An Introduction to African Malaria

Malaria is one of the most important infectious diseases in tropical Africa. It ignites 100–200 million bouts of illness annually, most mild and some severe. It kills by current estimates around 650,000 to 1.2 million Africans every year. Although there is no agreement on the best methodology for determining the number of malaria deaths – and thus the wide range of estimated mortality – specialists agree that the annual deaths are lower than those of just a few years ago.[1] A campaign to promote the use of bed nets, spray insecticides on the interior walls of dwellings, and provide antimalarial drugs is driving the numbers down.

Malaria has been an epidemiologically significant disease in tropical Africa for many millennia. Today, tropical Africa is the global epicenter of malarial infections. Malariologists estimate that approximately 90 percent of all malaria deaths occur in tropical Africa. The parasites that cause malaria and the mosquitoes that transmit the parasites are under assault, yet the infections are tenacious, and the dynamics of transmission are complex, volatile, and difficult to extinguish. Into the foreseeable future, malaria will remain a heavy disease burden under which Africans work and raise families.

[1] For the lower estimate, see World Health Organization, World Malaria Report 2011 (Geneva: World Health Organization, 2011). Available online: http://www.who.int/malaria/world_malaria_report_2011/en (accessed 15 May 2013). For the higher estimate, see Christopher J. L. Murray, Lisa C. Rosenfeld, Stephen S. Lim, Kathryn G. Andrews, Kyle J. Foreman, Diana Haring, Nancy Fullman, Mohsen Naghavi, Rafael Lozano, and Alan D. Lopez, "Global Malaria Mortality Between 1980 and 2010: A Systematic Analysis," *The Lancet*, vol. 379, no. 9814, 4 February 2012, 413–431.

THE EVOLUTION OF THE MALARIAL ENVIRONMENTS

On the basis of microbiological evidence and genetic studies, the broad picture of early human malarial infections is coming into focus.[2] Human beings have long been afflicted by several different species of one-celled parasites known as *plasmodia* that cause human malaria, and it is likely that four of the five species (*Plasmodium vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*) originated in tropical Africa, the birthplace of ancient humankind.[3] This malaria burden was probably very light during the early epochs of gathering, fishing, and scavenging, when our ancestors traveled in small bands and had only infrequent contacts with others. The earliest infections were zoonotic: they were transferred by species of mosquitoes that belonged to the genus *Anopheles*, which took blood meals from great apes who were infected by simian malarias and which then bit humans. The frequent displacements of early human groups typically meant that they moved beyond the flight range of the anopheline mosquitoes and thus that ongoing transmission of the parasites was rare.

One hundred thousand years ago – and perhaps even earlier – our ancestors began to settle along the banks of tropical African waterways to fish and to socialize during a few months of the year. These early camps provided a new epidemiological setting that facilitated a seasonal pattern of transmission of the malaria parasites.

[2] For an exploration of this early history, see James L. A. Webb, Jr., *Humanity's Burden: A Global History of Malaria* (New York: Cambridge University Press, 2009), 18–41.

[3] On falciparum, see Weimin Liu, Yingling Li, Gerald H. Learn, Rebecca S. Rudicell, Joel D. Robertson, Brandon F. Keele, Jean-Bosco N. Ndjango, Crickette M. Sanz, David B. Morgan, Sabrina Locatelli, Mary K. Gonder, Philip J. Kranzusch, Peter D. Walsh, Eric Delaporte, Eitel Mpoudi-Ngole, Alexander V. Georgiev, Martin N. Muller, George M. Shaw, Martine Peeters, Paul M. Sharp, Julian C. Rayner, and Beatrice H. Hahn, "Origin of the Human Malaria Parasite *Plasmodium falciparum* in Gorillas," *Nature*, vol. 467, 23 September 2010, 420–425.

For divergent interpretations of the origins of vivax, see Richard Culleton and Richard Carter, "African *Plasmodium vivax*: Distribution and Origins," *International Journal for Parasitology*, vol. 42 (2012), 1091–1097; Jane M. Carlton, Ararup Das, and Ananias A. Escalante, "Genomics, Population Genetics and Evolutionary History of *Plasmodium vivax*," *Advances in Parasitology*, vol. 81 (2013), 203–222.

Recently, researchers have discovered that a fifth species, *P. knowlesi*, infects human beings. Its distribution is limited to Southeast Asia. See Janet Cox-Singh and Balbir Singh, "Knowlesi Malaria: Newly Emergent and of Public Health Importance?," *Trends in Parasitology*, vol. 24, no. 9 (2008), 406–410.

For a graphic representation of the lifecycle of the malaria parasite, see page xxii.

The parasites caused disease.[4] In the case of vivax, malariae, and the relatively rare ovale infections, the disease frequently took the form of high fevers interspersed with chills, accompanied by nausea and diarrhea. It frequently produced anemia and an accompanying debilitation. These afflictions made it difficult to participate in the activities essential to group survival. Vivax emerged as the most important early malarial burden because the parasite had evolved with a dormant phase that allowed it to re-emerge from the liver after months or even years, and thus new rounds of infection were not dependent on the misfortune of the occasional cross-species infection.[5] The burden of vivax over time was sufficiently heavy to select for a human genetic variation that mitigated the damage.

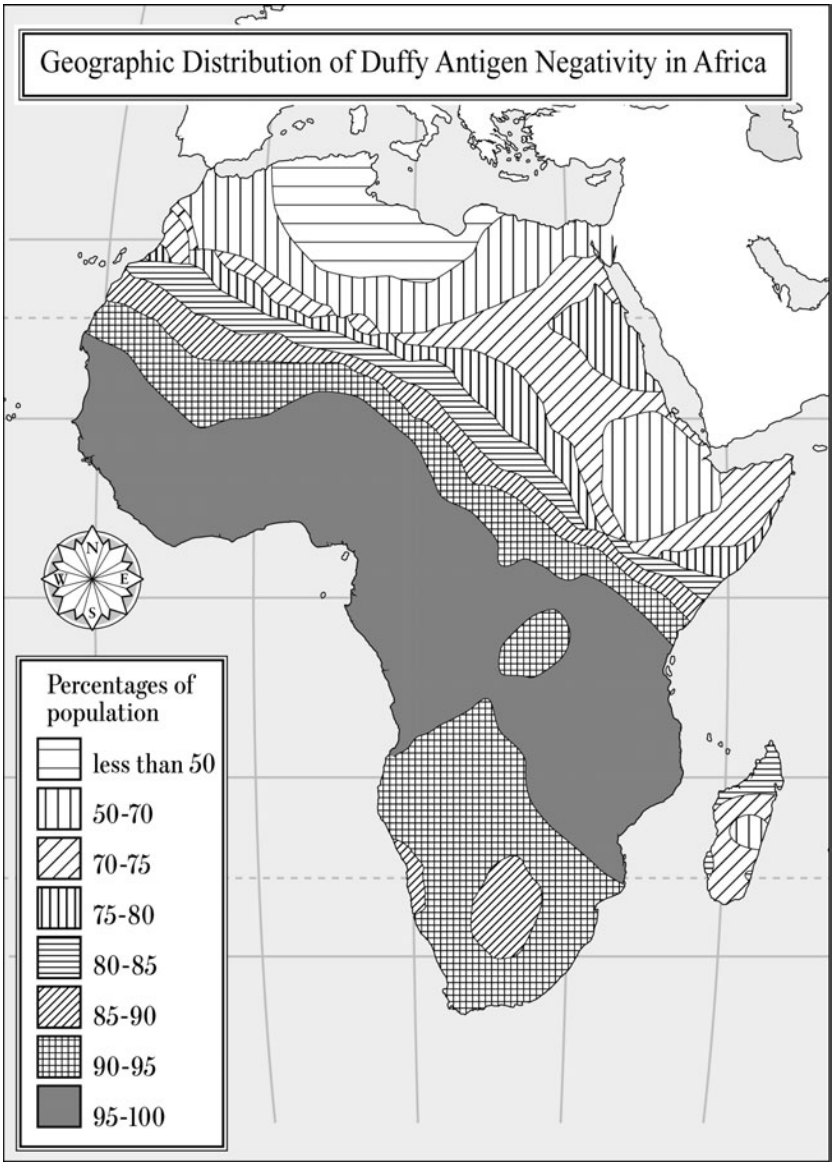
The critical genetic mutation took place in a surface antigen on the hemoglobin molecule. The mutation, known as Duffy Red Blood Cell antigen negativity – or Duffy negativity, was spectacularly successful. It prevented the parasite from infecting the red blood cell. The vivax parasite could not cause disease, and it could not reproduce. Duffy negativity was a definitive dead end for the vivax parasite.

Today, Duffy negativity is widely distributed in tropical Africa (see Map I.1). Its distribution probably reflects its early emergence tens of thousands of years ago and the competitive reproductive advantage of freedom from vivax infections and relapses enjoyed by those who carried the mutation. In a profound sense, the expanding expression of Duffy negativity was *the* determinative influence on the nature of African malaria. Vivax, the most common malaria parasite outside of tropical Africa, is rare in tropical Africa today.[6] Paradoxically, although Duffy negativity prevents vivax infections without health costs to the bearer, there have been enormous indirect costs borne by virtually everyone in tropical Africa.

[4] I use a shorthand when referring to an infection or disease caused by a malaria parasite: for example, a "falciparum infection" refers to an infection caused by *P. falciparum*.

[5] Ovale also developed a dormant liver phase. Relapsing ovale infections, in contrast to relapsing vivax infections, are often asymptomatic; the asexual parasite count rarely reaches high density; and the course of parasitemia is short compared to the other malaria parasite that cause sickness in humans. [William E. Collins and Geoffrey M. Jeffery, "*Plasmodium ovale*: Parasite and Disease," *Clinical Microbiology Reviews*, vol. 18, no. 3 (2005), 574, 578.]

[6] Vivax infections are transmitted among the small percentage of the population that is not protected by the Duffy mutation. See Franck Prugnolle, Virginie Rougeron, Pierre Becquart, Antoine Berry, Boris Makanga, Nil Rahola, Céline Arnathau, Barthélémy Ngoubangoye, Sandie Menard, Eric Willaume, Francisco J. Ayala, Didier Fontenille, Benjamin Ollomo, Patrick Durand, Christophe Paupy, and François Renaud, "Diversity, Host Switching and Evolution of *Plasmodium vivax* Infecting Great Apes," *Proceedings of the National Academy of Sciences*, vol. 110, no. 20 (2013), 8123–8128.



MAP 1.1. Geographic Distribution of Duffy Antigen Negativity in Africa
Adapted from L. Luca Cavalli-Sforza, Paolo Menozzi, and Alberto Piazza. *The History and Geography of Human Genes* (Princeton, NJ: Princeton University Press, 1994), genetic maps, 160. The data codings for Madagascar are derived from a map entitled "The Spatial Distribution of the Duffy Negative Phenotype Map in 2010 in Madagascar" made by the Malaria Atlas Project. Available online: http://www.map.ox.ac.uk/browse-resources/duffy-negativity/duffy-negativity/MDG/

Elsewhere in the global tropics, falciparum and vivax infections exist in a very rough equilibrium, jostling with one another as the locally or regionally dominant cause of malarial infection. (*P. malariae* generally plays a minor role; *P. ovale*, restricted to West Africa and the Pacific, is an infection of even lesser significance; and *P. knowlesi* is rare and restricted to Southeast Asia.) Tropical Africa is the grand exception. The near exclusion of vivax malaria from tropical Africa via the spread of Duffy negativity allowed for the broad dominance of falciparum malaria.[7] This constituted an epidemiological disaster. The African mosaics of malaria parasites came to be dominated by falciparum, the most dangerous parasite.

Falciparum infections, like those caused by the vivax, malariae, and ovale parasites, ignite a characteristic pattern of fever and chills with nausea and diarrhea and produce anemia. Falciparum infections, however, frequently cause more dire complications. Falciparum malaria can involve temporary or permanent coma, mental retardation, organ failure, and death. Falciparum, in the absence of medical intervention, may kill up to 20 percent of nonimmune individuals who are infected in the course of an epidemic.[8] By comparison, the death toll of vivax malaria is dramatically lower. Vivax, in the absence of medical intervention, may kill 1 or 2 percent of nonimmune individuals who are newly infected, and up to 5 percent in the case of individuals with a compromised nutritional or immunological status. No mortality estimates have been developed for malariae or ovale in tropical Africa, in part because these infections often occur in combination with falciparum.

Falciparum parasites thus posed a greater threat to tropical Africans than did vivax, malariae, or ovale parasites. The early history of falciparum infections is currently under laboratory investigation. Recent research suggests that a significant increase in falciparum infections may have occurred about 40,000–20,000 years ago.[9] The microbiological responses

[7] The dynamics of mixed infections are complex and only partly modeled. Longitudinal studies of mixed infections are rare. Mixed vivax and falciparum infections, however, are estimated to result in a far lower rate of severe clinical malaria. See Daniel P. Mason and F. Ellis McKenzie, "Blood Stage Dynamics and Clinical Implications of Mixed Plasmodium Vivax-Plasmodium Falciparum Infections," *American Journal of Tropical Medicine and Hygiene*, vol. 61, no. 3 (1999), 367–374.

[8] J. -F. Trape and C. Rogier, "Combating Malaria Morbidity and Mortality by Reducing Transmission," *Parasitology Today*, vol. 12, no. 6 (1996), 239.

[9] Hsiao-Han Chang, Daniel J. Park, Kevin J. Galinsky, Stephen F. Schaffner, Douda Ndiaye, Omar Ndir, Souleymane Mboup, Roger C. Wiegand, Sarah K. Volkman, Pardis C. Sabeti, Dyann F. Wirth, Daniel E. Neafsey, and Daniel L. Hartl, "Genomic Sequencing of

to heavy falciparum pressure, however, appear to have occurred in a more recent historical era. Falciparum may have begun to exert heavy selection pressure with the development of paracultivation of yams in the woodlands and forest-edge ecologies within the last 10,000–15,000 years. This falciparum pressure selected for genetic mutations that would convey a survival advantage, as vivax pressure had done in an earlier epoch.

Unlike Duffy negativity, however, the genetic hemoglobin mutations to falciparum pressure, known as *thalassemias*, conveyed significant costs as well as benefits. The bearers of these thalassemias can suffer severe anemia, growth failure, jaundice, and other complications. In tropical Africa, the mutation known as alpha-thalassemia is widespread. One of its most common variants is known as the sickle-cell trait, because it produces a sickle-shaped deformation of the red blood cell. These mutations are inherited, and when both parents biologically pass on the mutated gene, and thus the child is homozygous for the mutation, the health burden is great. Most children in tropical Africa who are homozygous for the sickle-cell trait do not live to the age of sexual maturity. Children who are heterozygous (with one mutated gene and one normal gene) inherit some protection from severe malaria.[10]

Plasmodium falciparum Malaria Parasites from Senegal Reveals the Demographic History of the Population," *Molecular Biology Evolution*, vol. 29, no. 11 (2012), 4327–4339.

[10] The normal hemoglobin molecule is made up of four chains of proteins, two alpha-globin and two beta-globin. The genetic mutations to malaria pressure involve changes in one or more of the genes that govern the production of these proteins. Hemoglobin S is a mutation caused by a particular amino acid substitution in the beta chain (valine for glutamic acid at position 6). For a brief overview of red cell polymorphisms and malaria, see Kevin Marsh, "Immunology of Malaria," in David A. Warrell and Herbert M. Gilles (eds.), *Essential Malariology* (London: Arnold Publishers, 2002), 253–256.

The thalassemias are a heterogenous group of conditions characterized by a reduced rate of production of one or more of the globin chains. In tropical Africa, the principal mutations are in the alpha-globin protein. For evidence of the protective value of alpha thalassemia, see Frank P. Mockenhaupt, Stephan Ehrhardt, Sabine Gellert, Rowland N. Otchwemah, Ekkehart Dietz, Sylvester D. Anemana, and Ulrich Bienzle, "Alpha +–thalassemia Protects African Children from Severe Malaria," *Blood*, vol. 104, no. 7 (2004), 2003–2006.

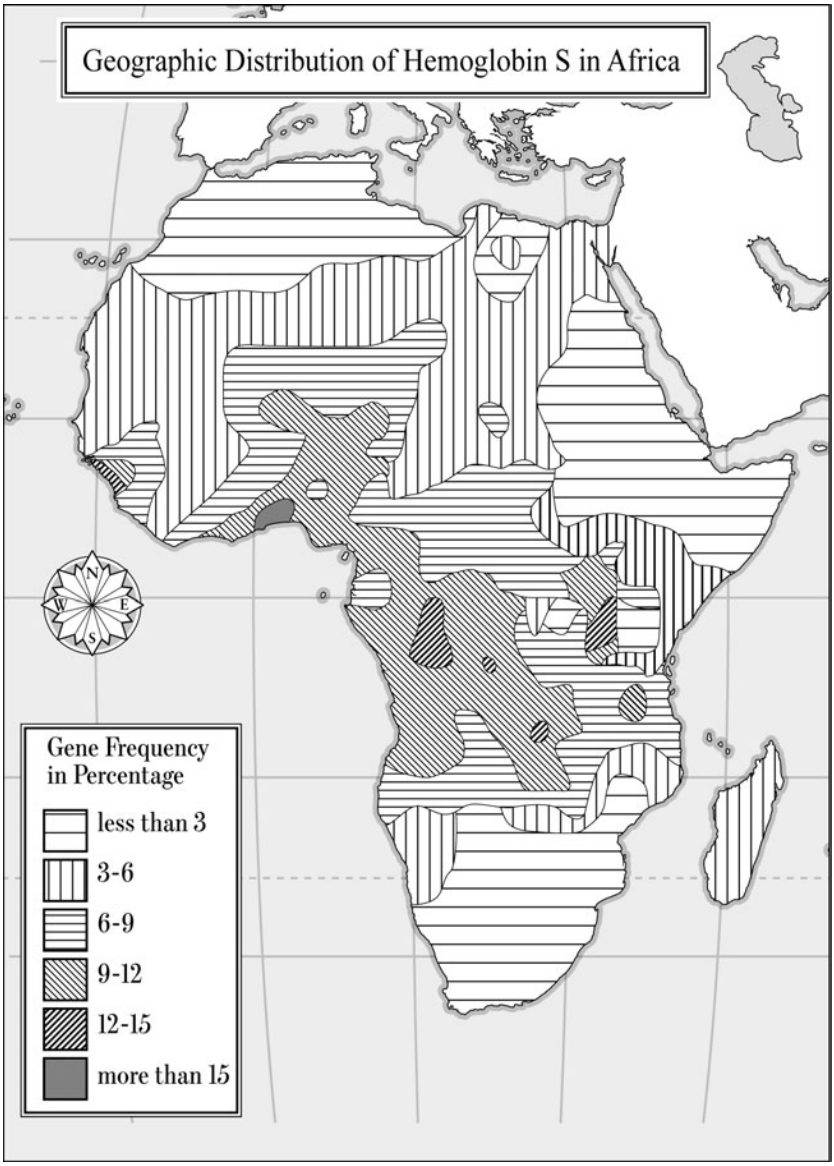
For the distribution and gene frequency of the alpha-globin mutations, see L. Luca Cavalli-Sforza, Paolo Menozzi, and Alberto Piazza, *The History and Geography of Human Genes* (Princeton, NJ: Princeton University Press, 1994), figures 2.14.5.A [world distribution] and 2.14.5.B [African distribution], 150; for world distribution of the beta-globin mutation, figure 2.14.6.B, 151.

It is possible that the hemoglobin mutation known as Hemoglobin C affords protection against malaria, although expert opinions differ. For the distribution and gene frequency of Hemoglobin C in Africa, see Cavalli-Sforza, et al., *History and Geography of the Human Genes*, figure 2.14.2, 148.

Over thousands of years, apparently well after the emergence and spread of Duffy negativity, as Africans extended their settlements throughout the continent, they carried malaria parasites with them in their blood (Map I.2). These were long-unfolding processes launched from West and Northeast Africa. The population movements from West Africa are known as the *Bantu migrations*; Christopher Ehret has analyzed the close connections between the languages spoken by the modern descendants of the original agricultural migrants and has argued for the relatively recent nature of the two-phase expansion, dated to 5500–4500 BCE and 1500 BCE–500 CE. From northeast Africa, the southward and westward movements of pastoralists and farmers known as the *Cushitic migrations* are dated to 4000–3000 BCE. Some of these pioneers reached southern Africa only in the early centuries of the second millennium CE.[11] There, agriculturalists and "mixed farmers," who practiced both agriculture and livestock herding, displaced hunting and gathering peoples and established new malarial environments. Even within long-settled zones, as African communities slowly built their numbers, they transformed their environments. In a broad sense, human communities inaugurated and/or intensified the malarial environments. In the forested zones, they cut holes in the forest canopy in order to grow food and inadvertently created new mosquito habitat. In the practices of vegeculture and seed-based agriculture, they created new contours to capture rainwater and created mosquito-breeding habitats. In building huts and compounds, they used local soils dug from "borrow-pits" that then filled with rainwater and in which mosquitoes bred. By settling, they improved the prospects for mosquitoes searching for blood meals in order to reproduce, and over time, the human settlements facilitated the evolution of anopheline species that had a strong preference for taking blood meals from humans rather than other animals. In these respects, the malarial environments of tropical Africa are relatively recent artifacts of human settlement.

As populations grew, societies became more complex. The tropical malarial environments, once highly localized, became increasingly integrated, with regional variations. This was true in all of the ecological zones – the sahel, savanna, woodland, lake coast, seacoast, and forest. In all zones, the parasite mosaics were dominated by falciparum. The environments differed in the intensity of transmission by virtue of the ecological behaviors of the different anopheline species that had adapted to the

[11] Christopher Ehret, *The Civilizations of Africa: A History to 1800* (Charlottesville: University of Virginia Press, 2002).



MAP 1.2. Geographic Distribution of Hemoglobin S in Africa
Adapted from L. Luca Cavalli-Sforza, Paolo Menozzi, and Alberto Piazza. *The History and Geography of Human Genes* (Princeton, NJ: Princeton University Press, 1994), figure 2.14.1.D, 147.

vegetation covers, patterns of rainfall, and the available blood meals in the regional habitats.

There were also important variations by altitude. Temperature was a principal limiting factor for both mosquitoes and human beings. In most highland regions above 6,500 feet, anopheline mosquitoes were rare, and the temperatures were typically too low to allow the parasites to reproduce. Settled human communities at these altitudes were sparse too, because cooler temperatures reduced the productivity of agriculture. Below 6,500 feet, the highland regions varied considerably, according to differences in physical relief, vegetation, and agricultural practices, but communities located between 3,500 and 6,500 feet altitude could be subject to occasional epidemics.[12] Humidity was also a limiting factor: to the north of the sahel, the environment was too dry to permit agriculture, and in the full desert, the transmission of malaria was limited to oasis settlements. There, the arrival of long-distance traders who had picked up infections elsewhere could set off an outbreak among oasis dwellers.

Parasite Mosaics

As falciparum became the dominant parasite in the regional configurations or *mosaics*, the *P. falciparum* parasite mutated into an array of different genotypes. The genotypes within a given mosaic played a central role in infections. During early encounters, African children acquired specific immunities through exposure to one or more of the genotypes. Cross-immunity between genotypes, however, was imperfect, and when a child or adult struggled with a new genotype for the first time, a severe bout of disease typically ensued.

The parasite mosaics in tropical Africa were unstable. Over millennia, African pioneers expanded into all of the ecological zones of the subcontinent and founded new communities. African merchants in trade diasporas carried goods across long distances, linking communities in different ecological zones. During the precolonial centuries before European military conquest of tropical Africa (1879–1914), predatory raiding and warfare between African states engulfed many African communities. Large numbers of people were forced to migrate within tropical Africa, and many were captured and sold as slaves. These internal slave trades, in

[12] Jean Mouchet, Pierre Carnevale, Marc Coosemans, Jean Julvez, Sylvie Manguin, Dominique Richard-Lenoble, and Jacques Sircoulon, *Biodiversité du paludisme dans le monde* (Montrouge: Éditions John Libbey Eurotext, 2004), 81–82.

conjunction with the chaotic displacement of populations during times of political and economic upheaval, brought about an unprecedented, rapid mixing of the parasite genotypes.

This was true as well of the external slave trades that brought captives into unfamiliar disease environments and thereby extended and reconfigured the parasite mosaics. This was the case, for example, during the long centuries of the external slave trades when many millions left tropical Africa in chains, sold into forced labor in North Africa, the Indian Ocean world, and the Americas. The Atlantic slave trade was the last of the three great outflows of African captives, and it is the best documented: during the seventeenth, eighteenth, and nineteenth centuries, the volume of slave exports into the Americas far outstripped those to other external markets. In the New World, the forcible transfer of some 12 million Africans transformed disease environments, creating lethal falciparum-rich malarial stews in the Caribbean and in regions of the South Atlantic fringe where African populations were in the majority.[13]

The parasitological details of these historical processes are not recoverable using current techniques. The broad picture within tropical Africa, however, is reasonably clear, with two salient features. First, in areas in which Duffy negativity was widely expressed – in all of tropical Africa – *P. falciparum* dominated the subcontinental mosaic and, by the early twentieth century, was involved in more than 90 percent of all malarial infections.[14] Second, many malarial infections involved more than one species of parasite, and most mixed infections involved *P. malariae*.[15] The usual peak prevalence of *P. malariae* in the parasite mosaics studied

[13] Webb, *Humanity's Burden*, 66–91; John R. McNeill, *Mosquito Empires: Ecology and War in the Greater Caribbean, 1620–1914* (New York: Cambridge University Press, 2010).

[14] The first studies of African parasites held that falciparum infections were the only kind to be found among the African communities of the west coast of the continent. Stephens and Christophers, on the basis of an analysis of 639 cases, found not a single vivax or malariae parasite and judged that they were nonexistent. [J. W. W. Stephens and S. R. Christophers, "The Malarial Infection of Native Children," in *Reports to the Malaria Committee of the Royal Society*, third series (London, 1900), 4–5.]

[15] In the wider world, malariae was far less common an infection than vivax, and among malariologists working outside of tropical Africa, it received little research attention. [Émile Marchoux, "La fièvre quarte et son mystère," *Revue coloniale de médecine et chirurgie*, 15 October 1930, 213–220.]

From the earliest investigations of parasite prevalence in clinical malaria, most findings agreed on the predominance of falciparum parasites and that *P. malariae*, which caused the distinctive seventy-two-hour fever known as *quartan malaria*, was the second most prevalent malaria parasite. Because malariae was far less lethal than falciparum, it attracted far less attention.