5 | UNDERSTANDING MALARIA

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5.1 | Introduction

In the 20th century, malaria caused 150 million to 300 million deaths, accounting for 2% to 5% of all deaths throughout the world. Today, malaria is curable and preventable, yet cases still number roughly 250–500 million worldwide, resulting in at least 1 million deaths each year.[1] Many wonder why so many people are still affected by malaria. The answer lies in the complex interplay of biological, sociological, and economic factors.

5.2 | Basic Biology

Malaria infection and illness start when a single-celled parasite of the genus *Plasmodium* invades the human bloodstream. Typically, four species of *Plasmodium* infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*; in Southeast Asia, *P. knowlesi*, a simian species, has also caused human illness. *P. falciparum*, which predominates in Africa, and *P. vivax*, which predominates in Asia and the Americas, produce the largest burden of disease.

More than 70 species of female mosquitoes of the genus *Anopheles* transmit human malaria. Of these, the greatest threat is *Anopheles gambiae s.s.* This African species is the world's leading vector for *P. falciparum* because it is long-lived and transmits with great efficiency.[2] Unlike some other malaria vectors,

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BOX 5.1 | Main Messages

- A basic knowledge of the biological, social, and economic factors underlying malaria is essential to understanding the road to elimination. Today's arsenal of tools includes interventions targeting key stages in the malaria parasite's life cycle in humans or mosquito vectors as well as strategies for case management, prevention, and surveillance. Choosing the right tools requires knowledge of specific social and eco-epidemiological characteristics of an elimination site.
- Concepts for malaria elimination build upon concepts for malaria control. The cornerstone of malaria control is case management and prevention. After transitioning to elimination, however, cases become rarer. At this point, surveillance, the identification of remaining foci of transmission, and prevention become far more important.
- The global burden of malaria—in terms of numbers of cases, severity of disease, geographical spread, and socioeconomic development—is tremendous. With today's tools, malaria elimination is feasible in some locales. Other sites with more-challenging epidemiological and socioeconomic conditions will require new and better tools and strategies.

which may seek blood from other animal hosts, *A. gambiae* may take 90% to 100% of its blood meals from humans. To describe other malaria vectors is beyond the scope of this chapter; however, it should be stressed that detailed knowledge of unique characteristics (e.g., density, biting behavior, resting behavior, sensitivity to interventions) of local malaria vectors is necessary for programs to achieve and maintain malaria elimination (Chapter 9).

The survival of the malaria parasite depends on the proximity of anopheline mosquitoes. Figure 5.1 demonstrates the life cycle of the parasite. The infected female mosquito injects motile parasites, known as sporozoites, into the victim's bloodstream while taking a blood meal. Within minutes, parasites invade liver cells and start to reproduce. In 1 to 2 weeks, infected liver cells rupture, releasing thousands of new parasites known as merozoites, which then invade red blood cells and undergo further cycles of asexual reproduction, during the course of which many erythrocytes will be ruptured. *P. vivax* and *P. ovale* can remain dormant in the human liver for weeks, months, or years; these dormant forms are the source of relapses of illness.

A few merozoites transform into male and female (sexual) stages capable of infecting new mosquitoes; these stages are called gametocytes. Once ingested by a new mosquito during a blood meal, male and female gametes are formed and fuse within the insect's gut, ultimately spawning forms that invade its salivary glands, from which they enter the next human host.[3] Depending on

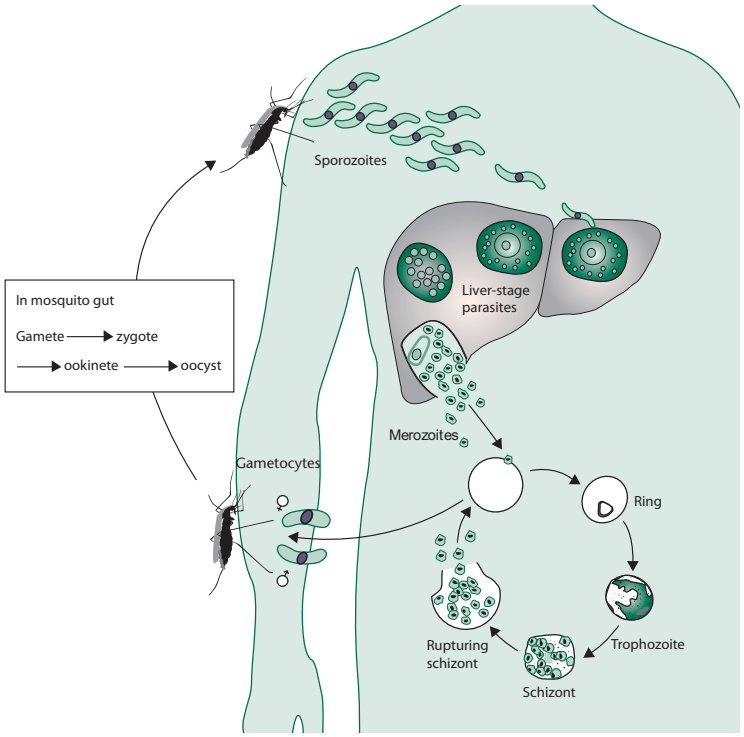

FIGURE 5.1 | Life cycle of the malaria parasite between mosquito vector and human host (Reprinted from *The Lancet,* 365 (2005): 1487-1498. Greenwood, B.M., Bojang, K., Whitty, C.J.M., & Targett, G.A.T. Malaria. With permission from Elsevier.[4])

the ambient temperature and parasite species, the entire sexual cycle within an infected mosquito takes about 14 days. Most adult *Anopheles* live for about 21 days.

5.3 | Individuals and Populations at Risk

In areas highly endemic for malaria, most notably sub-Saharan Africa, young children are particularly vulnerable to severe disease because they are heavily exposed and lack preexisting immunity. Pregnant women also constitute a high-risk group because of pregnancy-associated immune suppression and an affinity of *P. falciparum* for the placenta. Adverse outcomes in infected pregnant women include miscarriage, stillbirth, severe anemia in the mother, and low birth weight in infants, which, in turn, greatly increase the risk of infant mortality.

In contrast, acquired semi-immunity usually is seen in older children and adults who have grown up and reside in areas where *P. falciparum* is endemic and stable. Although such immunity does not preclude reinfection, it greatly reduces the severity of the illness. In many cases, it can even render an obvious bloodstream infection entirely asymptomatic. Therefore, in high-transmission settings, control interventions are focused more heavily on children and pregnant women.

A different pattern of disease is seen in temperate and subtropical regions of Asia and Latin America, where malaria transmission is more often unstable. Populations in these areas are more likely to suffer epidemics because their ongoing exposure is insufficient to induce or maintain immunity. Under these circumstances, residents of all ages can develop the full spectrum of disease, including severe complications. In fact, it is often adult men who are at highest risk of infection in Asia and South America because of occupational risks and migration. As malaria comes under control, its local epidemiology also changes within a given community. The proportion of clinical cases in adults increases, as does the community's risk of outbreaks.

In addition, genetic and acquired conditions affect the epidemiology of malaria. For example, carriers of certain inherited red blood cell diseases—in particular, sickle cell anemia—are less likely to die of *P. falciparum* malaria than their counterparts with normal hemoglobin.[5] Some genetically mediated protection also extends to *P. vivax*. This parasite invades red blood cells via a surface receptor called the Duffy antigen. In western and central Africa, most people are incapable of acquiring *P. vivax* infection because they lack the Duffy antigen. Malaria can also interact with other infections. HIV in Africa increases the likelihood of severe malaria in areas with unstable transmission, and in stable endemic areas, it increases the frequency and density of malaria infection in those with HIV as their immune suppression advances. Conversely, malaria transiently increases HIV viral load, thereby potentially increasing the likelihood of HIV transmission.[6]

5.4 | Socioeconomics and Drugs

The majority of deaths from malaria occur among the "bottom billion," or people who live on less than a dollar a day. Malaria also is primarily rural. The most common reasons why people die of malaria are socioeconomic and geographic. Sufferers may not have access to proper treatment because their families cannot afford it or they lack an understanding of the disease. Or they may simply live too far from a health care facility to obtain adequate treatment.

Sadly, even when people understand malaria and are able to secure medication, it may prove ineffective. Counterfeit and substandard antimalarial remedies are widespread. In recent studies, at least a third of medicines analyzed in Africa and Southeast Asia failed quality tests.[7, 8]

Drug resistance has contributed mightily to the world's recent upsurge in *P. falciparum* infections. Chloroquine resistance in *P. falciparum* first emerged in the 1950s and 1960s at the Thailand-Cambodia border and in South America;

in the 1980s, it began spreading in sub-Saharan Africa at a time when effective vector control was sorely lacking. The rise of chloroquine resistance in Africa has been temporally related to increases in malaria-associated mortality.

The loss of chloroquine, which was cheap, effective, safe, and widely available as an effective drug against *P. falciparum*, has proved a major setback for malaria control efforts. Chloroquine-resistant *P. vivax* poses another looming problem. Currently, these strains have been identified in Indonesia, Myanmar, Papua New Guinea, South America, Turkey, and Vietnam.[9]

Over time, other antimalarial drugs have also lost potency against *P. falciparum*. Mefloquine resistance is present in Asia, and sulfadoxine-pyrimethamine—the backup to chloroquine in Africa—has become progressively less effective worldwide. In combination with other antimalarial drugs, artemisinins (a family of highly effective compounds derived from the herb *Artemisia annua*) are the most potent first-line weapons remaining in the modern antimalarial arsenal for effective malaria control and elimination (see Section 5.6 below). However, recently at the Thailand-Cambodia and Thailand-Myanmar borders, some strains of *P. falciparum* have shown delayed clearance following artemisinin treatment.[10, 11]

5.5 Global Disease Burden

Today, as many as 3 billion people (roughly 40% of the world's population) risk exposure to malaria.[1] Not surprisingly, the most endemic areas are poor and tropical.

An estimated 2.37 billion people live in areas of *P. falciparum* transmission, the limits of which have recently been mapped. Predictably, Africa has the highest transmission levels (Figure 5.2). However, in northern and southern Africa, several countries have substantially reduced transmission, and outside of Africa, roughly 1 billion people reside in areas where their chance of contracting *P. falciparum* malaria is extremely low (less than one case per 10,000 population per year).[9] These areas are the initial foci for eliminating *P. falciparum*.

The current estimate of humans at risk from *P. vivax* is 2.6 billion people.[12,13] South and East Asia account for 52% of the total *P. vivax* burden, the Eastern Mediterranean region accounts for 15%, and South America accounts for 13%.[9] Because *P. vivax* develops in mosquitoes that thrive at lower temperatures than *P. falciparum* vectors, its geographical range is much wider, extending into temperate regions. The limits of *P. vivax* distribution are poorly defined, as our current understanding of its transmission and epidemiology lags behind what we

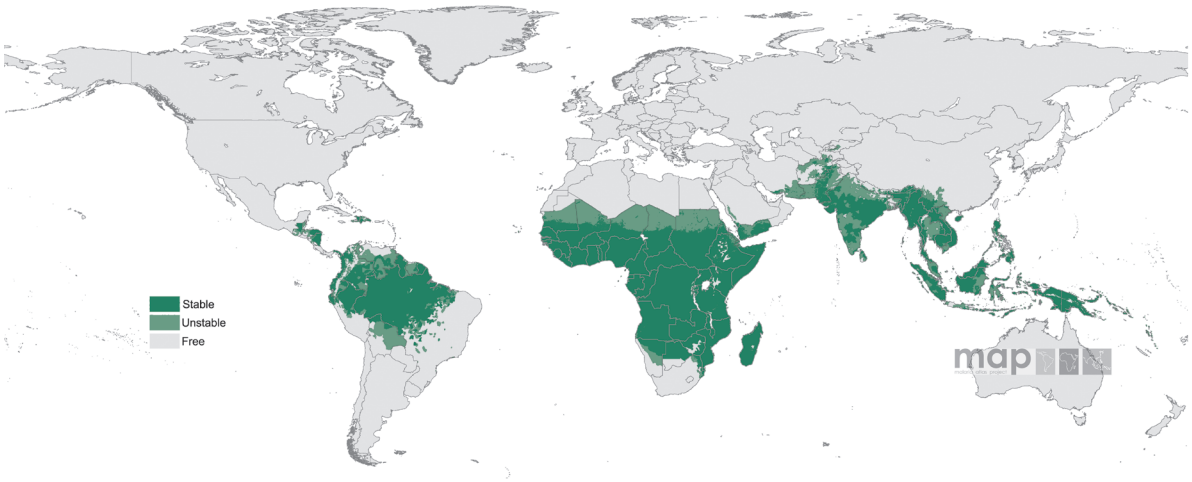

FIGURE 5.2 | Global distribution of *P. falciparum*. Areas are defined as stable (dark green areas, where *P. falciparum* annual parasite incidence, or *Pf*API, ≥ 0.1/1,000 persons per year), unstable (light green areas, where *Pf*API < 0.1/1,000 persons per year), or no risk (light gray). This distribution is governed to a large extent by temperature and aridity (from Guerra et al.[14]).

know about *P. falciparum*. Attempts are being made, nevertheless, to update the provisional limits of *P. vivax* transmission (Figure 5.3), using the same methods that were employed for *P. falciparum* (Figure 5.2).[14]

Worldwide, malaria is the fifth leading cause of death due to infectious disease, following respiratory infection, HIV, diarrheal disease, and tuberculosis. In Africa, malaria's death toll is exceeded only by HIV.[15] Despite harboring only 27% of the world's at-risk population, Africa has 89% of the malaria deaths and 59% of all clinical cases of malaria (74% of *P. falciparum* cases alone). Not surprisingly, this tremendous burden of disease is reflected in a chronic drain on health services. In Africa's most endemic areas, malaria accounts for 25% to 35% of all outpatient visits and 20% to 45% of hospital admissions.[16]

Globally, malaria kills 1 million people every year, 90% of whom are children under 5 years of age. In Africa, malaria is the leading cause of death in this age group, killing one African child every 30 seconds. There are also an estimated 400,000 cases of severe pregnancy-related maternal malaria per year, with an associated 10,000 maternal deaths.[17]

Beyond its devastating clinical toll, malaria thwarts productivity and economic growth. In 2002, malaria was the sixth leading cause of life lost and disability-adjusted life years (DALYs).[15] The majority of these occur among the world's poorest quintile, fostering a vicious cycle of infection, illness, and stunted productivity.

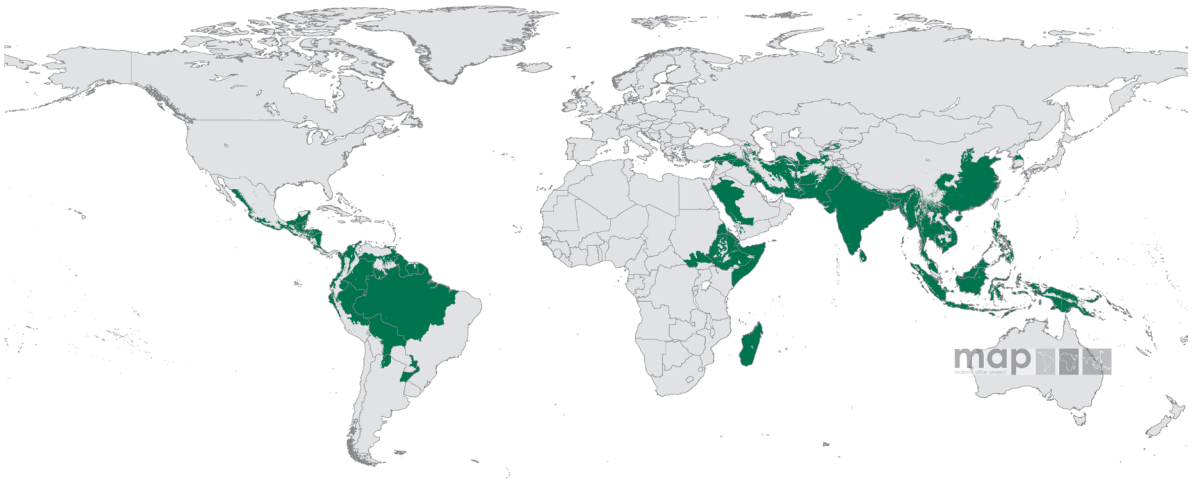

FIGURE 5.3 | Global distribution of *P. vivax* (from Guerra et al.[12, 13])

In strict economic terms, malaria costs African countries an estimated U.S. $12 billion per year, or 4% of their shared GDP. In the worst hit countries, malaria slows annual economic growth by 1.3%; conversely, a 10% reduction in malaria has been shown to yield a 0.3% increase in annual economic growth.[18]

Outside of Africa, Southeast Asia is the leading at-risk region for malaria, accounting for 66% of the disease burden. According to the WHO World Malaria Report of 2008, Afghanistan, Bangladesh, Brazil, India, Indonesia, Myanmar, Pakistan, and Papua New Guinea are the non-African countries with the highest estimated malaria cases.[1] Although most of these cases are nonfatal infections due to *P. vivax*, they are still responsible for significant illness and socioeconomic impact. Furthermore, there is growing evidence that *P. vivax* causes serious disease, especially connected to anemia in infants.[9]

Worldwide, an estimated 130 to 390 million *P. vivax* cases occur every year. The estimated global cost of *P. vivax*, including lost productivity and the cost of health care and transport to clinics, is between U.S. $1.4 and $4 billion per year.[9]

5.6 | Malaria Control and Elimination: The Toolbox

Historically, malaria control has spanned many interventions targeting vectors, parasites, and the human reservoir of infection. Because there is not a single blueprint or highly effective priority intervention such as a preventative vaccine, modern control and elimination will require a package of interventions customized to local conditions and specific programmatic goals.

With this caveat, modern malaria control can be divided into three broad categories: case management, prevention, and surveillance. Case management relies on prompt and effective treatment of symptomatic patients to cure disease and avert complications and death. Prevention includes everything from health education to vector control to prophylactic medication to vaccines. Surveillance refers to the systems in place for case detection as well as monitoring and evaluation.

How does malaria elimination differ from control? Control is concerned with reduction of the risk of malaria-associated morbidity and mortality to a point where they are no longer considered a public health problem. Control does not aim to prevent all transmission from occurring. On the other hand, elimination requires identification and treatment of all infected individuals, whether symptomatic or asymptomatic, so that transmission is prevented. During the shift to elimination, cases become rarer and are commonly restricted to defined foci. Therefore, prevention and surveillance become far more important.

CASE MANAGEMENT

Once a *P. falciparum* sufferer develops symptoms, prompt and effective treatment is crucial. Without it, the illness can progress to death or serious mental and physical impairment within hours. Before the patient receives treatment, however, a few key decisions take place. First, a patient (or patient's parent) recognizes a malaria-like illness, at which point the patient may receive "self-treatment" at home or consult with a formal or informal health care provider. The provider, in turn, may treat presumptively or rely on the results of a diagnostic test. Once a decision to treat for malaria has been made, the choice of a treatment regimen has to be made. The range of options is often limited and poor.

This same decision tree has led to a modern-day dilemma around "prompt and effective treatment." Presumptive therapy may reduce delays in initiating therapy and the risk of disease progression; however, it may also result in the substantial overuse of antimalarial drugs, the spread of drug resistance, treatment with a drug of inferior quality, and an increase in the risk of adverse drug reactions. Presumptive therapy may also delay the treatment of nonmalarial illnesses. Although treatment of laboratory-confirmed malaria has been increasingly advocated, many malarious communities lack diagnostic capacity. Even if tests are available, providers may choose to disregard negative laboratory test results and treat for malaria, resulting in wasted resources.

In an elimination setting where local transmission approaches zero, accurate diagnostic capacity is vital. Therefore, elimination will rely on rapid and accurate diagnosis and treatment.

DIAGNOSIS

Because malaria is a relatively nonspecific illness, diagnosis based on clinical grounds is unreliable. Since 1880, when Alphonse Laveran first found malaria parasites in human blood, a microscopic blood test has been the gold standard for malaria diagnosis. This test, when performed by a skilled professional, not only identifies malaria parasites within red blood cells, it distinguishes *P. falciparum* infection from infection with other malaria species, and it provides an estimate of the level of parasitemia. Disadvantages of microscopy include its need for trained personnel, proper equipment, and a power source.

More recently, rapid diagnostic tests (RDTs) for malaria have become available, providing an attractive alternative to microscopy. The main advantages of RDTs are their relative ease of use by unskilled personnel and the fact that they can be performed where there is no electricity. However, RDTs also carry disadvantages. Their average cost is U.S. $0.50 to $1.50. Also, most current RDTs are neither sensitive nor specific enough for *P. vivax*. Even with *P. falciparum*, RDTs can yield inaccurate results, requiring good quality control systems, which are difficult to maintain in remote, tropical settings.

Finally, RDTs cannot reliably detect gametocytes. Gametocytes do not cause symptoms but are necessary for transmission. When elimination is the goal, the ability to detect gametocytes in human blood becomes important. PCR-based tests that will reliably detect small numbers of both asexual and gametocyte stages are available; the technology is not complicated and they could soon be introduced routinely into central laboratory facilities. Key issues relating to diagnosis are discussed further in Chapters 8 and 10.

TREATMENT

The optimal treatment for malaria depends on the severity of disease, parasite species, local resistance patterns, and safety considerations. Generally, uncomplicated malaria is treated with oral drugs on an outpatient basis. Severe and complicated malaria, on the other hand, often require intravenous antimalarial therapy as well as other medical tests and technology found only in hospitals and well-equipped clinics.

Due to the spread of multi-drug-resistant parasites, the recommended treatment for uncomplicated *P. falciparum* malaria has undergone dramatic changes in recent years. Previously recommended monotherapies have been replaced by combination antimalarial therapy, which is defined as the simultaneous administration of two or more drugs that work independently against blood-stage malarial parasites (Table 5.1).

TABLE 5.1 | Important antimalarial drugs available for control and elimination efforts

Drugs	Primary indications
Artemether + lumefantrine Artesunate + amodiaquine Artesunate + mefloquine Artesunate + sulfadoxine-pyrimethamine Dihydroartemisinin-piperaquine	ACTs recommended by WHO for treatment of uncomplicated malaria[19]
Quinine Artesunate, artemether	Recommended treatment for severe and complicated malaria (*P. falciparum* and *P. vivax*)
Chloroquine	Treatment for non-*falciparum* malaria
Primaquine	Preventative against relapses and/or radical cure for *P. vivax*

Artemisinin and its derivatives (artesunate, artemether, dihydroartemisinin) produce rapid clearance of blood parasites and resolution of symptoms. Combining a short, generally 3-day course of the rapidly eliminated artemisinin compound with a longer-acting partner drug with a different mode of action is the rationale behind artemisinin-based combination therapy (ACT). ACTs also kill young gametocytes, thus reducing transmission and facilitating elimination.

Treatment options for *P. vivax, P. ovale,* and *P. malariae* infections are more limited. Although chloroquine remains the current treatment of choice for most cases, in areas of Southeast Asia and South America harboring chloroquine-resistant *P. vivax*, ACTs are now being used for treatment. Patients with *P. vivax* and *P. ovale* infections also need a second drug to eliminate latent liver parasites. The only regimen currently licensed for this use (a 14-day course of primaquine) is rarely completed. Primaquine can also cause hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a genetic condition for which a point-of-care test is not widely available.

Elimination of *P. vivax* is further complicated by the fact that gametocytes are usually released into the bloodstream just as a patient becomes ill. In contrast, *P. falciparum* gametocytes are released several days after the onset of illness. This lag allows ACTs to decrease the transmission of *P. falciparum*, whereas *P. vivax*–infected patients often propagate infection to others before receiving treatment.

CHEMOPREVENTION

Antimalarial drugs have long been used to prevent illness and reduce transmission. Chemoprevention can be divided into two categories: chemoprophylaxis and intermittent presumptive therapy (IPT). Chemoprophylaxis, which is traditionally given to nonimmune travelers to malaria-endemic areas, entails frequent subtherapeutic doses of an antimalarial drug to stave off infection for a defined period of time. Although the same strategy also could reduce malaria-associated morbidity in permanent (i.e., semi-immune) residents of malaria-endemic areas, this application of chemoprophylaxis has never gained wide acceptance, in large part because of cost, logistics, resistance, and concerns about a "rebound" in malaria following its discontinuation. The second category of chemoprevention is IPT, defined as the use of full treatment doses of drugs given at a few pre-specified time points not linked to symptoms or infection. IPT is given to pregnant women and is being considered for infants and children in areas of high transmission where many will be infected. Since it is not appropriate as part of an elimination strategy in areas that have already greatly decreased infection rates, it is not considered further here.

5.7 | Vector Control

The two leading means of vector control are use of insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS) of insecticide. Over the last two decades, a number of randomized controlled trials have clearly demonstrated that ITNs, in particular, can significantly reduce clinical disease and child mortality due to malaria.[20]

At present, long-lasting ITNs (LLINs) are the preferred technology. These nets have pyrethroid insecticide directly incorporated in their fibers. A great challenge is to achieve universal ITN coverage and usage.[21] Social marketing, subsidies, and provision of free ITNs are three strategies that have worked in program-driven initiatives, but will require further significant and sustained donor support for greatest effect.

Like chloroquine, the pyrethroid insecticide class will not remain effective forever. The recent emergence of pyrethroid-resistant *Anopheles* mosquitoes in several parts of Africa has underscored the urgent need for additional insecticides suitable for application to nets and other protective materials.[4]

In the mid-20th century, indoor residual spraying of DDT was fundamental to successful malaria elimination efforts. Today, spraying with several licensed insecticides has attracted renewed interest, especially in sub-Saharan Africa. In southern African countries with unstable malaria, DDT, carbamates, and

pyrethroids, in concert with ACTs, have dramatically lessened the local transmission of malaria.[22]

In parts of Asia, Africa, and South America, forest malaria presents unique challenges to vector control. IRS and ITNs may not provide adequate protection because forest malaria vectors mainly bite and rest outdoors.[21] For many countries, these highly efficient vectors contribute significantly to the burden of disease.[23]

To achieve elimination of malaria, novel vector interventions that spring from an improved understanding of local transmission, as well as environmental management, land-use, and housing innovation, will also be needed. Measures that kill mosquito larvae have been effective in some locales. New repellents, based on novel mosquito targets and genetic manipulation of natural vector populations, are additional strategies that hold promise for the future.

5.8 | Tracking Progress Toward Elimination

The ultimate measure of malaria transmission is its yearly toll of clinical illness and death as a result of local transmission. An elimination program must be technically and operationally capable of determining a progressive drop in morbidity and mortality due to malaria and of verifying when all local transmission has stopped.

An index of cases often used is the annual parasite index (API), which is the number of confirmed malaria cases per 1,000 population per year. API is the product of the ABER, the annual blood examination rate (or percentage of the population examined) and SPR, the slide positivity rate, or proportion of blood slides or RDTs found to be positive among all slides examined (see also Chapter 7).

WHO guidelines consider a country ready to consider transition from control to pre-elimination when the SPR < 5%, and from pre-elimination to the launch of an elimination program when the API is < 1/1,000. Other experts support a more conservative threshold of 0.1/1,000,[14] especially with respect to *P. vivax*. As stressed in Chapters 1 and 2, such policy decisions must be based on a range of political, economic, and organizational factors, as well as those measures that reflect the changing epidemiology. In addition, API can be very unreliable because of poor health information and underreporting, and it does not pick up the proportion of the population that is asymptomatic but still makes an important contribution to transmission. Although surveys of children are commonly used as a measure of parasite prevalence, as an elimination strategy proceeds, it becomes increasingly important to recognize that it

is the whole population, not just these children, that is the source from which mosquitoes become infected.

To overcome the challenge of assessing large population samples, the PCR-based diagnostic tests previously mentioned in this chapter as well as serological measures currently being developed for ongoing evaluation of an elimination program (Chapter 10) will be valuable—but they will also be costly and labor intensive.

5.9 | Conclusion

Malaria is a complex disease. In any given setting, understanding the dynamics of infection is of equal importance to making essential political, economic, and organizational investments in an elimination strategy. The infection characteristics vary, in turn, with the local species of *Plasmodium* and an array of human and vector characteristics.

Surveillance poses a particular challenge because, for elimination, it must determine not just who is clinically ill with malaria but also who is infected and possibly asymptomatic. Finding these people is the key to getting to zero.

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