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Climate Change and Mosquito-Borne Disease

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Global atmospheric temperatures are presently in a warming phase that began 250–300 years ago. Speculations on the potential impact of continued warming on human health often focus on mosquito-borne diseases. Elementary models suggest that higher global temperatures will enhance their transmission rates and extend their geographic ranges. However, the histories of three such diseases—malaria, yellow fever, and dengue—reveal that climate has rarely been the principal determinant of their prevalence or range; human activities and their impact on local ecology have generally been much more significant. It is therefore inappropriate to use climate-based models to predict future prevalence. *Key words:* *Aedes aegypti*, anopheles, climate change, dengue, global warming, malaria, mosquito, public health, vector, yellow fever. — *Environ Health Perspect* 109(suppl 1):141–161 (2001).

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Climate Change

The earth's climate has always been in a state of change (1–3). For nearly three centuries it has been in a warming phase. This was preceded by a cold period, the Little Ice Age, which was itself preceded by a warmer phase known as the Medieval Warm Period, or Little Climatic Optimum. Such changes are entirely natural, but there is evidence that in recent years a portion of the current warming may be attributable to human activities, particularly the burning of fossil fuels (4–6). The potential impact of this global warming on human health is a major subject of debate (7–10).

Many of the diseases that currently occur in the tropics are mosquito borne (11). It is commonly assumed that their distribution is determined by climate and that warmer global temperatures will increase their incidence and geographic range (12–14). This review explores the validity of both assumptions by examining the history of three mosquito-borne diseases—malaria, yellow fever, and dengue—in the context of past climates and of other factors that can influence their transmission.

Climate

Climate (Greek κλίμα, *an inclination or slope*—e.g., of the sun's rays; a latitude zone of the Earth) is commonly understood to mean the *average weather* in a given region or zone. In its older form, *clime* also included all aspects of the environment, including the zonal distribution of plants and animals. Both definitions are unsatisfactory because they imply that, unlike the obvious year-to-year variations of daily weather, long-term climate is a constant. By contrast, modern climatology recognizes that change is an inherent and fundamental feature of climate. Therefore, climatic values cannot be quoted without specifying the time span to which they refer.

Natural factors that cause climatic variability include fluctuations of the sun's radiant energy, alterations in the transparency of the atmosphere (due to sand, volcanic dust, and other airborne particles), and cyclic changes of the earth's rotation on its axis and its orbit around the sun. In addition, the circulations of the atmosphere and the oceans, which are major components of the climate machine, are subject to internal variations on time scales ranging from weeks to millennia. It is the complex interaction of all these variables that generates the continually changing patterns of climate. As a result, just as the yearly averages of climatic elements—such as temperature, humidity, rainfall, wind, and airborne particles—differ from one another, so too do the averages for decades, centuries, millennia, and millions of years (Table 1).

Climate is a major parameter in all ecosystems and has always been a fundamental factor in human settlement, economy, and culture. Episodes of second-order climate change, such as the end of the Ice Age, the drying of the Sahara, the waning of the Medieval Warm Period, and the onset of the Little Ice Age, have had an important impact on human history (1,2,15). However, awareness of such change has remained shadowy at best, probably because the inherent time scales are beyond the span of individual human experience.

During most of geologic history, temperature conditions extended to the polar circles, and the planet was relatively ice-free (3,16). Indeed, in the perspective of the past 600 million years, present global temperatures are relatively cool. In the context of these long-term averages, the warming trend that began in the late 1970s (see below) is a minor fluctuation, less than a first-order variation.

Weather

Weather, the short-term condition of climate, has a much more direct and tangible impact on daily life. Since earliest times, weather has been fundamental to the success of human activities, from agriculture to seafaring, from warfare to leisure. The universal belief in weather deities, the prominence of weather events in folklore, and the ubiquitous preoccupation with weather signs and portents are evidence that an awareness of weather, particularly a fear of inclement events, has been a major feature of the human psyche throughout history.

The significance of weather has not diminished in modern society. Indeed, in the past few decades, weather awareness, particularly in the global context, has reached unprecedented levels. Weather forecasting has become an important science, fundamental to the success of agriculture, transportation, trade, tourism, and virtually every other aspect of human enterprise. Weather data are collected from every corner of the globe and disseminated in digested form by government and private agencies as an aid to decision making in all walks of life. Continually updated forecasts and other information are available to the public via the popular media. Disastrous weather events from around the world are a major news feature, with detailed descriptions and graphic illustration. With this awareness of weather has come a new realization of the changeability of climate.

Recent Climate Change

Currently, world climate is in a warming phase that began in the early decades of the eighteenth century. Temperatures, at least in the Northern Hemisphere, are now broadly similar to what they were during the Middle Ages, in the centuries before the Little Ice Age (2). Awareness of this warming has led to a new preoccupation: concern that human activities may be affecting the natural climatic

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Table 1. Time scale of climatic variation.^a

Order	Interval (years)	Descriptor	Example of variation
1	30–100	Instrument record	Cooling trend from 1940 to late 1970s
2	100–1,000	Historical	Medieval Warm Period, Little Ice Age
3	1,000–10,000	Glacial	Variation within an Ice Age
4	10,000–1 million	Minor geologic	Ice Age
5	1–100 million	Major geologic	Interval between Ice Ages

^aGlobal events such as the El Niño Southern Oscillation phenomenon occur at a frequency well below that of the first order of variation.

regime, just as they are changing many other aspects of the environment. From the 1940s to the late 1970s, when global temperatures were in decline, there was concern that particulate industrial pollutants might be exerting a global cooling effect (17–19). Since then, as world climates returned to a warming mode, interest has switched to the greenhouse effect, a natural phenomenon by which atmospheric gases trap solar radiation in the form of heat.

Although the principal greenhouse gas is water vapor, about 2% by volume, public attention focuses mainly on carbon dioxide, a gas that is essential as the ultimate source of carbon for nearly all life on the planet. From the mid-nineteenth century onward, massive clearance of forests for agriculture, followed by an exponential rise in the combustion of fossil fuels (coal, oil, gas), has produced a measurable increase in atmospheric CO₂ from around 0.029% in 1890 to 0.037% today. Many climatologists agree that this 28% increase in atmospheric CO₂ together with an increase in other anthropogenic greenhouse gases may be contributing to the warming trend of recent decades (4–6,20). The extent of this contribution remains far from clear, but the mere possibility that human activities may be involved implies that the trend could be reversible, and has generated a spirited scientific (5,7,21–23) and public (24–26) discussion. Human health—and mosquito-borne disease in particular—is a prominent topic in this debate (12,27–32).

Mosquito-Borne Disease

Mosquitoes As Vectors of Disease

Mosquitoes are found throughout the world except in places that are permanently frozen. There are about 3,500 species, of which nearly three-quarters are native to the humid tropics and subtropics. The largest populations of individual species occur in the Arctic tundra, where colossal numbers emerge in a single brood each summer from snowmelt pools that overlie the permafrost.

In nearly all mosquito species, the female obtains the protein she needs for the development of her eggs by feeding on vertebrate blood. Some species are highly selective, restricting themselves to one or at most a few closely related host species. Others have a less clearly defined host preference and

may alternate among birds, mammals, and even reptiles. A complex salivary secretion facilitates feeding. It is the direct injection of this fluid into the capillaries that enables several life forms—viruses, protozoa, and nematode worms—to exploit mosquitoes as a means of transfer between vertebrate hosts. In nearly all cases, there is an obligatory phase within the insect. This includes a stage in which they multiply prodigiously in the salivary glands, from which they can be inoculated into a new host during a later blood meal. Although most such organisms do not appear to affect either the mosquitoes or their vertebrate hosts, some are pathogens of important human and animal diseases.

Factors That Influence Transmission

Climatic factors. The ecology, development, behavior, and survival of mosquitoes and the transmission dynamics of the diseases they transmit are strongly influenced by climatic factors. Temperature, rainfall, and humidity are especially important, but others, such as wind and the duration of daylight, can also be significant. The same factors also play a crucial role in the survival and transmission rate of mosquito-borne pathogens. In particular, temperature affects their rate of multiplication in the insect. In turn, this affects the rate at which the salivary secretions become infected, and thus the likelihood of successful transmission to another host. Of course, if the development time of the pathogen exceeds the life span of the insect, transmission cannot occur. It is the complex interplay of all these factors that determines the overall effect of climate on the local prevalence of mosquito-borne diseases (11,33).

Seasonality is a key component of climate. Summer temperatures in many temperate regions are at least as high as in the warmest seasons of much of the tropics. The crucial difference is that the tropics do not have cold winters. Tropical crops such as rice and groundnuts can be cultivated in temperate regions if they are planted in springtime. Similarly, if tropical mosquito-borne pathogens are introduced in the right season, they can be transmitted if suitable vectors are present; in most cases they are eliminated when winter sets in.

Mosquitoes native to temperate regions have had to evolve strategies to survive the winter, as have the pathogens that they

transmit. In the tropics, comparable adaptations are necessary for surviving in unfavorable dry periods, which can last for several years. In both cases, such adaptations impose a seasonality on transmission. For example, before eradication, the transmission season for *Plasmodium falciparum* in Italy was July–September (34). The same 3 months constitute the malaria season in Mali, where the disease is still endemic (35).

The physical environment is an important modifier of local climate (36). In dense forest, daily mean temperatures at ground level can be as much as 10°C lower than in adjacent open areas (37). Similarly, natural daytime temperatures indoors can be several degrees higher or lower than outdoors, depending on design, construction materials, and ventilation. Mosquitoes use a variety of strategies to exploit the timing and location of such microclimates to maximum advantage. For example, in *Anopheles gambiae* (38), a physiologic “clock” ensures that whatever the rate of metamorphosis in the pupal stage, the adults always emerge from the water at sundown or in the early hours of the night. In the laboratory, if *An. gambiae* pupae are maintained in constant light, the duration of the pupal stage is a direct function of temperature: It lasts about 2 days at 22°C but only 1 day at 32°C (Figure 1A). However, in a light regime of 12 hr light and 12 hr dark (LD 12:12), the timing is modified (Figure 1B) to minimize emergence in daylight (39,40). Similar circadian rhythms ensure that other behaviors such as feeding, resting, and oviposition are restricted to optimum times, regardless of ambient temperature (41). Thus, *An. gambiae* can survive in the Sudan (mean monthly temperatures of 42°C; actual outdoor temperatures can be over 55°C) by emerging after sunset, hiding in the thatch of buildings in the daytime, feeding after midnight, and ovipositing at dawn or dusk (42).

Analogous survival strategies operate in temperate climates. *Culex pipiens*, a vector of the St. Louis encephalitis virus (and the recently imported West Nile virus), is common in North America as far north as New Brunswick and Nova Scotia, Canada. It overwinters in the adult stage, sequestered at sites protected from the cold. Here again, light (in this case, daylength) is the *zeitgeber* or cue that initiates the survival strategy. Studies (43) in Memphis, Tennessee, revealed a remarkably high winter survival rate ($p = 0.97$) in an underground storm sewer. Survival was the same in a cold winter (1981–1982: 42 days of freezing temperatures, mean daily minimum temperature [December 1–February 28] -0.74°C ; 9 days with minimum of less than -10°C) as in a much warmer “El Niño” winter (1982–1983;

25 days of freezing temperatures; mean daily minimum temperature [December 1–February 28] +2.9°C; 1 day of less than –10°C, maximum temperatures as high as 27.2°C).

Memphis has a typical temperate continental climate. There are normally about 65 days per year with maximum temperatures above 32°C (temperatures above 38°C are not unusual) and about 60 days when the minimum falls below 0°C (lows of –15°C are not unusual) (44). *Aedes aegypti*, the principal urban vector of dengue and yellow fever, is a tropical species for which temperatures below 0°C are fatal. Nevertheless, at the time of the studies mentioned above (and probably for at least 200 years before), *Ae. aegypti* was present throughout the southern United States, and was common in Memphis. Presumably it survived during winter in niches protected from the cold. Despite the effectiveness of this strategy, in the past 15 years the species has disappeared from much of the region, including Memphis, displaced by another non-native species, *Ae. albopictus* (45). This example and the others given above emphasize that meteorologic variables alone are of limited value as a guide to the development times, behavior, and geographic range of vector species and the pathogens they transmit.

Human factors. Human activities are also crucial to transmission. Forest clearance eliminates species that breed in water in tree holes (e.g., the forest *Aedes* species that transmit yellow fever) but provides favorable conditions for those that prefer temporary ground pools exposed to full sunlight (e.g., many of the *Anopheles* species that transmit malaria). Drainage of wetlands eliminates the marshy pools exploited by many species but can provide the open channels preferred by others (e.g., some important European vectors of malaria, and *Culex tarsalis*, a vector of St. Louis encephalitis). Agricultural fertilizers can promote the growth of algae and other larval nutrients, whereas herbicides may eliminate them altogether. Cisterns, pit latrines, sewage-polluted ditches, storm drains, and blocked gutters can support large populations of *Cx. quinquefasciatus*, an important vector of Bancroftian filariasis. Wells are often a significant source of malaria vectors. Water-storage jars and drums, cemetery urns, discarded rubber tires, buckets, pots, and other man-made containers can be prolific sources of *Ae. aegypti*, an important peridomestic vector of yellow fever and dengue and other species that originally bred in tree holes.

Additional factors arise from behavior and cultural traits. Daily activity patterns—work, rest, and recreation—the location of homes in relation to mosquito breeding sites, the design of buildings, the materials used to build them, the use of screens and

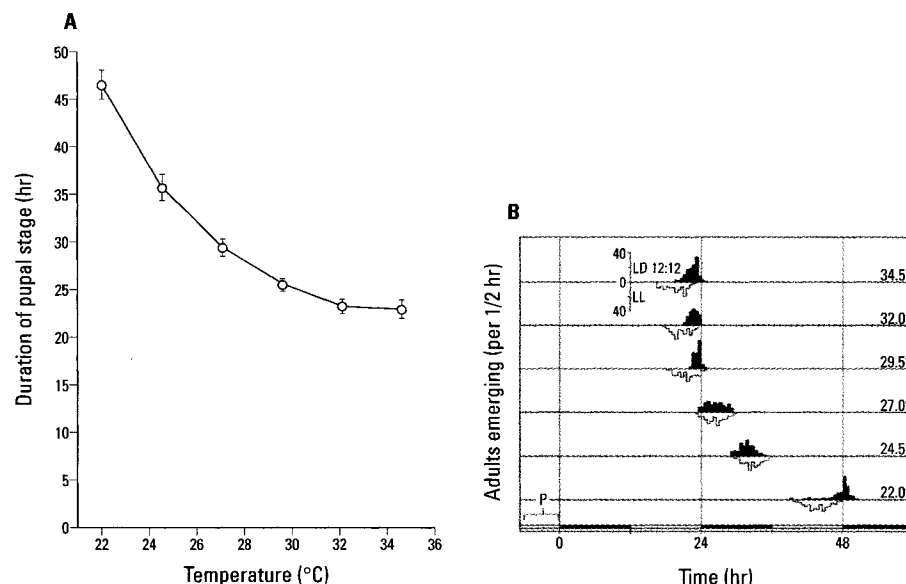


Figure 1. The influence of light regime on the timing of the emergence of adult *An. gambiae* from the pupal stage at different temperatures in the laboratory. (A) Duration (mean + SD) of the pupal stage in constant light (LL). (B) Timing of emergence in LL and in a daily regime of 12 hr light:12 hr dark (LD 12:12). In the LL regime (open histograms, downward) eclosion occurs as soon as metamorphosis is complete. In the LD 12:12 regime (open histograms, upward) emergence is delayed to give a peak near the time of light-off. P indicates the 6-hr period during which the pupae were collected in hourly batches. In the laboratory, pupation normally peaks 3–4 hr before the end of the light phase (41). In the field, pupation and pupal/adult eclosion are both delayed until sunset (187) or thereafter. Physiologic “gates” of this type maintain regular rhythms of physiology and behavior regardless of the effects of temperature. Figure reprinted from Reiter and Jones (39), with permission of Blackwell Science Ltd.

bed nets, and many other factors can be significant. Finally, chemotherapy, vaccination, and mosquito control have played major roles in reducing transmission in many parts of the world.

Predicting the Impact of Climate Change

Transmission models. Much of the recent speculation on the possible effects of climate change on mosquito-borne disease has focused on rudimentary concepts of their transmission dynamics (30,46–48). An example is vectorial capacity, a convenient way of expressing transmission risk:

$$C = \frac{ma^2 p^n}{-\log_e p}$$

where m is the mosquito density per human, a is the average number of bites per day for each mosquito, p is the probability of a mosquito surviving through any one day, and n is the extrinsic incubation period—the time taken for the pathogen to develop in the mosquito until the insect becomes infective. The only factor directly affected by a climate variable is n , which is inversely related to temperature. Because p is less than unity, p^n will increase at higher temperatures, although p itself may decrease as a result of other factors. However, the denominator is an exponential function, so p , survival rate, is dominant.

Caged mosquitoes can live for 3–4 months, but their median age in the field is commonly about 4–6 days. Clearly, in nature few die of senescence; most are killed by predators, disease, and other hazards long before they reach old age (49). Feeding and the search for oviposition sites are probably the most hazardous activities. Species that become inactive (e.g., in winter or in the dry season) are known to survive for as long as 9 months.

Vectorial capacity and similar elementary models were developed to explore the fundamental features of the transmission of mosquito-borne disease (50–53), mainly in the context of mosquito control operations. Except for n , the calculation of C depends on quantitative values that can be obtained only in the field. However, it is hard to estimate these values realistically because their measurement depends heavily on a complex range of assumptions (54–57). Moreover, C is limited to entomologic parameters and the duration of extrinsic incubation; it does not incorporate the parasite rate in humans or mosquitoes, nor any of the many ecologic and behavioral factors outlined in the previous section. Thus, although helpful in our understanding of transmission dynamics and as a practical tool in specific situations, such models have a limited value for assessing the impact of long-term climate change on disease transmission (58,59).

An alternative approach is to look at the past. The history of mosquito-borne diseases at different latitudes and in different climatic eras can help us assess the significance of climate variables in the context of the many other factors that affect transmission.

History of climates. Climatology is a relatively young science. Apart from a handful of sites, systematic records of climate variables are available only for the past century, mainly from land-based stations in the Northern Hemisphere. Global data, obtained by weather satellites, are available only for the past few decades. Thus the time span of direct studies of climate is within the first order of climatic variation, less than the period for valid long-term change (Table 1).

Fortunately, a large amount of alternative data is available. Documentary information from annals, chronicles, audited accounts, agricultural records, tax ledgers, and a wealth of other archival material provides a rich source of indirect information, particularly on the timing and occurrence of extreme weather events such as drought, flood, or unusual cold. Descriptions of wind direction, wind speed, cloud formations, and other weather indicators are available from private diaries, ships' logs, accounts of military campaigns, and similar sources. Substantial lines of evidence are also available from archaeologic, geologic, fossil, and other sources. They include the study of glacial moraines, lake and ocean sediments, pollen strata, deposits of insects, tree rings, coral structure, radiometric analysis of ice cores, and many other indicators. All this evidence makes it possible to realistically reconstruct past climates over the course of time (2,16).

History of mosquito-borne disease. The scientific study of mosquito-borne disease is also limited to the past 100 years. Fortunately, the symptoms of three important diseases—malaria, yellow fever, and dengue—are fairly distinctive. Thus, as with climatology, we can turn to a variety of sources for evidence of their occurrence in past climates. The bulk of this review is devoted to such evidence. Particular emphasis is placed on the temperate latitudes because of the wealth of historical materials that is available and because models suggest that the impact of global warming may be greatest at these latitudes.

Malaria

The Disease

Malaria (Italian *mala aria*, bad air) is a protozoan (genus *Plasmodium*) infection transmitted by mosquitoes of the genus *Anopheles*. The four species of *Plasmodium* that infect humans appear to have evolved from a common ancestor during the early Tertiary period, some 60 million years ago (60). Thus, some or all of them probably co-evolved with

the genus *Homo* and have affected humans since their earliest days.

The clinical course of malaria (33) generally involves distinctive bouts of fever alternating with periods of freedom from illness. Each episode begins with a short period (15 min–1 hr) of violent shivering, with the patient having cyanotic lips and fingers, a rapid but weak pulse, and a feeling of intense cold (rigor). This cold stage is followed by 2–6 hr of distressing heat, accompanied by flushed skin, intense headaches, nausea, and a full, bounding pulse. The hot stage is followed by profuse sweating and a rapid drop in temperature, often to levels below normal.

A prominent feature of the febrile bouts is their periodicity: They tend to recur every third day with *Plasmodium vivax*, *P. falciparum*, and *P. ovale* and every fourth day with *P. malariae*. From earliest times this periodicity gave rise to the descriptors *tertian* and *quartan* fevers. Another common term was *aestivo-autumnal* or *harvest fever* because in temperate regions epidemic transmission tended to occur in late summer and autumn (33).

Malaria in Temperate Climates

Prehistory. About 60 species of *Anopheles* can transmit human malaria. Those that exist in Europe probably began colonizing the region as the ice caps retreated at the end of the Pleistocene epoch. Human populations, also moving northward, almost certainly brought malaria parasites along with them. The prevalence of the disease in the Neolithic period and the Bronze Age is uncertain, but it is unlikely to have been very high because human groups were generally small and widely scattered. Nevertheless, early Neolithic skeletal remains from Anatolia and Macedonia exhibit pathologic changes that have been attributed to chronic anemia caused by *P. falciparum* infection. The widespread presence of thalassemia (Mediterranean anemia), a genetic condition that gives some protection against malaria, may also indicate a long history of contact with the pathogen.

Ancient Greece and Rome. The introduction of agriculture, around 7000 B.C., led to increased populations of relatively settled people and increasingly favorable conditions for malaria transmission (34). The extensive deforestation that began at this time may also have contributed to prevalence by creating additional habitat for anopheline mosquitoes. Similar ecologic changes in modern times have caused major increases in the prevalence of the disease.

Contemporary accounts together with fossil and other evidence suggest that a gradual warming and drying occurred in the Mediterranean region throughout classical

times until about A.D. 400 (2). Landscape studies suggest a gradual rise in sea level over this period. Around 300 B.C., beech trees (genus *Fagus*) grew in Rome, the Tiber River froze in winter, and snow lay for many days. However, by the first century A.D. the Romans considered the beech a mountain tree, and winters were definitely less severe. Over these centuries, the cultivation of the vine and olive moved gradually northward along the Italian peninsula. The Romans were even able to introduce wine growing to Germany and Britain, and import data suggest that Britain became self-sufficient in wine production by around A.D. 300. The warming trend is clearly indicated by tree-ring studies in California, so it may have been a worldwide or at least a hemispheric phenomenon (2).

The first literary mention of an autumnal fever is in Homer's *Iliad* (800 or 900 B.C.), as Achilles sets out to fight Hector (61):

And old King Priam was first to see him coming,
surging over the plain, blazing like the star
that rears at harvest, flaming up in its brilliance—
far outshining the countless stars in the night sky,
that star they call Orion's Dog—brightest of all
but a fatal sign emblazoned on the heavens,
it brings such killing fever down on wretched men.

We cannot be certain that this was malaria, but the reference to killing fevers at harvest time is one that recurs many times in other descriptions of malaria. Later texts confirm that the disease had become a significant feature in Greek life. Indeed, there is evidence that a major wave of malaria began with the flowering of Greek civilization and transmission rates continued to increase throughout the period of the Roman Empire (2,62). Hippocrates (460–377 B.C.) gave exquisitely detailed descriptions of the course and relative severity of tertian versus quartan infections (63). He also noted their association with wetlands and even observed that splenomegaly (enlarged spleen, often a symptom of chronic malaria infection) was particularly prevalent in people living in marshy areas.

Praxagoras, Heraclides, and other medical writers gave similar descriptions, from which it appears that much of Greece had become highly malarious (62).

There is a wealth of evidence that malaria was common in imperial Rome (34). Horace, Lucretius, Martial, and Tacitus were among many Latin authors who mentioned the disease. The Pontine Marshes, close to the city, were notorious as a source of infection. Marcus Terentius Varro (116–127 B.C.) described these *loca palustria* (fever areas) and attributed the disease to *animalia quaedam minuta quae non possunt oculi consequi* (animals too small to be seen). He advised that houses should be built in high, well-ventilated places so that the *bestiolae* that bred

below would be blown away, and even mentioned the use of nets to protect against the bites of mosquitoes (64). Later, in the second century A.D., the detailed writings of Galen and Celsus on the symptoms and treatment of “intermittent fevers” give clear evidence that three species of parasite—*P. falciparum*, *P. ovale*, and *P. vivax*—were commonly present (2,65).

The Dark Ages. Relatively little is known of climate after the Roman era, during the Dark Ages, but there seems to have been a cooling trend from the fifth century onward. There were certainly some outstandingly cold winters. In A.D. 763–764 there was ice on the sea in the Dardanelles, and in 859–860 the sea ice on the Adriatic was strong enough to support heavy wagons. In 1010–1011 it was even cold enough for ice to form on the Nile. Again, tree-ring data from California indicate that this cooling was not restricted to Europe. Nevertheless, the armies of Visigoths, Vandals, Ostrogoths, and other barbarians that swept the continent had to contend with malaria, often as a major setback to their campaigns. Several popes and churchmen, including St. Augustine, the first Archbishop of Canterbury, died of malaria during their journeys to Rome. Around the turn of the millennium, the armies of Otto the Great, Otto II, and Henry II suffered severely from the “Roman Fever” during their sieges of the Holy City.

The Middle Ages. The Medieval Warm Period, which reached its peak around 1200, coincided with major advances in technology and agriculture and a significant increase in population throughout most of Europe. The Vikings were able to establish self-sufficient colonies, based on oats and barley, in northern Scandinavia, Iceland, and Greenland. In the British Isles, tillage was extended to much higher altitudes than is possible today—so high that sheep farmers complained that too little land was left for grazing. English vintners were able to maintain a flourishing production of high-quality wine despite efforts by Bordeaux traders to have their exports restricted by treaty.

The explosion of economies and culture that occurred during this warming period has been attributed at least partly to the beneficial impact of the warming climate. From caliphate Spain to Christian Russia, numerous medieval writers mentioned agues, intermittent fevers, tertians, quartans, and the like. A classic example appears in *The Inferno*, where the Florentine poet Dante (1265–1321) wrote (66):

... Like those who shake,
Feeling the quartan fever coming on—
Their nails already blue, so that they shiver
At the mere sight of shade—such was I then;

Later, in *The Canterbury Tales*, the English poet Chaucer (1342–1400) wrote (67):

Your face is choleric and shows distension;
Be careful lest the sun in his ascension
Should catch you full of humours, hot and many.
And if he does, my dear, I'll lay a penny
It means a bout of fever or a breath
Of tertian ague. You may catch your death.

Favorable temperatures and rainfall may have enhanced transmission of malaria in earlier years, but Chaucer's lifetime coincided with a cooling trend that culminated in a series of severely cold winters in the first decades of the fifteenth century (68). Much of the earlier agricultural expansion was reversed. There were many years of famine and a large-scale abandonment of farms. Despite this cooling, malaria persisted, even in northern regions (34).

The Little Ice Age. The first half of the sixteenth century was warm again. Temperatures were probably quite similar to those of the period 1900–1950. In the middle of the century, however, a remarkably sharp change occurred. After a decade or so of particularly warm years—warm enough for young people to bathe in the Rhine River in January—the winter of 1564–1565 was bitterly cold (2). The next 150–200 years—dubbed the Little Ice Age—were probably the coldest era of any time since the end of the last major ice age, some 10,000 years ago (16). Yet despite this spectacular cooling, malaria persisted throughout Europe (34).

William Shakespeare (1564–1616) was born in the year of that first fierce winter, yet there are 12 mentions of ague in his writings. He also made several allusions to the association between swampy land and disease, and the name Sir Andrew Aguecheek presumably referred to the trembling cheeks of his obese hero. The years 1594–1597 were so cold and wet that wheat harvests were a disaster, yet William Harvey (1578–1657) missed much of his final year at the University of Cambridge, England, in 1597 because of malaria (69). In later years he made careful observations of malaria cases in London. The marshes in the Borough of Westminster, where the Houses of Parliament now stand, were notoriously malarious. In his treatise *On the Motion of the Heart and Blood in Animals* (1628) Harvey described the clinical pathology of the febrile episodes, including the changes in the consistency of blood that occur in serious cases (70):

In tertian fever, . . . in the first instance . . . the patient [is] short-winded, disposed to sighing, and indisposed to exertion, . . . the blood [is] forced into the lungs and rendered thick. It does not pass through them (as I have myself seen in opening the bodies of those who had died in the beginning of the

attack), when the pulse is always frequent, small, and occasionally irregular; but the heat increasing, . . . and the transit made, the whole body begins to rise in temperature, and the pulse becomes fuller and stronger. The febrile paroxysm is fully formed . . .

Another notable physician, Thomas Sydenham (1624–1689), also lived through some of the coldest years of the era, yet made frequent reference to tertians and quartans (34). He even remarked, “When insects do swarm extraordinarily and when . . . agues (especially quartans) appear early as about midsummer, then autumn proves very sickly” (34).

Not all the summers of the Little Ice Age were cool. The overall mean temperature was probably at least 1°C cooler than in the twentieth century, but there also seems to have been an enhanced variability of the climate, with wide differences between clusters of up to 6–8 years. Thus, diarist Samuel Pepys (1633–1703), who suffered from malaria, remarked that the summers of 1661, 1665, and 1666 were remarkably hot (34), and Sydenham described an epidemic of “tertian and some quartan” fevers that broke out in 1661, which “was doing frightful mischief” by August [quoted in Bruce-Chwatt and de Zulueta (34)].

Warm summers may have contributed to this and other outbreaks, but transmission was not restricted to such years. In 1657–1658, snow lay on the ground for 102 days—exceptionally cold even with respect to the climate of the times—yet Oliver Cromwell (1599–1658) died of malaria in September 1658 just as another severe winter was setting in. Temperatures were probably at their lowest from 1670 to 1700, yet this was the very period that Robert Talbot (ca. 1642–1681) was able to persuade the aristocracy of England and Europe to buy the prescriptions, based on cinchona bark, that he had developed in the marshlands of Essex (34,71–74). In the same period, Daniel Defoe (1660–1731) described life in the Dengie marshes of Essex, England (75):

a strange decay of the [female] sex here. . . it was very frequent to meet with men that had had from five to six, to fourteen or fifteen wives . . . the reason. . . was this; that they [the men] being bred in the marshes themselves, and seasoned to the place, did pretty well with it; but that they always went into the hilly country. . . for a wife: that when they took the young lasses out of the wholesome and fresh air, they were healthy, fresh and clear, and well; but when they came out of their native aire into the marshes. . . they presently changed their complexion, got an ague or two, and seldom held it above half a year, or a year at most; and then. . . [the men] would go to the uplands again, and fetch another; so that marrying of wives was reckoned a kind of good farm to them (75).

Dobson (76–79) has masterfully researched the demography, epidemiology, and social impact of malaria in England in this period. The disease was especially prevalent in areas of brackish marshland, the preferred habitat of an effective vector, *An. atroparvus*. Data from burial records show that mortality rates in “marsh parishes” were much higher than those in upland areas and were comparable to those in areas of stable malaria transmission in sub-Saharan Africa today (80).

After the Little Ice Age. From the early eighteenth century until the present, temperatures have gradually returned to levels that prevailed before the mid-sixteenth century. However, the marked variability of the Little Ice Age persisted for at least 150 years. Indeed, in the 1770s, much as is happening today, there was alarm that the climate was becoming increasingly erratic, and this prompted a new emphasis on the recording of weather variables. Some of the cold periods, particularly those between 1752 and the 1840s, were probably caused by major volcanic eruptions. Whatever their causation, such episodes—accompanied by major advances of the Alpine glaciers from 1820 to 1850—persisted until a more lasting warmth was established in the late nineteenth century (2,16).

A wealth of records in the eighteenth and nineteenth centuries reveals the northern limits of malaria transmission. In the British Isles, the disease was common in most of England and in many parts of Scotland, with occasional transmission as far north as Inverness. It was endemic throughout Denmark, coastal areas of southern Norway, and much of southern Sweden (81) and Finland (82). In Russia it was common in the Baltic provinces and eastward at similar latitudes throughout Siberia. The current average January temperature in some of these regions is less than -20°C (-4°F). Clearly, the distribution of the disease was determined by the warmth of the summers, not by the coldness of the winters. The northern limit of transmission (83) was roughly defined by the present 15°C July isotherm—not the 15°C winter isotherm, as stated in several widely cited articles on climate change (27,28).

Decline of malaria. In the second half of the nineteenth century malaria began to decline in much of northern Europe. Denmark suffered devastating epidemics until the 1860s, particularly in the countryside around Copenhagen, but thereafter transmission diminished and had essentially disappeared around the turn of the century (84). The picture was similar in Sweden (Figure 2), although isolated cases were still being reported until 1939 (81). In England, there was a gradual decrease in transmission until the 1880s, after which it dropped precipitously and became relatively rare except

in a short period following World War I (34,85). In Germany, transmission also diminished rapidly after the 1880s; after World War I it was mainly confined to a few marshy localities (34). The last outbreak of locally transmitted malaria in Paris occurred in 1865 during the construction of the Grands Boulevards, and the disease had largely disappeared from the rest of France by the turn of the century (86,87). In Switzerland, most foci had disappeared by the 1890s (88).

The decline of malaria in all these countries cannot be attributed to climate change because it occurred during a warming phase when temperatures were already much higher than in the Little Ice Age. However, a host of other factors can be identified.

First, improved drainage, reclamation of swampy land for cultivation, and the adoption of new farming methods (there is an old Italian saying: “malaria flees before the plough”) all helped eliminate mosquito habitat. Second, new root crops such as turnips and mangel-wurzels were adopted as winter fodder. These enabled farmers to maintain larger numbers of animals throughout the year, thus diverting mosquitoes from feeding on humans. Third, selective breeding of cattle plus new introductions (e.g., the Chinese domestic pig) in combination with the new fodder crops enabled farmers to keep large populations of stock in farm buildings rather than in open fields and woodland. These buildings provided attractive sites for adult mosquitoes to rest and feed, diverting them from human habitation.

Changes in demographics and human living conditions were also significant. Rural populations declined as manual labor was replaced by machinery. This further reduced the availability of humans (vs. animals) as hosts for the mosquitoes and of humans as hosts for the parasite. New building materials and improvements in construction methods made houses more mosquito-proof, especially in winter, another factor that reduced contact with the vector. Finally, greater access to medical care and wider use of quinine reduced the survival rate of the malaria parasite in its human host.

Much of the decline in malaria came before recognition of the role of mosquitoes in its transmission. Thus, for most of the region, deliberate mosquito control played little or no role in its eventual elimination.

Persistence of malaria in the then-Soviet Union and neighboring countries. In countries where profound changes in crop production and stock rearing were absent, malaria did not decline.

In Russia, from the Black Sea to Siberia, major epidemics occurred throughout the nineteenth century, and the disease remained

one of the principal public health problems for the entire first half of the twentieth century (34). In 1900, annual incidence in military garrisons was 6.6 per 1,000 in St. Petersburg, 31.0 per 1,000 in Moscow, and several hundred per 1,000 in the more southerly provinces. Mean annual incidence from 1900 to 1904 was 3,285,820, but by the period from 1933 to 1937, it had risen to 7,567,348. Some of this increase can be attributed to more effective reporting, but there is no doubt that the disease became much more prevalent after World War I and the 1917 Revolution. In the 1920s, in the wake of massive social and economic disruption, 2 years of severe drought, and a year of widespread flooding, a pandemic swept through what was then the entire Soviet Union. Official figures for 1923–1925 listed 16.5 million cases, of which not less than 600,000 were fatal (89). Tens of thousands of infections, many caused by *P. falciparum*, occurred as far north (Figure 2) as the Arctic seaport of Archangel ($61^{\circ} 30' \text{N}$).

The Soviet government appeared to make some headway against the disease in the 1930s, mainly by drainage schemes, afforestation, and naturalistic methods such as the use of mosquito-eating fish. World War II interrupted these efforts and transmission soared, particularly in the Ukraine, Belorussia, and other occupied areas. Finally, in 1951, a huge multifaceted antimalaria campaign was initiated. It involved widespread use of DDT and other residual insecticides, antimalarial therapy, land reclamation, water management, public health education, and many other approaches. This mammoth effort finally brought about a dramatic reduction of transmission, so that by the mid-1950s the national annual incidence was below 1 per 10,000 (34).

In neighboring Poland, the disease was still present after World War I, and a large-scale epidemic coincided with the 1920s pandemic in the Soviet Union. In the 1930s, efforts to control the disease were largely successful, although endemic foci persisted throughout the country (34). However, a new wave of transmission followed World War II (90). This peaked in 1948, after which an intensive campaign of DDT spraying and antimalarial therapy finally eliminated the disease (Figure 3). In Finland, malaria was still a problem after it had practically disappeared in neighboring Sweden. Significant transmission occurred during the Finno-Russian war (1939–1940). The disease finally died out in the late 1940s (82).

The contrast between the devastation caused by malaria in the Soviet Union until the 1950s, and its quiet withdrawal from other countries at similar latitudes in the previous century illustrates the importance of

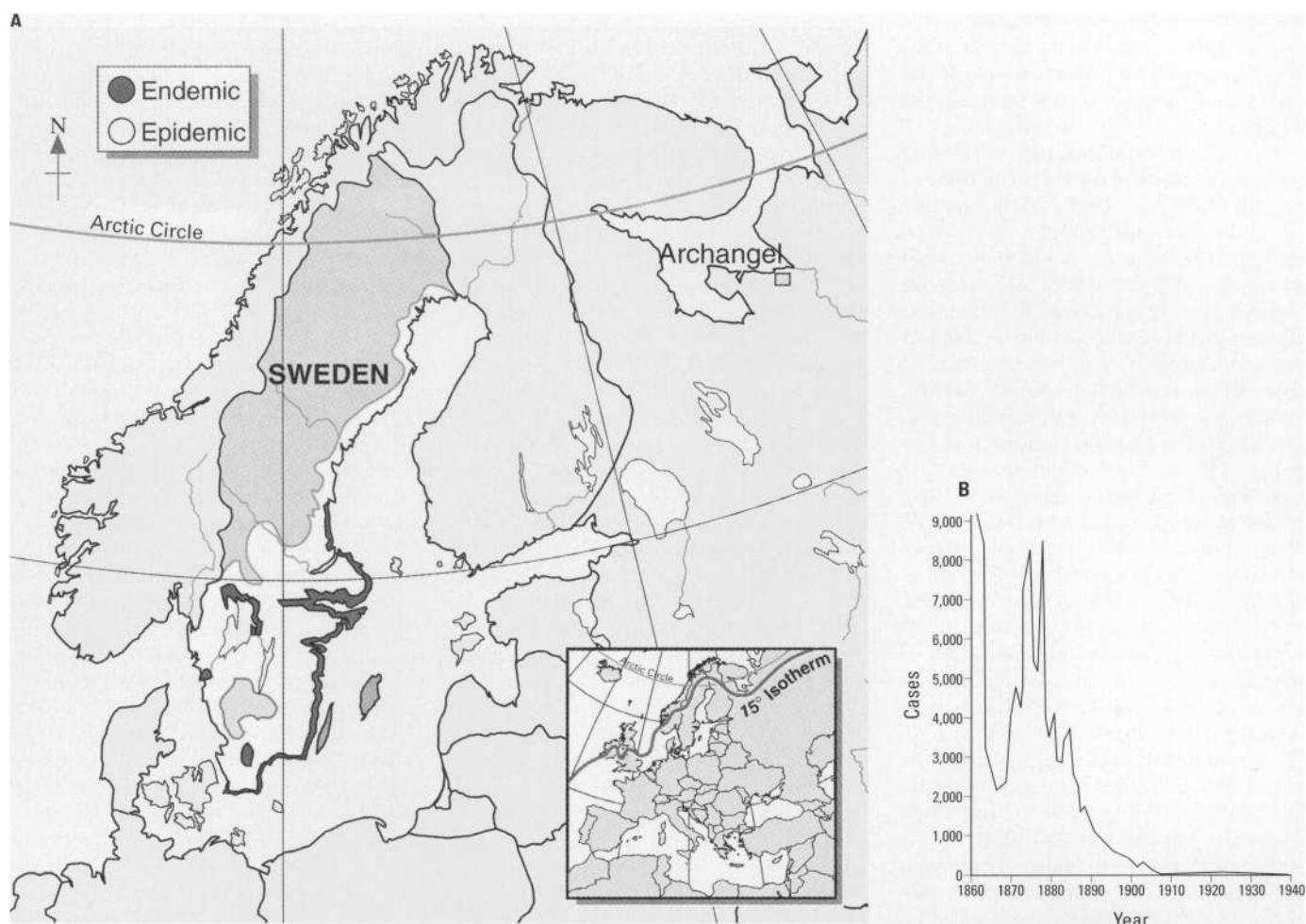


Figure 2. (A). Distribution of malaria in Sweden in the late nineteenth century, showing endemic and epidemic areas. (B) The annual death rate (1860–1940) attributed to the disease. Modified from Ekblom (81) and Renkonen (82). The 15°C July isotherm was the approximate northern limit of transmission. Note the location of Archangel, Russia, site of a major epidemic of *P. falciparum* in the 1920s.

nonclimatic factors in transmission. Until the collectivization of farmland that began in the winter of 1929–1930, the Soviet Union had been largely unaffected by the agricultural revolution. By 1936, all farming was essentially in government hands, but in protest many peasants had slaughtered their horses and livestock and destroyed their equipment. These events ran counter to many of the changes that had reduced transmission in much of Europe. In neighboring Poland and Finland farming was also less advanced than in much of the rest of northern Europe, but the slow modernization that occurred over this period probably contributed to the steady downward trend in malaria cases.

Malaria in southern Europe. Malaria remained highly prevalent in much of Mediterranean Europe, the Balkans, and the countries bordering the Black Sea until after World War II (89). The presence of several effective vector species, an abundance of prolific mosquito breeding sites, the warm climate, and the long summer season were all highly conducive to transmission. In addition,

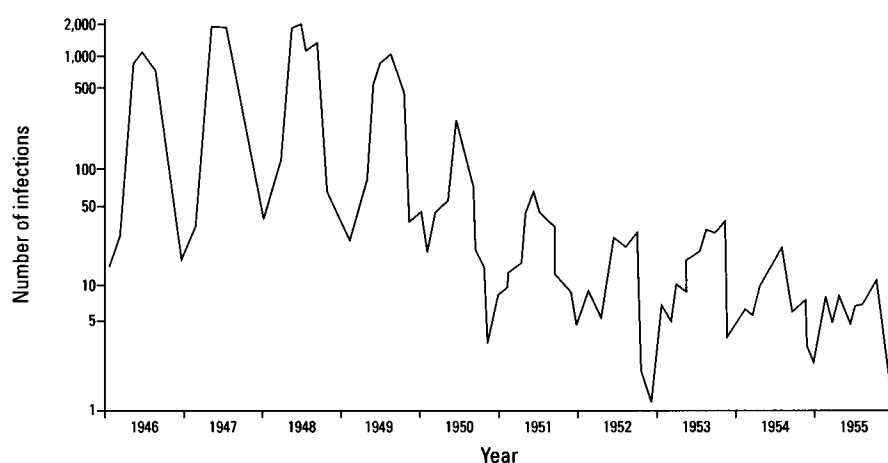


Figure 3. Malaria in Poland, 1946–1955. Malaria persisted in Finland, Poland, and the Soviet Union long after it had disappeared from other parts of northern Europe. Derived from Dymowska (90).

much of the region was relatively unaffected by the environmental changes associated with modern agriculture. Part of this lack of change can be attributed to the disease itself, for poverty and lack of progress characterized

many of the highly malarious regions. In northern Italy, for example, much of Piedmont and Lombardy was free of transmission. By contrast, large portions of the rest of the country, particularly Sardinia, Calabria,

and Sicily, remained virtually uncultivated until the 1950s, at least partly because of the ravages of the disease. The same was true for major regions in Spain, Greece, Romania, and Bulgaria (34).

In World War I, British and French allied operations in Macedonia were paralyzed by an epidemic of malaria (34). By 1918, incidence among British troops had risen to 459 cases per 1,000. Between the world wars, major malaria epidemics caused enormous economic hardship in the same region. Rail transport was often interrupted in the summer, and harvests were badly affected by the shortage of labor. Serbia, Bosnia-Herzegovina, Kosovo, and Croatia were also seriously affected. *P. vivax* was the principal parasite species in spring, followed by *P. falciparum* and *P. malariae* in late summer and early fall (91).

The elimination of malaria from Europe. Until end of World War II, the only effective approach to mosquito control was to eliminate the breeding sites by environmental modifications such as drainage and landfill and by the application of insecticidal oils or chemicals. These methods were costly, so they were applied mainly to urban centers and other areas of high economic importance. The advent of DDT revolutionized malaria control (92). It enabled cheap, safe, effective treatments to be targeted at the site where most infections occur—in the home.

The principal treatment method was to apply 2 g/m² of DDT to indoor surfaces once every 6 months. Mosquitoes were killed by contact when they alighted on the treated surfaces. Initial efforts in Italy, Cyprus, and Greece were so successful that a decision was made to eradicate malaria from all of Europe (33,93). The campaign was based on a careful application of scientific principles, meticulous planning, efficient administration, generous financing, and continuous emphasis on evaluation. It was orchestrated by several international agencies, particularly the World Health Organization (WHO) and the United Nations Children's Fund, as well as numerous national bodies including the U.S. Public Health Service. The International Health Division of the Rockefeller Foundation also provided generous financial and technical support. By 1961, eradication had already been achieved in many countries. The entire continent was finally declared free of endemic malaria in 1975 (94). One of the last countries affected was The Netherlands.

The complexity of malaria transmission: The Netherlands.

Everything about malaria is so moulded and altered by local conditions that it becomes a thousand different diseases and epidemiological puzzles. Like chess, it is played with a few pieces, but is capable of an infinite variety of situations (89).

The persistence of malaria in The Netherlands, a country that has held a central position in the economic life of Western Europe since the Middle Ages, is a good illustration of this complexity.

In the nineteenth century, despite great progress in drainage and cultivation, the heavily populated Low Countries were the most malarious region of northern Europe. During the Napoleonic Wars the failure of the British Walcheren expedition (1809) was blamed on malaria after 4,000 troops died of fever. Severe outbreaks also attributed to the disease occurred in 1826, 1834, and 1846, with many thousands of deaths (95).

The dominant vector, *Anopheles maculipennis*, was present throughout the country. However, the disease was particularly prevalent in areas that had been reclaimed from the sea, especially in Noord Holland, a province that includes the cities of Haarlem and Amsterdam. Moreover, a major peak of incidence occurred in the spring rather than summer or fall.

The unraveling of this puzzle was one of the classic triumphs of medical entomology (89). Investigation revealed that *An. maculipennis* was not one but several sibling species (96): *An. atroparvus*, which lays its eggs in brackish water; *An. messeae*, which prefers fresh water; and *An. maculipennis*, *sensu strictu*, which occurred inland in nonmalarious areas. In the laboratory, *An. messeae* and *An. atroparvus* were both excellent vectors of malaria. In the field the picture was very different. Both species preferred to feed on domestic animals rather than humans, but whereas *An. atroparvus* rested in stables, *An. messeae* preferred uninhabited sheds and other unheated outhouses. In the fall, *An. messeae* built up a fat body that allowed it to hibernate. By contrast, *An. atroparvus* remained semiactive, feeding at regular intervals throughout the winter. Although most of its meals were taken on farm animals, it occasionally wandered into adjacent human dwellings. If persons infected with the malaria pathogen were present, the mosquito acquired the infection. Thus, as in many tropical countries, transmission occurred at all times of the year despite winter temperatures that could dip below -20°C. However, the mosquito's ovaries did not develop eggs until the advent of spring, a condition known as gonotrophic dissociation. An additional twist to the story was that the local strain of *P. vivax* had a particularly long incubation period, so persons infected in the fall and winter showed symptoms of illness only in the spring after the first new brood of mosquitoes had emerged (34,89).

In 1932 a dyke was built to enclose the Zuider Zee, a vast area of brackish water to the east of Noord Holland. The accumulation

of river water behind this dyke caused a gradual decrease in the salinity of the surrounding land, greatly reducing the larval habitat of *An. atroparvus* (97). In addition, there were major changes in the living conditions of humans. New farmhouses were less intimately associated with cattle sheds and stables, and their structure and heating technology made them much less hospitable to overwintering mosquitoes (34).

Thus, although the disease was finally eradicated by routine DDT applications and the administration of antimalarial drugs, the ecology, physiology, behavior, and survival of the vector, plus the interaction of the pathogen with both vector and host, all contributed to its demise.

Malaria in North America. Several efficient malaria vectors are indigenous to North America and are common in many areas. The pathogen probably arrived in the hemisphere in infected European colonists and African slaves. The history of its decline is similar to that of Europe. In the 1880s, the disease was widespread in nearly all states east of the Rocky Mountains (Figure 4), from the semitropical Gulf Coast states to the northern U.S. border (98) and into Canada (99,100). It was also present west of the Rocky Mountains, particularly in areas where rainfall is abundant.

As living conditions improved and antimalarial drugs became more widely available, the incidence of the disease declined. During World War II, the U.S. military created an Office of Malaria Control in War Areas, which was responsible for military bases throughout the country. In a symposium published in 1941 (101), the disease was described as "of moderate endemic intensity in the sixteen southeastern states . . . with scattered epidemics at intervals of approximately seven years." In 1946 the U.S. Congress established a new agency, the Communicable Disease Center. This was the forerunner of the U.S. Centers for Disease Control and Prevention (CDC), and its principal mission was to eradicate malaria from the entire country. It was based in Atlanta, Georgia, because the southern states were the main region still affected by the disease. When operations began, foci of transmission were already hard to find, but the disease was not totally eliminated until the late 1950s. Today, as in Europe, there are many parts of the country where anopheline vectors are abundant, but the transmission cycles have been disrupted and the pathogens are absent.

Malaria in the Tropics

Epidemiology. The epidemiology of malaria in the tropics is even more complex than that in temperate climates and varies greatly with location (33). In much of equatorial Africa,

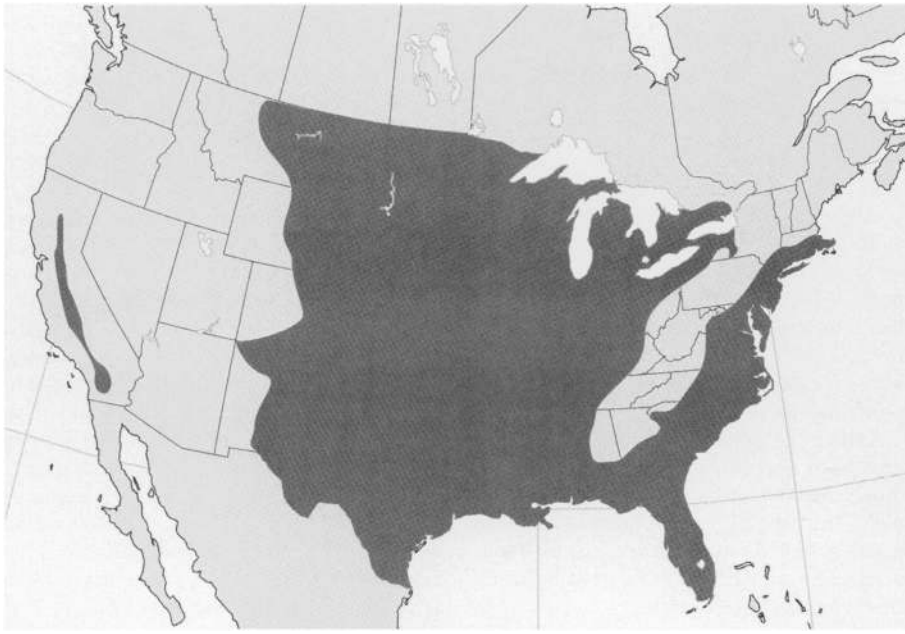


Figure 4. Malaria in the United States and Canada in 1882. The dark shaded areas are regions where the disease was probably endemic. Modified from Faust (98), Stewart (100), and Williams (188).

parts of northern India, Indonesia, and South America transmission is termed stable because it is fairly constant from year to year. The disease is endemic, but epidemics are uncommon. In other regions, including much of India, Southeast Asia, and Central and South America, the disease is also endemic but is termed unstable because transmission can vary greatly from year to year, and the potential for epidemics is high.

Stable endemic malaria. This occurs in regions where the anophelines are anthropophilic (they prefer to feed on humans) and have a high survival rate. Temperature and humidity are generally high and there is often relatively little seasonal variation. The disease is hard to control because transmission is extremely efficient—it can occur with relatively low mosquito populations—and transmission rates are so high that most people experience many infective bites per year. Severe illness and fatality are generally restricted to “new arrivals,” i.e., children and nonimmune immigrants. Older inhabitants harbor the parasites but have survived multiple infections and maintain a high degree of immunity by repeated reinfection. Epidemics in the local population are rare but can sometimes occur after a major increase in mosquito populations.

Unstable endemic malaria. This occurs in regions where the anophelines are generally zoophilic (they tend to bite animals in preference to humans), where their survival rates are low, or where both apply. Transmission rates can vary greatly, with epidemics often separated by many years of relatively low activity. The factors that precipitate such epidemics are

often difficult to identify. The disease may appear suddenly for no apparent reason, only to disappear again without obvious cause. In general, transmission is relatively inefficient and therefore requires high mosquito populations. In theory this implies that the disease is easier to control.

Index of stability. The causes of stability versus instability have been the subject of much study and controversy (33). In reality, the terms are merely convenient labels, for they describe the extremes of a wide range of situations. Mathematically the index of stability is given by the expression

$$\frac{a}{-\log_e p}$$

where a is the preference of the principal vector for human versus nonhuman blood and p is its daily survival probability. Note that a) the denominator is an exponential function—small changes in survival rate have a major impact on the index; and b) neither of the two variables is directly affected by climate variables

The concept of stability has proven valuable in understanding and solving control problems. The same approach is useful in addressing the question of climate change.

Climatic influences on malaria transmission in the tropics. Climatic factors are important in the tropics. Their influence is complex and varies according to region and the ecology of the vectors concerned.

Temperature. In theory, high temperatures should increase the likelihood of transmission because they reduce the extrinsic incubation

period. However, activities such as biting and egg laying are also likely to be accelerated. These are high-risk activities, so survival rate, and thus transmission rate, may also be affected.

In equatorial regions, vectors such as *An. gambiae* are commonly found as high as 3,000 m above sea level, but endemic malaria disappears above 1,800–2,000 m (102,103). A limiting factor is presumably the temperature required for effective extrinsic incubation, analogous to the temperature limits defined by isotherms at high latitudes.

Humidity. Survival rate may also be reduced when hot weather is accompanied by low humidity, but in areas where such conditions are normal, local species have adapted to cope with them. For example, in the severe drought and extreme heat of the dry season in semiarid parts of the Sudan, female *An. gambiae* survive up to 11 months of the year by resting in dwelling huts and other sheltered places. Blood feeding continues, so transmission is not interrupted, but the ovaries do not begin to develop eggs until the rains return (42,104). This strategy of gonotrophic dissociation is remarkably similar to the winter survival mechanism of *An. atroparvus* in The Netherlands. In both cases, inactivity leads to a high vector survival rate and continued transmission of malaria, even under adverse climatic conditions.

Rainfall. Rainfall can promote transmission by creating ground pools and other breeding sites, but heavy rains can have a flushing effect, cleansing such sites of their mosquitoes. Drought may eliminate standing water but cause flowing water to stagnate. Thus in arid areas prolonged drought may cause malaria to decline (105), whereas in areas where rainfall is normally abundant, vast numbers of mosquitoes can be produced and “drought malaria” may follow. Similar patterns apply to artificial streams in irrigated regions and storm drains and sewers in urban areas. Drought may also stimulate people to store water in cisterns, drums, and other manmade containers that serve as breeding sites.

Seasonality. Climatic factors often impose seasonality on transmission. Even in regions of high stability, transmission may peak at a specific time of year, although such modulations have little impact on the long-term health of the population because overall infection rates are so high. However, indices of stability are often lower in regions where seasonality is more pronounced. In some cases, the phenomenon is clearly defined but may vary according to circumstance.

The complexity of the influence of climate on malaria transmission in the tropics is well illustrated by the history of epidemics in Sri Lanka (106). In the 1930s, the disease was common. In a normal year 1.5 million people,

about a quarter of the total population, were treated for malaria in hospitals and dispensaries. However, from 1934 to 1935 a catastrophic epidemic is estimated to have killed 100,000 people. Worst hit was the southwestern quadrant of the country, a region with an average annual rainfall of more than 250 cm.

The dominant vector in that part of the country is *An. culicifacies*, a species that breeds along the banks of rivers. In normal years it was not abundant. Malaria was endemic, but the stability index was low; in most years the disease was relatively unimportant.

The monsoons in the preceding 5 years had been exceptionally favorable, with abundant heavy rainfall leading to excellent rice crops. Under such conditions, river flow was high, *An. culicifacies* was rare, and the population was exceptionally healthy. However, when two successive monsoons failed, the rice crops were lost and hunger was widespread. Colossal numbers of *An. culicifacies* were produced in the drying rivers and irrigation ditches.

The epidemic that followed was exacerbated by the weakened condition of the people. In addition, the herd immunity was especially low because the previous 5 years had been wet and therefore relatively free of malaria. By contrast, in the drier parts of the island, where *An. culicifacies* was dominant but the stability index was higher, immunity protected the population from the worst ravages of the epidemic (107).

Malaria was almost eradicated from all of Sri Lanka in the 1960s, but in recent years it has returned as a major public health problem, with almost 0.3 million infections reported annually in its population of 17 million (108).

Nonclimatic influences on malaria transmission in the tropics. As in temperate regions, human activities and socioeconomic factors have a major impact on transmission.

Population. The world's population was 4 billion in 1960, 5 billion in 1987, and more than 6 billion in the year 2000. Ninety-six percent of this increase has occurred in developing regions of Africa, Asia, and Latin America, many of which are malarious (109). For example, in sub-Saharan Africa, there are now nearly four times as many people (approximately 450 million) as there were in 1955. The population of Kenya was 8 million in 1963, 24 million in 1990, and is expected to be double this figure within the next 10 years. Many of the other factors listed in this section can be attributed to or associated with this rapid population increase.

Forest clearance. Many important malaria vectors breed in open sunlit pools. Forest clearance provides abundant new habitat for these species and is a classic cause of the emergence of malaria problems (110). Massive clearance also modifies local microclimates by reducing shade, altering rainfall

patterns, augmenting air movement, and changing the humidity regime.

Agriculture. Rice and other irrigated crops often create an ideal habitat for the mass production of mosquitoes. The construction of dams for irrigation or hydroelectric power can also lead to high populations of anophelines. Abandoned fish farming projects have had similar results in several countries. Cattle hoofprints can provide a prolific breeding site for anthropophilic species such as *An. gambiae*. Conversely, as in temperate regions, the proximity of cattle to human habitation can deflect bites from humans in areas where the mosquitoes are predominantly zoophilic.

Other ecologic factors. The removal of reeds from river margins increases water flow and eliminates the shelter preferred by many—but not all—vector species. Similarly, in still water, floating plants such as duckweed and water lilies are favored by some species but discourage others.

African papyrus produces an oil that inhibits anopheline development. The elimination of this aquatic plant for rice cultivation provides an environment better suited to *An. gambiae* and *An. funestus*. Conversely, the cultivation of ground depressions in the Sahel can suppress *An. funestus* and thereby reduce transmission (105).

In the High Andes of South America, malaria can be transmitted at 2,700 m. At this altitude, the vector *An. pseudopunctipennis* breeds in volcanic thermal springs (111). The outdoor climate is too cold for *Plasmodium* to develop, but the adult mosquitoes rest indoors, where temperatures are several degrees higher. Indoor resting sites also enable *An. gambiae* to transmit malaria in the East African Highlands.

Movement of people. Infected people moving in pursuit of work can introduce malaria to areas where it is absent or relatively rare. Conversely, nonimmune people are at high risk if they move to an area of transmission. In recent years, extensive road building and modern transportation have greatly exacerbated this factor. Even in the poorest countries, it is now common for people to travel large distances by road or rail to work, visit relatives, or seek medical attention. Tens of thousands of infected people also arrive by air in nonmalarious temperate countries each year, and many people from those countries become infected when they travel to malarious regions for work or leisure.

Urbanization. In rapidly expanding urban areas, extensive water storage and inadequate water disposal can lead to disastrously high mosquito populations. The absence of cattle can promote stable transmission by forcing zoophilic species to feed on people.

Many tropical cities are surrounded by large satellite settlements that retain rural

characteristics. Their dense populations promote conditions that are ideal for transmission. Infection rates in these semirural habitats are often higher than in the cities themselves.

Resistance to insecticides. There is a natural variability in the susceptibility of insects to insecticides. Insecticidal control exerts a selection pressure on the target population, promoting the survival of the least susceptible individuals. These survivors eventually give rise to strains that are physiologically resistant even to high dosages. Various biochemical and physiologic processes can be involved. In many cases resistance to one insecticide confers cross-resistance to chemically similar compounds and even to families of compounds that are chemically unrelated. For example, knockdown resistance (*kdr*) to DDT may also confer *kdr* to the pyrethroids, a family of synthetic insecticides related to natural compounds derived from plants of the genus *Chrysanthemum*.

Control operations can also select for behavioral resistance, i.e., changes in behavior that reduce contact with the insecticide. For example, species that prefer to feed and rest indoors (endophilic) can switch to outdoor (exophilic) activity in response to indoor residual treatments with DDT. Both types of resistance have proven a major obstacle to malaria control (33,112).

Resistance to antimalarial drugs. A range of drugs can be used to prevent malaria infection (malaria chemoprophylaxis) or to cure infections (malaria chemotherapy). The same selection process that leads to insecticide resistance in the vector can foster the emergence of strains of drug-resistant *Plasmodium*. In recent years, malaria control activities have frequently placed more reliance on antimalarial drugs than on insecticidal strategies. Resistance to several of these drugs is now widespread and is a significant factor in the worldwide resurgence of malaria (33,112).

Degradation of the health infrastructure. The public health sector of many countries has been eroded by lack of funding, institutional difficulties, rapid urbanization, and other problems associated with rapid development. In much of Africa and parts of Southeast Asia the increasing prevalence of AIDS has overwhelmed the ability of authorities to deal with other diseases. In such circumstances, people often rely on ineffective self-administration of antimalarial drugs.

War, civil strife, and natural disaster. Mass movements of people, e.g., soldiers and refugees, often promote malaria transmission. The breakdown of public health services, damage to water distribution and drainage systems, and the destruction of homes often exacerbate the situation. High concentrations of people in camps for displaced persons can also be disastrous.

The recent recrudescence of malaria. It has been suggested—on the basis of the simple models mentioned earlier—that the incidence of malaria in the tropics could increase by up to 60% as a result of global warming (12,13,113). It has even been claimed that the recent recrudescence of the disease may be caused partly by warming that has already occurred (13,28,114). In the context of such discussion, it is important to review the multiple factors that have shaped the recent history of the disease.

The malaria eradication program. The advent of DDT after World War II enabled WHO to encourage many newly independent countries to attempt malaria control. Results were so promising that a worldwide campaign to eradicate the disease was formally endorsed by the Eighth World Health Assembly in 1955.

Initial results were spectacular: Thirty-six participant countries had been certified as free of endemic transmission by 1977. Eighty-three percent of the world's population was living in areas from which the disease had been eradicated or where control activities were in progress. However, despite this encouraging success, the momentum of the program was already faltering (92), and the disease began a rapid recrudescence (115). Today malaria has returned to nearly all its former territory. Its prevalence continues to increase, and the goal of eradication has had to be abandoned. Prevalence is again high in many parts of Central America, the northern half of South America, much of tropical and subtropical Asia, some Mediterranean countries, and several of the republics that were once part of the Soviet Union. Annual cases worldwide are roughly estimated at 250 million, with 2 million deaths. As before, a large portion of these deaths are in areas of high stability, particularly in sub-Saharan Africa, where large-scale control was never seriously attempted (112).

The failure of the eradication program is often attributed to the emergence of resistance to insecticides and antimalarial drugs and the inability of many governments to sustain control operations in the face of competing priorities. However, in nearly every country, ecologic changes wrought by rapid development, population increase, civil strife, and war have also been highly significant. These are the same factors that enabled malaria to expand and flourish in Europe from the time of Homer until the nineteenth century.

Highland malaria. In equatorial regions, vectors such as *An. gambiae* are commonly found as high as 3,000 m above sea level, but endemic malaria disappears above 1,800–2,000 m. A limiting factor is presumably the temperature required for effective extrinsic incubation.

In recent decades, outbreaks of malaria have been reported from many such mountain regions. For example:

- Serious outbreaks of malaria have recently been reported in the New Guinea Highlands. Until the 1950s, the disease had rarely been reported in the region.
- A devastating malaria epidemic occurred on the central plateau of the Madagascar Highlands from 1986 to 1988.
- Malaria has become a serious public health problem in the West Kenya Highlands over the past 20 years. In previous decades, transmission was relatively low.
- The Amani hills of northeastern Tanzania were once virtually malaria-free, but prevalence has risen to very high levels in the past three decades.
- In the highlands of southeastern Uganda, records at a well-staffed mission hospital show a 70-fold increase in malaria incidence from the late 1960s to the mid-1990s, with a significant epidemic in 1994.
- In southern Rwanda, malaria records at another well-staffed facility show a slow increase in incidence from 1983 onward, with a sudden jump in 1987 to more than twice the previous rate.

Several authors have suggested that climate change may have contributed to these outbreaks (13,28,116,117). It is therefore instructive to review them in some detail.

New Guinea Highlands. In the early 1930s a human population estimated at 1 million, previously unknown to outsiders, was contacted in the mountains of New Guinea. It appeared that these so-called Stone Age people were malaria free, and this was attributed to their unique state of isolation (118). By contrast, the lowland coastal regions were highly malarious.

At first, the highlanders became a new source of labor for the coastal plantations, but after World War II, there was a rapid increase in the number of small landholders growing Arabica coffee and other crops in the mountains. In the late 1940s government scientists warned that the increasing contact between the regions could bring disaster, for epidemic malaria had already appeared in several highland areas at around 1,500 m (119). By the mid-1950s several alarming outbreaks led to the enforcement of a law that required employers of highlanders working on the coast to supply them with anti-malarials and to ensure that the medications were actually taken. Highlanders were held by the government in compulsory quarantine for 2 weeks and given curative malaria therapy on repatriation (120,121).

These regulations failed to stop the emergence of the disease and its spread to many isolated valleys. The increase in prevalence was clearly attributable to a rapid

increase of anopheline populations after forest clearance and to the construction of roads, airstrips, plantations, mines, water impoundments, and other human artifacts (122). Several vectors were involved, including *An. farauti* and *An. punctulatus* (122). These species breed in open sunlit pools and are in many ways analogous to *An. gambiae* and *An. funestus* in sub-Saharan Africa.

There is some evidence that malaria may have been well established in the highlands before the arrival of Europeans, but it did not become evident until forest clearance and development were more widespread (119,123). Whatever the chronology, the recent history of the disease is clearly attributable to the introduction of the parasite to nonimmune populations and the proliferation of its vectors as a result of large-scale ecologic change.

Madagascar Highlands. Irrigated rice culture was introduced to the plateau regions of Madagascar around 1800, and the population expanded rapidly. Malaria appears to have been absent for much of the century, but in 1878 a catastrophic epidemic occurred around the capital, Tananarive (present name: Antananarivo; altitude approximately 1,200 m). A second major epidemic occurred in 1895. Thereafter the disease became endemic. As in most of sub-Saharan Africa, *An. gambiae* and *An. funestus* were the principal vectors (124). In 1949 the French administration initiated a major control campaign involving annual treatment of homes with DDT, and an extensive network of malaria clinics and dispensaries. Within 10 years the disease had all but disappeared, but the clinics remained operational to treat sporadic outbreaks.

The country became independent in 1960 and later realigned itself with the Soviet Union. After a military takeover in 1975 and the enforcement of a new plan of scientific socialism, the economy went into disastrous decline. Medication was in short supply and in 1980 all but one of the clinics were closed. The ferocity of the transmission that followed was fueled by the population's lack of immunity, the absence of treatment centers, and the shortage of medication. In addition, as a result of the breakdown of law and order, people began keeping their cattle inside their houses at night to guard against theft, thereby bringing themselves in greater contact with the primarily zoophilic vector, *An. arabiensis*. During the epidemic, there were press reports of 100,000–400,000 deaths, although investigators concluded that the true figure was probably 10,000–25,000 (103,124). The situation was corrected in 1993–1995 by reinstituting DDT treatments and reopening the dispensaries. Despite several claims that transmission was the result of unusually warm temperatures, the meteorologic record shows remarkable

stability of temperatures over the past 30 years (124). All the evidence indicates that the tragedy was brought about by the breakdown of successful control in a highly endemic area as a result of socioeconomic factors (103).

Kenya Highlands. Malaria was not recorded in the Kenya Highlands until the second decade of the twentieth century (125,126). It began to appear after the clearance of forests for the development of tea estates and the importation of infected laborers. Initially the disease was seen mainly below 1,500 m and was rare in Nairobi (1,680 m), the capital. The first sizable epidemic (1918–1919) was attributed to the return of local soldiers from Tanzania. Thereafter, transmission moved to progressively higher altitudes, with major transmission in Nairobi and in the farming district around Eldoret (2,040 m). Six epidemics were recorded between the two World Wars. During World War II, epidemics occurred in the Londiani district (2,250–2,490 m) and even at a farm near Mount Timboroa, at 2,490–2,550 m (127). Transmission could occur at these altitudes because the adult mosquitoes rest indoors, where temperatures are 3–5°C higher than outside. In the 1940s, British entomologists referred to this as “hut malaria” and even suggested that the disease could be eliminated by persuading the women to move their cooking fires outdoors to make their homes colder!

The fundamental cause of this progressive upward advance of malaria was widespread deforestation and development associated with large farming ventures (127). The construction of roads and railways generated innumerable flooded “borrow pits,” depressions left by excavation for materials, and also contributed to the dispersal of the mosquito. The introduction of the ox wagon caused a proliferation of rough cart roads; water in the wheel ruts provided a prolific breeding site for vectors. Milldams on rivers interfered with natural drainage. These and many other factors were components of a drastic ecologic change, and this change brought transmission of malaria to the highlands. The disease continued to be a serious public health problem until the 1950s, when the colonial government organized an extensive control program, after which the area was essentially malaria free until the 1970s.

The tea-growing estates (1,780–2,225 m) in the Kericho district have an extensive medical service for employees and their dependents that was initiated in 1925. Health care at the central hospital of Brookebond Kenya Ltd. is extended to some 100,000 inhabitants of the region. However, there is no attempt at mosquito control, and malaria has reemerged as a serious problem. A recent study showed epidemics in almost every year from 1990 to

1997, with a mean annual attack rates of approximately 50% (128). Peak transmission was from May to July, after the principal rainy season and before mean monthly temperatures drop below 18°C. A questionnaire survey (June 1997) indicated that only 8% of patients had traveled to areas with known malaria transmission in the previous 30 days.

It has been suggested that the main factor in this recrudescence may be increased resistance to antimalarial drugs, as well as the unsupervised use of ineffective medications, but the picture is not entirely clear (129). Whatever the cause, the history of multiple epidemics in the earlier part of the century, including many at higher altitudes, makes it unnecessary to infer climate change as a contributory factor. Moreover, a set of well-maintained meteorologic records shows no significant change in temperature over recent decades (103,128), and a retrospective study of 33 years of monthly incidence data from the Brookebond tea-growing estates did not reveal any relationship between climate variables and the timing or duration of inter-epidemic periods (130). Indeed, in a detailed report to WHO (131), a group of malaria specialists based in Nairobi dismissed those who claim a global warming link as “scientific Nostradamuses.”

Amani Hills, Tanzania. In 1902, the German colonial administration built a field station at 1,000 m in the Amani Hills (altitude 600–1,000 m) of the eastern Usambara Mountains in northeastern Tanzania. The heavily forested area had a relatively cool climate and was considered malaria free. For many years Europeans living on the coast would spend time there during the hotter months of the rainy season.

Logging and extensive clearance for agriculture and general settlement began in the 1960s. Malaria specialists (132) predicted that this deforestation, along with road construction and the proliferation of dams, ponds, ditches, furrows, road ruts, and other breeding sites, would be highly favorable to *An. gambiae* and *An. funestus*; both species had been scarce or absent because they prefer open sunlit breeding sites. From 1967 to 1978, the human population doubled, mainly through an influx of people from the highly malarious coastal region. At the same time, malaria became increasingly common. By 1980–1982, 61% of infants less than 1 year of age who attended a clinic were positive for malaria; most of the infants (91%) had not left the area in the weeks preceding their illness (133).

As in the Kericho tea estates, the Amani station maintained a good meteorologic record. In the first half of the century, mean annual temperatures ranged from 12.8° to 15.6°C. In the 1960s there was a sudden

warming directly attributable to the elimination of shade by deforestation. After this warming the recorded temperatures are remarkably consistent for about 10 years, ranging from 20.0° to 20.8°C until reforestation produced a steady cooling trend of about 0.46°C per year. By 1975 the mean annual average was back to 17.4°C, but the malaria incidence remained high, apparently because indoor temperatures were several degrees higher than those recorded at the field station. In a recent study mean annual prevalence of parasitemia among children 6–71 months of age ranged from 33 to 76% (134).

The factors leading to the emergence of malaria in Amani were similar to those in New Guinea and Kenya: A major ecologic disturbance—deforestation—created a new habitat for effective vectors, and the elimination of shade produced a marked change in local climate. In addition, the prevalence of the parasite was augmented by an influx of infected people. More recently, substantial resistance to chloroquine has been documented in all three areas, although the drug is still widely used by the local populations.

Uganda Highlands. Over the past 30 years a marked emergence of malaria has been noted in the Rukungiri and Kabale districts of southeast Uganda. Incidence of the disease has steadily increased among outpatients at Kisizi Mission Hospital (altitude 1,650 m), and a significant epidemic occurred in 1994. Peak transmission is generally in July, the driest, coldest month of the year (103).

Endemic foci of the disease at 1,800–2,000 m were recognized in the area as early as 1919, and epidemic transmission has been known since 1948 (135). When a malaria eradication program was established in 1961, extensive surveys showed that prevalence was very low at altitudes above 1,500 m, except at certain lakesides up to 1,900 m. As in Kenya, Tanzania, and neighboring countries, transmission could occur at these higher altitudes because the adult mosquitoes rest indoors, where temperatures were 3–5°C higher than outdoors (136). Indoor spraying continued from 1963 to 1966.

In maps drawn before 1961, the human population was distributed mainly on hill-sides above 1,500 m. The valley bottoms were mostly papyrus marsh. Since then, population growth has been rapid (more than 3% per year). Many inhabitants have moved off the hills to cultivate the marshland with food crops and fish ponds. The elimination of papyrus has created a habitat for *An. gambiae* and *An. funestus*, leading to increased transmission (137). In 1994, rainfall was more than twice normal, so the vector was probably especially abundant. Thus, the increasing prevalence of the disease is attributable to the

changes in agriculture and ecology that accompanied a massive increase in population in an area of unstable endemic transmission (103), not to any change in climate.

Rwanda Highlands. Rwanda lies close to the equator, adjacent to Uganda. Most of the country is at an elevation above 1,500 m. Population density is the highest in Africa, although more than 90% of the population is rural. Traditional settlement is not in villages but in homesteads scattered across the hillsides of the mountainous terrain, with several hundred persons per square mile. In the past few decades, population increase has been extremely high—more than half the inhabitants are less than 16 years old—and is far above the productive capacity of the environment. In 1972 this situation was exacerbated by an influx of 60,000 refugees from neighboring Burundi.

Data from around the country indicate that the incidence of malaria has risen steadily in recent decades. The reasons for this increase have not been investigated but are probably similar to those in neighboring countries. For example, outbreaks in the 1980s were attributed to a new road that facilitated travel to malarious lowland areas (138). Also, as in Uganda, population pressures have led to increased use of valley bottoms, where settlements are more concentrated and transmission is more likely. Indeed, an association between marsh clearing and an increase in malaria was noted around Butare as early as 1946 (139). In neighboring Burundi, a country with similar topography and culture, an association between rice cultivation and malaria in the Rusizi Valley was noted in the 1980s (140).

The Gikonko Health Center in southern Rwanda is a well-staffed facility that serves a population of 38,000 people who live at a mean altitude of 1,500 m. Malaria records for 1983–1990 show a slow increase in incidence from 1984 to 1986 and a sudden jump in 1987 that appeared to be especially high among people living at higher elevations (a 501% increase in incidence in the second half of the year) (114). Temperatures in that year were approximately 0.9°C warmer than the mean for 1961–1980 and rainfall was about double. Loevinsohn (114) suggested that this jump was an example of the “substantial epidemiologic effect” of the impact of climatic factors on malaria “near or astride the altitude and latitude limits” of its transmission. He supported this claim with a regression model that showed an autocorrelation coefficient (incidence vs. temperature and rainfall) of 0.89 ($p < 0.001$). He ruled out the likelihood that other factors—cessation of control measures, chloroquine resistance, population movement, road construction, rice cultivation, and the timing of

a famine—had contributed to the sudden change. His paper is perhaps the most widely quoted example of a putative link between climate change and transmission.

At first glance, Loevinsohn's conclusions appear persuasive. The Gikonko data are considered unusually reliable and the coincidence between the sudden jump in incidence and the warm, wet weather of 1987 is striking. However, if the area were truly at the limit of transmission, we would expect incidence to have declined in 1988 and 1989, when temperatures returned to normal and to have increased again in 1990, when it was nearly 0.5°C warmer. In fact, the raised level of incidence remained stable from 1987 onward. However, a factor that has escaped mention in the climate change debate is that WHO supervised a complete reorganization of the national disease surveillance system at the very time that the malaria “increase” began. The 2.5-year project involved a redefinition of the list of reportable diseases, an ongoing *in vivo* study system designed to improve reporting of confirmed malaria, follow-up supervision to check surveillance data, and a routine of regional feedback letters and graphs. It is highly likely, therefore, that the massive jump in incidence in 1987 was the result of improved surveillance and diagnosis rather than a consequence of climatic factors (141).

In summary, these examples underscore the need to avoid simplistic reasoning in explaining the appearance of “new” malaria at high altitudes. In every case, transmission was well below the local maximum altitudinal limit (Figure 5), and there is no evidence that climate change played any role in the increase of incidence. As in South America (142), a major factor was the cessation of house spraying with residual insecticides such as DDT. Most of the other significant variables are ultimately attributable to the population explosion and an increased mobility of the population.

Yellow Fever

The Disease

Yellow fever is a viral disease native to tropical Africa (143). In its original woodland habitat it circulates among wild monkeys. It is transmitted by at least 14 species of mosquito—all of the genus *Aedes*—that breed in tree holes and other natural cavities. Humans can be infected if bitten by infected mosquitoes. Symptoms include high fever, jaundice, and spontaneous bleeding. The severity of illness is quite variable, but 20–50% of jaundice cases are fatal.

The virus can also be transmitted between humans by mosquitoes that are more closely associated with human habitation. One of these is the peridomestic form of *Ae. aegypti*, a species that readily breeds in water jars and other man-made containers. It is widespread in villages and urban areas throughout the tropics and can also thrive in temperate climates. In the United States its permanent range extends to North Carolina (144), although breeding populations have been recorded as far north as New York, New York, and Boston, Massachusetts (145).

History of Yellow Fever

Africa. The endemic zone of yellow fever in Africa extends from the southern borders of the Sahara to Angola. The disease occurs in a wide variety of habitats and its epidemiology is correspondingly complex. The broad picture is of wandering epizootics that move slowly across vast areas of the continent, generating sporadic human cases in woodland regions and sparking interhuman transmission in heavily populated areas where peridomestic *Aedes* species are common.

In the early twentieth century major epidemics were associated with the rapid growth of townships, particularly in West Africa. From the 1940s onward, mass immunization in territories administered by France (Benin, Burkina Faso, Cameroon, Chad,

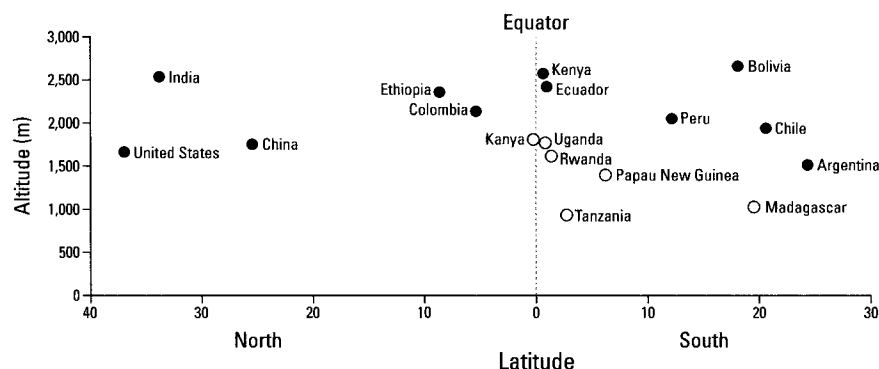


Figure 5. Occurrence of malaria at various altitudes. Solid circles indicate the maximum recorded altitude of transmission from 1880 to 1945. Derived from data in Hackett (111). Open circles indicate recent outbreaks (103, 114, 122, 128, 129, 133, 134, 136, 137).

Congo, Gabon, Ivory Coast, Guinea, Senegal, and Togo) greatly reduced the prevalence of human disease (146), while epidemics continued to occur in regions without immunization programs. Despite this success, preventive immunization was discontinued in the mid-1960s. During the past two decades the frequency of reported outbreaks has increased dramatically (143,147). To date, this increase has occurred mainly in rural areas, but the risk of urban transmission is high. Yellow fever is now classified as an important reemerging disease, with 34 sub-Saharan countries at risk (148).

The Americas. Both *Ae. aegypti* and yellow fever were brought to the Western Hemisphere from Africa with the slave trade. Transmission could continue at sea because the slave ships carried breeding colonies of the mosquito in their freshwater tanks (145). From the late seventeenth century onward, urban epidemics plagued the Caribbean and the tropical Americas. In addition, a forest cycle was initiated among New World primates, transmitted by several indigenous species of mosquito, particularly of the genus *Haemagogus*. Today, as in Africa, epizootics move across vast areas of the South American rain forest in cycles of 5–9 years. These sometimes extend to forested regions outside the enzootic zone. Thus, during 1948–1954 the disease moved via Panama and the Atlantic Coast of Central America to Mexico, and during 1964–1966 it spread from southern Brazil into Misiones Province, Argentina (143).

Until the twentieth century, the virus was frequently introduced to temperate regions. The first major outbreaks in the Thirteen Colonies were recorded during the Little Ice Age. New York was hit in 1668 and Philadelphia, Pennsylvania, and Charleston, South Carolina, in 1690. Epidemics became more devastating as urban populations grew, causing widespread terror and havoc. For example, 17,000 cases occurred in Philadelphia, a city of 55,000 persons in 1793 (149,150). Five thousand died and a further 12,000 fled the city. The disease returned in 1797, 1798, 1799, 1802, 1803, and 1805. Many other Atlantic coast cities were affected, including Norfolk, Virginia; Baltimore, Maryland; New York; and Boston (Table 2). Below the equator, major transmission was recorded as far south as Buenos Aires, Argentina.

Epidemics were even more frequent in the southern United States. New Orleans, Louisiana, was particularly vulnerable, and experienced repeated outbreaks from 1793 onward. In 1853, there were 40,000 cases with 11,000 deaths. Seventy-five thousand people were said to have fled the city. In 1878, the disease swept northward along the Mississippi and Ohio Rivers, with an estimated 100,000

cases and 20,000 deaths. Worst hit was Memphis, Tennessee, where at least 9,000 died and many inhabitants fled, never to return (151). When the disease struck again in 1879, there was serious national debate over a suggestion that the federal government issue an executive order to destroy Memphis and all its property by fire. This was not carried out, but the city, which had been the principal commercial and cultural center of the South, lost its charter and has never regained its former importance.

In 1881 Carlos Finlay proposed that the disease was transmitted by *Ae. aegypti*. His hypothesis was finally confirmed by Walter Reed and his team in 1900 (152). Strict mosquito control measures were applied, first in Havana, Cuba, and later in the United States and most of the major tropical ports. The last outbreak in the United States occurred in New Orleans in 1905. The development of an effective vaccine in the 1930s helped eliminate the urban disease from the rest of the Americas (143).

Europe. *Ae. aegypti* was present in southern Europe and North Africa until shortly after World War II. Its disappearance is not well documented but was probably associated with the malaria eradication campaigns. As in the Americas, yellow fever was never endemic, but many episodes of summertime transmission were initiated by ship-borne infections (143,153). Spain, with its extensive overseas colonies, was particularly vulnerable. For example, in 1856, more than 50,000 deaths were recorded in Barcelona, Cadiz, Cartagena, and Jerez. In the same year, 18,000 died in Lisbon, Portugal, and the disease also hit Livorno, Italy, and the French ports of Brest, Marseilles, and Saint Nazaire. In some years, small outbreaks were reported in ports as far north as Dublin, Ireland; Southampton, England; and Swansea, Wales (143,153).

Asia. *Ae. aegypti* is widespread in Asia, but for reasons that are not clear, yellow fever transmission has never been recorded there.

Table 2. Notable epidemics of yellow fever in North America, north of Mexico.^{a,b}

Year	Location	Year	Location
1668	New York, NY; Philadelphia, PA; and other settlements	1807	Charleston
1690	Charleston, SC	1811	New Orleans, LA; Florida; New Jersey
1691	Boston, MA	1817	New Orleans, Charleston, Baltimore
1693	Charleston, Philadelphia, Boston	1819	New Orleans, Charleston, Baltimore, Philadelphia, New York
1694	Philadelphia, New York, Boston	1820	New Orleans, Philadelphia
1699	Charleston, Philadelphia	1821	New Orleans, Mississippi Valley, Alabama, Charleston, Baltimore, Philadelphia, New York, Boston
1702	New York	1822	New Orleans, New York
1703	Charleston	1823	Key West, FL
1728	Charleston	1824	New Orleans, Charleston
1732	Charleston	1825	Mobile, AL; Natchez, MS; Washington
1734	Charleston; Philadelphia; New York; Albany, NY; Boston	1827	New Orleans, Mobile
1737	Virginia	1828	New Orleans, Memphis
1739	Charleston	1829	Key West, Mobile, Natchez
1741	Virginia, Philadelphia, New York	1837	New Orleans, Mobile, Natchez
1743	Virginia, New York	1839	Galveston, TX; Mobile; Charleston
1745	Charleston, New York	1841	Key West, New Orleans
1747	New Haven, CT	1843	Galveston, Mobile, Mississippi Valley, Charleston
1748	Charleston	1847	New Orleans, Mobile, Natchez
1751	Philadelphia, New York	1852	Charleston
1762	Philadelphia	1853	New Orleans
1778	Philadelphia	1854	New Orleans, Mobile, Alabama, Charleston
1780	Philadelphia	1855	Mississippi Valley, Norfolk
1783	Baltimore, MD	1856	New Orleans, Charleston
1791	Philadelphia, New York	1858	Charleston
1792	Charleston	1867	Key West, Galveston, New Orleans, Mobile, Philadelphia
1793	Philadelphia	1870	New York
1794	Philadelphia	1873	New Orleans, Mississippi Valley, Alabama, Memphis
1795	Philadelphia	1876	Charleston
1796	Philadelphia	1877	Port Royal, SC
1797	Philadelphia	1878	New Orleans; Memphis; Mississippi Valley; St. Louis, MO; Chattanooga, TN; many other cities
1798	Philadelphia	1879	Memphis
1799	Philadelphia	1905	New Orleans
1800	Philadelphia		
1801	Norfolk, VA; New York; Massachusetts		
1802	Philadelphia		
1803	Boston, Philadelphia		
1804	Philadelphia		
1805	Philadelphia		

^aModified from a table published by WHO (186). ^bSome records refer to states or regions without specifying the cities involved.

Factors that Influence Yellow Fever Transmission

Vaccination. Yellow fever vaccine is cheap and highly effective. Nevertheless, as already mentioned, enzootic transmission occurs in many countries that no longer support comprehensive preventive immunization. In the last 20 years incidence has increased rapidly, particularly in rural villages in West Africa; some urban epidemics have also occurred (154). The alarming rate of increase of urban dengue throughout the world, also transmitted by *Ae. aegypti* (see below), suggests an increasingly serious risk of such outbreaks.

Climate. Rainfall. In many enzootic areas, yellow fever is a highly seasonal disease. Rainfall is the principal determinant because the tree-hole breeding sites of the mosquitoes are scarce during long dry periods. Vertical transmission from one generation of mosquitoes to another via the egg stage is well documented. In areas of interhuman transmission, outbreaks can continue during the dry season if water storage containers provide a significant source of mosquitoes (143).

Temperature. As with malaria, the extrinsic incubation period of the yellow fever virus decreases with increasing temperature, but the effect of temperature on mosquito survival and behavior is complex and hard to predict. In many endemic areas, temperatures in the yellow fever season are cooler than in the dry season but are much higher than the minimum for effective transmission, so variation among years is probably a minor factor in disease incidence.

In temperate regions where summer transmission once occurred, the climate was clearly adequate for epidemic transmission even before the present warming phase. Cool weather was a limiting factor only when winter approached. Indeed, in many cities, normal summer temperatures were well above those of tropical regions where the disease is endemic.

Nonclimatic factors. As with malaria, transmission is influenced by a range of nonclimatic factors. Many of these are associated with rapid population growth, urbanization, and economic development.

Contact with the forest cycle. In forested areas, hunting, clearance for agriculture, logging, road building, mining, oil prospecting, and other occupations promote contact of nonimmune humans with the forest transmission cycle. These activities eliminate the habitat that supports the cycle, but their associated human settlements provide a favorable environment for peridomestic species such as *Ae. aegypti*, thus increasing the risk of interhuman transmission.

Urbanization. The rapid growth of densely populated towns and cities throughout the tropics provides an increasingly favorable environment for epidemic transmission.

Even when piped water is available, the supply is often intermittent, so reserves of water are stored in containers that are a source of *Ae. aegypti*. Other artifacts—buckets, flowerpots, bottles, cans, defunct household appliances, discarded tires, and many other items—can also serve as breeding sites if they accumulate rainwater.

Movement of people. Extensive road building and cheap air travel, even in the poorest countries, have opened up remote areas to exploitation and development. In South America the resultant movement of nonimmune people into forested areas has been a major factor in the incidence of yellow fever. Infected people traveling from endemic areas could introduce the virus to urban populations (155), but despite widespread recognition of this increasing risk, many countries do not enforce vaccination laws.

Cheap international air travel also has emerged as a significant factor in disease dissemination. For example, in 1996 an unvaccinated man died of yellow fever in Tennessee after returning to the United States from a fishing trip on the Amazon River (156), and there have recently been similar cases in Europe.

Urban mosquito control. Little attempt has been made to control yellow fever vectors in Africa. Residual treatments for malaria control were effective against *Ae. aegypti* because the species tends to rest indoors. However, many countries are now abandoning the method in favor of bed nets impregnated with insecticide. These are not effective for yellow fever control because, unlike anophelines, *Ae. aegypti* bites mainly in the daylight hours. During recent epidemics in West Africa, urban indices of *Ae. aegypti* were more than 100 times the minimum for epidemic transmission (157,158).

The *Ae. aegypti* eradication campaign. With the advent of DDT after World War II, an attempt was made to avert the threat of urban yellow fever by eradicating *Ae. aegypti* from the entire Western Hemisphere. The initial years of this campaign were remarkably successful. By 1961, 22 countries had been declared free of the species. However, as with the attempt to eradicate malaria, control was not sustained and some areas were not affected. The mosquito has now recolonized all its former territory, even the relatively remote island of Bermuda. Below the equator it has recently extended as far south as Buenos Aires. Until recently it remained widespread in the United States but has now been displaced from many regions by *Ae. albopictus*, an Asian species that was introduced in shipments of used tires (159–161). This displacement of one species by another illustrates a major flaw in the popular debate

on climate change: Biotic responses to climate change cannot be predicted on the mere basis of climate envelopes. The distribution of a species is determined by its interaction with other species and by many other behavioral and ecologic factors. It is therefore naïve to suggest that species will move to higher latitudes and altitudes simply on the basis of temperature change (162).

Since the eradication attempt, many cities have grown exponentially. Most countries in the Americas have a program for *Ae. aegypti* control, ostensibly to prevent dengue transmission, but their efforts are largely ineffective and infestation rates are generally high. Thus, in the aftermath of the eradication campaign and with the decline in preventive immunization, the risks of urban outbreaks of yellow fever are probably greater than at any time in the past 100 years (163).

Dengue

The Disease

Dengue fever is a viral disease closely related to yellow fever (164). As with yellow fever, forest-dwelling *Aedes* mosquitoes transmit dengue virus among wild monkeys, and peridomestic species, particularly *Ae. aegypti*, are responsible for interhuman transmission in villages and urban areas. Thus, many of the factors that influence transmission of yellow fever have a similar significance for dengue.

Dengue is caused by any of four closely related viruses. Illness usually begins with a sudden onset of fever and can include a variety of other signs and symptoms such as intense headache, severe pain behind the eyes, pains of the muscles and joints, nausea, vomiting, and a skin rash. Most dengue infections are self-limiting, but a small portion develop into a more serious illness—dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS)—characterized by spontaneous hemorrhage, increased permeability of the blood vessels and a condition known as physiologic shock. Fatality rates in untreated DHF/DSS can be as high as 50%. The incidence and geographic distribution of dengue have increased dramatically in recent decades: More than half the world's population now lives in areas at risk of infection (165). At present, no vaccine is available.

Dissemination of Dengue Worldwide

There are four immunologically distinct dengue viruses. In the forest cycle, all have been documented in Asia, whereas only one has been detected in Africa. This may be evidence that the viruses are of Asian origin. In China, descriptions of a dengue-like illness with hemorrhagic manifestations date back to at least the Northern Sung Dynasty, about 1,000 years ago (165).

From the seventeenth century onward there are records of major epidemics of denguelike illness in Asia, Africa, and the Americas. As with yellow fever, the disease and the vector traveled the world aboard ships. For this reason, most early outbreaks—in Panama; Alexandria and Suez, Egypt; Jakarta, Indonesia; Philadelphia; Madras, India; Mombasa, Kenya; Cadiz; Lima, Peru; and Zanzibar, Tanzania—were associated with seaports, and their frequency increased as ocean trade grew. From the late eighteenth century onward, pandemics of human dengue lasting 3–7 years swept around the world—much like the wandering epizootics of yellow fever in the forests of Africa and South America—and the disease became endemic in many tropical cities. In the Americas, the *Ae. aegypti* eradication campaign eliminated transmission in many countries, but the disease invariably reappeared within a few years of infestation (165).

In recent decades, rapid expansion of urban populations, the proliferation of mosquito breeding sites, and the failure of mosquito control efforts have exacerbated the risk of transmission. In addition, the worldwide movement of the virus has been greatly facilitated by international air travel. Today dengue is by far the most prevalent mosquito-borne virus of humans and is endemic in most populations of the tropics. Some estimates indicate 50–100 million cases per year, with 250,000–500,000 cases of dengue hemorrhagic fever (165). As with malaria, many recent publications have discussed the prevalence of dengue in the context of climate change (13,14,27,28,47,48,166,167).

Dengue in the United States. The first recorded epidemic of denguelike disease in North America occurred in 1780 in the port city of Philadelphia (168). The virus probably arrived from the Caribbean, where it was already widespread. In succeeding years dengue was a regular visitor to the United States. Eight major pandemics were recorded from 1827 to the 1940s. In 1922, an estimated 500,000 cases occurred in Texas alone. In that year, the disease spread eastward through Louisiana, Florida, and the adjoining states, and eventually moved south into the Caribbean. Thirty thousand cases were reported in Savannah, Georgia, of which 28% had hemorrhagic manifestations (169).

Since the 1950s, the disease has been relatively rare. Millions of people arrive each year from the tropics and there are undoubtedly many imported cases, yet there is very little autochthonous transmission even in areas where *Ae. aegypti* is common. In a single year, 1997, U.S. immigration authorities reported nearly 70 million personal crossings from three Mexican states—Coahuila,

Nuevo León, and Tamaulipas—into Texas. Nevertheless, in the 20-year period from 1980 to 1999, 62,514 suspected cases were reported to the health authorities in those Mexican states, whereas only 64 locally acquired cases of dengue were confirmed in Texas (Figure 6). The difference has nothing to do with vector prevalence: In 1999, during a dengue outbreak in the contiguous border towns of Nuevo Laredo/Laredo, the Breteau index (a measure of the level of *Ae. aegypti* infestation; an index of 5 is widely considered sufficient for epidemic transmission) was 38 on the Mexican side but 91 on the Texas side of the border (170). Thus, as with malaria, the mere presence of a competent vector is not a guarantee of disease even if weather conditions are adequate. The contrast in transmission rates can be attributed to several factors:

Layout of cities. The layout of modern U.S. cities is based on the automobile. Population density is relatively low. Housing areas are often discrete, interspersed with shopping precincts, industrial parks, and other nonresidential land. Much space is devoted to wide roads, parking lots, and other open areas. Plot sizes are large, and the spacing between houses is often greater than in many tropical cities. The number of persons per house is smaller because couples have fewer children, and the extended family is less

prevalent. All these factors limit the number of humans that are accessible to mosquitoes, thereby reducing the likelihood of epidemic transmission.

Building structure. *Ae. aegypti* is a day-active species that prefers to bite indoors or in the shade. In the United States, windows are usually fully glazed to maximize heating/cooling efficiency and are often kept permanently closed. The junctions between walls and roof are well sealed. Insect screens are ubiquitous in doorways and windows; many communities still have screen-enforcement laws that date back to the time of malaria eradication. By contrast, most homes, schools, and workplaces in the tropics rely on natural ventilation. Windows and doors are often kept open, especially during daylight hours. Many buildings do not have screens, and there is often a gap between the top of the wall and the underside of the roof. In such circumstances *Ae. aegypti* has far greater access to people than is usual in the United States.

Air conditioning and human behavior. In the United States, particularly in the South, air conditioning is widely used, even by low-income households. People spend much of their daily life sequestered in sealed, air-conditioned buildings. Even if infected mosquitoes gain entry to these buildings, the low ambient temperature and artificially dry

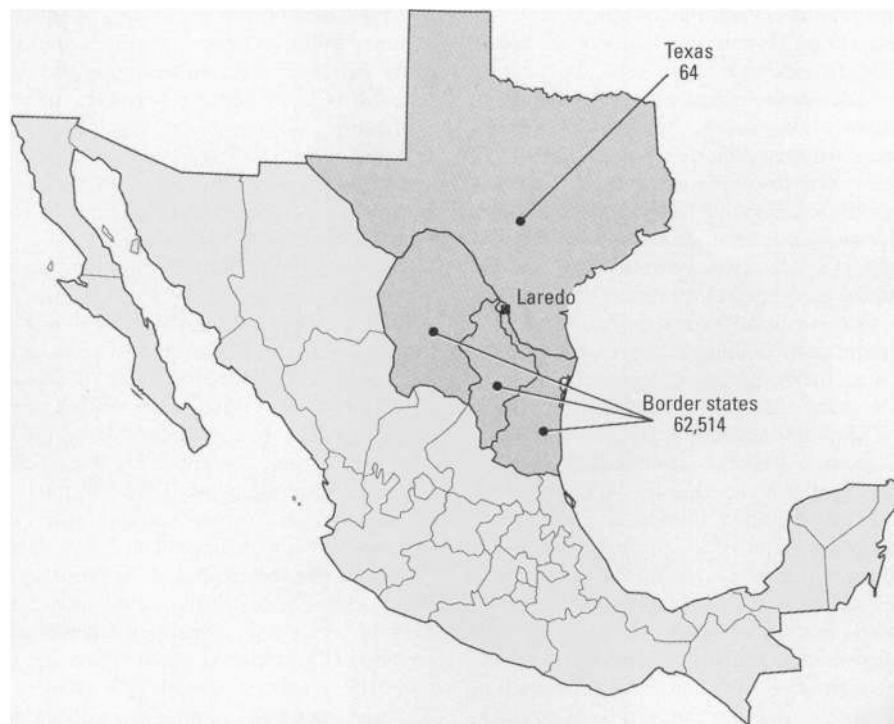


Figure 6. Dengue at the Texas/Mexico border from 1980 to 1999 (170). The Texas data refer to laboratory-confirmed, locally acquired infections. The Mexico data refer to clinically diagnosed cases reported to the state health authorities of Coahuila, Nuevo León, and Tamaulipas. In 1999, during a dengue outbreak in the contiguous border towns of Laredo/Nuevo Laredo, indices of *Ae. aegypti* infestation were considerably higher in Laredo (Texas) than in Nuevo Laredo (Tamaulipas, Mexico).

atmosphere will lessen their survival rate and extend the extrinsic incubation period, thus reducing the likelihood of transmission (171).

Air conditioning is much less common in the tropics. People seek the coolness of shaded, well-ventilated areas, precisely the sites where *Ae. aegypti* prefers to feed. In many countries the afternoon siesta is taken in such places and coincides with the peak biting period. The bite of *Ae. aegypti* is relatively painless so bites are often unnoticed. After the mosquito has fed, indoor closets and other dark places provide ideal sites for it to rest. All these factors promote contact with the insect, help ensure its survival, and thus increase the likelihood of transmission.

Dengue in Europe. A denguelike epidemic was recorded in Cadiz and Seville in Spain from 1784 to 1788. In mid-June 1801, the queen of Spain had an illness with denguelike symptoms, including hemorrhage, which she referred to as dengue (172). In the course of the nineteenth century, outbreaks of similar description occurred in the Canary Islands and in various places around the Mediterranean: Cadiz; Athens and Crete, Greece; Turkey; Beirut, Lebanon; Jerusalem, Israel; Alexandria and Port Said, Egypt (165). The first dengue epidemic to be confirmed serologically (in this case, retrospectively) swept through refugee camps in Greece in 1927–1928. It was one of the most catastrophic outbreaks on record anywhere in the world: An estimated 1,000,000 people were infected, and more than 1,000 died of DHF/DSS (173,174). After World War II *Ae. aegypti* disappeared from Europe, perhaps as a result of the widespread use of DDT, and dengue transmission ceased.

In the past 20 years a closely related species, *Ae. albopictus*, has infested much of Italy and large areas of Albania (175). A native of Asia, it was imported in cargoes of used tires, a larval habitat that it frequently shares with *Ae. aegypti*. A worldwide commerce in used tires has been responsible for infestations of *Ae. albopictus* in many other countries, including a large portion of the United States (160,176) and much of the Americas. The Italian infestation has been attributed to tire imports from Atlanta, Georgia, a city where both *Ae. aegypti* and *Ae. albopictus* are present (177). The Albanian infestation probably came from China. *Ae. albopictus* is also a vector of dengue, although in most parts of the world its importance is secondary compared to *Ae. aegypti*. An American species, *Ae. triseriatus*, has also become established in Italy after introduction in used tires (178). It is not known to transmit human disease, but these examples of recent introductions are a clear warning that *Ae. aegypti* could also return to the region.

Outlook for the Future

Models of climate change that attempt to project the potential impact of increased levels of greenhouse gases indicate that the degree of future warming is likely to be greatest close to the poles (4,179). This change of the temperature gradient would alter the world's wind and ocean circulations. In turn, such changes would affect precipitation, humidity, seasonality, and other climatic factors. The complexities of these systems, along with the complexity of all the behavioral and ecologic factors that influence transmission, make it impossible to predict their impact on the incidence of mosquito-borne diseases. However, some generalizations are permissible.

Temperate Climates

Malaria. In many countries at higher latitudes, changes in lifestyles and living conditions were the most important factors in the elimination of malaria. Even in countries where these factors were less dominant, eradication of the disease did not require total elimination of the vector. Residual treatments were effective because they reduced the life span of the adult insect, reducing the probability of transmission and eventually leading to the elimination of the parasite. Thus, the anophelines responsible for transmission are still present in the brackish waters of The Netherlands, as they are in Florida. They still occur in the rice fields of Arkansas and Italy, the ponds of Pennsylvania and Poland, and the forest pools of Minnesota and Finland. In many of these regions, advances in agriculture and improvements in living standards have limited the mosquito populations and reduced their contact with humans, but this is not always the case. For example, in large areas of Italy, anopheline populations have returned to levels not seen since before the DDT era. In recent surveys the vectorial capacity of *An. labranchiae* near rice fields in Tuscany and along the west coast of Calabria was estimated as 7.3–26 for *P. falciparum* and 8.3–32.5 for *P. vivax*, with peak landing rates on humans of more than 200 mosquitoes per human per night (180). In entomologic terms, these infestations are comparable to those in endemic areas with extremely high transmission rates; in the Garki Project, a major study in northern Nigeria, mean vectorial capacity for *P. falciparum* during the peak transmission season (July–October) was 21.74 (181). Nevertheless, despite the similarity in this entomologic parameter, the malarigenic potential of Italy is considered very low, and reestablishment of the disease is unlikely unless living standards deteriorate drastically (182). Moreover, if the present warming trend continues, human strategies to avoid these temperatures—particularly indoor living and air conditioning—are likely to become

more prevalent. In consequence, the stability index, already very low, will continue to decline.

Of course, this does not mean the disease will be entirely absent. International travel and population movement will facilitate introductions from other parts of the world. For example, WHO recorded 12,328 cases of imported malaria in the European Region in 1997. Such cases occasionally lead to summertime transmission (183), recently reported as far north as Toronto, Canada, and Berlin, Germany. However, in the all the wealthier countries, such outbreaks are likely to be small, easily contained, and confined to a limited geographic area.

The same may not be true of less affluent regions. Rapid economic decline combined with political instability has already brought back epidemic typhus, diphtheria, and other infectious diseases to several countries of the former Soviet Union. In the 1990s epidemic malaria has made a dramatic reappearance in Armenia, Azerbaijan, Tajikistan, and Turkmenistan. Cases have also been reported from Dagestan (Russian Federation), Georgia, Kazakhstan, Kyrgyzstan, and Uzbekistan (184). It is quite possible that the disease could spread northward into Russia and westward around the Black Sea. The 1999 conflict in the Balkans is in the same region where hundreds of thousands were infected with malaria during World War I. Endemic transmission in such areas could be significant if the parasite were to be reintroduced. Climate change might augment this possibility, particularly at high latitudes (e.g., in Siberia), although low stability should facilitate control.

Yellow fever and dengue. In the past, except in Asia, yellow fever and dengue have shared a similar geographic distribution and so can be dealt with together. The existence of a safe and effective vaccine against yellow fever should prevent the return of the virus to temperate regions. The factors that currently prevent dengue transmission in the United States will remain dominant unless living standards deteriorate drastically. However, if *Ae. aegypti* were to reestablish itself in the Mediterranean region, it is more likely that the disease could return. Summer temperatures are more than adequate for transmission. Most cities are compact and densely populated. Air conditioning is rarely used and windows remain open for most of the summer. Many activities, particularly social gatherings, occur in outdoor situations such as shaded balconies, courtyards, and outdoor restaurants—all ideal for contact with the vector. Warmer summers would probably extend the potential range of the disease. However, as with malaria, the poorer countries, particularly in North

Africa, the Levant, and the Balkans, would be at greatest risk. In Macedonia, for example, current refugee camps are less than 200 km from the location of similar camps in Greece that were the site of the devastating dengue/dengue hemorrhagic fever epidemic of 1927–1928.

Tropics and Subtropics

Malaria. In regions of high endemicity and stability, particularly in sub-Saharan Africa, childhood infection rates have remained remarkably static over the past half-century. Transmission rates are so high that even the colossal increases in anopheline populations that result from the introduction of rice cultivation do not alter the indices of infection (185). In such circumstances it is unlikely that a warmer climate would have much effect on incidence. Moreover, climate models suggest that the low latitudes are least likely to be affected by any global trend.

Farther from the equator, in zones of unstable malaria, the picture is less clear. Transmission is more sensitive to climatic factors, so the impact of climate change could be significant. A long-term increase in average rainfall might promote high mosquito populations in areas that are currently arid but reduce them where drought malaria is now the norm. Lower rainfall could suppress transmission in arid areas, as appears to have happened in recent years on the southern edge of the Sahara (105), but promotes drought malaria in wetter ones. Increased temperatures could facilitate transmission in humid areas but reduce it if associated with low humidity. Such changes could alter the relative abundance of local mosquito species, and natural selection could modify the species themselves. Climate change would induce other ecologic changes, which could lead to agricultural and economic change that might increase or decrease transmission potential. The plethora of factors involved is complex, and the overall impact on endemicity and stability is even harder to predict.

Higher temperatures would probably raise the maximum altitude for transmission and could bring the disease back to major cities such as Quito, Ecuador, and Mexico City, Mexico, where it has not been seen for many decades. In most such situations, stability would remain low, so control measures should be relatively effective. However, at lower altitudes, which are at the present limits of transmission, increased stability and prevalence might be more of a problem.

Other factors could have a crucial impact. The recent history of *Ae. albopictus* demonstrates that modern transportation has greatly increased the mobility of many species. The introduction of an anthropophilic mosquito to a new location could

drastically alter transmission potential by altering stability. This has happened in the past—the worldwide distribution of *Ae. aegypti* is perhaps the best example. Climate change might affect the likelihood that such introductions would lead to disease transmission.

Yellow fever and dengue. Rainfall is a major determinant of transmission in the forest cycle of yellow fever. Climate models do not suggest major changes in equatorial regions of Africa but indicate that rainfall might decrease toward the Sahara. This could reduce the overall potential for enzootic activity, but the resultant reduction of immunity in the monkey population might exacerbate the rate of epizootic transmission during rainy episodes and enhance the likelihood of transfer of virus to the urban cycle. Transmission would also be modified if climate change affected the monkey populations.

Transmission by peridomestic mosquitoes is often highly seasonal. The causes of this seasonality vary in different regions and in many cases are complex and poorly understood. Thus, in areas where mosquitoes breed in stored water, their populations may be extremely high all year, yet peak transmission occurs in the rainy season. In many instances this probably occurs because it is also the hottest season and/or because the survival rate is greater at higher humidity. In other situations transmission may be enhanced during

drought, when water storage becomes more important. However, the mere fact that transmission is seasonal does not imply that, for example, warmer seasons will produce higher rates of transmission. This is well illustrated by the record of dengue in Puerto Rico: There is no reason to suppose that climatic factors affect transmission rates of the four serotypes of this virus in different ways, but it is clear from Figure 7 that the patterns of their incidence are not identical. Immunologic history, expressed as the herd immunity, is presumably the dominant factor. Moreover, a retrospective analysis of 33 years of monthly data on DHF incidence in Bangkok, Thailand, did not reveal any relationship between climate variables and the timing of epidemics (130).

Final Comment

The natural history of mosquito-borne diseases is complex, and the interplay of climate, ecology, vector biology, and many other factors defies simplistic analysis. The recent resurgence of many of these diseases is a major cause for concern, but it is facile to attribute this resurgence to climate change. The principal determinants are politics, economics, and human activities. A creative and organized application of resources is urgently required to control these diseases regardless of future climate change.

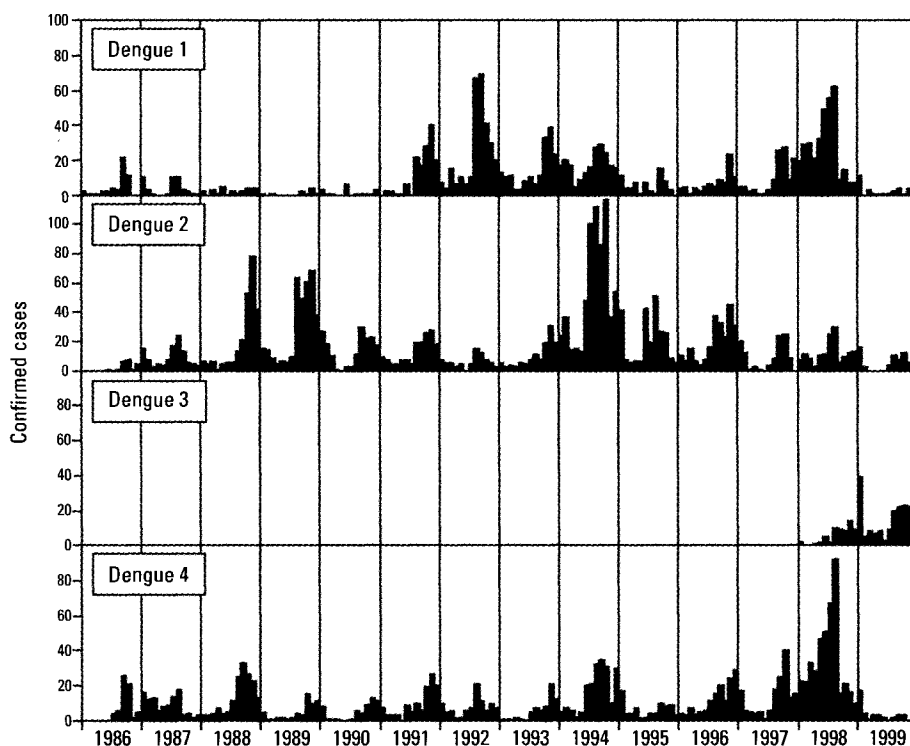


Figure 7. Monthly isolates of dengue virus, by serotype, in Puerto Rico from 1986 to 1999 (189). The viruses are essentially identical, yet the patterns of their incidence are not identical, indicating that factors other than climate are dominant in their rates of transmission.

Appendix. Glossary

Dengue. A disease caused by any of four closely related viruses that are transmitted by the bite of infected *Aedes* mosquitoes, principally *Ae. aegypti*. The illness usually begins with a sudden onset of fever and can include various other signs and symptoms such as intense headache, severe pain behind the eyes, pains of the muscles and joints, nausea, vomiting, and a skin rash. Dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) is a serious manifestation of dengue infection characterized by spontaneous hemorrhage, increased permeability of the blood vessels, and a condition known as physiologic shock. Fatality rates in untreated DHF/DSS can be as high as 50%.

Endemic transmission. Continuous transmission of a human disease pathogen within a given population group or geographic region. Enzootic transmission describes the same concept among animals.

Epidemic transmission. The occurrence of numbers of cases of human disease in a community or region that are clearly in excess of the normal expectancy for that location and time. The term is thus a relative one, based on average long-term frequency in a specified population at a specific time of year. Epizootic transmission describes the same concept among animals.

Malaria. A mosquito-borne infectious disease caused by protozoan parasites of the genus *Plasmodium*. Human malaria is transmitted by mosquitoes of the genus *Anopheles*, and is characterized by cycles of chills, fevers, and sweating.

Mosquito. Insects of the family Culicidae and order Diptera (two-winged flies). There are about 3,500 species, all of which lay their eggs on or near water and are entirely aquatic until the adult stage. The mouthparts of the adults are in the form of an elongated proboscis about half as long as the body. The females of most species can use this proboscis to pierce skin and imbibe blood from peripheral blood capillaries. A salivary secretion that is injected into the tissues during blood feeding can serve as a vehicle for the transmission of pathogens.

Quartan malaria. Malaria in which the febrile episodes occur every third day (i.e., days 1, 4, 7, etc.). This periodicity is characteristic of *P. malariae* infections.

Tertian malaria. Malaria in which the febrile episodes occur every alternate day (i.e., days 1, 3, 5, etc.). This periodicity is characteristic of *P. vivax*, *P. falciparum*, and *P. ovale* infections.

Vector species (of mosquito). A species of mosquito capable of transferring an infectious agent from an infected animal or human to a noninfected one. Transfer normally includes an obligatory incubation period that involves multiplication of the pathogen in various tissues of the insect, including the salivary glands.

Yellow fever. A viral disease of primates transmitted by the bite of infected mosquitoes. Symptoms in humans include high fever, jaundice, and spontaneous bleeding. The severity of illness is quite variable, but 20–50% of jaundice cases are fatal.

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