Analyzing the Impact of Malaria as a System

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Abstract

Malaria is a devastating infectious disease, afflicting millions of people each year, primarily in disadvantaged or marginalized regions of the world. This paper provides a comprehensive overview of malaria, analyzing it as an interconnected biological and social system.

The biology of malaria parasites, mosquito vectors, and human hosts is discussed in detail. This includes the *Plasmodium* parasites that cause malaria and the *Anopheles* mosquitoes that transmit it. Factors such as human genetics, the parasitic life cycle, and regional climate are all discussed, including their relationship to malaria transmission and severity.

The impact of malaria is explored, as well, as it exerts a heavy burden on affected populations. Its impact is focused in impoverished regions like sub-Saharan Africa, where it is a leading cause of childhood mortality. This paper analyzes the way malaria impedes economic development and perpetuates cycles of poverty, along with the unequal global distribution of malaria's effects.

Strategies for fighting malaria are assessed, including insecticide-treated nets (ITNs), indoor residual spraying (IRS), and promising vaccine candidates. While progress has been made, challenges remain due to malaria's complex biology, socioeconomic inequality, and inadequate funding for malaria research and control efforts.

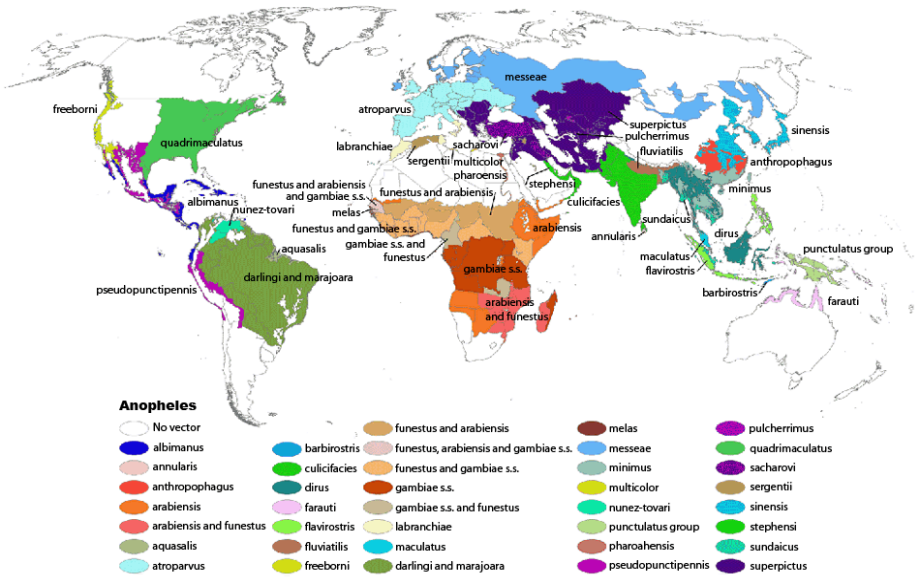
This paper demonstrates that malaria must be understood and addressed from biological, social, economic, and political perspectives. Sustained, coordinated efforts across disciplines and sectors are needed to alleviate malaria's burden worldwide, especially among marginalized populations. The insights provided can inform integrated strategies to make progress against this devastating disease.

Biological Description

Mosquitoes

There are 112 genera of mosquitoes, with about 3,500 species in total. Of these, only the *Anopheles* genus transmits malaria to humans. This occurs when females take blood meals for egg production, as part of their reproductive cycle (see Life Cycle for further details). Out of the 430 species of *Anopheles*, over 100 are able to transmit malaria to humans, but only about 30-40 do so in nature, referred to as "vectors" (Elbers, et al). The rest of the mosquitoes either cannot sustain parasite development (see Parasites for further details) or only rarely bite humans.

Anopheles species are found across the world, with different species transmitting malaria depending on geographic region, climate, and environment. They exist in both malaria endemic regions (e.g., south of the Sahara in Africa and Papua New Guinea in Oceania) and in areas where malaria has been eliminated by public health campaigns or economic development (e.g. the United States and Western Europe). Thus, there is always a risk of re-introduction of malaria. Such an event could potentially be extremely deadly considering the fact that many people in these regions do not have genetic or acquired immunity to malaria (see Genetic Factors and Acquired Immunity for further details, respectively).



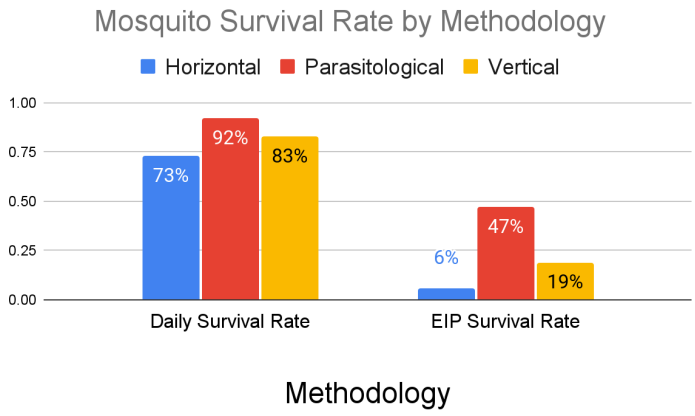
Malaria Transmission Ability

Some factors that affect a mosquito's ability to transmit malaria to humans include its preferred blood meal source and its lifespan

Regarding its preferred blood meal source, a mosquito may be anthropophilic (preferring humans), zoophilic (preferring animals), or opportunistic (feeding on whatever host is available). For example, *An. baimai*, *An. minimus*, and *An. annularis* are highly anthropophilic, while *An. kochi*, *An. aitkenii*, and *An. umbrosus* are far more zoophilic, rarely choosing to feed on humans. *An. pallidus* is considered an opportunistic mosquito, with multiple preferred hosts (Bashar et al).

In general, the more anthropophilic a mosquito is, the more potent it is as a vector, posing a greater danger to human beings.

Once infected by a parasite, a mosquito must survive the extrinsic incubation period (EIP), a quantity of time that is dependent on a variety of factors. These include temperature, the type of parasite, mosquito genetics, and the mosquito's food intake (Ohm et al). The average EIP is 9 days, with a range of 4-14 days, making it a significant limiting factor in the viability of a given mosquito species as a malaria vector. The easiest way to measure the lifespan of a mosquito is by measuring its daily survival rate - the probability a mosquito will survive on a given day. There are three methods to do this: horizontal, parasitological, and vertical, all of which yield different estimates. We will consider the vertical method estimate of p = 0.83, since more modern studies tend to use this method, and it has a smaller confidence interval of 0.80 - 0.86 (Matthews et al). This yields a probability of 0.83^9 = 19% of a mosquito to survive the EIP. This varies significantly by species, and is further complicated by a study showing that *Anopheles* mortality is age- and parasite-dependent (Dawes et al). Thus, this estimate should be taken with some skepticism.



Some other factors that may influence a mosquito's potency as a vector include its susceptibility to the malaria parasite (this varies greatly by species and type of parasite), when `they prefer to take blood meals (this impacts the efficiency of various treatments, see Methods of Fighting), and resistance to insecticide. However, there is considerably less data regarding these factors from each species of *Anopheles* across the world, which makes their relative impact challenging to compare.

Parasites

Plasmodium is a genus of unicellular eukaryote that can cause malaria. It is an obligate parasite, and there are over 100 species that infect animals such as birds, reptiles, and mammals. Five species are known to infect humans in nature: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. The first four infect through *Anopheles* mosquitoes, while *P. knowlesi* is transmitted by infected macaques. Other species of *Plasmodium* can infect humans under experimental or extreme circumstances, but this is rarely found in nature.

The five parasites each have a different geographical distribution according to their evolutionary traits. *P. falciparum* and *P. malariae* are both found worldwide, with the former predominating in tropical and subtropical regions (especially Africa). *P. ovale* is found mostly in West Africa and the western Pacific Islands, while *P. vivax* is found mostly in Latin America and Asia. These two parasites are very similar genetically and biologically, but their geographic distributions have very little overlap. *P. vivax* is rarely found in most of Africa as it cannot infect humans who are Duffy negative while *P. ovale* can (see Genetic Factors for more information on this). Finally, *P. knowlesi* is found mostly in Southeast Asia due to its unusual transmission mechanism. Malaysia is particularly affected due to deforestation, which causes humans in this region to have more frequent contact with long-tailed macaques, the *P. knowlesi* vector (Imai et al).

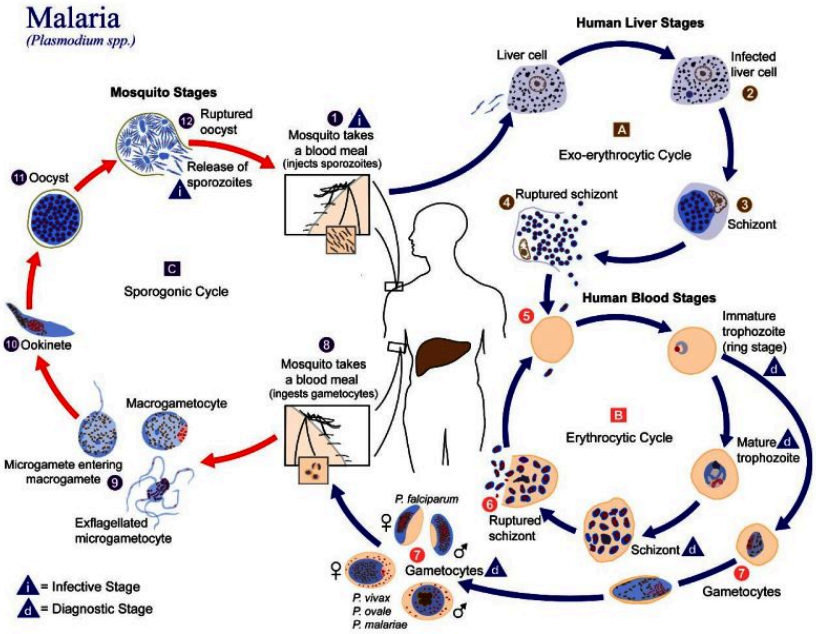
Malaria severity strongly depends on the particular species of parasite involved. For example, almost all cases of mortality are caused by *P. falciparum* due to the drastic difference in parasitemia (the amount of parasites found in an individual's blood). In non-falciparum malaria, the parasitemia rate is at most 2%, while *P. falciparum* is at least 50% (Trampuz et al). *P. falciparum* multiplies quickly in human blood, causing severe anemia (blood loss) and clogging small blood vessels (which can cause the often-fatal cerebral malaria if this occurs in the brain).

Non-falciparum malaria, while less severe, can still be very damaging to its victims. *P. malariae* can cause chronic infection if left untreated, and can persist throughout one's life. This can cause serious complications such as nephrotic syndrome (a kidney disorder). *P. ovale* and *P. vivax* have lengthy dormant liver stages that relapse many months or even years after the initial mosquito bite, invading the blood and causing illness. *P. knowlesi* has a very rapid 24-hour replication cycle, allowing it to quickly advance from a minor to a severe infection that can sometimes end in death. Regardless of whether malaria leads to death, it can severely reduce one's quality of life, making it a high-priority disease to prevent.

Temperature and humidity are important factors that influence parasite transmission rates, with higher temperatures speeding up parasite growth in *Anopheles* mosquitoes. This reduces the EIP and increases the proportion of mosquitoes that live long enough to infect humans. This creates a significant, and potentially deadly, link between climate change and malaria. Studies have shown that as the climate crisis progresses and temperatures rise, malaria outcomes are getting worse. The most significant effects will be seen in Africa, South America, and southeastern Asia - areas where malaria is already endemic. Further research must be done on this topic, due to the uncertainties involved in climate modeling and the interplay between various factors that influence malaria outcomes. However, the high death toll of malaria makes the threat all too real (Caminade et al).

Life Cycle

The joint life cycle of the *Anopheles* mosquito and *Plasmodium* parasite is an intricate process with many steps, with the host's blood and liver cycles playing an important role in the reproduction of both . organisms. It begins as an infected female mosquito takes a blood meal, injecting sporozoites (malaria's infective agent) into its host. The sporozoites spread to the liver, where they mature into schizonts, which eventually break apart, releasing merozoites (parasites that undergo asexual reproduction). After initially replicating in the liver, the merozoites enter the bloodstream and infect red blood cells which release more schizonts through the Erythrocytic Cycle. This is when symptoms of malaria appear, as malaria continues building up in the host's blood. Eventually, some parasites differentiate into gametocytes, the sexual stage, with microgametocytes (male) and macrogametocytes (female) being formed.



When a female *Anopheles* mosquito takes a blood meal from the host, it ingests male and female gametocytes, starting the Sporogonic Cycle (along with the EIP from the Mosquitoes section). The *Plasmodium* parasites multiply inside the mosquito, producing zygotes in its stomach, which develop into oocysts, which eventually release sporozoites. When this mosquito takes its next blood meal, it releases sporozoites into the host, beginning the next round of the cycle.

Understanding this life cycle is of paramount importance in developing new ways of fighting malaria. Its sheer complexity forms a formidable barrier to the development of a malaria vaccine. The constant development of new variations of this life cycle and new niches within the organisms it infects makes the problem reemerge time and time again. This is especially true for the human part of the life cycle, since there are so many areas involved in the growth and development of the *Plasmodium* parasite. Combined with the sheer complexity of having to deal with five different species of parasites, 5000 genes in the genome, and many layers and interweaving parts, malaria truly is a difficult challenge to overcome (Aly et al).

Climate

Malaria transfer occurs when all of the components of the life cycle are present: malaria parasites, *Anopheles* mosquitoes, and humans (see Life Cycle for more information on this). Factors that influence any of these key components play a strong role in the frequency and severity of malaria in a given region.

Climate is a major driving force behind the seasonality and geographic distribution of malaria parasites and *Anopheles* mosquitoes. For example, mosquitoes rely on precipitation to survive. Following a blood meal (which fuels egg production), female *Anopheles* mosquitoes lay eggs in bodies of water, with various preferences depending on the specific species of mosquito. Once hatched (usually a few days after being laid), the first 9-12 days are crucial for larvae, which may die if habitats dry up or flood due to a scarcity or overabundance of rain. Very few larvae survive this precarious period.

Plasmodium parasites thrive in warmer temperatures and higher humidities (as discussed in Parasites) because they produce more sporozoites that infect humans. These factors also influence mosquito longevity. Increases in relative humidity (e.g., the end of a rainy season) have been shown to decrease mosquito survival rates (Yamana and Eltahir). Mosquitoes have a complicated relationship with temperature. While low temperatures can decrease survival rates (the highest at 15°C and the lowest is at 35°C), high temperatures can drastically speed up mosquito life stage development time. For example, it takes 39.7 days for a mosquito to fully develop at 15°C and only 7.2 days at 35°C (Bellone and Failloux). Moreover, if it is too cold, the parasites cannot develop fully, preventing malaria transmission entirely. The minimum temperature depends on species, with *P. vivax* requiring 15°C and *P. falciparum* requiring 20°C, for example.

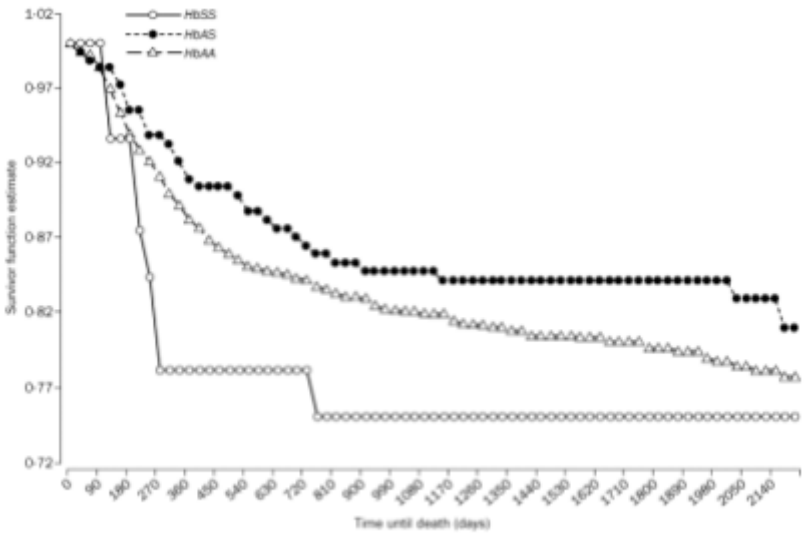
Climate can also influence human behavior, as people are more likely to sleep outside during hot days. There is also a seasonal and socioeconomic element to this, as agricultural workers are likely to sleep in fields during harvest season. Both of these practices increase the potential for malaria exposure at night. Combined with the nocturnal feeding patterns of certain *Anopheles* mosquitoes, this can have a significant impact on infection rates. This is also the reasoning behind bed nets as a way of preventing malaria (see Methods of Fighting for more information).

Genetic Factors

Many genes that control various aspects of human red blood cells also influence the risk, severity, and transmission rate of malaria. In areas where malaria is endemic, these genes are significantly more common, which has historically been used to genetically distinguish between

people of different ethnicities (Rodriguez). In addition, these genes sometimes come with undesirable side effects, either to oneself or to offspring.

Sickle cell anemia is a genetic blood disorder that is caused by an abnormal form of hemoglobin, the protein in red blood cells that transports oxygen. Genetic carriers have one normal hemoglobin gene and one mutated hemoglobin gene, and do not suffer from sickle cell anemia. However, carriers have a protective advantage against *P. falciparum*, since the rupturing of their red blood cells interrupts its life cycle. As a result, carriers have a lower risk of severe malaria complications and death. This is why sickle cell anemia has reached high frequencies in regions where malaria is endemic, such as Africa.



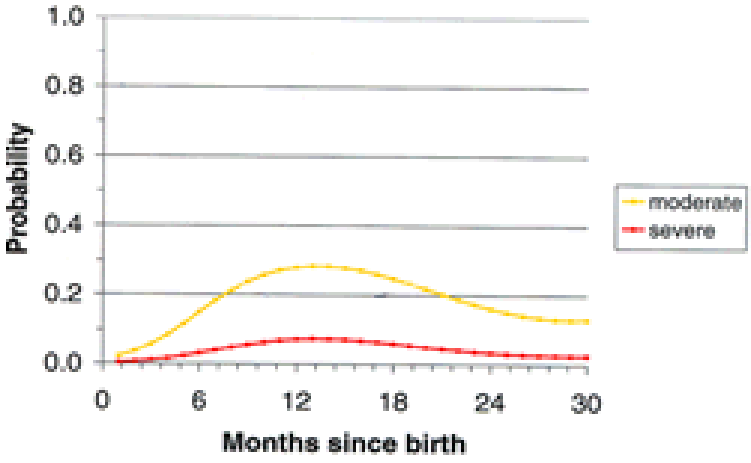
Aidoo et al. HbSS is the sickle cell genotype, HbAS is the carrier genotype, and HbAA has no sickle cell chromosomes

The Duffy negative blood group is a condition where red blood cells lack the Duffy antigen receptor, which is used by *P. vivax* to infect red blood cells. People who are Duffy negative are therefore resistant to infection by *P. vivax*. Over time, genetic pressure among humans selected for this trait in populations from regions where malaria is endemic. Today, the Duffy negative blood group is almost exclusively found in sub-Saharan African populations, with over 97% of West and Central Africans carrying the trait (Kepple et al). This is why the geographic distributions of *P. ovale* and *P. vivax* have such little overlap. They are very similar biologically, but *P. ovale* is able to infect Duffy negative people, and is found in areas where this gene is more common.

There are a variety of other genes that affect malaria outcomes in humans, and most are genes that affect red blood cells. For example, the HBA and HBB regions are critical since they affect the alpha and beta globin proteins found in red blood cells, with the sickle cell mutation being found in the HBB region (Kariuki and Williams). These genetic variations come with a myriad of side effects and can increase the risk of developing certain conditions. This may apply to the affected patient's children as well. However, in regions where malaria is endemic, they provided an evolutionary advantage, creating a genetic inequity that persists along global divisions of power and wealth, contributing to the cycle of poverty.

Risk Factors

There are several risk factors that impact the probability of getting malaria, as well as the severity of infection. These include age, behavior, and socioeconomic situation, along with the Genetic Factors discussed previously.



Babies living in regions where malaria is endemic often receive maternal antibodies that protect them against malaria. However this natural immunity wanes after their first few months of life. In addition, humans usually develop acquired immunity after being infected by malaria several times. While they are still vulnerable to being infected by *Plasmodium* parasites, they often show fewer or less severe symptoms. This means that young children, many of whom have not yet developed malaria immunity, are most at risk from this disease.

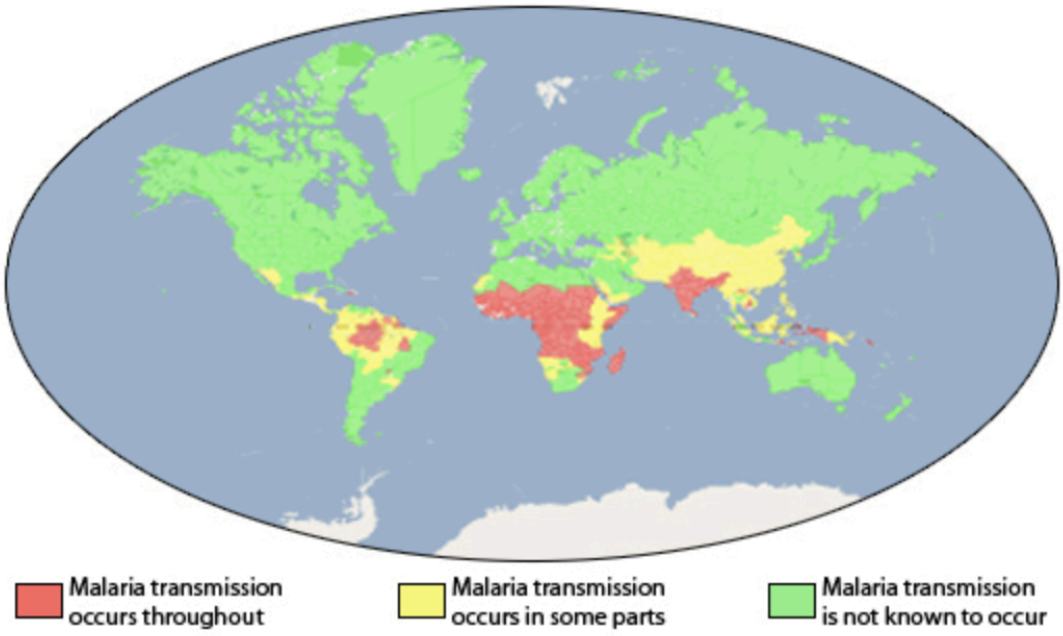
Various human behaviors also influence the severity and likelihood of exposure to malaria. This includes the accidental creation of larvae breeding sites through standing water in irrigation and increased night time mosquito bite exposure due to agricultural work. Some practices can also alleviate malaria, including keeping livestock and domestic animals near the home as an alternative blood meal source.

Socioeconomic factors also play a major role in malaria transmission. War-ridden regions may expose people to environments with high malaria transmission. Poor rural households often lack the resources to afford housing, effective bed nets, insect repellent, or medicine, which are all crucial in preventing or mitigating malaria infections. Due to knowledge gaps, traditional yet ineffective treatment methods are perpetuated by cultural beliefs. In areas where governments lack resources, there may not be sufficient equipment, medicine, or training for medical workers, who are often underpaid.

Impact and Equity

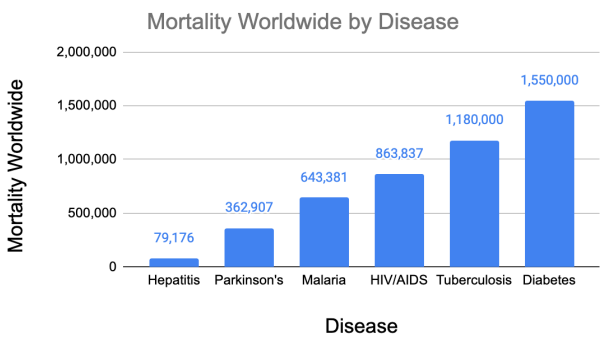
Geographic Distribution

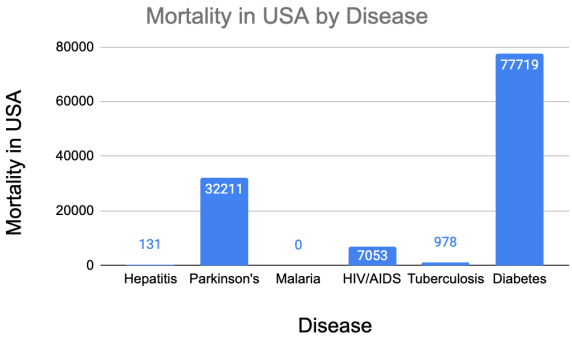
Malaria has the greatest impact in poor areas of the world. It has an outsized influence in the tropics and subtropics due to factors such as temperature, humidity, and rainfall amplifying *Anopheles* reproduction and survival rates. It is a primary cause of death in areas with high transmission, such as sub-Saharan Africa. Malaria inequality between nations is so severe that 95% of deaths in 2020 were in Africa.

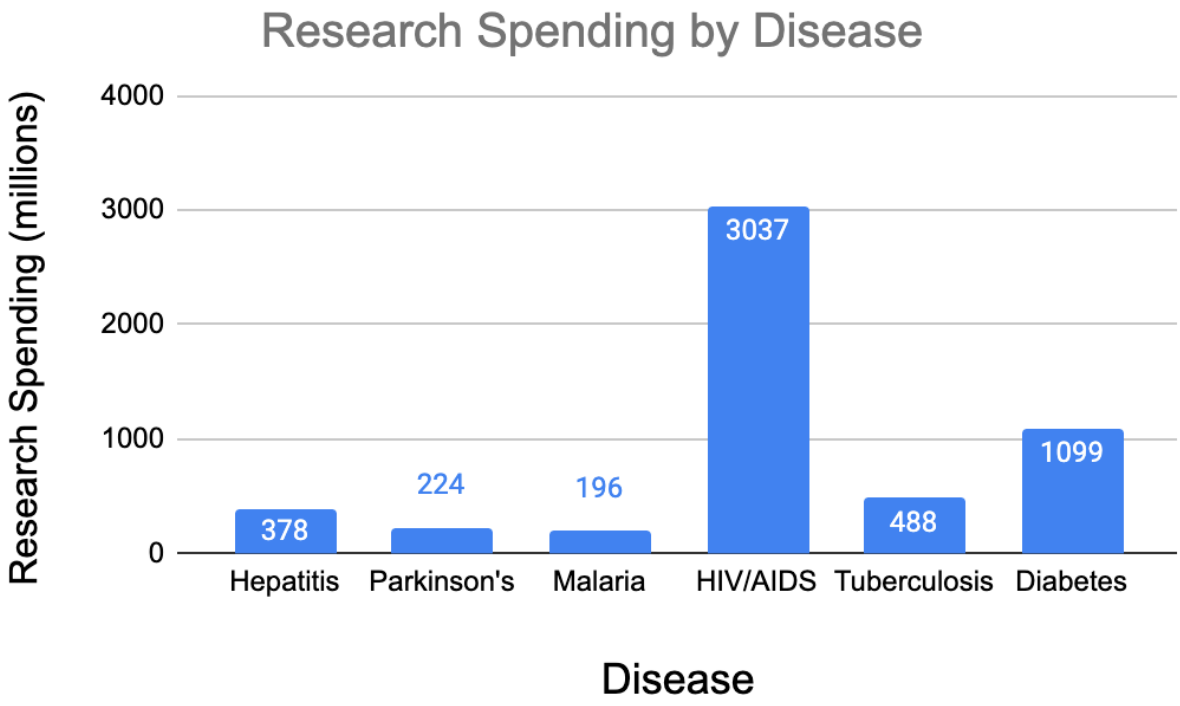


It is important to note that malaria does not necessarily occur uniformly across regions with high transmission rates. For example, during cold seasons, at very high altitudes, and in dry regions, malaria transmission will not occur. Temperature is the most important factor that determines this, with *P. falciparum* requiring 20°C to live and breed. However, in regions closer to the equator transmission is far more intense and occurs year-round.

Many developed nations in temperate regions, such as the United States and western Europe, have successfully eradicated malaria through public health campaigns aided by economic development. Due to this health equity gap, funding for malaria research is significantly lower than other diseases with similar or lower death tolls. Even for diseases with higher death tolls, the spending on research is not proportional to the difference in mortality.







All data is from 2019. Mortality data taken from Dattani et al. Funding data taken from NIH.

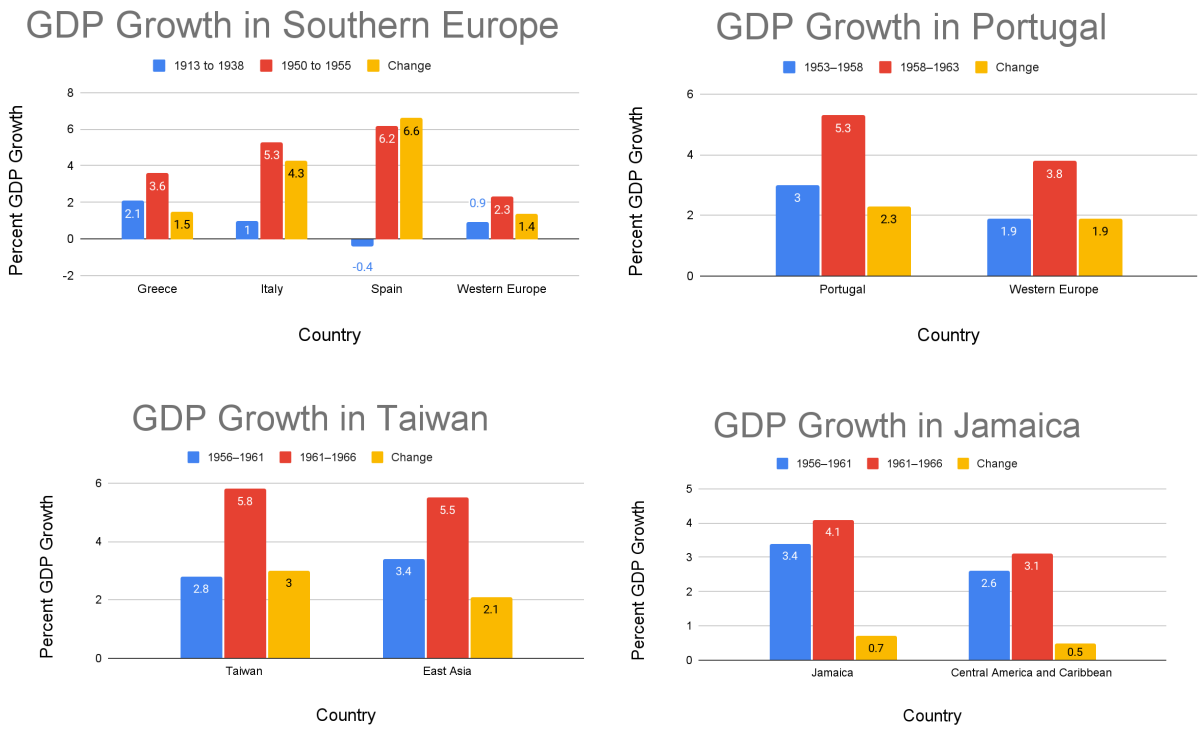
Socioeconomic Toll

Malaria is part of a devastating cycle of poverty, as it puts significant financial strain on the governments and individuals of the regions it affects. People in endemic areas must buy insecticide and nets to avoid this disease. Those who are infected by malaria need to travel and purchase medicine, and the loss of workdays affects both them and their employers. Tourism, which is often vital to the economies of these regions, is lessened by malaria outbreaks. Fewer economic ventures are undertaken by international companies due to the risks involved.

Direct costs due to healthcare, illness, and death are about $12 billion per year. However, lost economic growth is likely much greater than this. For example, even if climate, geography,

and past colonization are controlled for, the income level in 1995 for countries with a high rate of malaria was only 33% compared to countries without this high rate. Similarly, countries with a large malaria burden grew 1.3% less per person per year.

The extent of malaria's impact can be systematically seen in GDP growth before and after malaria eradication in various countries, compared to nearby nations where no change in malaria intensity occurred. An example of this would either be Western Europe where malaria was never very severe, or nearby regions that have never eradicated malaria.



Southern Europe eradicated malaria throughout the 1940s. Portugal eradicated malaria in 1958. Taiwan and Jamaica eradicated malaria in 1961.
All data taken from Gallup and Sachs.

Methods of Fighting

In this section, we will consider various methods of fighting malaria. We will analyze the way they work, their efficacy, and potential future improvements.

Insecticide-Treated Nets

Insecticide-Treated Nets, or ITNs, are bed nets treated with insecticide to protect people from mosquitoes while they are sleeping. This is strategic as most mosquito bites happen while people sleep. The insecticide repels and even kills mosquitoes, and other insects that try to feed on humans. With enough ITNs, the amount and lifespan of local mosquitoes can be reduced significantly, creating a form of herd immunity. This generally requires greater than half of the people in a given area to use an ITN.

The type of insecticide used is crucial, as they must be shown to have minimal health effects on humans but be deadly to insects. Only two are currently approved for ITN use: pyrroles and pyrethroids. However, with pyrethroid resistance being on the rise among mosquitoes, this is becoming less effective.

The main drawback of ITNs is the requirement for retreatment of nets with insecticide every 6 to 12 months. To combat this, long-lasting insecticide-treated nets, or LLINs, have been developed. These are effective for over three years and have been shown to be associated with malaria decreases in nations with high coverage.

Indoor Residual Spraying

Indoor Residual Spraying, or IRS, is a technique that involves covering the interior surfaces of a house with an insecticide. This is a highly effective method of preventing further transmission of malaria if done correctly since after taking a blood meal, most mosquitoes rest in houses. However, this requires applying insecticide to the interior of at least 80% of homes in a given community.

The type of insecticide used greatly influences the efficacy and cost of IRS. For example, DDT was greatly used in the 1950s and 1960s. However, its use declined due to environmental concerns associated with DDT. The perceived failure of these movements, with the Malaria Eradication Campaign being a prominent example, resulted in poor publicity for IRS and the abandonment of its use for several decades. However, recent success in South Africa has resulted in an 80% decline in malaria cases, revitalizing global interest in IRS.

Vaccines

Malaria vaccines have been notoriously difficult to develop, with efforts dating back to the 1960s. A large obstacle impeding such research is the historic lack of funding due to the absence of a first-world, traditional market (see malaria research spending in Geographic Distribution), meaning that few companies or organizations have actively worked on development. In addition, the complex life cycle of the *Anopheles* mosquito combined with poor understanding of the human immune system response to malaria has proven to be a formidable technical barrier. Nevertheless, there has been tremendous progress in the past decade, culminating with the WHO's approval of the RTS,S/AS01 vaccine for use in children living in regions with endemic malaria.

The RTS,S/AS01 vaccine has been shown to reduce malaria cases by a third in babies over the age of 5 months. It is extremely safe for humans, with over 2.3 million doses across three countries, easy to deliver equitably despite calamities such as the COVID-19 pandemic, and highly cost-effective in endemic regions. Further studies are being conducted on how to maximize vaccine effectiveness, including dose schedules and patient age.

Alternative vaccine candidates are also being explored. A prominent option is the whole sporozoite vaccine. This method uses the sexual form of the *Plasmodium* parasite, taken from an infected mosquito, which is administered to humans intravenously. To ensure safety, it is either accompanied by chemoprophylaxis or irradiated prior to injection. The PfSPZ vaccine, which uses this method, has been shown to be safe for humans, but with questionable efficacy at six months of age.

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