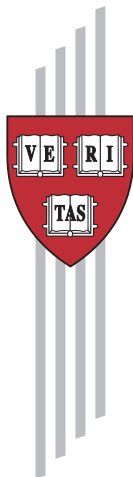


The Changing Global Distribution of Malaria: A Review

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Abstract

Organized efforts to reduce the burden of malaria are as old as human societies. Understanding the historical relationships between humankind and malaria is important for natural and social scientists studying the disease, as well as policy makers trying to control it. Malaria once extended widely throughout the old world, reaching as far north as 64°N latitude and as far south as 32°S latitude. Today, however, malaria is almost exclusively a problem of the geographical tropics. Analysis of historical changes in malaria prevalence suggests a number of factors which help to determine the likelihood and sustainability of success in malaria control. Among these are geography, evolutionary history of flora and fauna, infrastructure, and land use. It is due to these factors, much more than socio-economic ones, that attempts to control or interrupt transmission of the disease have historically been most successful on islands, in temperate climates, or at high elevations.

Keywords: malaria, geography, history

JEL Codes: I1, N5, N7, O1

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The Changing Global Distribution of Malaria: A Review

Amar Hamoudi and Jeffrey D. Sachs¹

Humankind shares a long and tumultuous history with the four protozoan parasites that cause malaria. In spite of numerous organized attempts to reduce their impact, these pathogens have prospered over the millennia, spreading far beyond their evolutionary origins in Africa and Southeast Asia. Even now, a century since its etiology and life-cycle were elucidated, malaria continues to present a daunting public health challenge. In 1990, the WHO estimated global malaria incidence at about 120 million clinical cases annually; in 1994, they estimated 300-500 million cases annually (1; 2). Understanding the historical relationships between humankind and malaria is necessary on at least three levels. First, in biological terms, it is necessary for our understanding of the evolutionary history of the disease (3). Second, in programmatic terms, it is necessary for the design of malaria control efforts which do not repeat past mistakes (4). Third, in economic terms, it is necessary for our efforts to determine the ways that malaria takes a toll on human communities, and to design targeted policies to alleviate the burden of the disease (5).

The life-cycle of vector-borne diseases like malaria is complex relative to that of many directly-transmitted human diseases (including bacterial or viral diseases like bacterial meningitis or HIV). On the whole, directly transmitted diseases require a threshold level and complexity of population agglomeration, and are therefore relatively recent phenomena—perhaps evolving within the last 10 millennia (6; 7). In contrast, the relationship between humans and malaria may date back several million years (8). Because malaria parasites appear to have coevolved with the human species, these two populations appear to be well adapted to each other. The various *Plasmodium* species may not even stem from the same ancestor; the genus may be polyphyletic. Although certain evidence suggests that *P. falciparum* coevolved with *Homo sapiens*, other observations indicate that it may have emerged first in a non-human host such as the chimpanzee. Either model would help explain some of the complexity of malaria's mechanisms for evading our immune system (9; 10). Historically, it has been proposed that diseases evolve toward reduced virulence for their hosts; using this logic, the relative age of the parasite-host relationship

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might be taken as a suggestion that malaria has become more tame than other, younger diseases. The proposition of such an evolutionary tendency, however, has been widely dismissed by scholars as inconsistent with empirical data. Malaria remains extremely burdensome, causing about 2 million deaths annually.

The archives of numerous ancient human societies refer frequently and in varying detail to intermittent fevers that may have been malaria (11). Malaria once extended widely throughout the old world, reaching as far north as 64°N latitude and as far south as 32°S latitude (12). Today, however, malaria is almost exclusively a problem of the geographical tropics. Figure 1 shows an overlay of data from World Health Organization maps of malaria risk in 1946, 1966, and 1994, illustrating the extent of this localization to the tropics. Of about 120 countries, islands, or colonies where malaria was endemic in 1945, the disease has disappeared from 15 European countries, about seven islands or archipelagoes, the United States, Israel, and Chile (13). José Nájera and others have broadly classified trends in the remaining countries where malaria is endemic (14). As table 1 shows, the current situation is not uniform. For example, only 9% of Malaysia's population lives in regions where malaria is transmitted, and in 1994 59,000 cases of malaria were diagnosed in health clinics serving a total population of 20 million people. In contrast, the whole of Tanzania's population of 29 million remains at risk of contracting the disease, with more than 8 million diagnosed in health clinics in 1994. About 40% of the world's population remains at risk for infection, of whom 19% live in Africa; in addition, about 90% of clinical malaria cases occur in sub-saharan Africa (2).

Data on malaria incidence, morbidity, and mortality are incomplete and often of questionable quality. In Africa, for example, it has been estimated that the approximately 28 million reported cases of malaria account for only 5-10% of total malaria incidence on the continent. Nájera et al. report that the most accurate reporting of malaria incidence likely takes place in Brazil, India, and Thailand, where about half of clinical cases are reported. The WHO estimates malaria to account for 1.5-2.7 million deaths each year, although it is noted that this statistic "may vary by a factor of 3, depending on the method [of estimation]."(2) Incidence data in Africa are so underreported that they are misleading, and therefore often excluded from assessments of the world malaria situation, although on the order of 90% of malaria cases occur on the continent. In many of the regions where malaria remains endemic, the situation is growing increasingly difficult to control. Parasite strains resistant to chloroquine, the most common anti-malarial drug, have spread throughout Asia, Africa, and parts of South

America. In some regions, particularly in Southeast Asia, multi-drug resistant strains are beginning to spread, posing a threat to all means of effective case management. An effective vaccine is still many years away. In addition, the spread of insecticide resistant vectors poses a challenge to epidemiological control efforts. According to the Malaria Foundation International, malaria incidence in Africa may be increasing by 20% each year (15).

Ronald Ross modeled the epidemiology of malaria mathematically, and his equations were refined in 1957 by George Macdonald (16). These models, although they have been extensively refined (17; 18), still form the basis of our understanding of malaria transmission. Macdonald defined the basic reproduction number (originally described as a “rate”) as the number of secondary infections which result from a single infection over the period of a case’s infectivity, assuming a perfectly immunologically naïve environment. As the basic reproduction number increases, it becomes more difficult to protect a community from infection, since each single case poses a danger to a larger proportion of the community. Macdonald denotes the basic reproduction number, z_0 , as follows:

$$z_0 = \frac{ma^2bp^n}{-r \ln p}$$

where m is defined as the abundance of anophelines relative to the human population

a describes the propensity of a vector to bite a human host

b is defined as the proportion of mosquito bites which are infective

p is defined as the probability that a mosquito will survive a single day (p is greater for longer-lived species)

n is defined as the extrinsic incubation period, or duration of the mosquito phase of the parasitic life-cycle

and r is the rate of recovery of the human host

² This equation is derived from:

$$z = \left(1 - \frac{ax}{ax - \ln p}\right) * \left(\frac{ma^2bp^n}{-r \ln p}\right)$$

where x is the proportion of the human population which is infected at any given time.

z_0 is the limit of z as x approaches zero—the postulation of a perfectly immunologically naïve community. In a context of sustained transmission,

Although numerous simplifying assumptions are embedded in these equations, they illustrate some of the most important determinants of malaria transmission.

m, mosquito abundance

Macdonald defines m as “the anopheline density relative to man.” More specifically, m is the quotient of the population of vector mosquitoes and the human population. It is in part determined by a number of environmental, geographical, and species-specific factors. Mosquito larvae mature in aquatic environments; therefore the presence of suitable water is a requirement for mosquito reproduction. However, there is enormous heterogeneity between mosquito species in the specific environmental factors which favor efficient reproduction. Some of these factors include the presence or absence of shade, brackish or fresh water, and deep or shallow pools. Since m is linearly related to z_0 , the abundance of mosquitoes can be shown to have a small impact on the efficiency of malaria transmission relative to other factors. Historically, therefore, efforts to control malaria by reducing mosquito populations have been aimed at mosquito breeding sites; only if breeding sites could be eliminated, the thinking went, could anopheline populations be reduced sufficiently to control malaria transmission. Outside of Europe and the United States, malaria transmission has almost never been dampened sustainably by reduction of anopheline abundance.

a, host specificity

Macdonald defines a as “the number of people bitten by a single mosquito in a single day.” Therefore, this variable provides an indication of the narrowness within which a vector’s attention is focused on humans—vectors which are more likely to be diverted from a person by the presence of a horse would, of course, bite fewer people than those which avidly forego the horse in favor of the person. Two factors largely govern a —first, the mechanisms of host seeking behavior of the vector mosquitoes, and second, the presence or absence of alternative hosts. The species-specific mechanisms of host-seeking behavior can be described as determining an underlying value of a , indicating how anthropophilic³ a local vector would be in an environment with an optimal distribution of potential hosts. The relative abundance of hosts, on the other hand, would determine a ruling value of a where the

however, this condition is contrary to fact. Therefore, in a static context, the “ruling reproduction number,” which gives the slope of the observed epidemic curve, is often far less than the basic reproduction number.

relative abundance of potential hosts was not optimal. The mosquito may prefer a cow to a human, but where no cows are available, the mosquito will content itself as an anthropophile. The mechanisms of host-seeking behavior in mosquitoes are the object of an enormous amount of research among entomologists, but there is general consensus that host preference is genetically determined within mosquito species by means of variations among olfactory organs (19). In addition to distracting more zoophilic vectors by introducing animal “barriers” these vectors may be diverted by improvements in animal husbandry, whereby sufficient distance is maintained from the animal hosts (these practices have been described as “zooprohylaxis”).⁴ z_0 is related to the square of a ; therefore, host specificity is one of the more powerful determinants of the efficiency of malaria transmission.

b , proportion of infective bites

Macdonald defines b as “the proportion of anophelines with sporozoites in their glands which are actually infective.” It describes the probability that a bite by an infected mosquito will cause the person bitten to contract malaria. It is governed by a number of factors, including the infectiousness or “quality” of the sporozoites injected by the feeding mosquito, the number of oocysts which form on the mosquito stomach wall, the number of sporozoites which emerge and infect the mosquito salivary gland, and the number of sporozoites injected. These factors vary between both vector and parasite populations. Although b relates only linearly to z_0 , control strategies have been designed which aim to reduce this variable by introducing a vaccine to prevent sporozoite invasion of the liver cells of vaccinated hosts.

p , probability of survival

Macdonald defines the variable p as the “probability that a mosquito will survive a whole day.” Therefore p^n is the probability that the mosquito will live for n days, diminishing as n increases. Of course, as p approaches its limiting value of 1, mosquito longevity increases. In nature, p has been observed to range between 0.6 and 0.95, varying between mosquito species (20). Macdonald’s equation shows that, holding all other things constant, z_0 is proportional to $p^n / \ln p$, which, it can be shown, is the same as $Ee^{E/n}$ where $E = -1 / \ln p$ is defined as the life expectancy of the mosquito. Therefore, this term plays by far the most powerful role in defining z_0 . Historically, control

³ A zoophylic vector prefers to feed on non-human animals; an anthropophilic vector prefers to feed on humans.

⁴ Of course, zooprohylaxis is often not a deliberate intervention strategy. As described below, in Europe, improvements in animal husbandry

strategies aimed at manipulating this variable have involved the residual application of insecticides on surfaces where recently blood-fed mosquitoes are likely to rest. This was the strategy of the World Health Organization's Global Malaria Eradication Program in the 1950s and 1960s.

n, extrinsic incubation period

n is the total number of days required for the completion of the mosquito portion of the parasite life-cycle, including the fusion of micro- and macro-gametes, ookinesis, oocyst formation, sporozoite formation, and sporozoite migration. After biting an infected human, a mosquito will not be able to infect another person until *n* days have passed. Therefore, p^n is the probability that a mosquito will live long enough to become infective. Under laboratory conditions, a number of factors may affect *n*, including temperature, chemical and biochemical factors (for example, pH), host abundance, competition, and nutrition. In nature, values for *n* usually only exist for ambient temperatures between 18°C and 30°C for vivax malaria, and between 20°C and 30°C for falciparum malaria, although this range varies between microhabitats. As shown above, *n* plays a very powerful role in defining z_0 , and in those climates and habitats where ambient temperature and species specific factors render p^n sufficiently close to zero, transmission of malaria is unstable or even impossible.

r, recovery rate

According to Macdonald, *r* is often considered to be constant in a perfectly naïve community ($r=0.0125$). He defines it as “the proportion of affected people, who have received one infective inoculum only, who revert to the unaffected state in one day.” However, *r* may be described as dependent on a number of factors. The “molecular arms race” between humans and malaria parasites may be millions of years old, possibly resulting in more evolutionary adaptations in humans than any other disease (9; 21). These adaptations, which vary between human population groups, help to determine varying susceptibility to infection and immune responsiveness. Among the most well known of these adaptations are sickle-cell trait, the Duffy blood group negativity, and Glucose-6-phosphate dehydrogenase deficiency. Sickle-cell trait and Duffy are most common in African populations, and may help to illustrate malaria's long history on the continent. Adaptations which reduce susceptibility to infection effectively reduce the value of *b*, while those which enhance immune responsiveness increase *r*. Of course, the

had a profound, yet unexpected, impact on malaria transmission during the interwar period.

effects of these adaptations may be mimicked by effective primary health care; the availability of effective prophylaxis affects b and therapy affects r . The variables b and r are unlike the others in Macdonald's basic equation in that they relate directly to individual infections. These variables, therefore, are the quantitative link between patient care and epidemiological control.

In considering Macdonald's model, it is also important to note that in nature there are complicated relationships between these variables which may make it difficult to manipulate one while holding the others constant. For example, "larval control strategies," designed to reduce mosquito abundance (m) by disrupting reproduction may actually result in selection for a stronger and healthier adult mosquito population, thereby increasing p (22).

Another important concept to consider in understanding the dynamics of malaria is the stability of equilibrium. A stable transmission equilibrium is one which is not sensitive to changes in z_0 . Macdonald originally described the stability of equilibrium as the rate of change of L_x , which is the limiting value of the infected proportion of the population, per unit change of z_0 , or $\frac{dL_x}{dz_0} = \frac{-\ln p}{a}$. Note that by this definition, the stability of equilibrium is inversely proportional to both host specificity and vector life expectancy. Therefore, a short lived vector which is not specifically inclined toward biting humans supports a lower initial value of z_0 and therefore provides a "head start" for antimalaria efforts. In addition, the transmission equilibrium in such a context is more sensitive to subsequent changes in z_0 .

The History of Control Efforts

Organized efforts to reduce the burden of malaria are as old as human societies. Russell, for example, provides detailed descriptions of the efforts from pre-Roman Etruscans to Napoleon to drain the marshes surrounding Rome, whose "noisome smells" were believed to cause pestilence (23). But it was considerably more difficult to fight an unseen enemy, and before the parasites were discovered and their life cycle characterized a century ago, malaria could only be associated with poor sanitation. Harrison explains that malaria was seen as a "disease of rural decay, spawn of ill-kempt, savage, and uncultivated land, yielding to good husbandry and civilization." (24) Hippocrates observed that "[where] there be rivers. . . which drain off from the ground the stagnant water. . . [the people] will be healthy and bright. But if there be no rivers, and the water that the people

drink be marshy. . . the physique of the people must show protruding bellies and enlarged spleens.”(23)

Accordingly, therefore, most early efforts at malaria control focused on sanitation and land use strategy. But the germ theory of disease, when it became universally accepted during the 19th century, suggested that underlying these environmental determinants, malaria had a fundamentally biological cause. The expansion of colonial powers into the malarious tropics brought new urgency to European efforts to understand the etiology of malaria. According to Harrison (25),

equatorial Africa, the principal arena of 19th century empire, had notoriously resisted white settlement. . . everywhere in the tropics the white men languished and died, wasted by the heat and ravaged by disease, above all by malaria.

Throughout the century, a succession of colonial army officers, as well as scientists from Italy (malaria endemic at the time), doggedly tracked the disease until its entire life-cycle, etiology, and epidemiology had been elucidated in detail. When Ronald Ross provided irrefutable empirical support for the mosquito theory, it seemed logical to focus anti-malaria efforts on the mosquito. Ross himself delivered a lecture in 1900 at University College, Liverpool, entitled “The possibility of extirpating malaria from certain localities by a new method.”(26) Every noted malaria intervention during this period was aimed at reducing vector populations (m in Macdonald’s equation, above—although, of course, this equation would not be published for another half century). Ross, for example, spearheaded an effort designed to reduce anopheline populations in Freetown, Sierra Leone by isolating and eliminating breeding sites, without success (his initial studies led him to conclude that there were about a hundred puddles which were likely to be *Anopheles* breeding sites; if these could be eliminated, malaria would be eradicated from the city. He anticipated that a successful effort would cost around £140) (25). Ross, in his memoirs, describes similar efforts in Havana, Lagos, and Hong Kong. Stephens and Christopher tried to improve on these efforts in the Indian city of Mian Mir, also without success. These efforts are described in detail elsewhere (4; 23; 25; 26), although it is fairly clear that the failure in controlling anopheline populations stemmed from poor understanding of the behavior of the vectors; the science of medical entomology was yet to emerge. Some early efforts at malaria control succeeded, however. For example, in 1901, Malcolm Watson was able to save colonial plantations in Malaya through “fine tuning of the environment” to eliminate the local vector, thereby reducing fevers by 90% in two years (25). Watson’s positive results have been attributed to the strategies of exfoliation and reduction of the salinity of some coastal swamps (he had built dikes to cut the swamps off from the sea). His success would lead to the concept of “species sanitation,” which employed environmental engineering designed to have specific and

devastating impact on local disease vectors. Ten years later, however, the disease returned to cause a cataclysmic outbreak, demonstrating the precariousness of malaria control. Similarly, in 1904, Gorgas' success in controlling malaria and eliminating yellow fever in the Panama Canal Zone—informed by successful vector control strategies in Havana and Panama city (of *Aedes aegypti*, a yellow fever vector)—allowed the United States to complete the canal project which the French had been forced to abandon. In an exhaustive history of the effort (27), Simmons describes Gorgas' intensive sanitary strategy in the Canal Zone, as well as the cities of Panama and Colon:

Listed in the order of their development the procedures advocated or used have passed through the following phases, which overlapped in some instances: (1) the therapeutic and prophylactic use of quinine; (2) the use of mosquito nets, and the screening of houses; (3) the killing of adult mosquitoes in dwellings and the elimination of harboring places by cutting away sheltering underbrush; (4) the destruction of mosquito larvae and pupae by the use of oil and other larvicides; (5) the elimination of breeding places by filling, draining, training streams, and by admitting the tide to replace impounded fresh or brackish water with circulating sea water; and (6) the attempt to drain all standing water by permanent sub-soil tiling and concrete-bottomed ditches.

Extremely detailed data were made available to Gorgas about the population of the Canal Zone, its topography and geography, the epidemiology of its diseases, and its climate and temperature variations. In addition, he was given enormous financial support for his efforts. He designed an extremely centralized programmatic approach, and achieved rapid and sustained success (4; 25). Gorgas' success was a watershed in the history of malaria intervention, and played an essential role in Panama's subsequent malaria control efforts. It is important to note, however, that his scheme was focused exclusively on the Canal Zone and the cities of Panama and Colon (situated close to the canal's endpoints). According to Simmons, “[b]ecause of the expense involved, intensive anti-mosquito work has been limited to the immediate vicinity of the more important towns and Army posts.”

Italy produced many of the world's most important early malariologists, owing possibly to its long and problematic history with the disease. Bruce-Chwatt, in summarizing this relationship, proposes that malaria may have figured prominently in the downfall of Rome (24). Angelo Celli was one of the great Italian malariologists and an avid social reformer. At the beginning of the 20th century, Celli devised a malaria control strategy for Italy which differed markedly from the emerging “species sanitation” approach. In fact, where virtually all contemporary interventions had been vector focused, Celli's approach focused entirely on the human victims of the disease, most

of whom were the rural poor of the Roman Campagna—peasant farmers in the employ of absentee landlords. Malaria in Italy, as in the rest of southern Europe, followed a cycle of seasonal epidemics, with outbreaks of vivax malaria in the spring, and falciparum malaria in the fall. These cycles interacted with the cycles of communal immunological memory⁵ to produce regular peaks in malaria mortality every 5 years. Beginning in 1883, when the first statistics were compiled, total malaria mortality had already begun to decline, in the absence of any intervention program. In 1900, Celli advocated the distribution of quinine, at a price equivalent to its cost to the government, across the Campagna. He also successfully campaigned for the institution of economic and social reforms designed to provide the local population with the necessary tools (e.g., better houses, nutrition, etc.) to avoid or overcome malaria (an approach dubbed the “*bonifica integrale*”). This approach appears to have greatly accelerated the naturally occurring decline in malaria mortality, and was the beginning of a steady trend which ended in Italy’s eradication of malaria after World War II.

In addition to spurring the development of modern malariology, the increase of global traffic during the colonial period resulted in the importation of many infectious diseases to areas where they had not previously been endemic. In the case of malaria, such an importation occurred in Mauritius in 1866. Part of the three-island Mascarene archipelago, Mauritius has been separated from Africa for millions of years, and was not inhabited either by humans or anophelines until relatively recently. The first human inhabitants of the island were probably slaves transported by the Dutch from Madagascar in the middle of the 16th century. Owing to the ravages of periodic hurricanes, however, the island defied continuous habitation and served primarily as a temporary resting place for malarial travelers on the way back to Europe, until control of the island devolved to Britain in 1810. The British deforested much of Mauritius in order to establish sugar cane plantations, and despite the importation of laborers from malaria-endemic regions, malaria was not transmitted due to the absence of anopheline vectors (28). Over the course of the next half century, *An.gambiae* and *An.funestus* were imported via ship traffic and, owing to the previous deforestation and irrigation of the island, became indigenous. The combination of malaria vectors and malarial humans set off a series of massive epidemics, starting in the port city of Albion and following trade routes along the coast, then moving inland. In less than a decade, the disease became endemic. The dynamics of these epidemics are described elsewhere (25; 28; 29). Similar introductions of malaria occurred at the same time on

⁵ Naturally acquired immunity to malaria only lasts a short time in the absence of frequent reinfection.

Grand Comoros Island and Reunion Island. Malaria remained endemic in Mauritius and Reunion for a century before being successfully eradicated. The Mascarene experience remains one of the most informative illustrations of the dynamics of malaria epidemics in naïve regions where climate, geography, and fauna favor endemicity—dynamics which were later observed in regions where interventions had drastically reduced transmission for a sustained period of time, but where small parasite populations escaped surveillance.⁶ This dynamic was also observed in the resurgence of malaria in Malaya in 1911, after Malcolm Watson’s successful intervention in 1901.

By the time of the outbreak of World War I, therefore, other than the emerging success stories in Panama and Italy, the crusades to control the transmission of malaria had largely failed, although they offered a number of important lessons. These efforts had spawned a few debates which would shape the emergence of later international control policies. Among these, the alternative conceptions of malaria as a primarily social disease (as suggested by Celli and others) which is naturally and inevitably eliminated with the elimination of poverty, and malaria as a primarily entomological and clinical problem (as suggested by Watson and others), which required proper scientific intervention strategy, vied with each other for decades.

The two World Wars, and the concomitant social upheaval and economic decay, as well as the end of the colonial period, transformed anti-malaria efforts around the world. Between the wars, the reorientation of priorities among the colonial powers restricted these efforts almost exclusively to the United States and Europe, where the prevalence of malaria had begun to decline, even in the absence of any concerted intervention efforts. This spontaneous decline is primarily attributable to changes attendant on rapid economic growth in three important ways. First, the drainage of swamps in order to establish new agricultural land had drastically reduced the indigenous anopheline populations of malaria endemic regions in southern Europe and the American rural south. Similarly, improved facilities in animal husbandry led to better separation of humans and livestock, and diverted the attention of more zoophilic vectors.⁷ Second, increased income provided at-risk individuals with the means to

⁶ A similar but historically more important story of malaria importation may involve the introduction of the disease in the Americas by the *conquistadores* in the 17th century. However, as Russell points out, evidence is inconclusive as to whether or not the disease was already endemic before their arrival. Malaria remains endemic and virulent in tropical regions of Latin America.

⁷ It is important to note that no environmental change leads inevitably to a reduction in vector populations, owing to the wide heterogeneity of reproductive and biting behavior among anopheline species. For example, eliminating forest cover, which had made Malaya hostile to *An.maculatus* in 1901, had made Mauritius hospitable to *An.gambiae* in the 1860s. In fact, it was this awareness of heterogeneous behavior which theoretically underlay the concept of species sanitation. It happened, however, that the changes concomitant with economic development in Europe and the United States also rendered the environment hostile to most of the local vectors. As we have tried to emphasize, understanding the heterogeneity of vector behavior is extremely important in understanding global differences in malaria transmission.

improve their health-seeking behavior, including limiting their exposure to mosquitoes and seeking drug treatment (“radical” treatment schemes are those which have the goal of not only eliminating clinical symptoms but also clearing all parasites from the patient’s blood, are an important part of many malaria control strategies). Similarly, increased national wealth allowed for the establishment of an extensive health infrastructure, making primary clinical care easily accessible throughout the region. Finally, the establishment of large cities created environments hostile to the spread of malaria.⁸ Of course, it is impossible to know (and trivial to speculate) whether this spontaneous decline would have led inevitably to malaria eradication in Europe, if not for the direct intervention efforts of the 1930s, 1940s, and 1950s, but the observation of spontaneous decline of the disease seems to lend credence to the conception of malaria as a “social disease,” borne of poverty and poor sanitation. Europe’s experience, however, is not necessarily universally applicable. Hackett offers an important caveat:

Agricultural progress, land reclamation, animal deviation, quinine, screening—these changes may have been able in various ways to tip the scales against malaria in temperate climates because they have worked where climatic conditions are relatively marginal for transmission. The same changes have failed in the tropics in large part because *Anopheles* and *Plasmodium*, flourishing through the long, wet, warm seasons, can overwhelm any relatively minor improvements in human defenses.

In terms of Macdonald’s equation, above, the two variables which played an extremely important role in Europe’s success in controlling malaria were *a* and *p*. (Examination of the equation shows that these are its most quantitatively powerful variables). The primary malaria vectors in southern Europe included *An. maculipennis*, *An. superpictus*, *An. sacharovi*, and *An. labranchiae* (11; 24). *An. maculipennis*, in particular, is a complex of sub-species, each of which has a varying degree of anthropophilicity. (At the end of the 19th century and until 1930, a lack of understanding of this variation was the basis for the conundrum of “anophelism without malaria,” about which much has been written^{9 10}). In comparison to European vectors, some tropical malaria vectors, including for example *An. gambiae* in Africa, are more anthropophilic (30). In Europe throughout the early part of the 20th

⁸ Some of the complex effects of urbanization on malaria transmission are summarized in Oaks et al. *Malaria: Obstacles and Opportunities* (1991). Urban areas can be divided into two zones: the central zone, where the lack of suitable standing water renders vector reproduction extremely rare and where malaria transmission is significantly reduced compared to more rural areas, and the periurban areas, where increased population density and poor sanitation provide a more hospitable environment for vector reproduction. Malaria transmission in periurban areas is particularly problematic where the resident populations are migrants displaced from more malaria endemic rural areas (see also Nájera JA, BH Liese, and J Hammer (1992) “Malaria: New Patterns and Perspectives” World Bank Technical Paper no. 183).

⁹ see Litsios, Harrison, Bruce-Chwatt and Zulueta, and Hackett

¹⁰ After this principle was understood, according to Litsios, R. Senior White “speculated that [in England] it had been the introduction of turnip culture in the middle of the [19th] century to provide winter food for cattle, which by saving the herds from annual slaughter had initiated the

century, improvements in animal husbandry effectively reduced a by distracting vector mosquitoes and thereby dampened the transmission of the disease. In addition, these vectors are generally much shorter lived than other tropical vectors (most notably *An. gambiae* and *An. funestus*, another African malaria vector). This reduced value of p had always rendered malaria transmission less stable in temperate Europe than in the tropics. Residual application of DDT in the late 1940s further reduced p , dealing the final blow to European malaria.

There may have been other factors which made malaria transmission relatively unstable in Europe. For example, in temperate regions, mosquitoes spend the winter in a state of hibernation or non-reproductive semi-hibernation. In order to maintain transmission, therefore, temperate strains of *Plasmodium* species required a variety of biological mechanisms, including delayed patency (whereby the parasite spends the winter in the human liver) or prolonged incubation (spending the winter in the mosquito gut). These adaptations leave the pathogens particularly vulnerable to direct intervention, whereby well timed and widely concerted regimes of drug therapy and insecticide applications could target all the re-emerging parasites at arrested points in their life-cycle. The Dutch Malaria Commission, for example, introduced the idea of “autumnal quinization” in 1939. From mid-August until early November, during the height of the relapse and transmission season, they proposed an intense regimen of community wide quinine distribution and insecticide spraying. The program was hindered by the onset of World War II, by communal non-compliance in the drug regimen, and by other factors, but nonetheless managed to suppress an epidemic in one region.¹¹

Another non-entomological advantage of temperate regions is the relative absence of asymptomatic parasite carriers. Unlike many diseases (for example, measles), infection by malaria does not lead to the development of protective, sterilizing immunity. Instead, after repeated bouts of illness in a relatively short period of time, an individual develops a non-sterilizing immunity which does not prevent parasites from developing and circulating in the blood after a new inoculation, but does suppress the development of clinical symptoms (31). As a result, a population of apparently healthy individuals provides a parasite reservoir from which subsequent infections are transmitted. This non-sterilizing immunity only lasts a short time in the absence of reinfection. In highly

decline of malaria.”

¹¹ As discussed below, the use of quinine therapy to contain *P. vivax* transmission faces a number of obstacles. Later, when the drug Quiniplex was introduced, it played an important role in the ultimate elimination of malaria from the Netherlands. (Verhave, Jan Peter (1995) “The use of quinine for treatment and control of malaria in The Netherlands,” *Trop. Geog. Med.* 47:252-8)

endemic areas, therefore, a very large proportion of the indigenous adult population are parasite carriers, albeit apparently healthy. As transmission declines due to successful intervention it becomes increasingly important to identify and manage this potentially deadly parasite reservoir. Disease surveillance is much less costly in less endemic regions, where clinical symptoms conspicuously identify a larger proportion of parasitemic individuals.^{12 13} Malaria case detection in highly endemic areas is further confounded by the presence of other diseases whose symptoms resemble those of malaria. Thus, even when clinical symptoms do present themselves, malaria is only one of several possible diagnoses; in contrast, these symptoms (e.g., intermittent fevers, anemia, “paroxysms”) in the temperate zones pointed more directly to malaria.

In addition, due to both climatic and species-specific factors, European malaria vectors tend to rely on swamps for breeding. This rendered them more susceptible to the “bonifying” changes in land use trends throughout the early portion of the 20th century. Macdonald’s variable *m*, therefore, was more vulnerable to manipulation in Europe than elsewhere. For example, whereas agricultural development and land reclamation was hostile to the vector population on the Roman Campagna, it may have proven beneficial to the vector population in the Ethiopian highlands, where *An. gambiae* larvae have been observed feeding on corn pollen in puddles on newly developed farmland (20). Similar land reclamation schemes in the United States (most notably, the Tennessee Valley Authority project of the 1930s) greatly reduced vector populations and helped to bring malaria transmission under control.

Malaria, however, did not spontaneously *disappear* from Europe.¹⁴ Throughout the interwar period, direct interventions continued with great success, mainly in the form of radical drug therapy, environmental engineering, and application of larvicides and insecticides. Interrupted (and rolled back) by the widespread displacement of refugees and economic devastation of World War II, this success resumed in the late 1940s, and by the end of the next decade malaria had disappeared entirely from most of Europe. Today, malaria is endemic in only one European country—Turkey (32). Interestingly, in several places (e.g., Greece, Cyprus, and Italy), some malaria

¹² see Litsios, Pp. 94-96

¹³ For a discussion of the debilitating cost of malaria surveillance in the tropics, see Nájera et al.

¹⁴ Although it did disappear accidentally from Greece. Facing budget constraints, the Greek government in 1951 was forced to cut back its consumption of insecticides by spraying them only in particularly malarious areas. They were surprised to note that, in the formerly malarious areas where spraying had been interrupted, transmission did not resume. This experience was formative and, according to Pamapana, played an important role in the establishment of the WHO’s Global Malaria Eradication Program (see below) (Bruce-Chwatt and Zulueta, Hackett, Harrison)

vectors remain, suggesting that the danger of resurgence persists—if a few imported cases go undetected, the reasoning goes, a series of rapid and devastating epidemics could result, followed by the return of seasonal endemic malaria (11). However, as long as a sophisticated primary health care infrastructure exists and human-mosquito contact remains relatively controlled, imported cases of malaria can easily be eliminated in a timely manner with few or no secondary infections.¹⁵ The experience of these countries (and others, including Mauritius, where *An. gambiae* remains indigenous, but malaria transmission is extremely rare) helps to illustrate the difference between the challenges of preventing the re-establishment of malaria once it has disappeared and those of controlling its spread where it remains endemic.

It is possible to overestimate the role of drug therapy in the effort to control malaria in Europe. By far the most widely used drug for malaria therapy at the time was quinine; chloroquine, the most popular contemporary anti-malarial drug, was still in its experimental stages by 1947, when Europe was witnessing the final decline of malaria. In addition, most European malaria was caused by *P. vivax*, which, unlike *P. falciparum*, is particularly well-adapted to seasonal transmission, existing in two schizont forms in the human liver—one of which emerges to cause blood infections and clinical symptoms, and the other of which remains latent in the liver. It is this second schizont form which is responsible for *vivax*'s characteristic relapses, up to a year after inoculation (12). While quinine has rapid effectiveness in controlling clinical symptoms like fever, its concentration in the blood is extremely short-lived, and it has no appreciable effect on parasites in the liver. Therefore, doses of the distasteful drug must be administered extremely frequently in order to have even limited prophylactic effect; furthermore, it is well-established among clinicians that it is very difficult to convince an individual who does not suffer from clinical symptoms to maintain a drug regimen. All of these factors combined to make quinine relatively ineffective as an epidemiological tool. Widespread drug therapy in Europe, therefore, mitigated malaria-associated morbidity and mortality, but may have had less effectiveness than environmental changes and vector control measures in controlling the spread of the disease.¹⁶ Tropical *falciparum* malaria, however, does not relapse; once parasites are

¹⁵ In terms of Macdonald's basic reproduction equation, a sophisticated primary health care infrastructure and controlled human-mosquito contact respectively increase r —the rate of recovery, and decrease ma —the human biting rate.

¹⁶ A long debate among malariologists during this period focused on the effectiveness of quinine as a tool for malaria control. There are those, like Celli and Robert Koch, who suggested that quinine's effectiveness as a killer of *P. vivax* gametocytes could help suppress transmission by drastically reducing the size of the parasite reservoir during the transmission season, while others, like Hackett, suggested that quinine use was in fact counterproductive, alleviating clinical symptoms without controlling transmission, thereby diverting resources and providing a community with a false sense of security. Therefore, while radical drug therapy was an extremely important component in the malaria control and eradication strategies of countries across Europe, it is difficult to rank its historical importance against that of vector control techniques and

eliminated, only reinoculation with new sporozoites can cause another blood infection in the same individual. Therefore, this type of challenge is not among the many daunting challenges faced by the use of radical drug treatment to control the transmission of tropical falciparum malaria.

Throughout the interwar period and afterward, malaria control efforts continued in Panama (still, however, restricted to the areas of the Canal Zone with large U.S. staff communities). According to Simmons, Gorgas' previous success, as well as the completion of the canal and subsequent urbanization of the zone, made malaria control considerably easier by the late 1930s. Previous resurgences, however, like that observed in Malaya, had amply illustrated the cost of abandoning control programs at a point of disequilibrium. Therefore, Gorgas' intensely centralized organizational design for malaria control remained in place long after the completion of the canal in the form of the "Division of Sanitation." The prevention of reintroduction of malaria (which most likely would have occurred from the Republic of Panama, just outside the Canal Zone) was maintained by an enormously intricate system of screening to reduce human mosquito contact, environmental engineering to reduce anopheline populations,¹⁷ intensive surveillance of mosquito breeding and behavior,¹⁸ larviciding, and the introduction of natural predators like larvivorous fish. Particular emphasis was placed on the drainage and filling of swamps, and subsequent destruction of mosquito breeding places. Six decades later, Panama remains a regional success story, with one of the lowest rates of malaria incidence per 1000 population at risk among Central American countries (second to El Salvador). In addition, malaria transmission occurs only in a comparatively small proportion of its area.

The Global Malaria Eradication Program, 1958-1969

From Macdonald's basic reproduction equation, it follows that for each disease generation (the inverse of the human recovery period) during which $z_0 < 1$, the total incidence of malaria in the community decreases. Therefore, it is theoretically possible, by manipulating one or more of the determinants of the basic reproduction rate, to eradicate the disease entirely. In this context, DDT emerged as a potential panacea, which, efficiently

"bonification." (see Litsios and Harrison for summaries of this debate)

¹⁷ "[A]ided greatly," according to Simmons, "by the fact that excellent, large scale, topographical maps of the whole Canal and much of its vicinity are available to the Health Department."

¹⁸ Inspectors were sent into the field to search for and identify mosquito larvae with portable compound microscopes, and laborers were employed in dwellings to use flashlights and catching tubes to trap mosquitoes overnight for later identification and dissection.

employed in any ecological context, could sufficiently reduce the variable p to hold $z_0 < 1$ for several years (until micro-evolutionary pressure caused insecticide resistance to emerge) and eliminate the disease. This was the basis of the Global Malaria Eradication Program, launched by the World Health Organization in the late 1950s.¹⁹ The four-phase strategy of the program (preparation, attack, consolidation, and maintenance) was designed to make maximum use of the continually shrinking time-horizon of DDT effectiveness (agricultural use of the insecticide had already begun to select for resistance before the eradication program had even begun). While it is clear that the designers of the program understood the ways in which topography, geography, climate, evolutionary history, and a host of other local factors influenced the dynamics of malaria transmission, these factors seemed to have been rendered effectively irrelevant by the enormous power of DDT to reduce mosquito longevity. During the first few years of the Global Eradication Program, Europe had finally succeeded in eliminating the disease using this strategy. At its apogee, the program had enlisted the participation of countries across Europe, Asia, and Latin America. Although Africa was considered to lack the necessary infrastructure to maintain an efficient spray campaign and was “excluded” from the program, both Mauritius and South Africa ultimately joined, among the last countries in the world to do so. Outside of Europe, after optimism had waned and the goal of eradication had been abandoned in 1969, the strategy of residual spraying of DDT had succeeded in eliminating malaria from 2 countries: Taiwan and Jamaica. In a few other countries, malaria incidence had been dramatically reduced, and the countries were able to complete the eradication effort on their own—among these were Mauritius, Cuba, and several Caribbean islands. Many appraisals have been offered of the failures of the Global Malaria Eradication Program in accomplishing its primary goal, and these are reviewed exhaustively elsewhere.²⁰ The goal of the attack phase of the program was to use residual application of DDT on the walls of houses to reduce Macdonald’s variable p . Emilio Pampana, who codified the programmatic design, points out that the extrinsic incubation period of the parasite

needs quite a few days. . . . During this period, most anophelines would feed every 48 hours, so that they would come back [several times] and risk being killed by the sprayed walls. Clearly the chances that the mosquito will be killed are high. . . . The consequence is that, if all houses have their inner walls appropriately sprayed with insecticide, transmission of malaria will be stopped, and no new infections will occur.”(33)

¹⁹ For a detailed history of the history behind the launching of this campaign, see Litsios and Harrison.

²⁰ see Litsios, Harrison, and Bruce-Chwatt and Zulueta.

However, as many appraisals of the program have pointed out, it failed to take into account vital differences in anopheline behavior. Domiciliary spraying of insecticides failed in many environments to control the spread of malaria appreciably, because some mosquito species never rest indoors after feeding, thus avoiding any contact with the insecticides. This “refractory behavior” appears to be determined genetically, and differed between species even before micro-evolutionary pressure began to select for refractory mutants within species. But initial dramatic reductions in malaria incidence in many countries around the world, including for example, Afghanistan, India, Sri Lanka, and Nicaragua, seemed to suggest that this approach had a generally sound theoretical basis. The consolidation and maintenance phases of the program required extensive drug distribution (for both prophylactic and therapeutic purposes), and the progression from one phase to the other was not often smooth. In terms of Macdonald’s equation, the attack phase was focused on p , the consolidation phase was focused on r and b , and the maintenance phase was simply intended to confirm that the parasite reservoir had been completely eliminated. However, the organizational design of national eradication programs had been extremely centralized. For example, countries were encouraged to establish malaria eradication offices outside established health ministries, in order to facilitate efficient spraying programs during the attack phase. However, the transition to the consolidation phase then proved difficult in many cases, where the primary health care infrastructure had been inadequately prepared during the course of the attack phase. This “verticality” of design was only sustainable for a short period of time, while execution of the program involved rote behavior by well-trained staff and morale remained high, and very little cooperation was required from outside the central offices of the national malaria eradication programs.²¹ In addition, this transition was often poorly timed; the parameters of the four phases were defined in principle by epidemiological goals, but in practice by specific time constraints; budgets, for example, had to be submitted several years in advance. Therefore, some countries proceeded into the maintenance phase with substantial parasitemia remaining in the community, while others continued spraying long after insecticide resistance had become widespread.²² The program was theoretically designed to manipulate local conditions for a short period of time, and thereby to eradicate the parasite reservoir permanently. As long as even a small parasite reservoir remained, the program could not be stopped without z_0 returning to its initial value and causing dramatic disease resurgence. As

²¹ For a reinterpretation of this debate, see Bradley, DJ (1998) “The particular and the general: Issues of specificity and verticality in malaria control” *Parassitologia* **40**:5-10.

²² For various viewpoints on the theme of time limitation, see Gramiccia and Beales, and Spielman et al. (1993) “Time limitation and the role of research in the worldwide attempt to eradicate malaria” *J.Med.Ent.* **30**:6-19.

hope of eradication and international commitment waned, this conundrum became more and more pronounced, and the pressure to rocket countries from one phase to the next became acute. Nonetheless, Gramiccia and Beales, among others, endorse the view that where the program had involved a country's primary health care infrastructure, it was often successful in bringing health services to historically neglected rural settings.

Pampana warned early in the eradication program of the danger of disease recrudescence if interventions are abandoned at a point of disequilibrium, where local conditions favor increased transmission. But as Gramiccia and Beales indicate, the re-evaluation of the goal of eradication did not substantially change the program. "In fact," they argue, "for a control programme, residual insecticides, wherever they had some effect, remained the cheapest and most effective means for the control of rural malaria." As insecticide resistance became more intense, however, community participation became more grudging, and international financial support dried up,²³ many communities abandoned or neglected their antimalaria efforts. In certain regions, most notably in southern Asia, where prevalence remained low and the community had been rendered immunologically naïve by years of interrupted transmission, devastating and dramatic resurgences occurred throughout the 1970s.

Resurgence usually occurs after a period of dampened transmission, and therefore in a community that is relatively immunologically naïve. Therefore the "ruling reproduction number" is much closer to the basic reproduction number than it would be in an endemic environment in an equilibrium state. It follows, therefore, that if conditions are sufficient to maintain endemic transmission and a very small parasite population is introduced into the environment, then the disease will spread more and more rapidly until equilibrium is achieved. The observed recrudescence is rendered more dramatic by the synchronous nature of malaria etiology; Harrison describes how entire communities fell ill at almost the same time in ever-increasing waves, until communal immunity is established and the disease settles to its relatively silent endemic equilibrium.

Control Efforts of the Past 30 Years

Since the end of the global eradication program, malaria has only disappeared from a few countries. Mauritius maintained its existing eradication program, well into the maintenance phase when the global program

²³ The formal end of the Global Malaria Eradication drastically reduced the amount of multilateral funding available to support local malaria control programs. For time-series data on funding allocation, see Gramiccia and Beales.

was abandoned, and reported its last locally transmitted cases in 1965. Mauritius control programs were as old as the endemicity of the disease; while still under British rule, Mauritius received advice on vector control strategies from Ronald Ross himself (25). Although there is some dispute about the initial success of malaria control efforts, by 1951 DDT spraying had eradicated *An. funestus*, one of the main vectors, from the island. Owing to its frequent cyclones, the density of anophelines on Mauritius is extremely variable, and a population explosion in the late 1970s led to a brief but costly recrudescence. Today, however, the primary potential vector on the island is *An. arabiensis*, and surveillance and control measures remain in place to keep the population as low as possible. Mauritius is fortunate that *An. arabiensis* is less anthropophilic than many other vectors, and most of the population remains sensitive to insecticides. At the same time, it is unfortunate that the vector prefers to rest outdoors, making it more refractory to insecticide spraying (34). The risk of resurgence in the absence of efficient surveillance, vector control, and prompt treatment of cases is very real—as demonstrated by the experience of the late 1970s. The state of malaria eradication, whether certified by the WHO or not, is rarely ever permanent, and requires more extensive maintenance in the tropics than in temperate zones.

The establishment of malaria control efforts in Africa lagged far behind the rest of the world. Although consolidated control efforts had been recommended WHO in Africa as early as 1950, the problem of African malaria was deemed sufficiently intractable to justify the exclusion of the continent from the eradication program. In the post-eradication years, many countries in sub-saharan Africa joined the successor Global Malaria Control Program. However, there were a few notable efforts to control the disease in Africa during this period, even outside of Mauritius and South Africa. For example, Nigeria had employed a spray program in its western region between 1954 and 1958, with very limited success. A few other efforts in Africa met with similar results, and experiences in Africa seemed to call into question the validity of the basic epidemiological models. Among the first careful international efforts conducted during this period was the “Garki project,” sponsored by the WHO in the Nigerian savanna between 1970 and 1976. The project was extensive and time-limited, designed not only to control malaria transmission in this region but also to characterize the epidemiologic dynamics of malaria in this historically under-examined context. After six years of operations costing over \$6.1 million, the study concluded that the use of indoor residual spraying and mass drug administration—precisely the prescription of the eradication program—should not be recommended as malaria control strategies in Africa. More than its conclusions, however, the historical

importance of the Garki project may stem from its illustration of the degree to which the problems of malaria in Africa had been neglected.

Latin America and the Caribbean islands have a relatively long history of malaria control efforts, dating back to the early part of the 20th century (including, for example, Gorgas' success in Havana, the Panama Canal Zone, and Panama²⁴). By 1952, virtually every country in the Americas had an organized malaria control program in place. Over forty years later, however, malaria remained endemic throughout the Americas, except in the United States, Canada, Chile, Uruguay, and the Caribbean islands with the exception of Hispaniola (Bahamas, Barbados, Bermuda, Cayman Islands, Cuba, Guadeloupe, Jamaica, Puerto Rico, St. Vincent/Grenadines, Trinidad and Tobago, and the Virgin Islands) (35) (32). Where eradication (or, more correctly, extremely efficient control) has been achieved, it has occurred through vector control and radical drug treatment techniques. These cases are informative, because the Caribbean islands are situated extremely close to malaria endemic neighbors (the highest malaria risk in the Americas exists in Guyana and French Guiana, both countries on the Caribbean coast). However, imported cases are relatively rare (in 1991, the highest number of imported cases in the region occurred in Cuba, where 215 cases were detected; this was followed by Guadeloupe, where 24 cases were detected), and have historically been controlled.²⁵ The Dominican Republic, in contrast, which has historically demonstrated sustained success in malaria control (and where malaria incidence in the early 1990s was rare by regional standards), remains subject to outbreaks from imported cases from Haiti (36), where the topography differs significantly and vector populations are extremely difficult to control.²⁶ These cases, and those of other islands (e.g., Singapore and Hong Kong—where urbanization has played an important role in malaria control), suggest that control is more sustainable on small islands. There are likely to be at least three reasons for this phenomenon. First, once controlled, the population of a vector species is less likely to grow quickly in a relatively isolated island context. When new

²⁴ Other examples may be found in Litsios and Harrison.

²⁵ Trinidad's experience in the control of imported malaria is particularly illustrative. There are three foci of transmission of imported malaria in the country. The largest is the capital city and main trade point, Port of Spain, where the vast majority of imported cases are falciparum malaria originating from Africa and introduced by returning laborers. The second is a smaller port along the western coast, and the third is a tiny rural region in the southwest corner of the country, less than 50 miles from the coast of Venezuela. The Trinidad government reacts to every reported case of imported malaria with a combination of radical treatment of the infected individual, blood testing and prophylactic treatment of the nearby population, intradomiciliary insecticide spraying, and extensive disease surveillance. The total cost of this strategy has been estimated at US\$10,000/case; an investment the Trinidad government sees as essential to the protection of its privileged health status and its vital tourism industry. (Kitron, Uriel "GIS and vector-borne disease surveillance and control," presentation at the Harvard School of Public Health, December 4, 1998.)

²⁶ According to Gramiccia and Beales, in the 1950s and 1960s, Haiti had initially had some success in controlling malaria, primarily through radical drug treatment, but this success was quickly rolled back when drug resistant malaria was observed and the local vector *An.albimanus* developed insecticide resistance.

vectors are imported, for example through international travel on airplanes or ships, it is generally in small numbers. In the presence of an intact infrastructure, efficient entomological surveillance can identify and eliminate foci before a vector population grows unwieldy (as, for example, with Mauritius' success in keeping *An.gambiae* and *An. funestus* populations very small). Second, importation of cases is less likely to occur as a result of mass migration. Mass migration, either in the presence or absence of infrastructural collapse, has accounted for malaria outbreaks throughout history, including for example those of Mauritius in the 19th century, or more recently, the re-establishment of endemic transmission in Tajikistan in 1990, or epidemics in the Dominican Republic in 1994 (32). Thirdly, they are less susceptible to infrastructural collapse in neighboring countries. Malaria outbreaks often result from civil strife or economic crisis (as, for example, in central Asia), and these outbreaks inevitably have repercussions in the border regions of neighboring countries, particularly when these regions do not provide a natural barrier against vector migration.

In Asia, where some of the most devastating resurgences occurred immediately after the end of the WHO's global eradication program, malaria continues to pose a threat to much of the population. According to the WHO, malaria transmission occurs in regions accounting for 85% of the population of southeast Asia and 4% of China (exclusively in its tropical southern states). Much of the malaria in southeast Asia is transmitted by forest-dwelling vectors, making vector control extremely difficult and also leaving large infected populations beyond the reach of the basic health infrastructure. In addition, multi-drug resistant malaria has been observed in the region. In Asia, as in Latin America, the small island countries (including Malaysia, Singapore, Hong Kong, and parts of Indonesia) have generally fared better in controlling malaria than their continental neighbors (including Thailand, Myanmar, Bangladesh, and India), although Sri Lanka is an important exception, reporting the second highest risk of malaria in the region.

Today, the WHO reports that of the approximately 100 countries in which malaria remains endemic, "over 90% have designed control measures in line with the Global Malaria Control Strategy (which replaced the eradication program)." Each of these countries have met with varying degrees of success, but all strategies involve some combination of vector control, reduction of human-mosquito contact and drug treatment. Any contemporary control strategy faces a variety of challenges. Vector control strategies are hindered by the rapid development of insecticide resistant vector populations. In addition, anthropogenic changes in the environment have sometimes had

unintended effects on vector populations (37-40). Drug treatment strategies are daunted by inadequate health care infrastructure, poor distribution of drugs, the explosion of drug resistant parasite populations, and inadequate self-treatment education of the community (41-44). Reduction of human mosquito contact is hindered by the presence of poorly constructed dwellings, exophagic vectors (that is, vectors which feed outdoors) and community non-compliance in bednet strategies (45; 46).

Analysis of historical changes in malaria prevalence suggests a number of factors which help to determine the likelihood and sustainability of success in malaria control. A few among these are geography, evolutionary history of flora and fauna, infrastructure, land use, and economic activity. Each of these factors operates independently and in concert with the others to produce an enormous heterogeneity of challenges. A few, including Nájera et al., have begun to try to design strategies which take these factors into account (see for example table 2, reproduced from Nájera (47)). This approach is extremely important for the success of future malaria control efforts, and ought to be discussed more widely and refined further. More generally, a number of broad lessons may be drawn from history; for example:

- Geography favors malaria control efforts in island and temperate contexts. As shown in table 1, in addition to the fact that historical success in malaria eradication has been almost exclusive to these contexts, effective control is also more sustainable in these contexts.
- Different geographical and biological contexts require differing degrees of surveillance and control to maintain past success. For example, in highland regions where malaria transmission is seasonal, vigilance is necessary to detect and dampen epidemics when they occur. Similarly, where vector breeding is difficult to interrupt, as for example in forest contexts, environmental management is unlikely to have positive effects (observe, for example, in table 2 the very limited number of contexts in which environmental management and epidemic surveillance have been observed to achieve success).
- Different epidemiological contexts make different demands on local and national infrastructure. Where resistance to the most commonly distributed drugs is widespread, for example, self-treatment is less likely to be effective in mitigating disease morbidity and mortality, and access to primary care clinicians and second-line drugs is more important. In addition, in parts of tropical Africa, where malaria is highly endemic

and other diseases with similar symptoms are also widespread, it is very difficult to determine with precision the number and distribution of malaria infected persons. Therefore, it is especially difficult in these contexts to determine the success of ongoing control programs, to isolate specific foci of transmission, and to use drug treatment techniques to control disease morbidity and mortality.

- Anthropogenic changes to the environment, both globally and locally, are likely to have varying and often unpredictable effects on local malaria situations. Often, these changes will demand creative social, economic, and public health policy responses.

These lessons have important policy implications for malaria control. More than simply demanding a more localized or “horizontal” approach to control programs, they suggest the identity of some of the variables behind those of Macdonald’s seminal equations. In the absence of breakthrough technologies, well designed strategies will take into account how factors including those listed above interact globally and locally. In addition, similar historical analysis, placed in its proper context, can help to illustrate the ways in which malaria transmission maintains both itself at the level of the patient and at that of the country. A longer view, for example, is required to understand micro- and macroevolutionary dynamics, while a wider one is required to understand the micro- and macroeconomic burden of malaria.

Figure 1.
Malaria risk - 1946, 1966, 1994

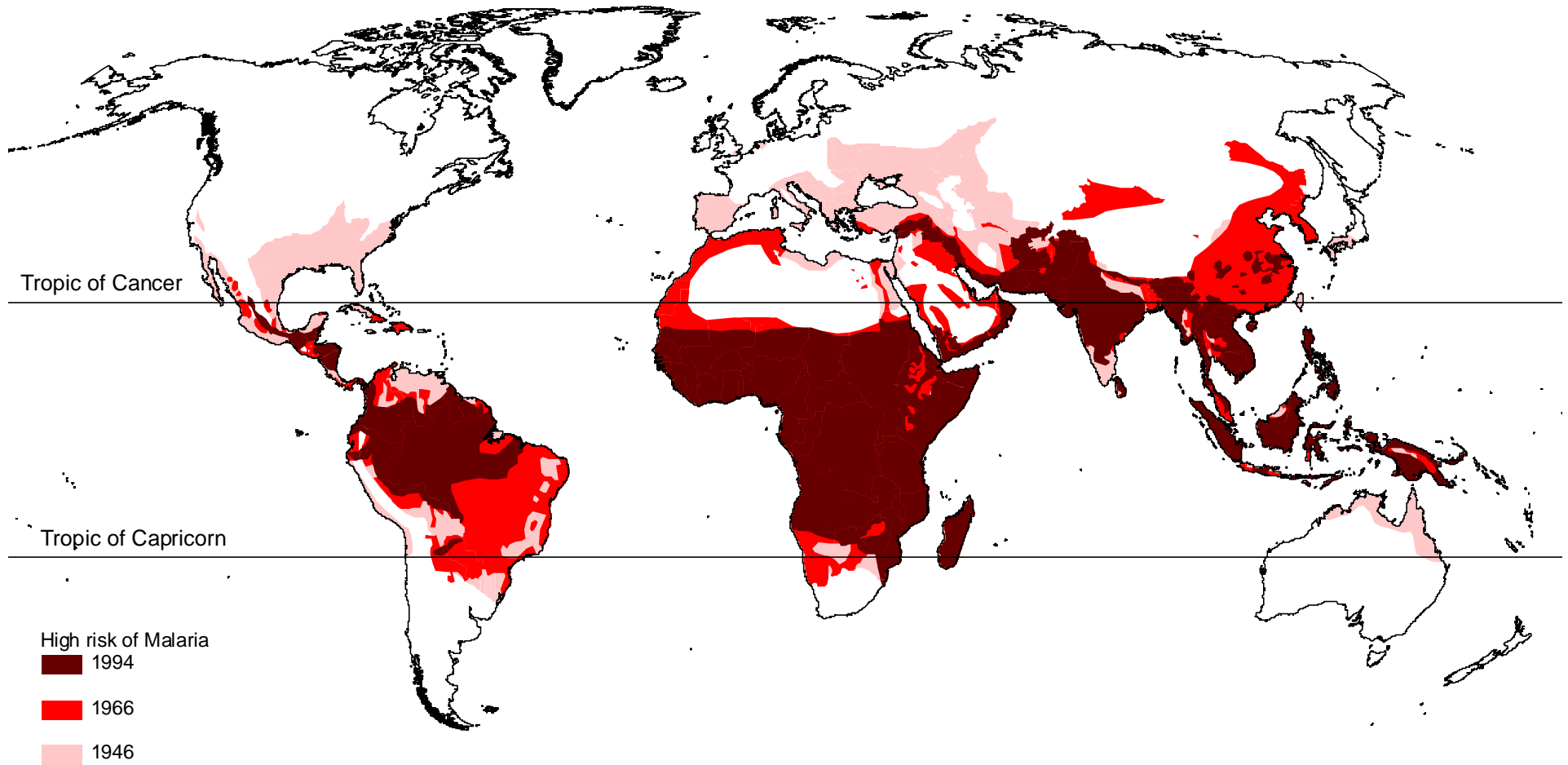


Table 1. Broad Classifications of the malaria situation, 1950s-present

Countries and regions where appreciable endemic transmission of malaria no longer occurs ^a	Countries or regions where “malaria declined and the situation has remained favorable” ^b	Countries or regions where “the incidence of malaria has oscillated. . . with a quasihorizontal general trend” ^b	Countries or regions where “malaria has increased markedly in certain areas” ^b
<p>Carribbean islands (excluding Hispaniola); United States; Chile</p> <p>Italy; Balkan region (excluding Turkey); France; Germany; Scandanavia; UK</p> <p>Cyprus; Israel; Jordan; Kuwait; Lebanon</p> <p>Mauritius; Lesotho; Seychelles</p> <p>Former Soviet Union (excluding Azerbaijan and Tajikistan)</p> <p>Australia; New Zealand; Brunei; Japan; Mongolia; Singapore; Hong Kong; Taiwan</p>	<p>Cuba; Costa Rica; Panama; Paraguay</p> <p>Egypt; Morocco; Tunisia</p> <p>Korea; Malaysia (excluding Sabah); China</p>	<p>Argentina; El Salvador; Honduras; Nicaragua; Surinam</p> <p>Yemen; Iran</p> <p>Indonesia; Malaysia (Sabah)</p>	<p>Belize; Bhutan; Bolivia; Brazil; Colombia, French Guiana, Guatemala, Guyana; Mexico; Peru</p> <p>Turkey^c</p> <p>Afghanistan; Saudi Arabia</p> <p>Madagascar</p> <p>Tajikistan</p> <p>Myanmar; Nepal; Papua New Guinea; Solomon Islands; Thailand; Vanuatu; Vietnam</p>

Note: Due to lack of data, it is difficult to place most African countries on this table. However, according to the WHO report *World Malaria Situation 1990*, tropical Africa accounts for most of the “areas where endemic malaria remains basically unchanged, and no national anitmalaria program was. . . implemented [by 1990].”

^a Sources: Bruce Chwatt and Zulueta; WHO (1997)

^b Source: Nájera et al. (1993)

^c Source: WHO (1997)

Table 2. Contexts in which control strategies have (+) or have not (-) proven effective.

Reproduced from Nájera et al. (46)

Table 3.2 Patterns associated with ecological and social conditions

<i>Control intervention</i>	<i>Major ecological conditions</i>						<i>Specific occupations/ social conditions</i>			
	<i>African savannah</i>	<i>Plains and valleys outside Africa</i>	<i>Forest and forest fringe</i>	<i>Highland and desert fringe</i>	<i>Seashore and coastal</i>	<i>Urban</i>	<i>Agricultural colonization of forest</i>	<i>Gold mining</i>	<i>Migrant agriculture labor</i>	<i>Displaced populations</i>
Management of clinical malaria										
Diagnosis and treatment	+	+	+	+	+	+	+	+	+	+
Care of treatment failures	+	+	+	+	+	+	+	+	+	+
Protection of pregnant women										
Chemoprophylaxis	+	-	+	-	-	-	+	-	-	-
Bednets and personal protection	+	+	+	+	+	+	+	+	+	+
Vector control										
Residual spraying	-	Selective	Selective	Epidemic control	Selective	Limited	Selective	-	Limited	Epidemic control
Fogging ULV	-	-	-	-	+	Limited	-	-	Limited	+
Impregnated bednets or curtains	+	+	+	-	+	-	+	+	-	-
Environmental control										
Drainage and source reduction	-	-	-	-	+	+	-	-	+	-
Larviciding	-	-	-	-	+	+	-	-	+	-
Biological control	-	-	-	-	Limited	+	-	-	+	-
Surveillance										
Epidemiological surveillance	+	+	+	+	+	+	+	+	+	+
Monitoring epidemic risk	-	+	+	+	-	-	-	+	+	+
Health education										
	+	+	+	+	+	+	+	-	-	-

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