7 | MEASURING MALARIA FOR ELIMINATION

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7.1 | The Role of Theory in Malaria Epidemiology and Control

The primary goal of this chapter is to describe the role of epidemiological theory and mathematical modeling in defining and updating an elimination agenda for malaria. Many relevant questions that come up in planning or monitoring malaria control begin with the words "How much . . . ?" or "What levels . . . ?" As an example, one question might be "How much would malaria epidemiology change if 80% of people owned and used an insecticide-treated bed net (ITN)?" Although statistical answers are found by starting from data and working backward to infer cause, mathematical answers are found by starting with a basic description of malaria transmission and working forward. Mathematics thus provides a precise language for discussing malaria epidemiology in all its complexity, and it gives such discussions a quantitative structure.

The parasite rate (PR) is a commonly measured aspect of malaria that is highly useful for malaria elimination planning. Intuitively, it is known that elimination will require greater effort in places where a higher fraction of people are infected (i.e., there is a higher PR). Mathematical models turn the notions of "higher fraction," "greater number," and "more effort" into quantitative statements. They can also draw useful comparisons about malaria control in different places, such as the hypothetical prediction "80% coverage with ITNs would reduce PR from a baseline of 20% to below 1% within 10 years, or from a baseline of 50% to 15% within 5 years." Quantitative answers are rigorously

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testable, and they make it possible to consider the nuances of malaria transmission, such as seasonality, differences in the vectors and their biting behaviors, and differences in the way malaria control is implemented.

Before starting a malaria elimination program, it would be wise to ask two questions: "What are the goals of the program?" and "How long will it take to reach those goals?" Useful goals have clear criteria for success or failure, and it is hard to imagine answering these questions without quantitative measurements, which can then be composed into a mathematical framework known as a mathematical model.

To be useful, mathematical analyses must describe changes in the quantities that are regularly measured, and they should also describe reasonable time frames for change. As an introduction, Box 7.1 defines the most commonly used measures.

THE ROLE OF THEORY IN THE GLOBAL MALARIA ERADICATION PROGRAM

Ronald Ross (1857-1932) demonstrated that mosquitoes transmit malaria and developed the first mathematical model for malaria transmission.[1] He was interested in the reason why the PR varied from place to place and in giving some practical quantitative advice about malaria control. Many of Ross's insights guided the first four decades of malaria control, when considerable efforts were made to eliminate malaria with larvicides and elimination of larval vector habitats.

By 1950, demonstration projects had proved that DDT spraying to kill resting vectors was an extremely potent tool for malaria control, but the key insight into why DDT was so effective came from George Macdonald's mathematical analysis.[2] Noting the long delay required for the parasite to complete sporogony in the mosquito, Macdonald showed that the longevity of mosquitoes is a weak link in malaria transmission. To put it another way, only old mosquitoes transmit malaria. DDT would shorten vector life span, and this would have a triple effect: It would reduce the fraction of mosquitoes that lived long enough to become infected with malaria, it would reduce the portion of infected mosquitoes that lived long enough to survive sporogony, and it would reduce the number of infectious bites given by an infectious mosquito. These three effects combined could explain why DDT spraying was so effective.

The Global Malaria Eradication Program (GMEP) established in the 1950s was based around indoor residual spraying (IRS) with DDT. After an ini-

BOX 7.1 | Measuring Malaria

Parasite Rate, or PR The prevalence of noninfective asexual blood-stage parasites varies with age. In a stable malarious area, people are rarely born infected, but PR rises with age until it reaches a plateau in older children. By 10 years of age, some immunity begins to develop and PR begins to decline. By the age of 20, it has fallen by a third from the plateau. By the end of life, it is at two-thirds of the plateau.[3] As immunity rises in older children and adults, parasite densities decline. Some part of the apparent decline in PR is caused by the inability to detect parasites. There may also be some real declines in PR because of immunity and other factors. The PR in children older than 2 years but less than 10 is called the standard PR.

Entomological Inoculation Rate, or EIR The EIR is the expected number of infectious bites per person per unit time, usually over a year. The EIR is found by multiplying the sporozoite rate (i.e., the proportion of mosquitoes with sporozoites in their salivary glands) and the human biting rate (i.e., the number of bites by vectors per person per year). Human biting rates are estimated by catching mosquitoes as they try to land or by catching them in traps.

Force of Infection The force of infection is the rate at which humans are infected. The force of infection is closely related to the EIR, at least conceptually. Although the EIR is measured by counting infectious vectors, the force of infection is estimated by looking at the rate at which humans become infected. It is defined as the number of new infections per person per year. One way to estimate the force of infection is to clear parasites and then observe people until they become infected. The signs of infection can be detected by the lingering immune response long after infections have cleared, so another way of estimating the force of infection is to plot the prevalence of an immune marker in the blood serum, or seroprevalence, against age and to look at the slope in young children. Such methods provide a sensitive assay of malaria transmission in low-intensity settings.

tial planning phase (Chapter 6), a 3-year attack phase of intensive spraying was envisaged, with the goal of interrupting transmission completely while minimizing the evolution of insecticide resistance. The 3-year time window was based on a mathematical model in addition to data from field trials and malaria therapy, which was the use of supervised clinical malaria infections to treat neurosyphilis before antibiotics were available. The data indicated that untreated infections naturally clear after approximately 200 days. A model showed that if transmission were interrupted, the PR would decline by about 80% per year, and PR would fall to 1% of its starting value within 3 years.[4] After

Annual Parasite Index, or API The API is designed to measure the number of confirmed malaria cases per thousand people per year in a defined geographical area. The proportion of the population examined is called the human blood or annual blood examination rate (HBER or ABER). People with suspicious fevers are examined for parasites, and the proportion of parasite-positive slides among suspicious fevers is called the slide positivity rate (SPR). API is defined as the product of the two (API = HBER × SPR) when data are available for the entire year. Most API data come from clinics where suspected fevers are examined for the presence of parasites, but it is often supplemented by active surveillance. When malaria becomes rare, it becomes increasingly difficult to detect ongoing transmission using PR.[5] Then API can be a reliable method for reporting new malaria infections in low-intensity settings with good reporting systems, especially when PR is too low to measure reliably. API data are difficult to interpret as a measure of malaria intensity, and they have low value for planning for elimination in places where PR is high enough to measure, but they may be the only way to measure progress toward elimination.

Vectorial Capacity Vectorial capacity is the expected number of infectious bites that will eventually arise from all the mosquitoes that bite a single person on a single day.[6]

Basic Reproductive Number, or R_0 R_0 is defined as the number of infected humans that would arise from a single infected human, or the number of infected mosquitoes that would arise from a single infected mosquito, after one complete generation of the parasite. It measures maximum potential transmission, so it describes populations with no immunity and no malaria control. It can be computed by summing vectorial capacity over the average duration of human infectiousness, but discounted for inefficient transmission.

Controlled Reproductive Number, or R_C While R_0 describes maximum potential transmission, R_C describes maximum potential transmission in a population with malaria control. R_0 measures the intrinsic potential for epidemics, while R_C measures the potential for epidemics after taking into account all of the measures that have been put into place to slow transmission.

a successful attack, there would be a consolidation phase leading up to malaria elimination (Chapter 6).

Although there has been substantial disagreement about the programmatic implementation of GMEP as a time-limited, intensive spraying program and the role of mathematical models in defining that agenda, few would disagree with Macdonald about the value of his basic insight. Malaria transmission is exquisitely sensitive to the mortality rate of adult mosquitoes, and modern malaria elimination programs must exploit that fact by attacking the adult vectors.

7.2 The Context for Malaria Transmission

As mentioned in Chapters 2 and 6, a common criticism was that the GMEP took a "one size fits all" approach that made it easy to scale-up malaria control and coordinate activities centrally.[7] The downside was program inflexibility and indifference to the local context for malaria transmission. A concrete example of how the rigid programmatic criteria may have led to an inappropriate decision comes from Pare-Taveta, a pilot program on the border between Kenya and Tanzania in an area where malaria was hyperendemic. The PR declined throughout the attack phase, but more slowly than the 80% decline stipulated by the programmatic criterion. After 3½ years, the PR was still declining; nevertheless, the spraying program was stopped. It is now clear that in the high-intensity settings more commonly found in Africa, PR will decline more slowly than 80% per year because of multiple infections. Such failure of the GMEP argues for a different approach to setting programmatic criteria, one that is capable of being tailored to the local situation.

Malaria transmission varies regionally, and sometimes over very short distances, as a consequence of factors such as transmission intensity, which vector species are dominant, and characteristics of the human populations. At a global level, there are important differences between sub-Saharan Africa and the rest of the world. The first is that the African vector *Anopheles gambiae* is the most efficient vector of malaria and the one with the strongest preferences for humans. Africa has two other anopheline species, *A. arabiensis* and *A. funestus,* that are also very efficient vectors. All three species tend to bite indoors and at night, and because of these three vector species, Africa overall has very intense transmission. The second difference is that *Plasmodium falciparum* is the dominant parasite in all of Africa, and *P. vivax* is generally absent. Outside Africa, there is a great variety of vectors and vector behavior, and the frequencies of both *P. falciparum* and *P. vivax* can also vary substantially from place to place. Most models and discussion have focused on *P. falciparum* and on the African vectors. Clearly, *P. vivax* and non-African vectors will require greater modeling attention.

7.3 Malaria Transmission

Our understanding of malaria epidemiology and the parasite life cycle has increased progressively and led to successive refinements of the original Ross-Macdonald model. Here, we discuss some of these ideas and their relevance to malaria elimination.

THE ROSS-MACDONALD MODEL

The Ross-Macdonald model is a basic quantitative description of the *Plasmodium* life cycle and the vector feeding cycle. The parasite enters the mosquito during a blood meal, and the mosquito becomes infectious 10 to 16 days later, after the parasite completes sporogony. In the meantime, the mosquito will have fed several times, and most infected mosquitoes will die before sporogony is complete. Mosquitoes that survive sporogony can then give several infectious bites before they die.

Human infections begin during the mosquito blood meal, when sporozoites enter the skin. Parasites are not obvious in the blood for about 11 days. The human with a *P. falciparum* infection is not infectious until a fraction of the blood-stage parasites become gametocytes and then mature, 8 to 10 days later. Untreated or improperly treated infections last approximately 200 days on average, and some infections last longer than a year. As long as the blood-stage parasites persist, some gametocytes will be produced. The number of mosquitoes that will become infectious depends, in part, on the number of mosquitoes that bite humans, the rate that parasites develop, and the longevity of the mosquitoes. This process is demonstrated in Figure 7.1.

One way to summarize transmission is to answer the simple question "How many infectious mosquitoes would be expected to come from a single infectious mosquito after just one generation of the parasite?" The complex answer to this question is the quantity called the basic reproductive number, R_0.[2] To answer this question, we count the number of infections by following the parasite through its life cycle:

- How many times is a person bitten by vectors each day?
- How many human blood meals does a vector take over its lifetime?
- What fraction of blood meals taken by infectious mosquitoes cause infections in humans?
- How long does a person remain infectious?
- What fraction of mosquitoes feeding on infectious humans become infected?
- What fraction of mosquitoes survive sporogony?

R_0 is computed by giving quantitative answers to these questions and taking the product.

The Ross-Macdonald model describes changes in the fraction of infected humans (i.e., PR) and the fraction of infectious mosquitoes (i.e., the sporozoite

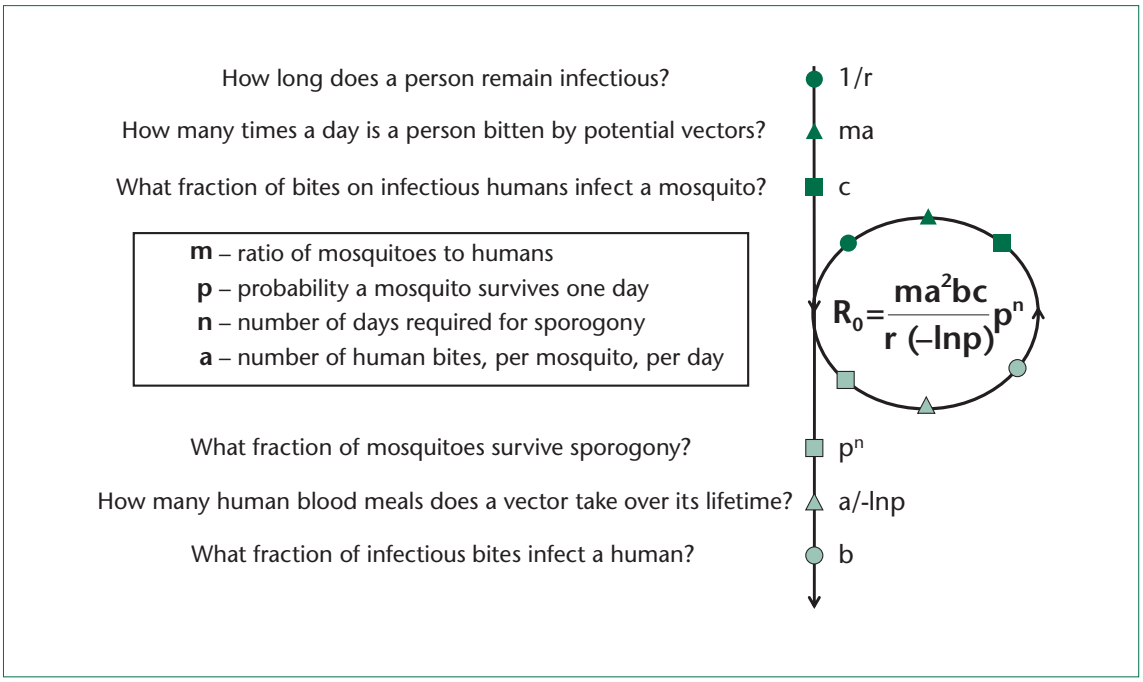

FIGURE 7.1 | Measuring R_0

rate) over time as infections are acquired and cleared. If $R_0 > 1$, then a single infectious mosquito would tend to leave more infectious mosquitoes, and as a consequence PR would increase until it reached a steady state when new infections were balanced by cleared infections.

The mathematical models and the concept of R_0 also describe most basic aspects of *P. vivax* transmission dynamics, but the parameters must be modified to describe the vectors and the dynamics of *P. vivax* infections in humans. There is one big difference that the Ross-Macdonald model does not accurately describe. Because *P. vivax* can lie dormant in the liver, a single infectious bite can result in multiple relapsing infections as new *P. vivax* broods emerge. Although this happens in only a fraction of infected people, the equations must be modified to consider dormant liver-stage infections and relapse, and R_0 for *P. vivax* must add up all the mosquitoes that arise from the primary infection and from all of the relapsing infections.

The concept of a steady state is usually interpreted as a long-term average, but this requires careful interpretation in the light of malaria immunity in humans, seasonal mosquito population fluctuations, multiple infections, and the fact that some people are bitten more than others. Elaborations on the Ross-Macdonald model have added each one of these factors alone and in com-

bination. In each model, there is a different way of computing R_0, and there is also a different quantitative relationship between PR and R_0. Mathematical models can provide a good qualitative description of malaria, even where there is some uncertainty about the underlying quantities. Despite the uncertainty and quantitative differences among these models, R_0 provides a unifying concept. When indexed to PR or other routinely collected malariometric indexes in a credible way, R_0 provides practical guidance about how much transmission would have to be reduced to eliminate malaria.

HETEROGENEOUS BITING

Humans differ from one another in their ability to transmit malaria to mosquitoes, in their susceptibility to disease, in their immunological responses, and in many other quantitative traits. For most of these differences, R_0 is proportional to the population average, but heterogeneous biting is different because it amplifies transmission intensity. Heterogeneous biting refers to the fact that some people are bitten more than others. Heterogeneous biting can be separated by three kinds of factors: how bites are distributed within households, among households, and among individuals over time.

The factors that determine who gets bitten within a household are complicated and include body size, sex, pregnancy, and olfactory cues that have not yet been identified.[8] Some households get more infectious bites than others, depending on their proximity to larval habitat, their use of ITNs or area repellents, the housing design, and odors that probably attract mosquitoes from very long distances.[8] All of these effects combine so that a few houses harbor the vast majority of the mosquitoes. It has been proposed that 20% of the people get 80% of the bites.[9] Not all vectors bite indoors and at night. Depending on the local vector present, heterogeneous exposure to malaria can have very different causes. When the primary vectors live in the forest, for example, the people who spend the most time in the forest are at greatest risk.

Heterogeneous biting amplifies malaria transmission when PR is low, and it hides very intense transmission when PR is high.[10] Consider the contrasts of two populations where the PR is 10%. In a population where 10% of people are bitten twice a day, but 90% of the population is never bitten, R_0 would be much higher than in a population with a PR of 10% with uniform biting rates. Thus, it should be obvious that when biting is extremely uneven, the prevalence of malaria can disguise subpopulations where biting is extremely intense. The message is simple. Holding PR fixed, the higher the degree of biting inequity, the more difficult it will be to eliminate malaria.

ESTIMATING R_0

Given the importance of R_0 in planning for malaria control, it is surprising how infrequently it is measured. Mathematical models define relationships between PR, R_0, and other commonly measured indexes, and this provides a useful method for estimating R_0.[11]

A problem with this method is that it must take into account all of the factors that affect endemic malaria, such as human immunity, heterogeneous biting, seasonality, malaria control, and density dependence. If transmission is highly seasonal and focal, for example, then the value of R_0 will be highly influenced by the time and place with the highest transmission. It is possible to develop a wide range of plausible models.[10] Which factors matter and which model should be used?

One way forward is to build many different models and challenge them with various kinds of data and then select models that best capture both the underlying mechanisms and the observed patterns.[12] The process of iteratively building models and validating them leads to refinements of the theory and suggests new tests of the theory. In the end, the process of building models allows us to make a better assessment of the potential for malaria elimination.

Using this process, one study estimated R_0 in 121 African populations.[11] Those estimates suggest that R_0 ranges above 1,000, and perhaps much higher. This suggests that malaria will be extremely difficult to control in Africa and in some areas outside of Africa where transmission intensity is very high. To put this into a more quantitative context, it is necessary to give quantitative estimates of how effective malaria control can be.

7.4 | Malaria Control

In the design of malaria control programs, a question often arises about how to set target coverage levels of malaria interventions to achieve some predefined goal. In order to eliminate malaria, for example, it will be necessary to reduce malaria transmission by a factor that exceeds R_0, and to sustain this level of control until no parasites remain in the human or vector populations. To explain this better, we define the concept of an "effect size."

A power analysis for malaria control should focus first on the likely effect size that can be achieved from a package of interventions and their distribution and intensity. For malaria elimination, the relevant effect size is the overall reduction in potential transmission. As a reminder, R_0 describes potential transmission in the absence of control. In the presence of control, potential

malaria transmission is described by the controlled reproductive number, R_C. In effect, R_0 defines the maximum possible transmission in an area, while R_C describes what would happen in light of, for example, ITN use, regular medical care, and the public health response to an outbreak of malaria.

Power analysis estimates the effect size, defined as the ratio R_C/R_0. As an example, if ITNs reduced vectorial capacity by 90%, the effect size would be $R_C/R_0 = 10$. The overall effect size for integrated malaria control is found by multiplying the effect sizes for reductions in vectorial capacity achieved separately through adult vector control, larval vector control, and the reduction in infectiousness achieved through the use of antimalarial drugs.

INTEGRATED MALARIA CONTROL

To understand how well malaria control will work when several different interventions are deployed simultaneously, the first step is to estimate the effect size of each one of the interventions separately.

Insecticides can repel or kill mosquitoes and reduce mosquito longevity, delay feeding, and deflect vectors so that they feed with greater frequency on nonhuman hosts.[13] IRS works in much the same way as ITNs, but the mosquitoes might take a blood meal first. Clearly, ITNs and IRS reduce the risk of malaria for those people who use them, but at high rates of use, they also reduce the risk of malaria and protect people who don't use an ITN or who live in unsprayed houses nearby. However, leaving some low-risk populations unprotected will allow malaria transmission to continue and will increase malaria exposure for high-risk populations. An example is the better protection of children that may occur when adults were provided with ITNs.[14] Analyses of malaria transmission therefore need to consider whole populations, not just the high-risk groups.

Another way to reduce transmission is to control larval mosquitoes at the source.[15] Although larval control may not be cost-effective in every situation, it can be extremely cost-effective in others, and it can bring about dramatic reductions in vector populations that make other forms of control more effective. Given the extremely high estimates of R_0, it may not be possible to eliminate malaria with the combination of ITNs and drugs. Without new tools, larval control may be required to achieve elimination, although, given the diversity of breeding sites that *A. gambiae* can utilize across Africa, larval control is often not an option for this vector.

The effects of drugs on malaria transmission are more difficult to describe because of clinical immunity and the potential for reinfection. Intuitively, it

is clear that a drug that radically cured an infection by removing all of the parasites in all of the life stages would cut short the infectious period. A radical cure at the beginning of an infection could reduce infectiousness from several months, on average, to no infectiousness at all. In areas with immunity and frequent reinfection, many new infections tend to go untreated, and the control power of drugs is substantially diminished.

There are a few important caveats about drugs and transmission, however, as each drug affects the parasites at a different phase in their life cycle. The first-line drugs all kill at some asexual stage of the parasites; some of these (e.g., artemisinins and chloroquine) kill immature gametocytes, and others (e.g., primaquine) kill mature gametocytes. In areas of low transmission, where health care systems manage to treat all new infections, transmission would continue from people who carry only gametocytes.

Drugs also have other effects. Drugs with long half-lives would have a natural prophylactic effect and prevent some new infections.[16] Intermittent presumptive treatment (IPT) of pregnant women or infants at scheduled prenatal or pediatric visits does provide some protection from clinical disease, and it may also reduce infection, for as long as the drug concentrations remain high.

The effects of reducing malaria transmission through larval control, adult vector control, and antimalarial drugs all complement each other. When these different modes of control are combined, their effect sizes are multiplicative. Thus, an effect size of 10 achieved through ITNs and an effect size of 10 achieved through drugs would be multiplicative and produce a total effect size of 100 (i.e., a 99% reduction in transmission intensity). Each additional mode of malaria control further improves the total control power. One caveat is that malaria control can create heterogeneity or interact with existing biting heterogeneity.[17] Heterogeneity presents enormous modeling challenges, in light of variations between people in their use of health services and ITNs. If malaria control could focus on those who are bitten the most, the effects would be quite dramatic.[18] Conversely, a segment of the population that was not reached by any form of malaria control could sustain transmission regardless of how intensive malaria control was applied to everyone else.

All of this raises an important question: given the arsenal of malaria control weapons, what is the optimal package of malaria control interventions, depending on the context for transmission? This is an important question that can only be answered with some modeling, combined with malaria control and elimination experiences in a variety of contexts.

MAPPING R_0 AND R_C

The map in Figure 7.2 illustrates data that are a nonlinear transformation of the model-based geostatistical point estimates of the annual mean *Pf*PR$^{2-10}$ for 2007 within the stable spatial limits of *P. falciparum* malaria transmission, displayed as a continuum of light to dark green from 0 to >200 (see map legend). The rest of the land area was defined as unstable risk (medium gray areas, where *Pf*API < 0.1) or no risk (light gray, where *Pf*API = 0).

The spatial distribution of R_C illustrated in Figure 7.3 shows areas categorized as the following: easy to control with simple improvements in access to health care and antimalarial drugs (R_C = 0 to <2, lightest green); possible to control by achieving the equivalent of an 80% ownership with long-lasting insecticide-treated nets (LLINs) and 80% use (R_C = 2 to <10, light green); possible to control by dramatically improving access to health care and scaling up of LLINs as above (R_C = 10 to <100, medium green); and difficult to control even with the scale-up of a complete suite of existing interventions (R_C = >100, dark green). The rest of the land areas were defined as either unstable risk (medium gray areas, where *Pf*API < 0.1) or no risk (light gray). It should be noted that there are considerable error margins in the conversion of R_C to *Pf*PR$^{2-10}$ and that places that have already scaled up control will find it more difficult to improve control. These estimates should thus be interpreted cautiously and used only as an informative guide. In addition, the time taken to achieve the interruption of transmission can still be considerable, on the order of decades, and is reduced by the margin by which the implemented control exceeds R_C.

REVISED ENDPOINTS AND TIME LINES

One practical use for models is to set realistic expectations about what can be achieved through existing programs. The PR is a commonly measured index of transmission intensity that provides reliable information about R_0 (or R_C), so it forms the best evidence base for large-scale planning, although other malariometric indexes improve the diagnostic ability of monitoring and evaluation. An important question for planners to consider is, for some fixed level of ITN and other intervention coverage, how much can PR be reduced and how fast will it change?

The logic for developing a PR-based theory is fairly simple. Given a baseline estimate of PR, it is possible to infer R_0, albeit with some uncertainty. Given a specific package of interventions and specific coverage levels, it is possible to estimate R_C. The new PR is predicted by a mathematical model using the new value R_C. Changes in PR can, thus, be predicted for any package of interven-

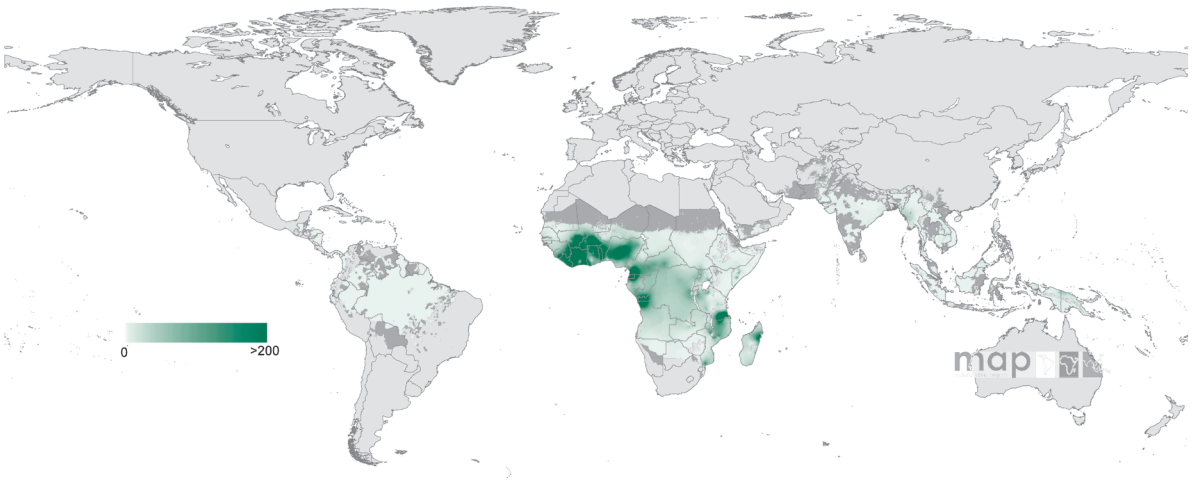

FIGURE 7.2 | The spatial distribution of the estimated basic reproductive number of *P. falciparum* malaria at present levels of control (R_C)

tions, as long as it is possible to estimate the control power. A simple lesson that comes out of this sort of analysis is that the same package of interventions will have different effects depending on the baseline PR, seasonality, and heterogeneous biting. When PR is high, the reductions will be comparatively small. When seasonal fluctuations or biting heterogeneity is high, the reductions will also be comparatively small.

The expected waiting time to reach the new PR can also be computed using mathematical models. The waiting times to reach the new steady state are longest when the packages of interventions are barely sufficient to eliminate malaria. The rate of decline in PR is much faster when malaria transmission is interrupted completely, but it is much slower than the GMEP criterion when the baseline PR is high (>60%).

These methods provide a way of establishing testable predictions and concrete advice about the coverage levels required to reach program goals. This same process also works when malaria control is changed from one level of coverage to another, so it can weigh the value of changing a package of specific interventions, such as increasing ITN coverage from 50% to 60%. By extension, it should also be possible to identify the control power that is required to reduce PR below some prescribed lower limit within a fixed time frame.

While these methods can provide some useful projections about the changes in PR, the entire basis for monitoring begins to break down as PR declines below 1% and becomes harder to measure, and API may be the only measure for progress toward elimination. By extension, the factors that affect malaria control

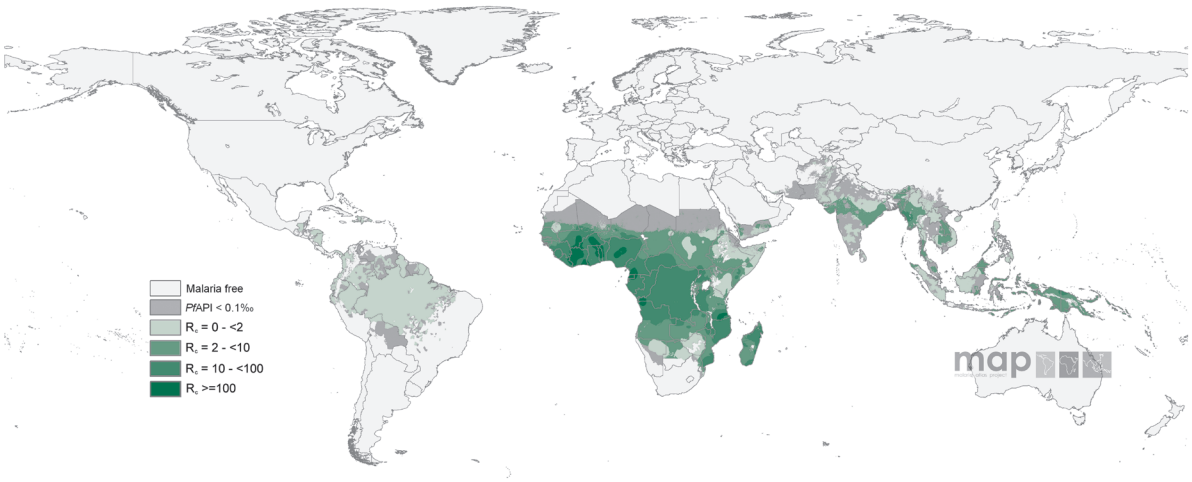

FIGURE 7.3 The spatial distribution of the estimated basic reproductive number of *P. falciparum* malaria at present levels of control (R_C) stratified according to the ease of the additional control required to interrupt *P. falciparum* malaria transmission

and ongoing transmission also change. In high-intensity areas, when there is a commitment to elimination, the emphasis must be on reducing transmission. As the reservoir of malaria begins to decline and transmission is controlled, the emphasis may shift. Currently, transmission at low intensity has not been the subject of extensive modeling (Box 7.2). Low-intensity transmission in areas where a large fraction of clinical episodes are treated, for example, may be sustained by broods of mature gametocytes. Gametocyte densities decay slowly, like the serum concentrations of drugs. An important consideration for *P. vivax* elimination time lines is that relapsing infections from the largely invisible liver-stage infections can substantially extend the waiting time to elimination. The relative importance of these factors for elimination awaits investigation using mathematical models.

OUTBREAK RISK AND IMPORTATION RISK

For malaria eradication to succeed, it must be possible for every country to sustain elimination. As described in Chapters 1 and 3, two key concepts for describing malaria after elimination are outbreak risk and importation risk. Outbreak risk, also known as receptivity, is defined as the potential for malaria outbreaks, and importation risk, also known as vulnerability, is the risk of importing malaria from nearby malaria-endemic populations.

In modeling terms, outbreak risk is described by the concepts of R_0 and R_C. In areas where elimination has been achieved, it must have been true that $R_C < 1$

BOX 7.2 | Stochastic Models of Malaria Epidemiology and Control

There are many kinds of mathematical models. The Ross-Macdonald model and most other models commonly used in malaria epidemiology are called "deterministic models" because nothing happens by chance. Deterministic models are useful when the law of large numbers applies, when small fluctuations that happen by chance can be ignored as a kind of irrelevant noise.

There is a need to develop new sorts of models that consider the consolidation phase, when malaria is rare, and the maintenance phase, after malaria has been eliminated. Under these conditions, there are very few events, so the law of large numbers does not apply. Different sorts of models must be developed to consider the random fluctuations and chance events. These are called "stochastic models."

Two concepts that are critical for post-elimination planning are the rate at which malaria is imported (i.e., importation risk) and containment of the malaria outbreaks that follow (i.e., the outbreak risk). The tendency for an epidemic to occur is described by R_C, but the size and duration of an outbreak will be highly variable. Important factors include the immune status of the population, which affects whether infected people are likely to report to health facilities, as well as micro-heterogeneity in transmission, that is, whether imported malaria infections are likely to remain in localized foci or to spread widely. Stochastic malaria models have been developed, including a computer simulation developed by the Swiss Tropical Institute.[19] There is an urgent need to extend such analyses to low-transmission settings, with the modeling of surveillance systems as a priority.

occurred for long enough to clear parasites from all the human and vector hosts. This statement would not be true if elimination were achieved through mass drug administration, or if malaria were easier to eliminate because of high levels of transmission, blocking immunity in humans. An important concern is that the levels of control that are required to achieve elimination may not be sustained, especially after malaria has ceased to become a burden and when it competes with more-pressing public health needs. When malaria is rare, it is important to consider individuals and stochastic behavior. This shifts the emphasis to estimating R_0 using baseline estimates of transmission intensity, and to assessing the standing capacity for malaria control. Does a country have the ability to rapidly and efficiently detect imported malaria and the start of an epidemic and then contain an outbreak?

In practical terms, importation risk can be assessed from the malaria endemic statuses of countries, population densities and distributions, and the rates of migration among countries.

To put these concepts into a metaphor that is more readily understood, consider an analogy to forest fires. Outbreak risk describes aspects of a forest that leave it susceptible to fires, such as large amounts of standing timber, the density of dead trees, and the moisture content of living trees. Importation risk is analogous to the risk of lightning strikes and human activities that spark the fire.

7.5 | Before and After Elimination

The ability to sustain elimination once it has been achieved depends on the methods used to control malaria and achieve elimination in the first place. In areas with low importation risk where elimination was achieved by combining intensive vector control with effective surveillance and prompt effective treatment with antimalarial drugs, it may be possible to relax the level of vector control and shift some of those resources to detect and control outbreaks (Box 7.3).

It is probably easier to keep malaria out of a place than to eliminate it. When malaria is rare, antimalarial drugs can be extremely effective tools for controlling transmission and stopping outbreaks, but drugs are much less effective where malaria is endemic. The reason is that ongoing infection maintains clinical immunity so that some infections go untreated and individuals remain infectious for months, thus making it easier for malaria to keep up a chain of asymptomatic infection. Since an individual with an infection that was cured radically ceases to become infectious, an outbreak could be stopped immediately by treating every person. When malaria is rare and every new case of clinical malaria is detected and promptly and radically cured, malaria transmission never gets started. In the same place, malaria transmission can continue until clinical immunity wanes sufficiently.

The conditions that allow outbreak control to work are extremely effective surveillance combined with prompt treatment to achieve a radical cure. It is intuitive that having effective contact tracing and aggressive outbreak control focused around confirmed cases will make outbreak control more effective. The long delay between infection and the point when a person presents at the clinic, the waiting time for gametocytes to mature, and the delay for sporogony all open a window of opportunity for malaria outbreak control to contain epidemics in the post-elimination state.

BOX 7.3 | Is Elimination a "Sticky State"?

To achieve global malaria eradication, each country that achieves malaria elimination must sustain it. Mathematical models generally suggest that this will be quite difficult, especially in places where R_0 is very high.[11] Transmission models suggest that the PR tends to a long-term average, depending on R_C. The relationship is like the temperature in a room and the set point of a thermostat. Vector control, such as ITNs or IRS, lowers R_C and changes the set point, and PR drops until it reaches the new set point. If vector control were relaxed, the set point would change, and PR would increase. In other words, these models suggest that intensive malaria control must be sustained for decades to keep the set point at zero.

Some recent theories suggest that this metaphor may not be entirely correct.[20] After malaria control brings the incidence of malaria near zero, there may be other changes that make malaria elimination easier to sustain. Increases in wealth and housing quality can permanently reduce R_0, change the market forces for health care, and change people's attitudes toward malaria. After a prolonged reduction in transmission, adults can lose their immunity, but this is a double-edged sword. On one hand, an uncontrolled epidemic in a nonimmune population would probably cause massive mortality. On the other hand, after the loss of malaria immunity, malaria transmission would be obvious because every person who got infected would also get sick, and this could make malaria easier to control. Contact tracing could be very effective. Measures that are generally impractical or ineffective against endemic malaria, such as mass spraying with insecticides and mass drug administration, could become much more effective because of the smaller scale of the problem. As attitudes change, a small outbreak of malaria can cause a huge outcry for action. If attitudes about malaria, wealth, and health infrastructure change enough, the outbreaks can be prevented.

Mathematical theory suggests that the same place can have two set points. One set point corresponds to endemic malaria and well-developed immunity, and the other set point corresponds to no malaria and no immunity. These set points are only possible if the response to clinical malaria, such as prompt effective treatment with antimalarial drugs and effective outbreak response, is very effective. To put it another way, if malaria elimination is sustained for long enough, and if the health systems and outbreak response are good enough, the absence of malaria can be "sticky." The success of global malaria eradication is greatly enhanced if malaria transmission dynamics are sticky, because it becomes easier to hold the ground that has been won.

This possibility is conditional on having strong health care systems and effective surveillance in place to be able to identify a high proportion of clinical malaria episodes. This helps to explain how some countries have managed to stay malaria free, despite having a history of endemic malaria, healthy vector populations, and frequently introduced malaria.

THE INFORMATION NEEDED FOR ELIMINATION

Strategic planning at the regional and global levels will require a considerable evidence base, including information on human population distribution, outbreak risk, and importation risk. Some of these databases are already being assembled on a global scale. As mentioned previously, the parasite rate is commonly measured, and it provides a useful index of malaria transmission intensity. Maps of malaria endemicity (i.e., PR) provide a basic estimate of outbreak risk. When combined with population distribution maps and other information, they can also be used to estimate importation risk. The ability to move the modeling agenda into an explicitly spatial context is a luxury that was not available to the former GMEP. Although considerable effort will be required to quantify the uncertainty in predictions, global maps of malaria endemicity not only provide a platform to help inform strategic planning through scenario analyses but also provide a mechanism to monitor change and evaluate intervention effects.[21]

7.6 | Conclusion

Mathematical modeling is one of many tools that can be used to plan for and carry out elimination. In forming a strategic plan, it is not enough to set vague goals. The elimination program, like any program, will need plans with defined time limits and concrete targets with well-defined parasitological, entomological, and epidemiological endpoints, such as 80% coverage within 5 years to reduce PR to less than 1%. There is little benefit to making a goal that is not realistic and cannot possibly be met. Mathematical models can help to establish realistic goals and time lines based on existing tools, they can help to inform the monitoring and evaluation and make course corrections, and they can also help to describe the big picture for malaria elimination in quantitative terms. As we have stated, mathematical models are nothing more than thinking carefully and quantitatively about malaria.

References

1. Ross, R. *Report on the Prevention of Malaria in Mauritius*. London: Waterlow and Sons (1908).
2. Macdonald, G. *The Epidemiology and Control of Malaria*. London: Oxford University Press (1957).
3. Smith, D.L., et al. Standardizing Estimates of the *Plasmodium falciparum* Parasite Rate. *Malar. J.* 6 (2007): 131.

4. Macdonald, G., and G.W. Göeckel. The Malaria Parasite Rate and Interruption of Transmission. *Bull. World Health Organ.* 31 (1964): 365-377.
5. Hay, S.I., et al. Measuring Malaria Endemicity from Intense to Interrupted Transmission. *Lancet Infect. Dis.* 8, 6 (2008): 369-378.
6. Garrett-Jones, C. Prognosis for Interruption of Malaria Transmission Through Assessment of the Mosquito's Vectorial Capacity. *Nature* 204 (1964): 1173-1175.
7. Gramiccia, G., and P.F. Beales. The Recent History of Malaria Control and Eradication. In Wernsdorfer, W., and I. McGregor (Eds.). *Malaria: Principles and Practice of Malariology* (2nd ed.). New York: Churchill Livingstone (1988): 1335-1378.
8. Takken, W., and B.G.J. Knols. Odor-Mediated Behavior of Afrotropical Malaria Mosquitoes. *Annu. Rev. of Entom.* 44 (1999): 131-157.
9. Woolhouse, M.E., et al. Heterogeneities in the Transmission of Infectious Agents: Implications for the Design of Control Programs. *Proc. Natl. Acad. Sci. U.S.A.* 94, 1 (1997): 338-342.
10. Dietz, K. Mathematical Models for Transmission and Control of Malaria. In Wernsdorfer, W., and I. McGregor (Eds.). *Malaria: Principles and Practice of Malariology* (2nd ed.). New York: Churchill Livingstone (1988): 1091-1133.
11. Smith, D.L., et al. Revisiting the Basic Reproductive Number for Malaria and Its Implications for Malaria Control. *PLoS Biol.* 5, 3 (2007): e42.
12. Smith, D.L., et al. The Entomological Inoculation Rate and *Plasmodium falciparum* Infection in African Children. *Nature* 438, 7067 (2005): 492-495.
13. Le Menach, A., et al. An Elaborated Feeding Cycle Model for Reductions in Vectorial Capacity of Night-Biting Mosquitoes by Insecticide-Treated Nets. *Malar. J.* 6 (2007): 10.
14. Killeen, G.F., et al. Preventing Childhood Malaria in Africa by Protecting Adults from Mosquitoes with Insecticide-Treated Nets. *PLoS Med.* 4, 7 (2007): e229.
15. Killeen, G. F., et al. Advantages of Larval Control for African Malaria Vectors: Low Mobility and Behavioural Responsiveness of Immature Mosquito Stages Allow High Effective Coverage. *Malar. J.* 1 (2002): 8.
16. Okell, L.C., et al. Modelling the Impact of Artemisinin Combination Therapy and Long-Acting Treatments on Malaria Transmission Intensity. *PLoS Med.* 5, 11 (2008): e226; discussion e226.
17. Koella, J.C. On the Use of Mathematical Models of Malaria Transmission. *Acta Trop.* 49, 1 (1991): 1-25.
18. Woolhouse, M.E., et al. Heterogeneities in the Transmission of Infectious Agents: Implications for the Design of Control Programs. *Proc. Natl. Acad. Sci. U.S.A.* 94, 1 (1997): 338-342.
19. Smith, T., et al. Mathematical Modeling of the Impact of Malaria Vaccines on the Clinical Epidemiology and Natural History of *Plasmodium falciparum* Malaria: Overview. *Am. J. Trop. Med. Hyg.* 75, 2 (Suppl.) (2006): 1-10.
20. Aguas, R., et al. Prospects for Malaria Eradication in Sub-Saharan Africa. *PLoS ONE* 3, 3 (2008): e1767.
21. The Malaria Atlas Project (http://www.map.ox.ac.uk) has assembled more than 12,000 estimates of *P. falciparum* PR into a database for the purposes of mapping malaria.