Shrinking the Malaria Map

A Prospectus on Malaria Elimination

Edited by
Richard G.A. Feachem,
Allison A. Phillips,
and Geoffrey A. Targett
On Behalf of
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The Global Health Group
UCSF Global Health Sciences

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PREFACE

Malaria is responsible for 250–500 million cases and nearly 1 million deaths per year, imposing an enormous burden of suffering on too many lives in tropical regions of the world. The Global Malaria Eradication Program (1955–1969) achieved considerable success in removing the threat of malaria from about a billion people but, for much-discussed reasons, the program could not be sustained and stopped well short of its goal. We are again encouraged by recent and significant progress in "shrinking the malaria map," with many countries dedicating resources and making great efforts toward releasing their nations from the threat of malaria. This evolution has been linked in part to a substantial increase in investment in tackling malaria globally, leading to development of much-improved means of treatment and control and in the ability to make these available where they are most needed.

An overarching strategy has been developed to exploit this major new initiative. The new strategy, defined in the Roll Back Malaria Global Malaria Action Plan, has three parts to it:

1. **To strengthen the aggressive control of malaria in its heartland**
   This should happen in the 61 highly endemic countries where the most deaths and disease occur. This is the part of the overall strategy on which most investment must continue to be focused.
2. **To shrink the malaria map from the endemic margins inward**
   By achieving elimination, countries will, in addition to gaining the intrinsic benefits of that success, continue the global strategy that has occurred de facto since the early 20th century—spatially progressive elimination.

3. **To continue researching and developing new tools** New tools, such as improved drugs, diagnostics, insecticides, and eventually a vaccine, are essential to the success of ongoing and future elimination efforts. Looking forward, and using the lessons from malaria history of the past 50 years, many of the interventions that work at present will need to be replaced because they will inevitably become less effective over time.

In order for the ultimate goal of eradication to be achieved, all three components of this strategy must proceed simultaneously.

The Malaria Elimination Group (MEG) was convened in late 2007 by the Global Health Group at the University of California, San Francisco, to support the relatively neglected second part of the strategy. The MEG plays a supportive role to countries that are embarked on the path to elimination of malaria or are considering whether or not elimination is a viable option for them.

The MEG is an international multidisciplinary group that has taken on the task of identifying and providing informed discussion on the substantial questions of whether, when, and how to eliminate malaria. Strategic planning and feasibility, the operational and technical challenges of reducing transmission to zero, importation risk, outbreak risk, and cross-border transmission—all of these considerations and risks, as well as others, need to be carefully evaluated by countries pursuing or contemplating elimination.

A Prospectus on Malaria Elimination aims to provide practical advice that can guide countries in thinking through their decisions on whether, when, and how to eliminate malaria. It is prepared for key stakeholders who work on the front lines of elimination, and for those who provide technical insight to governments, donors, and potential investors. The *Prospectus* is not prescriptive, because the specific decisions surrounding the direction that the malaria program should follow must be made in each country, with the context carefully taken into consideration. The *Prospectus* does, however, outline a strategic vision and serves to inform the decision-making process by providing a range of considerations that a country must evaluate in context before, during, and after the elimination decision. A companion document to the *Prospectus* has also been published by the Global Health Group at the University of California, San Francisco: *A Guide on Malaria Elimination for Policy Makers,* written by Sir Richard Feachem and the Malaria Elimination Group.

The majority of the authors of the *Prospectus* are members of the MEG. Authors of specific chapters were chosen for their expertise in particular areas relevant to an elimination program; some outside expertise was drawn from

as needed. Authors collaborated as small working groups, reflecting upon the rich history of malaria elimination and eradication while brainstorming new ideas based on their knowledge of opportunities presented and challenges to be expected. As a group, the MEG discussed and debated the first draft of the *Prospectus* in October 2008 and reviewed the final draft remotely.

The *Prospectus* is a living document and will undergo periodic updates and supplements. The *Prospectus* is available on the Web (www.malariaelimination group.org) and in hard copy. It is the first part of a much larger MEG agenda that will provide more extensive data and updates on the progress of elimination, accomplished by using new data or through dialogue with countries as they plan to carry out their elimination progams. Case studies on countries that have achieved elimination or are implementing an elimination strategy are in progress, and these will help inform the elimination agenda and will lead to additional improvements and updates to the *Prospectus*. We encourage all those working on the front lines of elimination to comment on and contribute to this evolving work through a forum available on the MEG Web site (www.malariaeliminationgroup.org).

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San Francisco
April 2009

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In conclusion, the editors and authors acknowledge our many partners, too numerous to mention by name, in the malaria elimination focus countries, who strive to turn the ambition behind this initiative into a reality.

EXECUTIVE SUMMARY

Thirty-nine countries across the world are making progress toward malaria elimination. Some are committed to nationwide elimination, while others are pursuing spatially progressive elimination within their borders. Influential donor and multilateral organizations are supporting their goals of achieving malaria-free status.

With elimination back on the global agenda, countries face a myriad of questions. Should they change their programs to eliminate rather than control malaria? What tools are available? What policies need to be put into place? How will they benefit from elimination? Unfortunately, answers to these questions, and resources for agencies and country program managers considering or pursuing elimination, are scarce.

The 39 eliminating countries are all positioned along the endemic margins of the disease, yet they naturally experience a variety of country characteristics and epidemiologies that make their malaria situations different from one another. The Malaria Elimination Group (MEG) and this *Prospectus* recognize that there is no single solution, strategy, or time line that will be appropriate for every country, and each is encouraged to initiate a comprehensive evaluation of its readiness and strategy for elimination. The *Prospectus* is designed to guide countries in conducting these assessments.

The *Prospectus* provides detailed and informed discussion on the practical means of achieving and sustaining zero transmission. It is designed as a road map, providing direction and options from which to choose an appropriate path. As on all maps, the destination is clearly marked, but the possible routes to reach it are numerous.

The *Prospectus* is divided into two sections:

Section 1 Eliminating Malaria, comprises four chapters covering the strategic components important to the periods before, during, and after an elimination program.

Section 2 Tools for the Job, comprises six chapters that outline basic information about how interventions in an elimination program will be different from those in a control setting.

Chapter 1, **Making the Decision**, evaluates the issues that a country should consider when deciding whether or not to eliminate malaria. The chapter begins with a discussion about the quantitative and qualitative benefits that a country could expect from eliminating malaria and then recommends a thorough feasibility assessment. The feasibility assessment is based on three major components: operational, technical, and financial feasibility. Cross-border and regional collaboration is a key subject in the chapter.

Chapter 2, **Getting to Zero**, describes changes that programs must consider when moving from sustained control to an elimination goal. The key strategic issues that must be addressed are considered, including supply chains, surveillance systems, intersectoral collaboration, political will, and legislative framework. Cross-border collaboration is again a key component in **Getting to Zero**.

Chapter 3, **Holding the Line**, provides recommendations on how to conduct an assessment of two key factors that will affect preventing the reemergence of malaria once transmission is interrupted: outbreak risk and importation risk. The chapter emphasizes the need for a strong surveillance system in order to prevent and, if necessary, respond to imported cases.

Chapter 4, **Financing Elimination**, reviews the cost-effectiveness of elimination as compared with sustained control and then presents the costs of selected elimination programs as examples. It evaluates four innovative financing mechanisms that must support elimination, emphasizing the need for predictable and stable financing. Case studies from Swaziland and two provinces in China are provided.

Chapter 5, **Understanding Malaria**, considers malaria from the point of view of elimination and provides a concise overview of the current burden of the disease, malaria transmission, and the available interventions that can be used in an elimination program.

Chapter 6, **Learning from History**, extracts important lessons from the Global Malaria Eradication Program and analyzes some elimination efforts that were successful and some that were unsuccessful. The chapter also reviews how the malaria map has been shrinking since 1900.

Chapter 7, **Measuring Malaria for Elimination**, provides a precise language for discussing malaria and gives the elimination discussion a quantitative structure. The chapter also describes the role of epidemiological theory and mathematical modeling in defining and updating an elimination agenda for malaria.

Chapter 8, **Killing the Parasite**, outlines the importance of case detection and management in an elimination setting. Options for diagnosis, the hidden challenge of *Plasmodium vivax* in an elimination setting, and the impact of immunity are all discussed.

Chapter 9, **Suppressing the Vector**, explores vector control, a necessary element of any malaria program. It considers optimal methods available to interrupt transmission and discusses potential changes, such as insecticide resistance, that may affect elimination efforts.

Chapter 10, **Identifying the Gaps—What We Need to Know**, reviews the gaps in our understanding of what is required for elimination. The chapter outlines a short-term research agenda with a focus on the operational needs that countries are facing today.

The *Prospectus* reviews the operational, technical, and financial feasibility for those working on the front lines and considers whether, when, and how to eliminate malaria. A companion document, *A Guide on Malaria Elimination for Policy Makers,* is provided for those countries or agencies whose responsibility is primarily to make the policy decisions on whether to pursue or support a malaria elimination strategy. The *Guide* is available at www.malariaeliminationgroup.org.

KEY DEFINITIONS

Malaria **Elimination** is:

The interruption of local mosquito-borne malaria transmission in a defined geographical area, creating a zero incidence of locally contracted cases. Imported cases will continue to occur and continued intervention measures are required.

Malaria **Eradication** is:

The permanent reduction to zero of the worldwide incidence of malaria infection.

DEFINITIONS BY THE WORLD HEALTH ORGANIZATION

Importation Risk (also known as vulnerability) is:

The probability of malaria reintroduction based on an area's proximity to other malarious areas and the movement of infected humans or infected Anopheles mosquitoes.

Outbreak Risk (also known as receptivity) is:

A measure of the potential of an area or focus to allow transmission to occur, or once elimination has been achieved, the propensity for reintroduced malaria to give rise to malaria outbreaks.

DEFINITIONS BY THE MALARIA ELIMINATION GROUP

1 | MAKING THE DECISION

Bruno Moonen,[a] Scott Barrett,[b] Jim Tulloch,[c] and Dean T. Jamison[d]

1.1 | Introduction

Malaria elimination, according to the WHO definition, is "the interruption of local mosquito-borne malaria transmission in a defined geographical area," which implies that imported cases may occur and that continued interventions will be required after elimination has been achieved.[1] For the MEG, a "defined geographical area" does not necessarily imply national boundaries, as the epidemiological zones where malaria elimination might be feasible from a technical perspective do not always follow administrative borders.

The MEG global strategy for malaria elimination, as set out in this *Prospectus*, encourages countries at the current global boundaries of malaria transmission, and countries that benefit from other geographical characteristics that favor elimination (for example islands), to explore the option of pursuing an elimination strategy.[2] Depending on the malaria epidemiology within the country or region, countries may want to target specific zones at the subnational level or participate in wider regional initiatives, including cross-border collaborations toward elimination. This chapter identifies considerations that countries may wish to take into account as they address the elimination decision.

THE ELIMINATION UNIT

As shown in Figure 1.1, there are currently 39 countries that are either planning for elimination or already in the pre-elimination or elimination phase.[3-10] These

[a]Clinton Foundation, Nairobi, Kenya; [b]School of Advanced International Studies, Johns Hopkins University, Washington, DC, USA; [c]Australian Agency for International Development, Canberra, Australia; [d]Institute for Health Metrics and Evaluation, University of Washington, Seattle, USA

BOX 1.1 | Main Messages

The Malaria Elimination Group (MEG) makes the following recommendations:

- All countries unsure about the appropriateness and timing of moving to an elimination program should conduct a rigorous and structured feasibility assessment, taking into account technical, operational, and financial feasibility.
- Mathematical modeling of outbreak risk and importation risk is an integral part of the methodology to assess technical feasibility. When both are estimated to be low, countries should seriously consider elimination. From a technical point of view, elimination should not only be assessed on a regional or country level but, rather, be based on ecological zones and their malaria epidemiological contexts.
- The assessment of operational feasibility takes into account the commitments a government can or is willing to make to fulfill the necessary programmatic requirements and to create an enabling environment to facilitate the elimination process.
- Donors and governments interested in elimination need to rethink financing and probably adopt new financial mechanisms. Financial feasibility requires institutional change as well as long-term and reliable monetary resources.
- Countries should pursue a multinational elimination target based on epidemiological factors rather than arbitrary national borders. Regional and/or international bodies should not only provide the institutional structure to encourage and assist in achieving this goal but also financially reward countries that adopt and contribute to achieving regional and global targets.
- The importance of benefits such as expected reduction in morbidity and mortality, a better climate for foreign direct investment, satisfaction resulting from a national accomplishment, and the fact that elimination is potentially a cost-reducing investment should be factored into the overall judgment about whether to commence explicit elimination efforts.

The MEG, while supporting ambitious future strategic thinking, also places high value on honest feasibility assessments and rigorous operational planning. These key elements, in combination with novel approaches to guarantee sustainable financing, will determine the success of any elimination effort. The MEG also strongly supports the idea that broad regional targets and collaborations are often the most effective approach to cross-border challenges.

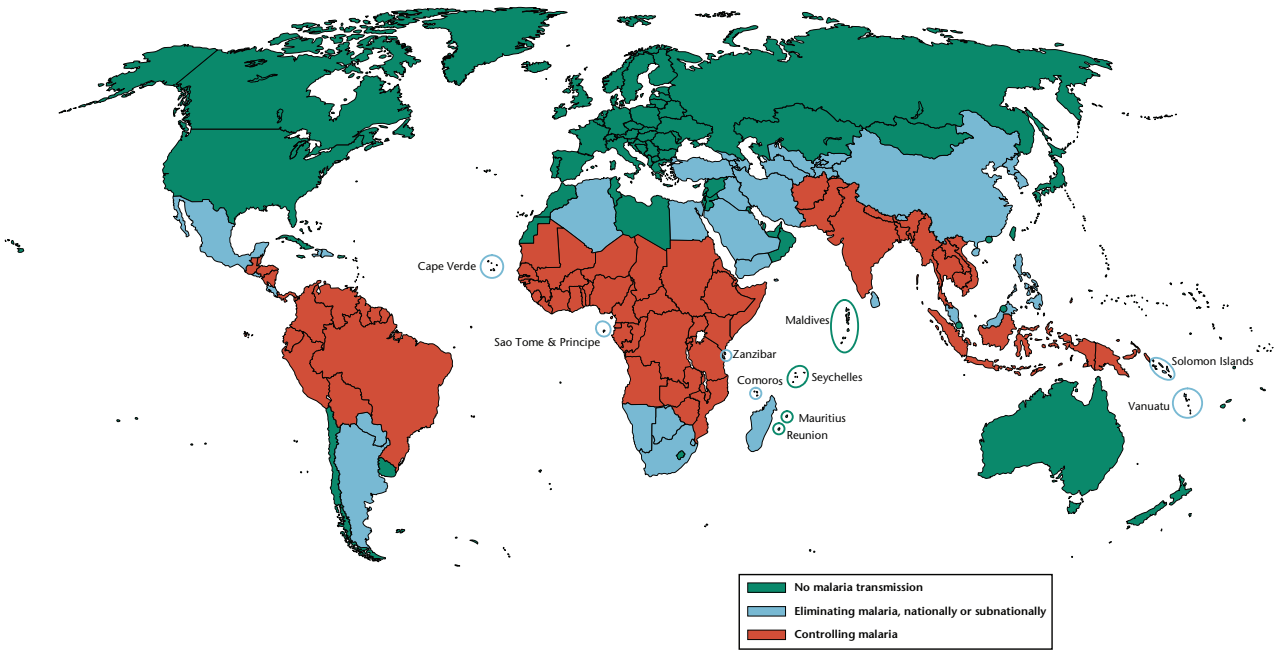

FIGURE 1.1 | Malaria freedom, elimination, and control, by country, 2009

countries—for example, Algeria, Botswana, and Mexico—lie on the fringes of areas of malaria transmission. Over time, when such fringe countries have achieved elimination, neighboring countries—including in this example Niger, Zambia, and Guatemala, respectively—will find themselves on the boundaries of areas of transmission, and they will de facto be faced with the decision of whether or not to pursue the same goal, either for their border areas or for the whole country. Figure 1.1 shows that countries in large parts of Eurasia, Asia, and South America, as well as island countries from the Caribbean, Africa, and Oceania, have made the decision to go for elimination.

While it is countries that typically embark on malaria elimination and are eventually certified by WHO as malaria free, there are important subnational and supranational components to this effort. Countries can choose to pursue malaria elimination in limited areas pending a move toward a nationwide effort to eliminate. For example, a country composed of many islands, such as Vanuatu or the Solomon Islands, may undertake spatially progressive elimination by pursuing elimination island by island. Similarly, large countries, such as China, India, and Indonesia, may focus initially on malaria elimination in certain states and provinces before launching national elimination efforts.

THE ELIMINATION DECISION

The decision to begin the elimination process is complex and should not be made lightly, as the consequences of failure can be discouraging and costly. A premature elimination target can lead to false expectations and may be followed by resurgence of malaria, damaged credibility because of the failure to achieve expected results, and consequent erosion of national and international support. At the same time, excessively conservative control targets can carry similar risks in that populations, governments, and donors may eventually tire of ongoing activity despite low disease risk. For some countries, political interest in and consensus on the feasibility of achieving and sustaining zero transmission will be strong enough initially so that the decision can be made with little analysis. This has been the case with some countries that have adopted elimination in recent years. With other countries, a more rigorous and evidence-based decision-making process will be needed. In line with previous and current WHO guidelines, the MEG recommends that countries unsure about an elimination program (subnational, national, or regional) should undertake a rigorous and structured study. The appropriateness and timing and the technical, operational, and financial feasibility of moving toward or participating in a program should be considered. Before a discussion of these issues takes place, some background is provided here on the potential economic (and other) benefits to a country of moving from a high degree of control to elimination.

1.2 Potential Benefits of Elimination

Successful, sustained elimination can yield substantial benefits for a country. These benefits range from the reduced burden of malaria and its sequelae, such as anemia, to the corresponding increase in educational attainment[11] and productivity in the population, to the potential stimulation of the tourist industry and greater foreign direct investment.

Eliminating malaria from a country requires current investment; the returns are realized later. These returns can come in one or both of two forms. First, elimination may simply be less costly than sustained control in the long run. Second, even if the long-term costs of elimination exceed those of sustained control, the ultimate benefits may still exceed the costs. A brief history of the economic consequences of attempts to eliminate other diseases may provide insight before the benefits and costs of malaria elimination are considered.

ECONOMIC CONSEQUENCES OF ELIMINATING OTHER DISEASES

A review of the economic effects of disease elimination naturally begins with smallpox, which was globally eradicated in 1979. This is compared with the very different situation with measles. Table 1.1 addresses smallpox and measles, as well as the ongoing elimination/eradication programs for polio, Guinea worm, and river blindness.

Before the smallpox eradication campaign began, many countries had already unilaterally eliminated smallpox within their borders. Elimination by individual countries served as an indicator that eradication might be feasible. Eradication yielded specific dividends—removing the need to vaccinate, as well as the absence of risk of any future infections. This expectation of high benefits was met by the extremely high benefit-cost ratios, which were estimated later. It was possibly the greatest single public investment the world had ever made.[12] The key to the success of this investment was that smallpox eradication benefited the world, as well as every country. Yet, the effort almost did not succeed; its greatest challenge was international financing.[12]

The economics of malaria eradication differs from that of smallpox because in the latter case, every country had to vaccinate to a critical and even level everywhere (80%). Malaria has an ecological basis, and because of this the steps needed to eliminate malaria vary substantially from country to country. In this way, feasibility is inherently different between the two diseases, suggesting the desirability of the MEG's strategy to eliminate first in less-challenging countries on the endemic margins of malaria.

Measles has recently been eliminated in the Americas and in Asia; in other places, the number of cases has declined dramatically because of increased control. The benefit-cost ratio shown in Table 1.1 is small compared with smallpox eradication, partly because measles has a low mortality rate in resource-rich countries. It is also because, as yet, there is no dividend analogous to the cessation of vaccination that followed smallpox eradication. Because measles is highly infectious, sustaining elimination in the face of a substantial risk of reintroduction requires that countries maintain very high levels of immunization coverage. As we shall see, in countries technically well positioned for an elimination effort for malaria, there may be more economic similarity to smallpox eradication than to measles elimination, despite the differences outlined above.

ELIMINATION AS A COST-REDUCING INVESTMENT

Before we conduct an analysis of malaria elimination relative to sustained control in a country, we need cost and epidemiological data, including estimates of

the inherent potential within a country to spread malaria (outbreak risk) and its risk of new infections from abroad (importation risk). If epidemiological and cost assessments are sufficiently favorable, elimination may prove to be a cost-reducing investment.

On the cost side, we first need to obtain the baseline costs of sustained control. Next, we need information about the most efficient combination of interventions that can eliminate malaria and about what that combination will cost. Ideally, we will have not just a point estimate but also an understanding of how costs vary with the level of control. The costs of approaching elimination are likely to be high in countries with a high importation risk or high outbreak risk. Elimination may not be economical in these countries, even if it is deemed technically feasible.

Finally, we need data on the costs of sustaining elimination after it has been achieved. As noted previously, for measles the marginal costs of achieving and sustaining elimination are the same. In both elimination and prevention of reintroduction, population immunity must be kept at the critical level through continued immunization. For malaria, it is possible that the measures needed to sustain elimination will be different from the measures that were used to achieve elimination. If the costs of sustaining elimination are lower than the costs of sustaining control, there will be an investment dimension to elimination.

The first step in an economic analysis of malaria elimination is to explore whether elimination could be a cost-reducing investment. Current historical information is highly limited for all three types of cost—sustaining control, pushing toward elimination, and sustaining elimination. Careful empirical case studies would provide much firmer guidance than is now possible about the circumstances that are likely to make elimination ultimately cost reducing. That said, cost analyses have been undertaken for a number of regions contemplating elimination, and these studies give an idea of the range of costs that might be expected. To take one example (which Chapter 4 further discusses, along with several others), our analyses suggest that Hainan Island, China, is now spending about $2.9 million per year to sustain a high level of control. The estimated cost of a push to elimination would be about twice as high annually for approximately 5 years. After transmission interruption, the estimated cost of holding the line would be about $1.6 million a year—substantially less than is now being spent. The 5-year investment period ultimately yields cost savings. For Swaziland, however, planning estimates point to the likelihood that sustaining elimination is likely to result in a permanent increase in costs. This increase can be justified by the benefits if their magnitude is sufficient.

Table 1.1 | Economic studies of the elimination of selected diseases

Disease	Target	Status	Economics
Smallpox	The goal of eradication was declared by the World Health Assembly (WHA) in 1959.	The last endemic case was in 1977; smallpox was declared eradicated in 1979.	The benefits-costs ratio for global expenditure was 159:1; for international financing, 483:1.[13]
Measles	WHO Americas agreed to eliminate by 2000; WHO Europe by 2007; WHO Eastern Mediterranean by 2010.	It was eliminated in the United States in 2000 and in the Americas in 2002. Imports occur regularly.	Pelletier et al.[14] show that, for Canada, moving from a one-dose to a two-dose immunization program to eliminate measles yields a benefits-costs ratio between 2.6 and 4.3.
Guinea worm (dracunculiasis)	The goal of eradication was established by the Centers for Disease Control in 1980 and later reinforced by several WHA resolutions.	It was eliminated from 11 countries, including all of South Asia. It remained endemic in 9 sub-Saharan African countries at the end of 2006.	Kim et al. estimate a positive net present value,[15] implying benefits > costs; but see Miller et al.[16]
Poliomyelitis	The goal of eradication was declared by the WHA in 1988.	Wild poliovirus type 2 has not been detected since 1999. The other two wild viruses are endemic in 4 countries (Afghanistan, India, Nigeria, and Pakistan), down from 125.	Barrett and Hoel[12] showed that benefits > costs.[17] However, these analyses assume that eradication is certain to occur and that vaccination can cease post-eradication.
River blindness (onchocerciasis)	Two regional control programs, OCP and APOC, are in sub-Saharan Africa. WHO Americas pledged to eliminate onchocerciasis by 2007.	As of 2007, no new cases of blindness in the Americas have been due to onchocerciasis. Control efforts are successful in sub-Saharan Africa, but elimination has not been achieved.	Analysis shows benefits > costs for the OCP[18] and APOC.[19]

OTHER BENEFITS OF MALARIA ELIMINATION

Beyond the potential for cost reduction, there are other benefits of elimination efforts, notably, marked reductions in morbidity and mortality, an improved climate for tourism and foreign direct investment, and the satisfaction of a national accomplishment. These benefits may sometimes be of quantitative significance, but others are likely to prove difficult to measure. Even so, a judgment concerning their importance should be factored into the overall decision about whether to commence explicit elimination efforts.

In addition to the benefits within the country of achieving elimination,

there are international effects that may be important. Neighboring countries will no longer need to worry about importing cases from the eliminating country. The world as a whole will have taken a step toward the global public good of eradication, and many will have learned something from each country's experience. And, finally, the country will no longer be a source of potential resistance to antimalarial drugs, which will benefit all countries.

EQUITY IMPACT

Every member of a country remaining at risk of malaria will benefit from malaria elimination. One consideration relevant to the decision of whether to eliminate is the equity consideration: will disadvantaged members of society share fully in the benefits of the program? Economists and others regularly conduct "benefit-incidence" analyses to ascertain which portions of a population benefit from a particular public sector program. Typically, but far from uniformly, programs favor the better-off. In the Philippines in 1998, for example, immunization coverage was about 75% overall, but in the poorest quintile, coverage was only about 50%. Given this starting situation, moving from 75% to universal coverage would differentially benefit the poor. It is plausibly similar with malaria elimination: because control efforts are likely to have first reached the better off and more engaged populations, elimination programs will, by reaching remaining segments of the population, almost surely prove to be equity enhancing.

In conclusion, our analyses point to the importance of considering the investment potential when elimination's initial costs are counterbalanced by a situation in which maintaining elimination is less costly than sustaining high levels of control. The possibility of such a situation is suggested by our analyses for Hainan Island; a country's actual importation and outbreak risks will determine the reality. Additionally, but harder to measure, elimination will improve a country's environment for tourism and foreign direct investment. The experience of malaria elimination in the United States and polio elimination in South America suggests that, if properly undertaken, these programs can contribute to overall health system strengthening. Finally, there is strong reason to believe that malaria elimination programs will enhance equity by principally serving disadvantaged subpopulations. These conclusions must be viewed with the caveat that the evidence available at this time is limited. It is important that malaria elimination efforts gather data as they progress so the economics of elmination can be reassessed on an ongoing basis.

1.3 The Feasibility Assessment

TECHNICAL FEASIBILITY

According to WHO, elimination is technically feasible if it has been demonstrated in a similar eco-epidemiological setting in the recent past.[1] For the moment, this excludes, de facto, the whole of sub-Saharan Africa, where elimination has not been achieved recently. Pampana (1969) defined technical feasibility as "evidence that conditions in a country are such that a particular technique . . . will succeed in an acceptable period of time and that, once obtained, absence of transmission could be maintained."[20] The MEG further defines technical feasibility as the probability that malaria transmission can be reduced to zero in a given area using the currently available tools and that elimination can be maintained in that area. Achieving elimination thus depends on the effectiveness of the control tools used, which is influenced by the strength of transmission in a given area. Maintaining zero not only depends on the local strength of transmission but also on the probability that an infected person or mosquito does not reintroduce malaria into the area. The technical feasibility of maintaining elimination in a given area depends on the following:

- the malaria transmission potential of that area, or outbreak risk (receptivity)
- the likelihood that malaria will be reintroduced once elimination has been achieved, or importation risk (vulnerability)

Recent efforts to quantify both outbreak and importation risks are discussed in Chapter 7. Although there are no definite criteria for establishing the exact levels for both variables,[1] mathematical modeling should be an integral part of the methodology used to assess technical feasibility.

Modeling of outbreak risk is important for the elimination decision because the actual transmission levels at which countries should begin elimination efforts may vary significantly. Zanzibar, before 2000, was considered to be moderately to highly endemic and therefore not a country that, according to WHO guidelines, should aim for elimination. However, it achieved such levels of control that it recently decided to assess the feasibility of malaria elimination on the islands. Even though they had not reached the recommended WHO milestone of a slide positivity rate (SPR) of less than 5%,[1] the modeling of their outbreak risk demonstrated that elimination would be technically feasible in the next 6 to 10 years (David Smith, University of Florida, personal communication, February 2009).

Mathematical modeling of importation risk not only will quantify the risk of

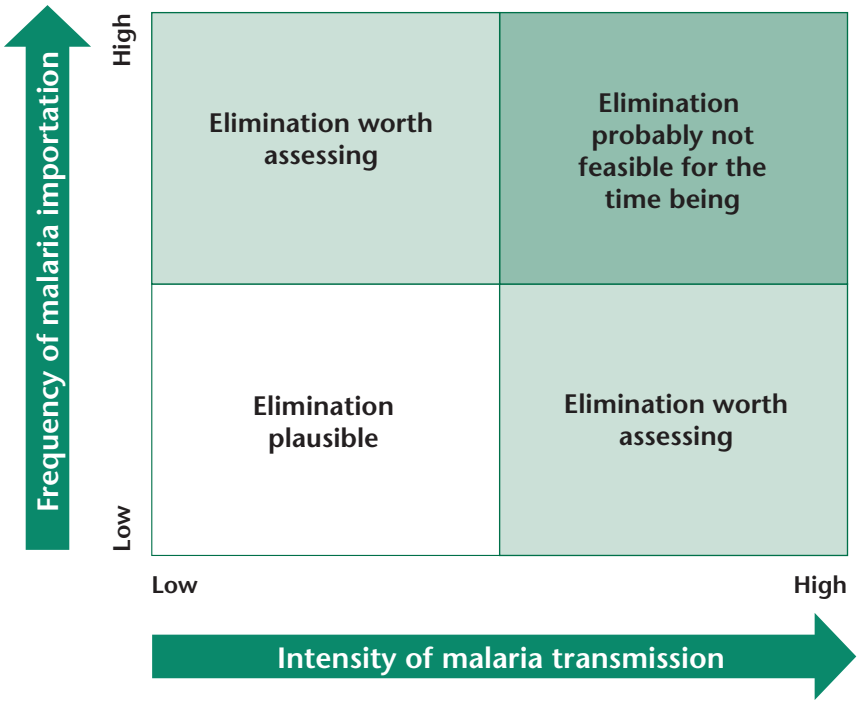

FIGURE 1.2 | Some factors determining technical feasibility

reintroduction but also might identify specific groups that need to be targeted with surveillance to avoid reintroduction of malaria. It will also provide the necessary arguments to convince governments, regional bodies, and donors of the importance of cross-border operations such as the Lubombo Spatial Development Initiative (LSDI) in Mozambique, South Africa, and Swaziland. Modeling outbreak and importation risks provides a more quantitative basis on which to determine technical feasibility, to complement WHO's qualitative definition of "proof in a similar eco-epidemiological setting."[1]

The decision to eliminate malaria is ultimately determined by its technical feasibility. If assessment of this feasibility concludes that technically it is unlikely that malaria can be eliminated, further evaluations of operational and financial feasibility become unnecessary. As illustrated in Figure 1.2, the concepts of outbreak and importation risk can help countries to grasp the technical feasibility even before rigorous evaluations are finalized.

When both factors are deemed to be high, as in Nigeria, the elimination decision should most probably be postponed. Instead, countries with high importation risk and high outbreak risk should scale up their malaria control for impact, both to reduce burden and to make it possible for themselves and

their neighbors to eventually move toward elimination. If the importation risk is low but outbreak risk high, as in certain island settings, feasibility will mainly depend on the country's ability to maintain high levels of control, reduce the vector capacity, provide prompt and effective treatment, and rapidly respond to detected cases. If a country's outbreak risk is considered to be low but importation risk is high because of population movements from endemic countries, elimination will only be possible if a near-perfect surveillance system detects all imported cases immediately. An example is in Bhutan, where 77% of all malaria cases originate from three districts located on its southern border with India.[21] Thailand provides a similar example of a country with high importation risk, where a vast majority of cases are imported from neighboring countries that do not have as strong malaria control measures. Both examples demonstrate that malaria is a regional issue. When both outbreak and importation risks are low, countries should seriously consider elimination.

OPERATIONAL FEASIBILITY

Historically, operational feasibility was subdivided into administrative and practical feasibility. Administrative feasibility was defined as "the possibility to create a national organization that can carry out a malaria elimination program with a strong long-term governmental commitment, a conducive legal environment for malaria elimination control activities especially spraying and surveillance, and the availability of sufficient funds." Practical feasibility meant "countrywide access for personnel and materials, sufficient human resources for the malaria control program and the health facilities, and cooperation of the general public."[22] Given the importance of financial feasibility, the MEG proposes that it should be considered separately, and operational feasibility should focus on requirements related to the implementation of all activities needed to achieve and maintain elimination. The operational feasibility component thus tries to answer the questions around if and how the interventions needed to achieve and sustain elimination can be implemented given the capacity of the national malaria program and the health system. Unlike technical feasibility, which is defined by the malaria epidemiology in a given area that does not necessarily follow administrative borders, operational (and financial) feasibility can only be addressed using defined regional, national, or subnational units. While technical feasibility is paramount in the decision to go for elimination or not, operational feasibility is much more dependent on whether a government can or is willing to meet the necessary programmatic requirements and to create an enabling environment to facilitate the elimina-

tion process. If elimination is deemed technically feasible and the financial means and political will are available, almost anything can be done.

It is prudent to note that a variety of operational shortcomings were an important part of the failure of the Global Malaria Eradication Program, even when political commitment and financial means were available.[20] Key operational issues related to "getting to zero" and "holding the line" are therefore discussed in detail in the later chapters. When assessing the different aspects of operational feasibility, it is important to keep two main questions in mind:

1. What activities are essential, and for how long, to achieve and maintain elimination?
2. How are these activities different from "sustained control"?

Operational feasibility is extremely context dependent, but the following operational requirements can be considered universal components for any malaria elimination program:

- A health system that is capable of providing near-universal access to high-quality diagnosis and treatment—access and quality are important in order to guarantee sufficient coverage and specificity for passive case detection. This can be achieved through both the private and public sector and, as discussed in the following chapter, might be possible even when the health system is not yet fully developed. In addition, this will require sufficient capacity, both managerial and technical, at the central or district levels.
- The capacity to implement a near-perfect surveillance system; to design and run an effective information, education, and communication program; and to establish a monitoring and evaluation (M&E) system for measuring elimination-specific targets—the delivery of these key interventions is discussed in detail in the two following chapters. They are not unique to an elimination program but require either a higher level of perfection in their execution or a shift in focus or methods, which necessitates a careful evaluation of the operational implications.
- An enabling environment with political stability, genuine political buy-in and support, a legal framework adapted to the operational needs of elimination, good collaboration between the different sectors involved (e.g., immigration, education, and agriculture), community participation, and cross-border collaboration—all are important, but political stability can be considered an absolute.

> Political support has to reach beyond high-level, politically motivated declarations, and it requires direct involvement of political leaders to make elimination a matter of national priority and pride. In addition, it is important that malaria elimination be treated as a regional and global public good, with regional initiatives complementing national decision-making. In many ways, the ideal approach for most countries would be to join the pursuit of a multinational elimination target, which defines the scope of a program based on epidemiological factors rather than arbitrary national borders. As such, the MEG supports the idea of broad sub-regional or multi-country targets and collaborations as being the most effective approach to cross-border challenges.

FINANCIAL FEASIBILITY

The efficient administration of any health program requires long-term stability. Providers need to learn their jobs within the system, and patients need to learn when and where to seek care. Stability, in turn, requires adequate levels and continuity of financing. Malaria elimination is no exception. Where then will the required financing come from? The annual amounts involved may reasonably be in the order of $0.25 to $25.00 per person in the population at risk (with the higher end ($25) being substantially more in difficult-to-reach locations [see Chapter 4 for more detail]). For middle-income and upper-income countries (9 of the 39 elimination countries in Table 1.2), domestic public financing can suffice. For the 11 low-income countries and for many of the 19 lower-middle-income countries, external assistance will be required and must be assured. (Low-income countries spend only $6 to $8 per person per year on health through the public sector.)

Beyond the concern for adequacy of financing, malaria elimination requires two additional elements of financial design. First, the country must sustain financing after the disease has ceased to exist in the population and has therefore lost political salience. Second, cross-border transmission will often call for international financing. The magnitude of the need for cross-border financial arrangements will increase with the country's importation risk. Chapter 4 proposes mechanisms to sustain financing after transmission in a country has ceased. These mechanisms include long-term loans or grants, earmarked taxes, and where feasible, creation of endowments. International financing can come from a relatively rich eliminating country to a poorer, malarious neighboring country. More typically, international financing will involve support by bilat-

TABLE 1.2 | Demographic, economic, health, and aid characteristics of the 39 elimination countries[1]

Country	Population (millions)	Life expectancy at birth (years)	GNI per capita (U.S. $)[2]	Health expenditure per capita (U.S. $)[2]	Private health expenditure (% of total health expenditure)	GFATM[3] R9 malaria eligibility (Y/N)	PMI[4] selected (Y/N)	World Bank IDA[5] eligible (Y/N)
LOW-INCOME ECONOMIES								
Comoros	0.6	65	650	14	47	Y	N	Y
Haiti	9.6	61	420	28	69	Y	N	Y
Korea (North)	23.7	66	—	14	14	Y	N	N
Kyrgyz Republic	5.2	66	450	29	60	Y	N	Y
Madagascar	19.7	59	290	9	38	Y	Y	Y
Sao Tome and Principe	0.2	61	800	49	15	Y	Y[6]	Y
Solomon Islands	0.5	67	630	28	8	Y	N	Y
Tajikistan	6.7	64	330	18	77	Y	N	Y
Uzbekistan	26.9	68	530	26	52	Y	N	Y
Yemen	22.4	61	650	39	58	Y	N	Y
Zanzibar[7]	1.0	43	340	17[8]	43[8]	Y	Y	Y
LOWER-MIDDLE-INCOME ECONOMIES								
Algeria	33.9	71	2,720	108	25	Y	N	N
Armenia	3.0	69	1,470	88	67	Y	N	Y
Azerbaijan	8.6	64	1,260	62	75	Y	N	Y
Bhutan	0.7	64	1,270	52	29	Y	N	Y
Cape Verde	0.5	70	1,980	114	18	Y	N	Y
China	1,320.0	73	1,740	81	61	Y	N	N
Dominican Republic	9.8	70	2,310	197	67	Y	N	N
Egypt	75.5	68	1,270	78	62	Y	N	N
El Salvador	6.9	71	2,530	177	53	Y	N	N
Georgia	4.4	70	1,300	123	80	Y	N	Y
Iran	71.0	71	2,580	212	44	Y	N	N
Iraq	28.5	56	—	—	26	Y	N	N
Namibia	2.1	61	2,950	165	35	Y	N	N
Paraguay	6.1	75	1,230	92	64	Y	N	N
Philippines	87.9	68	1,270	37	63	Y	N	N

TABLE 1.2 | *(continued)*

Country	Population (millions)	Life expectancy at birth (years)	GNI per capita (U.S. $)[2]	Health expenditure per capita (U.S. $)[2]	Private health expenditure (% of total health expenditure)	GFATM[3] R9 malaria eligibility (Y/N)	PMI[4] selected (Y/N)	World Bank IDA[5] eligible (Y/N)
Sri Lanka	19.9	72	1,170	51	54	Y	N	Y
Swaziland	1.1	42	2,210	146	36	Y	N	N
Turkmenistan	5.0	63	1,234	156	33	Y	N	N
Vanuatu	0.2	69	1,580	67	35	Y	N	Y
UPPER-MIDDLE-INCOME ECONOMIES								
Argentina	39.5	75	4,460	484	56	N	N	N
Botswana	1.9	52	5,320	362	36	N	N	N
Costa Rica	4.5	78	4,660	327	24	N	N	N
Malaysia	26.5	72	5,070	222	55	N	N	N
Mexico	105.3	74	7,300	474	54	N	N	N
South Africa	47.6	51	4,810	437	58	N	N	N
Turkey	73.9	73	4,750	383	29	N	N	N
HIGH-INCOME ECONOMIES								
Korea (South)	48.0	79	15,880	973	47	N	N	N
Saudi Arabia	24.2	70	12,540	448	24	N	N	N
Total countries	39							
Total population	2,173,020,000							

1. All data are from standard Web sources provided by the World Bank; World Health Organization; British Broadcasting Corporation; Central Intelligence Agency; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and the Government of Tanzania. Data are from the most recent year available, mostly 2005-2008.
2. Atlas method (U.S. dollars): The Atlas Conversion Factor is used by the World Bank in order to facilitate cross-country comparisons of national income and health expenditure. The method uses the 3-year average of the local currency exchange rate to U.S. dollars, adjusting for inflation.
3. GFATM is the Global Fund to Fight AIDS, Tuberculosis and Malaria. R9 refers to applicant eligibility for Round 9 in 2009.
4. PMI is the President's Malaria Initiative of the U.S. Government.
5. World Bank IDA is the International Development Association.
6. Sao Tome and Principe is not among the PMI 15 focus countries but is receiving support from from the governments of Brazil and the USA for its elimination program.
7. Throughout this document we treat Zanzibar as if it were a country, because its malaria situation and intentions are different from those of mainland Tanzania.
8. These data include both Tanzania and Zanzibar.

eral or multilateral development assistance agencies for regional cross-border elimination projects.

The dynamics of malaria elimination point to the critical need for mechanisms to achieve sustainable international financing. In particular, the following considerations are important:

- After individuals are no longer exposed to the malaria parasite, they progressively lose what immunity they have acquired. The harm to a newly infected infant will be the same pre- and post-elimination. But for an adult who had acquired immunity through repeated exposure, and then lost it during elimination, the risk will be larger should malaria be reintroduced years after elimination. This biological feature of malaria increases the adverse consequences of reintroduction. Therefore, programs to eliminate malaria should ensure they maintain the highest levels of vigilance and the ability to respond.
- Elimination may have implications for drug resistance. According to the Global Malaria Action Plan, "sustained control increases the chances of resistance spreading; achieving elimination removes the risk of resistance."[8] Moving to elimination clearly has a potential role to play in containing resistance, and this has important implications for financial design. If drug resistance is particularly likely to occur in some regions (e.g., Southeast Asia), there is an important global public good associated with elimination. Containing resistance will not only place demands on sustained financing but also require development of appropriate international financial mechanisms.
- Malaria elimination is likely to shift the structures of costs and finances from those of a relatively independent control program to those of a program more fully integrated within a health system. In particular, it is natural to envisage shifts toward integrated vector control activities, multi-disease surveillance programs, and improved clinical management of imported malaria through generally strengthened clinical services. Sustaining the malaria component of these integrated activities may best be done by maintaining separate malaria elimination financing in the context of integrated operations.

In essence, transition to an elimination effort requires rethinking financing and, probably, adoption of new financial mechanisms. Financial feasibility requires institutional change as well as monetary resources. Regional or inter-

national bodies should provide the institutional structure not only to encourage and assist countries in achieving elimination but also to financially reward countries that pursue regional targets.

1.4 Conclusion

The decision to eliminate malaria is complex and should not be made lightly, as the consequences of an ill-informed or wrongly motivated decision can be serious. In the end, it is the role of each government, with local and international guidance as appropriate, to select and weigh the final set of factors that are relevant to its decision. The MEG strongly encourages countries to assess the technical, operational, and financial feasibility of elimination so that policy makers can make an informed choice on whether or not to pursue malaria elimination. Technical feasibility is a prerequisite for elimination, but certain aspects of operational feasibility, such as political stability, are equally important. Financial sustainability for activities aimed at a disease that will become increasingly rare will be a major challenge, and many malaria-endemic countries will most probably need long-term international financial support.

Donors and governments alike therefore need to be informed about the potential substantial benefits that successful and sustained elimination discussed earlier can yield. In that regard, it will be important to consider the investment potential of having elimination's initial costs counterbalanced by a situation in which maintenance of elimination is less costly than sustaining high levels of control.

It is important that malaria elimination be treated as a regional and global public good, with regional initiatives complementing national decision-making. In many ways, the ideal approach for most countries would be to join the pursuit of a multinational elimination target, and the MEG supports the idea of broad regional targets and collaborations as being the most effective approach to cross-border challenges. The MEG encourages countries and regions to be ambitious in their strategic thinking but believes that honest feasibility assessments followed by rigorous operational planning, in combination with novel approaches that guarantee sustainable financing, are key factors that will determine the success of any elimination effort.

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2 | GETTING TO ZERO

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2.1 | Introduction

This chapter considers the actions that must be taken to attain the required level of coverage of a range of essential interventions that are needed to interrupt malaria transmission. Goals that may seem straightforward in the abstract often involve immense logistical and operational challenges when attempted among the complex realities of an elimination program. As such, this chapter is fundamentally about the backbone of successful elimination programs—sound management and strong systems. The experience of the Global Malaria Eradication Program (GMEP) underscores the central role of management and systems in getting to zero. Emilio Pampana, one of the architects of the 1955-1978 eradication program, recognized this need in the principal manual of that era: "In malaria eradication we must prevent the very last case of malaria. There is no such thing as a partial success. . . . Consequently no other public health program needs such a careful and complete planning and such an efficient and smooth running administration."[1]

An examination of the GMEP reveals that it was the inability to meet the onerous management criteria that hindered many programs and was the main

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BOX 2.1 | Main Messages

- Malaria elimination initiatives should be planned and executed in a spatially progressive manner, considering goals at the subnational, national, regional, and supranational levels where appropriate.
- Countries should assess and plan activities and a sound strategy for interrupting transmission and preventing reintroduction prior to embarking on an elimination program.
- Transitions between phases of the malaria program continuum from control to elimination should be based on a range of factors, including political, economic, and epidemiological, not just on epidemiological measures.
- Interventions in malaria elimination programs should be carefully targeted based on identification and analysis of transmission foci.
- Universal diagnosis is critical to elimination and can be effectively achieved through appropriate use of rapid diagnostic tests (RDTs) and microscopy as well as DNA PCR.
- Robust passive case detection is essential to elimination. This should be incorporated into the basic health system as soon as appropriately possible.
- Elimination initiatives should only employ large-scale active case detection interventions after careful analysis of feasibility and cost-effectiveness.
- Cross-border collaboration and regional initiatives should be vigorously pursued. Where cross-border initiatives are developed, there should be clearly defined funding and coordinated implementation.
- Countries should develop a comprehensive strategy for ensuring the sustained commitment and engagement of key stakeholders prior to transitioning to an elimination program.
- Elimination can and should be pursued even if the public health system is not capable of conducting all interventions, if there are other entities able and willing to fulfill those responsibilities.
- Central malaria units should be incorporated into the broader health structure gradually, as opposed to rapid dissolution, after the achievement of elimination, in order to prevent reintroduction.

reason that the program failed to reach its ultimate goal of eradication. In Latin America, for example, stalled progress in the early 1970s was most frequently attributed to "serious administrative and/or operational problems," the code at the time for poor leadership and management, in addition to weak systems and logistics.[2]

While Chapter 1 explores the necessary forethought that contributes to the decision of whether or not it is reasonable to set the goal of eliminating malaria, this chapter evaluates the transition that is required for a program to achieve that goal. We explore a number of essential components and considerations to ensure successful implementation, including the interface with the basic health system and robust surveillance. Last, we discuss the imperative of cross-border collaboration and regional initiatives for both achieving and sustaining malaria elimination in mainland countries.

It is important to keep in mind that the recommendations in this chapter are not fixed or static. What works for one country may not work for another; there is no "one size fits all" approach that will work universally. The GMEP's greatest flaw was attempting to apply a single approach—extensive DDT spraying—across immensely diverse eco-epidemiological, socioeconomic, cultural, and political settings. While lessons can and should be learned from other countries, each program must be designed to fit the unique characteristics of the local environment, tailoring available tools to the specific epidemiological and systems settings. Recommendations in this chapter are intended to guide an elimination program's decision-making process and contribute to their strategy to interrupt transmission.

2.2 | From Control to Elimination

Once a decision to pursue elimination has been made, the program must begin to plan and execute appropriate changes to its strategies and interventions. There is no defined moment when a malaria effort ceases to be a control program and becomes an elimination program. The program continues to pursue many of the same activities, including vector control, case management, and monitoring and evaluation (M&E), and the changes in interventions are subtle, with shifts in the emphasis, intensity, and targeting of certain key interventions.

WHO has provided a guideline (Figure 2.1) to assist countries in defining and planning the sequence of changes in the transition from control to elimination.[3] As shown, it recommends that countries engage first in a "pre-elimination" phase, in which initial shifts in emphasis and capacity are made, before pursuing complete interruption of transmission. The decision to engage

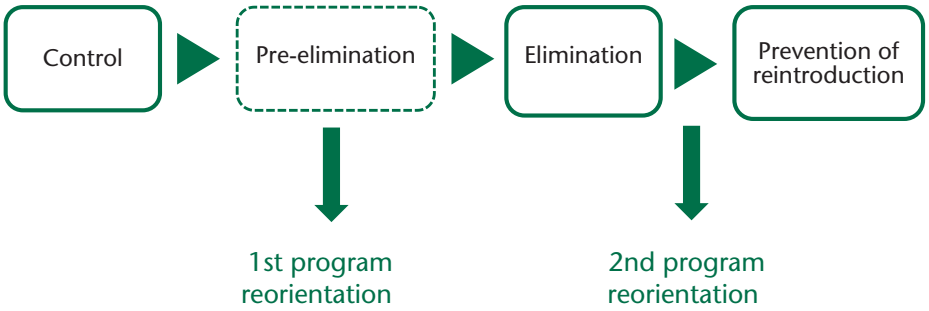

FIGURE 2.1 | Major intervention transitions by program phase

in the first two transitions (the last occurs automatically when elimination is achieved) should be based on a range of political, economic, and epidemiological factors (Chapter 1).

For some countries, the prevention of reintroduction will be the most challenging phase (Chapter 3). Substantial interventions may have to be sustained for decades in the face of constant reintroduction of parasites and public fatigue, and significant advance planning for this phase is an integral component of the elimination program. The MEG therefore strongly recommends that when preparing to interrupt transmission, all countries carefully assess and plan the measures that will be used to prevent resurgence before making the decision to embark on an elimination program.

All core malaria interventions must be adapted in some way in the transition from control to elimination. For some interventions, these changes will be relatively minor. For example, some countries may decide to initiate limited larviciding as part of their vector control strategies for an elimination program.[4] For other interventions, a fundamental shift in the approach or intensity of implementation is required. Table 2.1 summarizes those interventions and/or program components that must undergo the most significant change and the general approach required in each program phase. This list is not exhaustive and does not include all interventions that can be used for elimination.

SPATIAL TARGETING OF PROGRAMS

Malaria, like most health issues, is typically financed and controlled at the national level. In many areas, however, there is a strong rationale for subnational (e.g., a low-endemic province), supranational, or regional (e.g., an epidemiological zone shared among several countries) malaria elimination targets and programs. While WHO will only certify an entire country as malaria free, this should not deter countries from pursuing elimination in more-limited

TABLE 2.1 | Major interventions needed as program phases change

Activity	Control	Elimination	Prevention of reintroduction
Intervention target	Entire or broad areas of country	Residual and potential transmission foci	Potential transmission foci and individual imported cases
Diagnosis	High reliance on clinical diagnosis*; limited quality assurance	All cases confirmed with microscopy and/or RDTs; robust quality assurance	All cases confirmed with microscopy and/or RDTs; robust quality assurance
Private sector	Diagnosis and treatment provided in private sector (with support from public sector in some settings)	No diagnosis or treatment in informal private sector; formal private facilities fully integrated into surveillance system	No diagnosis or treatment in informal private sector; formal private facilities fully integrated into surveillance system
Program management and legislation	Often limited central capacity, including M&E; limited or no cross-sectoral collaboration and enabling legislation	Strong central capacity with extensive analytical and technical capacity; substantial cross-sectoral collaboration and relevant legislation	Reduced or reoriented, targeted central capacity; potential additional legislation (e.g., border screening)
Surveillance	Limited reporting and analysis of cases through passive system	All new cases rapidly reported and analyzed through both passive and active systems	Sustained, comprehensive, and rapid detection of new cases through passive system
Border measures	Limited or no cross-border initiatives	Initiatives pursued to dramatically reduce transmission in key neighboring areas; prophylaxis for travelers to endemic areas	Cross-border initiatives and provision of prophylaxis maintained; potential border screening of travelers from endemic areas; potential screening and treatment of migrant workers and refugees

*Clinical diagnosis should also be phased out as soon as possible in order to improve control programs.

national areas or regionally. The MEG recommends that national, subnational, and supranational elimination targets be established as appropriate given the epidemiological, political, and economic realities.

One of the greatest distinctions between control and elimination efforts is the geographical focus of key interventions. While there may be some variation between epidemiological zones, most interventions are uniformly applied to the target areas during the control phase. As the caseload approaches zero, however, remaining transmission is increasingly restricted to specific areas, and more precision in the application of interventions is needed. These "foci" are the primary targets of the elimination program, as continued heavy investment in areas where transmission has been interrupted is not cost-effective, nor always necessary.[5]

BOX 2.2 | Attacking Remaining Malaria Foci in Morocco[4]

In the decade between 1963 and 1973, Morocco reduced the number of annual new indigenous malaria cases from more than 30,000 to several dozen. Local transmission of *Plasmodium falciparum* was eliminated, and continuing *P. vivax* transmission was contained to limited areas of the country. While *P. vivax* resurged modestly in some areas in the ensuing decades, the government of Morocco committed in 1999 to fully eliminating malaria from the country by 2002. To do so, it developed a new strategy to target and interrupt the remaining sources of transmission and limit the introduction of new cases from abroad.

The heart of the new strategy is the classification of different transmission foci throughout the country and the tailoring of interventions to effectively address each. Two foci with continuing transmission were targeted with indoor residual spraying (IRS) and larval control, robust surveillance, and case management. Areas where transmission had been interrupted recently were targeted with a slightly less-aggressive approach to vector control (larval control only) and surveillance (once- instead of twice-monthly home visits). The areas where transmission has been historically present but where indigenous cases have not been detected in more than 15 years receive limited vector control and surveillance targeted only at locations with high importation risk. In this way, Morocco has prioritized its resources to achieve elimination. No locally transmitted case of malaria has been recorded in Morocco since 2004. In 2008, after more than 3 years of zero transmission, the country applied to WHO for certification of malaria-free status.[6]

Interventions should be appropriately targeted based on the characteristics of the foci identified. To be able to determine and target the most effective interventions, a program must be capable of identifying foci, which requires the following:

- accurate universal diagnosis
- prompt reporting of new cases
- active case investigation
- entomological surveillance
- detailed spatial analysis

TRAINING AND RETRAINING

The transition from control to elimination is crucially dependent on countries giving a high priority to a full range of malaria program and allied-staff training. These will be required for different categories, including senior and junior

health care professionals and other program-related staff. Many countries have far too few people trained in the essential skills as the capacity required for successful elimination is developed.

Program planning from inception through to prevention of reintroduction requires detailed training, retraining, and supervision. The extent of this training will reflect the requirements of the whole elimination strategy and thus needs to be comprehensive. For training, each country would use a standard operational manual that would be updated as evidence and experience accrued. Training must be locally relevant but should be based on a model elimination syllabus that is then adapted by each country or region.

DIAGNOSIS

Effective diagnosis of all cases will require some of the most challenging changes for many programs. While pursuing control, most countries, even those with low transmission, confirm only a minority of suspected malaria cases; clinical diagnosis is still prevalent among health workers.[7] This is not acceptable in an elimination program: as transmission approaches zero, all new cases must be confirmed and treated so that remaining transmission may be monitored. Achieving this will require a comprehensive set of measures across the health system, most of which are not in place in many countries. They include the following:

- education and communication campaigns to increase the awareness of signs and symptoms of malaria, the prompt seeking of treatment at formal health facilities, and the acceptance of diagnosis results by patients and health care workers
- provision of diagnosis and treatment free of all charges (including consultation fees) to all malaria patients, including those attending the formal private sector
- sufficiently trained and motivated staff in primary health facilities to conduct diagnostic tests (either RDT or blood slide)
- consistent supply of high-quality diagnostics and treatment at all levels of the health system
- well-equipped laboratories with trained and motivated staff and adequate transport for efficient transfer of tests and results between facilities and labs
- a strong central reference laboratory and a robust quality control system for diagnosis conducted at all levels of the system

BOX 2.3 | Selecting Diagnosis Tools and Strategies

Full coverage with microscopy is not feasible in some settings,[8] and other approaches, such as use of RDTs with appropriate quality control, should be adopted instead. Moreover, replacement of clinical diagnosis is important, particularly as endemicity goes down, to avoid overestimation of malaria cases and wastage of drugs.

Each country should carefully tailor its diagnosis strategy to the local context, taking into account operational realities within the health system and malaria epidemiology. Potential alternative strategies to the traditional exclusive focus on microscopy might include the following:

- microscopy used at health facilities to diagnose and confirm cases with a robust quality control system based on DNA PCR at national or regional reference laboratories
- RDTs used at health facilities for primary diagnosis and case management with microscopy at regional and national level for verification and quality control
- RDTs used at health facilities for primary diagnosis and case management with DNA PCR at national reference laboratories used for verification and quality control

- a solid reporting structure in place to ensure that all positive diagnoses are reported to the central level with requisite speed

PRIVATE SECTOR

In many countries, a significant proportion of malaria patients seek treatment outside the public sector.[9] In a control program, the priority is to endeavor to ensure that such patients will be given access to effective treatment. Some countries are actively supporting this through subsidies and/or other interventions. In an elimination program, only the public sector and the accredited premium private hospitals and clinics can provide the high-quality diagnostic facilities required as the basis of treatment. In most cases, the often-prevalent informal and unaccredited sources of treatment, including small drug shops, cannot be expected to provide quality diagnosis and treatment or appropriately report new cases to the central level.

BOX 2.4 | The Legal Framework for Elimination

Some of the key activities of an elimination program may require changes in national legislation. Some countries have adopted a number of legislative measures to facilitate elimination, including mandatory acceptance of IRS.[1] The recommended specific measures that countries should consider fall into four broad categories, including the following:

1. mandatory implementation of certain activities by health workers and authorities, for example, prompt notification of cases
2. mandatory acceptance by households and private businesses of elimination measures, for example, vector control
3. increased regulation of private sector health providers, including potential removal of over-the-counter antimalarial medicines
4. border control measures such as mandatory screening at ports of entry and case follow-up

Given the personal privacy and human rights implications of some of these measures, the appropriate legislation will have to be carefully designed and adapted to each country, taking into account international conventions and local legal code. In some countries, enforcing these legislative measures will be challenging. However, even if they are not fully enforceable, adopting these measures establishes societal norms, creates awareness, and contributes to behavior changes that will benefit elimination programs.

Countries that are ready to pursue elimination and that have a strong informal network of providers will need to implement a comprehensive and innovative approach to incorporate these facilities into the elimination program. Strategies should include incentives, training, and patient-behavior change approaches, as well as increased regulation, accreditation, and a reliable reporting system to ensure that informal private activity enables the elimination effort rather than undermining it.

PROGRAM CAPACITY

The level and intensity of interventions used in an elimination program require a corresponding increase in the capacity of the national program. New technical staff in areas such as surveillance and data management will need to be added, as well as more general program staff, to closely oversee and support the implementation of key interventions. It will be necessary to enroll

staff at all levels of the elimination program in regular training and retraining programs in order for them to learn new techniques and refresh their skills. Performance throughout the program and the health system will also need to be monitored and enforced to achieve elimination. In Oman, for example, there is a clear performance framework in which members of the program are held accountable for the appropriate management of new cases and other outcomes.[10]

Much more so than in the control phase, there is also a need for the national program to coordinate activities with other units within the government. For example, the ministry of defense must ensure that interventions are appropriately implemented for all military locations and personnel, while the ministry of immigration may need to take measures to limit the introduction of new cases.

2.3 Knowing the Enemy: Building Strong Surveillance

Surveillance is perhaps the most important component of an elimination program. As will be further discussed in Chapter 3, a program must be able to detect, investigate, and respond rapidly to every individual case of malaria in order to achieve and sustain zero transmission. This enables it to treat remaining cases appropriately, identify and address transmission foci, and eventually confirm and receive certification for the achievement of elimination.[11] As a program moves to elimination, it must invest heavily in its surveillance system to ensure that it meets a high standard of speed and sensitivity. A surveillance system is composed of three core phases:

1. collection of case data through active and passive detection methods
2. analysis and interpretation of data, including case investigation
3. appropriate response, including radical treatment and targeting of foci

PASSIVE CASE DETECTION

A robust passive case detection system, which includes reporting of cases captured through normal patient visits to health facilities to a central team that carefully analyzes and tracks patterns, is the cornerstone of any approach to surveillance—if new malaria cases identified at health facilities are not being adequately reported and followed up, elimination will not be achieved. In most

elimination programs, the passive case detection system will have to be substantially improved to ensure that all new cases are reported to the central level with the requisite speed (e.g., within 24 hours, once at or near zero local transmission). In addition, many countries will need to strengthen their central units that record, analyze, and mobilize responses to reported cases, which can involve improving skills and obtaining appropriate technology.

Key considerations for elimination programs related to the passive case detection system include the following:

- Strengthening the system will require significant and sustained investment in equipment, personnel, training, and communication.
- In some countries, it may be necessary to create a malaria-specific reporting system that is distinct from the core health management information system. However, parallel reporting systems are not desirable, should be used only if elimination will not be achieved otherwise, and should be incorporated into the basic system as soon as responsibly possible.
- While some countries have extended their passive case detection beyond the formal health system to community health workers, this approach is not recommended for elimination programs.[12]

ACTIVE CASE DETECTION

Prior to implementing an elimination program, most countries will be unable to identify a sufficient number of new cases through the health system to interrupt transmission and will accordingly need to employ some form of active case detection, or the proactive screening of certain segments of the population for malaria parasites. Active detection provides the distinct benefit of enabling treatment of asymptomatic parasite carriers, who are often a major source of continued transmission. Many different approaches to active detection have been used.[13] Figure 2.2 shows a spectrum of active case detection methods that have been employed from least to most complex and resource intensive.[14] There is currently no evidence to suggest that the approaches on the right end of the spectrum (i.e., mass screening) are more effective and/or cost-effective than the more-limited measures. The MEG therefore recommends that countries only adopt these measures following detailed analysis of feasibility and cost-effectiveness.

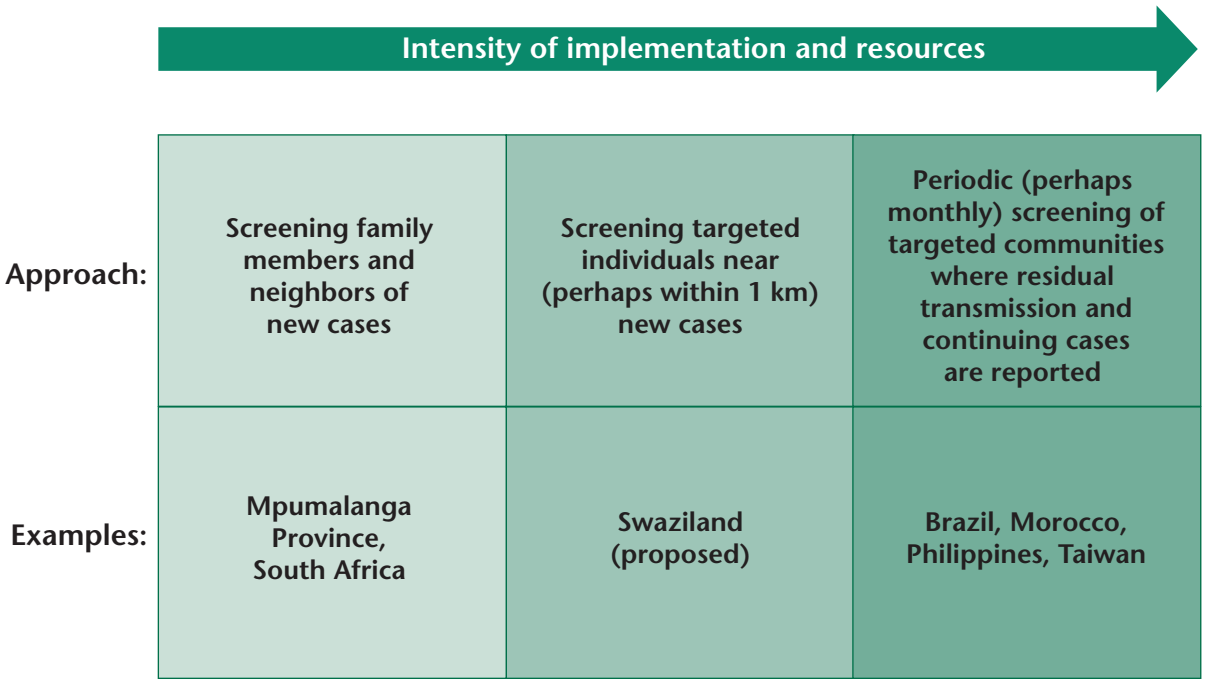

FIGURE 2.2 | Approaches to active case detection

ANALYSIS AND RESPONSE

The surveillance system is only as useful as the response it elicits. As described above, strong surveillance enables the program to identify and target its interventions at residual and potential foci. To do so, the program must first understand and interpret the often complex data gathered by the system. This is done through the following:

- active investigation of all new cases to determine parasite species, source of infection, and history and duration of illness (e.g., for potential *P. vivax* relapse)
- collection of relevant entomological data in targeted areas (Chapter 9)
- prompt analysis of both epidemiological and entomological data in a central elimination database, ideally with a strong geographic information system component

Given the constant risk of resurgence, countries will need to maintain sufficient emergency stocks of key commodities, such as insecticide and medications, to rapidly respond to emerging epidemics ("epidemic preparedness and response"). In addition, the requisite systems must be in place nationally and at district level to ensure that provision of the commodities can be guaranteed as needed.

2.4 The Imperative of Cross-Border Collaboration

As discussed in Chapter 1, all countries that will pursue national elimination in the coming years will have to face the challenge of continued malaria transmission in neighboring countries. This is particularly the case for countries that share lengthy land borders, but also applies to island countries with multiple entry points or areas pursuing subnational elimination. Borders are typically porous with increasingly high levels of human traffic, not only due to migrant laborers but also as a consequence of social and political unrest. As such, unless eliminating countries can ensure a significant and sustained reduction in transmission in the border areas of neighboring countries, it is unlikely that they will be able to achieve zero local transmission.

A number of different approaches to cross-border initiatives have been pursued in the past, including the following:

- An eliminating country, which has greater capacity and resources, directly implements or provides detailed support for interventions in the neighboring country. This approach has been followed in the Lubombo Spatial Development Initiative (LSDI), a highly successful collaboration between Mozambique, South Africa, and Swaziland that has reduced malaria prevalence in targeted areas by more than 90%.[15]
- The eliminating country provides limited or remote technical and financial assistance to the targeted areas. An example of this is an intermittent collaboration between Saudi Arabia and Yemen, where the principal activities have included training of Yemeni staff in Saudi facilities.[16]
- Participating countries engage only in targeted coordination of policies and increased communication between their programs.[17] This is the de facto approach used by most regional initiatives.

The MEG recommends that, as much as possible, countries develop regional initiatives that employ the first two of these approaches.

There are substantial challenges to developing and executing successful cross-border initiatives. Many initiatives have been conceived and planned, but few have had notable impact. Drawing on lessons learned from the LSDI, there are a number of apparent success factors for cross-border efforts:

Political and administrative support The negotiation of cross-border arrangements typically needs to occur at levels above the respective

malaria program managers, and a clear mandate from ministers of health or other political leaders can greatly facilitate regional or cross-border operational arrangements.

Technical leadership Strong alignment of approaches and guidance on technical issues across the participating countries is essential to any cross-border initiative. For example, the LSDI is led by a regional malaria control commission of technical and operational experts from the region, which designed the initiative and guides its ongoing work.[14]

Significant and independent funding As will be discussed more in Chapter 4, innovative financing mechanisms are required to facilitate regional or cross-border programs. Cross-border initiatives typically require substantial additional funding, and in most areas, it is unlikely that governments alone will devote adequate national resources to controlling malaria in neighboring countries. The LSDI has been largely financed by private sector donors, South Africa, and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Strong centralized management In the LSDI, the Medical Research Council in South Africa (MRC) has established a robust management structure and closely monitors and manages performance across the initiative in line with the accountability standards and reporting requirements set by its donors.

2.5 | Sustaining National Political Will

Although recent experience has reconfirmed that dramatic reductions in malaria incidence can be achieved in a short time, fully eliminating local transmission is a war of attrition in most settings. Finding and clearing the last cases and foci, particularly of *P. vivax*, often requires five or more years of effort, even in relatively conducive settings such as in Europe and the Middle East.[18] As history has consistently shown, attention, resources, and diligence cannot waver during this time or malaria will resurge and the gains of the preceding years will be lost.

Fatigue among key stakeholders, ranging from local communities and implementers to national politicians, is one of the greatest threats to a malaria elimination program. It is challenging to convince individuals to engage in elimination-conducive behavior, such as sleeping under insecticide-treated nets (ITNs), and to convince politicians from endemic countries and donors

to commit funds and attention once malaria is no longer a major threat. The MEG therefore recommends that each country develop a comprehensive strategy for ensuring the sustained engagement of key actors before it launches its full elimination program.

Key components of the strategy to maintain national and political will include the following:

Secure sustained, high-level political support The highest levels of the government must view elimination not just as a short-term political benefit but as a long-term investment in the development of the country or region. This can be fostered through incorporation of elimination goals and activities into broad development strategies and medium-term budgets as well as consistent, well-designed advocacy campaigns, ideally supported by high-profile champions from within the government.

Build community engagement Programs will greatly benefit if communities fully understand and take ownership of the elimination goal.[19] While there has been increased attention to community-led malaria-control initiatives in recent years, there is little evidence of the impact of these approaches on a large-scale.[20, 21] Appropriate approaches must be developed within each country and adapted to local community structures and cultural practices.

Target vulnerable populations In many countries, special attention will need to be paid to particular subgroups within the population. The last sources of transmission are often found among groups such as cultural and ethnic minorities, nomadic or forest populations, and/or migrant workers, which often have less contact with the formal health system. Ensuring the necessary participation of these groups in elimination interventions will often require adaptation of approaches to unique social, cultural, and political dynamics. The failure of the first elimination campaign in Mexico, for example, has been partly attributed to resistance among indigenous populations in the south of the country.[19]

Set expectations and promote vigilance It is important that advocacy efforts set appropriate expectations of the duration and benefits of elimination with politicians and communities. Overselling the program will quickly lead to disappointment and reversals.[22] In addition, once cases begin to near zero, it is critical that the program

TABLE 2.2 | Framework for an elimination advocacy campaign by stakeholder group[1]

Stakeholder	Outcome	Message	Information needs
National leaders (e.g., heads of state)	Commitment to long-term support for elimination	Elimination will bring great benefits to your country and your neighbors.	Health and economic impact estimates; elimination commitments by neighbors
Ministry of finance	Significant and long-term financial support	Malaria elimination is good for economic development and is cost-effective.	Economic impact and cost-effectiveness estimates
Ministry of health	Leadership of elimination program; appropriate investment in and management of the health system	Eliminating malaria will reduce the burden on the health system. Maintaining elimination requires constant vigilance.	Detailed analysis of health system needs to achieve and sustain elimination
Local government leaders	Effective sustained management of activities; commitment of local resources and leadership	Elimination is a national priority that will greatly benefit communities in your area. Activities need to be sustained, or dangerous epidemics will occur.	Commitments by national and regional leaders; local budget and management needs for effective implementation
Business leaders	In-kind and financial contribution to elimination activities	Malaria elimination is good for business (e.g., greater productivity and more tourism and investment).	Economic impact estimates; mapping of opportunities for business contribution
Donors	Substantial and sustained funding for elimination program	Elimination will contribute to health and economic development goals. Elimination funding must be long-term and predictable.	Inclusion of elimination in national development strategies; analysis of long-term financing needs and mechanisms for predictability
NGOs	Active participation in malaria elimination activities	Elimination will save many lives and benefit communities. NGOs have an important role to play.	Mapping of opportunities and needs for NGO engagement
Public	Sustained engagement in elimination activities and appropriate health behavior	Malaria remains a deadly threat even once it has been eliminated.	Simple examples of malaria resurgence from other countries

1. Courtesy of Dr. Matthew Lynch, Johns Hopkins Center for Communication Programs

consistently reinforce the continued threat of resurgence and need for sustained investment vigilance. This can be done through advocacy and education campaigns (e.g., through schools), as well as by promoting national unity and pride in the achievement of elimination.

Develop robust financial arguments Many stakeholders, including ministries of finance and international donors, will question whether malaria elimination is the best use of limited resources. It is thus imperative that the economic case for elimination also be well presented. When this is done, the indirect impact of elimination on the health system (strengthening systems and reducing patient burden), foreign direct investment, and tourism should be considered, as should the strong arguments for considering elimination a regional public good (see Chapter 1).

Well-targeted and sustained advocacy and communications campaigns will be critical to executing strategies and achieving the objectives outlined above. An example of a comprehensive elimination advocacy campaign is outlined in Table 2.2. In most cases, it will be important for organizations other than the National Malaria Control Program (NMCP) to implement aspects of such a campaign (e.g., targeting national leaders and ministers). As such, it will be important for the NMCP to form strategic partnerships with NGOs and other organizations that can fill this important role.

2.6 Malaria Elimination and Constructive Engagement with the Health System

The strength of the basic health system is integral to elimination, and most countries will have to strengthen that system to achieve and sustain zero transmission. However, that is not to say that a health system must be perfect for elimination to be achieved. Rather, the MEG recommends a careful examination of which components of an elimination program must be pursued through a strengthened health system and which can employ alternative approaches.

The health system is often equated with the formal, government-led public health infrastructure in the country. However, there is often a range of other organizations and facilities that provide health care and other essential services related to malaria elimination, including private, nongovernmental, and faith-based organizations. In fact, elimination will only be achievable in some countries if these organizations play a substantial role. However, there are a

number of areas where government health system priorities and coordination are vital. These include the following:

Case management Appropriate diagnosis and treatment of patients presenting with fever at health facilities is essential to elimination. It is not feasible or effective to develop an infrastructure of human resources solely for primary malaria care. The health system must be strong enough to provide sufficient coverage and quality of case management, including the consistent supply of drugs and other commodities to the health facilities.

Surveillance and monitoring Health facilities will also be responsible for reporting the majority of new malaria cases to the central level. While a malaria-specific system may be adopted, it will need to build on the infrastructure of the general information system. If that system is weak, it is likely that malaria surveillance will also not reach sufficient levels of speed and accuracy, jeopardizing a rapid response.

Planning and coordination As already described, an elimination program faces significant risk of fatigue among policy makers and consequent financial volatility. If elimination efforts are planned and budgeted for "off-budget" or as isolated activities, the risks of uneven resource flows increase. It is therefore imperative that elimination be incorporated into all core planning and budgeting activities, and in decentralized systems, it must be part of district health plans to help to ensure sustainability.

Beyond these areas, it is possible, and in some cases advisable, for the program to employ approaches that are complementary to the basic health system. It may be necessary, for example, to complement a weak surveillance system with periodic surveys, which could be conducted by a health research institution. Distribution of long-lasting insecticide-treated nets (LLINs) may be more efficiently achieved through the private sector or a faith-based organization. Opportunities for using elimination resources to build the capacity of the basic system should be pursued as long as they do not detract from the elimination goal. They can include expanding initially malaria-specific systems to support other diseases, as has been done with polio surveillance in some countries, and additional broad performance incentives for general health professionals, among others.[23]

Although the government must lead and typically implement the majority

of the elimination effort, the nongovernmental sectors can, as we have indicated, contribute substantially in a number of key areas. These include, but are not limited to, the following:

Direct provision of services Some NGOs and private organizations are also well positioned to provide diagnosis, treatment, case management, and other services, particularly in remote communities. In addition, major businesses (e.g., tourism) with a stake in elimination can be used to provide services to their employees and surrounding communities.

Outsourcing of key functions Nongovernmental groups may be able to implement certain elements of an elimination program where government capacity or competency is weak. It may be efficient to outsource the implementation of complex technical functions, such as behavior-change communication, commodity procurement, and mass distribution campaigns, to private organizations that are particularly suited for logistically intensive functions.

Systems strengthening Others can play an important role in building and supporting the government's capacity to achieve elimination, including by contributing additional skilled staff or implementing key training programs. Some organizations can also assist in essential advocacy and resource mobilization. However, the integration of all actors, private as well as public, into district planning is vital to a strong system.

It is typically understood that once elimination is achieved, the national malaria program will be disbanded and any ongoing malaria activities will be incorporated into the general health services.[1] We question this assumption. The premature dismantling of eradication programs during the 1970s and 1980s created many challenges for subsequent malaria control, including significant loss of technical staff at all levels, and contributed to resurgence during that period.[24] Other elimination efforts, such as for Guinea worm, have faced similar challenges when integration has been pursued prematurely and resources and attention diverted away from essential activities.[23] Therefore the eventual integration of malaria elimination activities should occur gradually and be carefully managed to prevent erosion of the capacity to intervene, thus protecting against possible resurgence of infection. For this reason, in some settings it may be advisable to maintain a robust, distinct national program for some time after transmission is initially interrupted, as was done on Taiwan.[25]

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3 | HOLDING THE LINE

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3.1 | Introduction

Once elimination is achieved, the constant threats of reintroduction and reemergence, and thus severe morbidity and mortality, make some malaria control activities necessary. Prevention of transmission reemergence is an integral component of any elimination campaign and must be planned carefully before elimination is attempted. The risk of reintroduction after elimination is highly dependent upon two components:

1. the intrinsic potential for malaria transmission in the region, as determined by its vectors, geography, environment, and social factors
2. the rate at which new sources of malaria infection enter the region from other countries or regions where elimination has not yet been achieved

Even in regions with high intrinsic malaria risk, well-developed health systems and effective interventions can reduce the risk from this baseline prevalence, while measures such as targeted screening of immigrants can permit early identification and treatment. To "hold the line," the MEG recommends

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BOX 3.1 | Main Messages

- Countries or regions considering elimination must make detailed assessments of the factors listed below to ensure the feasibility of preventing malaria reemergence:
  1. importation risk, in terms of the number of infected individuals entering the country each year, in order to determine screening requirements
  2. outbreak risk, in terms of the intrinsic potential for reintroduced malaria transmission
  3. surveillance system capacity, in terms of its ability to identify, report, and respond to imported individual malaria cases and outbreaks
- Governments must commit to maintaining resources and encouraging community support for sustainable antimalarial interventions long after malaria has been eliminated.
- It may be appropriate to maintain a central unit with responsibility focused on malaria even after cessation of transmission, to ensure epidemic containment and effective case response, but these activities should be carefully integrated with the health system.
- Each country needs to assess its own needs for the ongoing activities required to deal with outbreaks, and the potential for importation, according to the overall risks to which it is exposed.
- A coordinated multicountry regional approach to elimination will greatly reduce importation and outbreak risks and should strongly be considered before, during, and after an elimination program.
- Screening high-risk individuals at ports of entry may help to reduce importation risk, but implementation and cost-effectiveness are important considerations. Key factors that determine whether port screening is likely to be cost-effective include the expected prevalence of infection in these individuals; the volume of travelers; and the importation risk, surveillance, and case response capabilities of the country to prevent missed cases from developing into epidemics.
- Eliminating vectors is generally not recommended as a strategy for preventing reemergence of malaria, although controlling receptivity through sustained, targeted indoor residual spraying (IRS), or net use may be appropriate.
- Maintaining a strong surveillance and outbreak response system is essential for containing infections before they can spark epidemics.

Mauritius

Achieved elimination: 1973

Malaria recurred: 1975–1976

Contributing cause: Increased migrant labor from endemic areas

Kazakhstan

Achieved elimination: 1980s

Malaria recurred: 1991-1996

Contributing cause: Weakened health system; increased migration (e.g., of soldiers from endemic areas)

South Korea

Achieved elimination: 1979

Malaria recurred: 1993

Contributing cause: Introduction of parasites and vectors from North Korea

interventions tailored to the specifics of a region or country, which should include guarding against the introduction of malaria parasites (to lower the importation risk) and preventing the spread of such parasites should they be introduced (to lower outbreak risk). The ability to identify and respond quickly to introduced cases must be maintained through strong surveillance and outbreak response capacity.

Many countries have successfully eliminated malaria and have instituted sound surveillance programs and policies that hold the line, and they have been able to respond effectively to limited reintroduction. By contrast, as funding for the Global Malaria Eradication Program (GMEP) began to wane, malaria reemerged in other countries that had come close to zero but had not adequately prepared for surveillance and sustained vigilance.[1] Examples of the occurrence of epidemics include, in diverse settings, Sri Lanka (1968-1969),[2] Madagascar (1986-1988),[3] and more recently, Azerbaijan, Tajikistan, and Turkey.[4] After insecticide spraying stopped or was scaled back in these areas, the vector populations recovered, resulting in high rates of transmission and thus severe malaria and mortality due to the waning of immunity.

Reaching zero is not the end of malaria; countries or regions must shift focus from eliminating internal transmission to preventing reemergence from external sources, whether from bordering nations or neighboring regions in which malaria is still endemic. In other words, planning for malaria elimination must consider not only how to get to zero but the equally challenging task of staying there; tactics for prevention of reemergence should be treated as integral components of the overall elimination strategy, and many of the same approaches adopted to reach zero may successfully be maintained to hold the line.

Planning for elimination is based, in part, on the quantitative concepts of outbreak risk and importation risk (Chapter 1). After elimination is achieved, these

BOX 3.2 | Modeling Outbreak Risk

Initial efforts to define outbreak risk semi-quantitatively have been described in Italy[5] and more recently in southern France (below)[6] using detailed entomological transmission risk maps based on meteorological data. Such methods may be useful in assessing risk in places where malaria has already been eliminated and in monitoring and evaluating malariogenic potential in countries considering elimination.

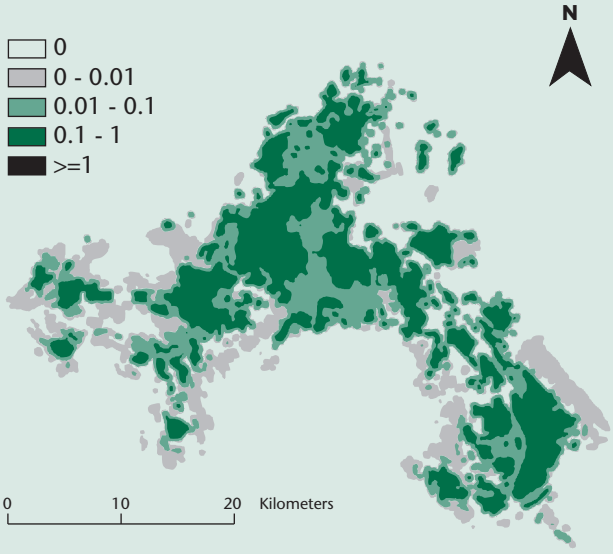

FIGURE 3.1 | Spatial variations in *P. falciparum* transmission risk estimate (ranging from 0 to greater than 1) in August in the Camargue. Corresponding calculations for *P. vivax* showed a much higher risk of outbreaks occurring at this time of year (from Ponçon et al.[6]).

concepts remain highly relevant. The WHO certification of malaria elimination is awarded after 3 years of continued absence of locally acquired cases, but malaria can still return years later. Preventing reemergence of malaria will rely upon a combination of keeping outbreak risk low through maintenance of good health systems, minimizing importation risk, and maintaining a strong surveillance system to monitor and catch cases that do appear. The combination of a region's outbreak risk and importation risk produces a measure called the malariogenic potential, which can be considered an indication of the overall risk that malaria will return.

Despite the widely recognized importance of malariogenic potential, there are no standardized measures for defining levels of outbreak risk or importation risk in any given geographical setting.[7] In the future, mathematical models will play an important role in helping to define quantitative thresholds of acceptability (Box 3.2). Any model will require detailed data on the epidemiological and entomological situation in a given country; collecting specific metrics, including age-specific parasite prevalence, vector density, human biting rate,

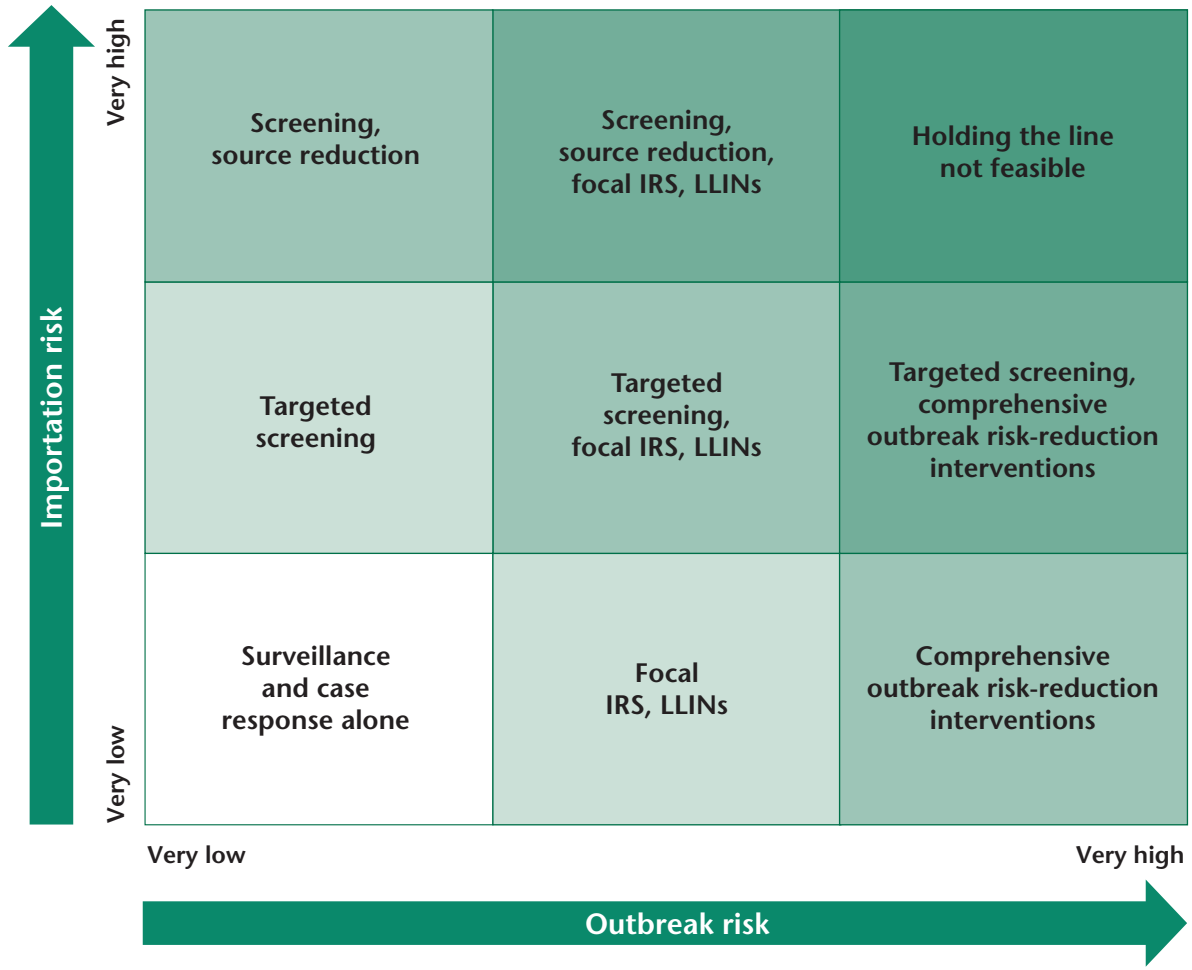

FIGURE 3.2 | An example of how the measures required to prevent reintroduction will vary according to relative levels of outbreak risk and importation risk. Specific interventions must be appropriate to country contexts.

entomological inoculation rates, and other parameters at geo-referenced locations, will help in defining malaria risk. This information can then be used to make maps to inform operations, to identify ongoing transmission foci or hot spots, and to focus elimination efforts.

Collection of this information is something some countries could undertake now. Even without these data, planning for elimination can still proceed while the capacity to obtain detailed risk information is gradually improving.

In the example cited in Box 3.2, the outbreak risk is quite high in certain regions of the Camargue during August; however, the overall malariogenic potential will remain low if there is little importation risk occurring in those areas where outbreak risk is high. In this situation, and also when importation

risk is high but outbreak risk low, it is possible to hold the line (Figure 3.2). In places with high importation risk and high outbreak risk, multiple sustained approaches and interventions will be required if malaria reintroduction is to be avoided. To hold the line, countries must reduce their malariogenic potential to a level that ensures a low risk of reintroduction. Again, there are no absolute standards for defining a low level of risk.

The MEG recommends careful analysis of the outbreak risk and importation risk of a particular region to help determine the relative emphasis that must be placed on different sorts of post-elimination interventions.

3.2 | Management and Implementation

Holding the line, like the campaign to get to zero, will necessitate a combination of strong commitment and effective management and leadership. Additionally, the national or regional health system will need to be sufficiently robust to permit timely identification and treatment of all new malaria cases to prevent an outbreak. Maintaining sufficient political will and capacity to sustain intervention against an invisible opponent will be a difficult task. Historical examples of countries that nearly eliminated malaria, only to suffer severe resurgences when control activities were stopped, illustrate the hazard in not maintaining disease-specific efforts after successful gains have been made.

The MEG recommends that countries attempting to hold the line consider maintaining a central malaria program in some form, integrated into the health system, to ensure sustainability of outbreak risk and importation risk-lowering interventions, as well as rapid and effective case management and epidemic containment (see Chapter 2).

Proactive planning is necessary to ensure that national commitment to malaria elimination does not end with achievement of zero transmission. Getting to zero requires an intensive campaign with defined resources, while holding the line needs an unbounded commitment to continue malaria prevention activities until malaria is completely eradicated. As a result, it is important to note that considerable financial resources may be required to maintain antimalarial operations even after elimination has been achieved (Chapter 4).

The MEG recommends that governments must commit to maintaining resources and encouraging community support for sustainable antimalarial interventions, even long after malaria has been eliminated.

As long as malaria remains endemic elsewhere, preventing its reintroduction requires strong political commitment, active community support, and in many cases, untiring interventions for reducing outbreak risk and importation risk.

BOX 3.3 | The Importance of Maintaining Interventions

In the central highlands of Madagascar, a combination of DDT spraying, IRS, and case detection and treatment successfully prevented reemergence of malaria from 1960 until cessation of control activities in 1980. At that time, the government halted spraying in the highlands, since the lack of malaria seemed to indicate that such activities were no longer necessary. With the discontinuation of spraying, *Anopheles funestus* gradually became firmly reestablished in rice field breeding habitats, and this, coupled with the migration of gametocyte-positive individuals from malaria-endemic lowland areas, resulted in an explosive malaria epidemic among a then-nonimmune highlands population in the late 1980s, causing an estimated 40,000 deaths over 5 years.[3] Although this example is of resurgence in a country that had not yet achieved elimination, it emphasizes that holding the line against reintroduction within a country is often deeply challenging and requires aggressive and sustained intervention.

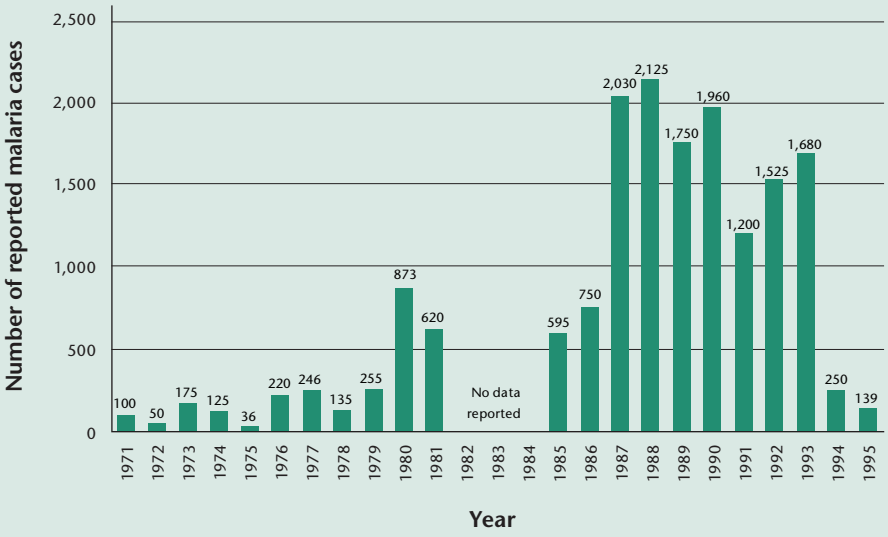

FIGURE 3.3 | Number of malaria cases in the Analaroa Health Center, Madagascar Highlands (no data reported from 1982-1984) (from Mouchet et al.[8])

Approaches that may help maintain such steadfastness include:

- community awareness campaigns, such as periodic "malaria day" reminders of the great economic and health advantages of preventing the potentially devastating reintroduction of malaria
- maintenance of small malaria-specific programs, or a multipurpose program with specific malaria expertise, to ensure vigilance in areas

BOX 3.4 | Sociopolitical Upheaval Can Spark Reemergence

In Tajikistan, malaria transmission had been reduced to very low levels by the 1980s, although occasional seasonal cases still occurred. The situation deteriorated in the 1990s. What changed? Altered agricultural practices associated with the introduction of rice crop irrigation significantly increased outbreak risk by creating favorable breeding habitats for local competent malaria vectors (*A. superpictus, A. pulcherrimus,* and *A. maculipennis*).[9] At the same time, armed conflict, civil unrest, and adverse economic conditions led to large population movements across the border with Afghanistan, where 2 to 3 million people are thought to have been infected in epidemics during the mid-1990s. Finally, malaria control in Tajikistan was disrupted during the 1992-1997 civil war. Although this example is of resurgence in a country that had not yet achieved elimination, it illustrates a central challenge that some eliminating countries will face as they attempt to hold the line.

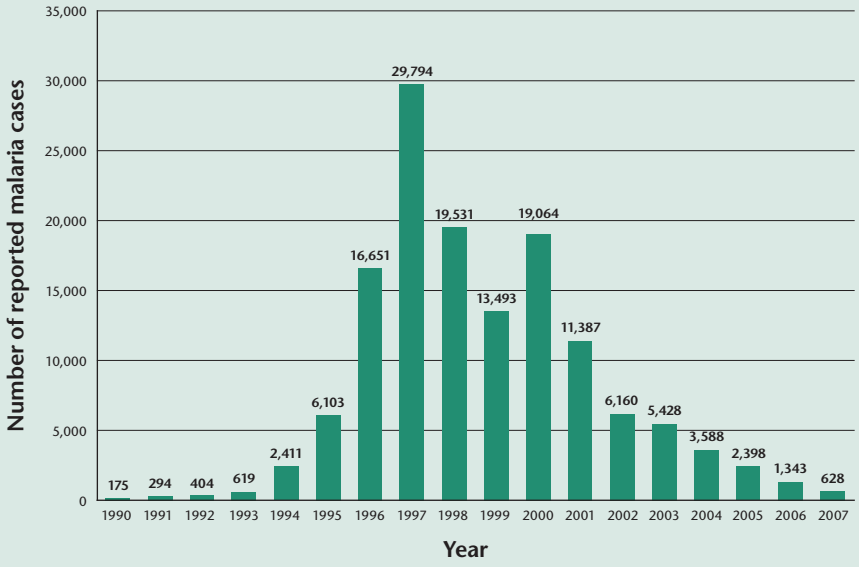

FIGURE 3.4 | Reported malaria cases in Tajikistan between 1990 and 2007 (from Matthys et al.[10])

with high malariogenic potential or weak health systems, even years after the perception of a threat from malaria has vanished

- establishment of innovative financing schemes to ensure that domestic and international resources are set aside for post-elimination antimalarial vigilance

Because a country's or region's importation risk and outbreak risk may change over time, assessments of these indicators must also be dynamic. Such a need

is especially important when development, agriculture, or conflict may cause significant changes in vector habitat or the risk of imported malaria. In areas undergoing major sociopolitical upheaval, rapid and simultaneous changes in importation risk and outbreak risk can result in resurgent malaria that quickly overwhelms available resources. For example, several countries of the former Soviet Union, notably Azerbaijan and Tajikistan, have experienced significant epidemics since indigenous transmission was reestablished in the 1990s.[4,11,12]

3.3 Importation Risk

As discussed in Chapter 1, importation risk, also known as vulnerability, measures the rate at which infected and infectious mosquitoes or humans come into a region each year. Importation risk can be conceived of on a national scale, but it is also a useful concept for malaria elimination within parts of countries, such as the Philippines, where spatially progressive malaria elimination is occurring province by province.

Malaria is constantly being imported and exported around the globe, a fact that was brought into sharp relief after eastern Africa imported chloroquine-resistant parasites from Southeast Asia, and as chloroquine resistance spread throughout the world from a few focal points of origin.[13] In areas with high levels of transmission, importing malaria is a minor public health concern, except, as in eastern Africa, when the imported parasites are much more difficult to treat. As local transmission is reduced, imported malaria becomes a higher priority, and after malaria has been eliminated from a region, importation risk increases to the point where it is of utmost concern. Movement of parasites is facilitated by migration of their mosquito and human hosts, and we consider each of these cases separately.

Mosquitoes typically fly only short distances, but they occasionally travel or get blown much farther, and they can be transported accidentally in the cargo holds of airplanes or in containers on ships. The risk of importing malaria over long distances is real, but a second issue is that countries can import a new vector species and dramatically increase their importation risk. Brazil imported the efficient African vector *A. arabiensis* in 1930, sparking a severe outbreak. In that case, the epidemic was stopped by eliminating the vector, albeit with great difficulty, but malaria persisted. The geographical spread of sub–Saharan African vectors north of the Sahara and the spread of efficient vectors to neighboring countries are important concerns, especially when those countries have eliminated malaria. These risks highlight the need for vector vigilance.

In almost all cases, human introduction of parasites, rather than acciden-

tal transportation of mosquito species, is chiefly to blame in countries where malaria has resurged. Asymptomatic malaria infections in humans can last months, and humans can fly around the world in a few days and cross national borders in an afternoon. Given the numbers of people who move across borders, human movement is the most important component of importation risk. Malaria can be introduced by soldiers, journalists, diplomats, or others who are returning home from foreign service; tourists who have recently visited malaria-endemic areas; migrant labor populations; nomadic populations migrating across borders; people with ethnic or tribal affiliations across arbitrarily drawn political borders; or refugees escaping political instability in their home countries. Quantifying all of these rates is a daunting task.

Certain travelers, however, are likely to be at much higher risk of transporting parasites than others. Poor migrant workers traveling overland from endemic countries are substantially more likely to harbor parasites than wealthy tourists on prophylaxis or business travelers arriving from nonendemic regions by plane and residing primarily in air-conditioned hotels. As a result, the magnitude of importation risk will be affected greatly by the endemicity in regions surrounding the borders of a country, as well as the socioeconomic status of the people in those regions. Elimination may be a tenuous, short-term victory for a nation bordering a poor, highly endemic country, especially if substantial migration occurs across porous borders.

One part of importation risk can be estimated by taking the product of the immigration rate and malaria endemicity in the immigrants' country of origin. This multiplication provides a first-order approximation that can be built upon for planning or comparison purposes. Other more comprehensive assessments of importation risk can be made by sectors of the government that are not typically included in malaria planning, such as the department of immigration.

The MEG recommends a comprehensive evaluation of migration into the region in which malaria is to be eliminated, in order to estimate overall vulnerability and to identify groups at particularly high risk.

Important considerations include the following:

- the magnitude of immigration rates
- the likelihood that migrants carry malaria
- the parasite species carried (e.g., *P. vivax* may be more difficult to detect and uproot)
- where migrants settle (e.g., many immigrants arrive in urban areas, where malaria transmission rates tend to be low, though this is not always so in poor and expanding peri-urban areas)

BOX 3.5 | Screening Travelers to Mauritius

In Mauritius, which has had no indigenous malaria transmission for a decade despite still having competent vectors, all visitors arriving from endemic countries are registered at the port of entry, and their names and addresses are recorded for follow-up by health surveillance officers. These officers may take a blood sample for screening, and private-sector doctors are also encouraged to take blood smears from those with suspected malaria cases. These measures have identified between 35 and 63 imported cases of malaria each year since 2000.

Although risk of reintroduction of malaria transmission will be driven by gametocyte carriers from malaria-endemic areas, in many cases the events necessary to spark a malaria outbreak will not occur despite the entry of an infected individual—that person may not be bitten by an anopheline mosquito during his or her time in the malaria-free country, or that mosquito may not survive long enough to transmit again. However, each additional case of imported malaria introduces the risk that all of these events will happen and that transmission will occur. There is, then, an urgent need to locate and treat the primary and secondary cases in order to stop the development of an outbreak. Knowing the rate of migration by potentially infected individuals from endemic regions allows a possibility to reduce importation risk. Two principal means of reducing importation risk should be evaluated:

1. Identify infected individuals and treat them promptly, ideally before entry, before they can infect competent local vectors and lead to secondary cases and sustained foci of indigenous transmission.[5, 12]
2. Address the source of infection directly by reducing transmission in the regions that are the primary sources of infected travelers.

IDENTIFYING INFECTED INDIVIDUALS AND TREATING THEM PROMPTLY

Screening with malaria rapid diagnostic tests (RDTs) or microscopy at port of entry and/or point of departure and providing follow-up treatment of infected individuals may play an important role in reducing the number of imported cases and outbreaks. For example, all individuals entering the island of Aneityum in Vanuatu have a blood smear at the point of entry with same-

Table 3.1 | Some examples of key populations that could be screened

Source region	Migrant group	Destination region
Mozambique	Migrant sugar laborers	Swaziland
Malaria-endemic regions of Burundi	Refugees from civil war violence	Highlands region of Burundi
Colombian nonendemic regions	Nonimmune agricultural workers	Colombia's malaria-endemic Naya basin

day testing and treatment, as appropriate. When migration rates are high, efforts should focus on screening high-risk groups, such as migrant laborers from endemic regions. Large influxes of laborers for agriculture or mining are a well-known source of imported malaria. As demonstrated in Table 3.1, targeted screening and treating of high-risk populations has been an effective tool for decreasing vulnerability in certain regions.

Countries generally adopt different border-entry procedures for their own citizens; in developed countries, citizens returning from malaria-endemic countries represent a dominant source of imported malaria. Citizens who plan to visit malaria-endemic countries should be encouraged to take prophylaxis while traveling and continue prophylaxis to control early-stage infections that appear after returning home. As malaria disappears from a country, doctors will tend to overlook malaria, so it is worth reminding doctors that they, too, need to remain vigilant and to ask patients whether they have been traveling and, if so, where.

Establishing effective internal border control measures to reduce the movement of malaria within a country is a particular challenge when planning to stage spatially progressive elimination (e.g., province by province). Legal and ethical acceptability must be considered carefully. In addition, screening internal migration may be an enormous burden for a country already fully engaged with preventing introduction of malaria parasites from external sources; for example, uncontrolled internal migration was a major factor in the resurgence of malaria within Indian states, such as Kerala, during the GMEP. However, when geographically feasible, countries pursuing spatially progressive elimination should monitor movement within their own borders just as if they were reducing reimportation from a neighboring country. Generally, the problems of staged progressive elimination are more difficult for large contiguous countries like India than for multi-island nations like the Philippines, where internal migration is more easily screened.

In resource-poor settings, it is unclear how much countries should rely on malaria screening at international ports of entry. Border screening can be costly and can entail direct monetary requirements, such as paying for RDT procurement and the human resources needed to conduct the tests, and nonmonetary costs, including the inconvenience to the individuals being screened. Some of these costs can be passed on to immigrants, but such charges will also increase the incentives to bypass official border crossings.

The MEG recommends that countries conduct effectiveness and cost-effectiveness analyses to determine whether and where screening measures should be implemented.

Total costs must be weighed against the potential benefits to determine the cost-effectiveness of screening programs. The following points should be considered:

1. Screening groups of travelers at very low risk of malaria infection will prove inefficient because a large number of individuals will need to be tested to find a single positive case.
2. Border screening is unlikely to be cost-effective in settings with high immigration rates but low importation risk, as large numbers of malaria-free individuals will have to be screened to find the few cases, as in the first point.
3. For a test with a given sensitivity and specificity, positive predictive value (PV^+, which indicates the probability that infection is truly present) will be lower if the population being screened has a low prevalence of infection (Figure 3.5).
4. The specificity of the screening test should be considered to ensure an acceptable rate of false negative results. In some cases, combining two tests—one highly specific and the other highly sensitive—may be appropriate.
5. The costs of screening can be reduced by focusing on high-risk groups, with calculations depending upon existing levels of outbreak risk and the capabilities for strong surveillance and outbreak response.

It is important to balance screening with other measures. For example, in the case of overland migration across a porous border, countries should increase the level of vigilance at the clinics in regions where migrants are likely to settle. The farms, mines, or other regions drawing migrant workers from endemic countries, for example, should be closely scrutinized for imported cases. If

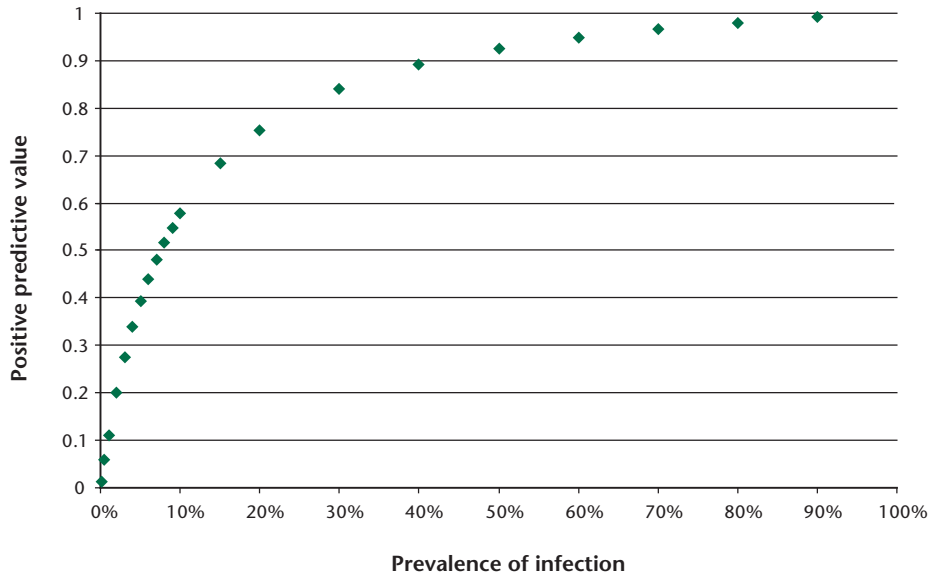

FIGURE 3.5 | Positive predictive value (shown here for a test with 95% sensitivity and specificity) increases as prevalence of infection increases in the population. At lower prevalence, a smaller fraction of positive test results is actually due to infections. Among groups of people crossing borders, overall prevalence rates may be low, so assessment of particularly high-prevalence subgroups will facilitate a more specific and cost-effective screening program.

screening is inherently inefficient, it may be more effective to focus resources on surveillance and outbreak risk reduction measures. There is no hard and fast rule for determining how valuable screening will be, but as a rule of thumb, the higher the malariogenic potential, the greater the need for all measures, including screening.

REDUCING TRANSMISSION IN SOURCE REGIONS

Risk of infection for a given migrant is dependent upon the endemicity of malaria in the region from which he or she travels. Oman, for example, reported importing less malaria after Zanzibar, a source of many travelers, controlled malaria with artemisinin-based combination therapy (ACT) and IRS and therefore greatly decreased transmission rates. Similarly, the burden of malaria in South Africa was reduced after Mozambique improved control of malaria. In resource-poor areas that share a border with endemic regions, zero transmission is unlikely to be sustainable without significant investment in cross-border initiatives. In addition, importation risk will increase if malaria

interventions falter or weaken in countries connected by national borders or immigration routes, emphasizing that countries have an interest in not only achieving control in neighboring countries but also sustaining it.

Importation risk is thus, to some extent, a factor that can be modified by coordinating national and international malaria control programs. Regional benefits of malaria control through transnational initiatives are what justify spatially progressive approaches to elimination.

The MEG recommends working with neighboring countries and those from which migrants originate whenever possible, to reduce importation risk.

Working with neighbors to reduce malaria in a multi-country region will increase the sustainability of malaria elimination. Because malaria control has regional implications for the public good, it should be incorporated into the international financing of malaria control (Chapter 4). Contributing resources to ensure sustained reductions in malaria in neighboring countries may prove to be a cost-effective investment toward preventing reintroduction following elimination.

3.4 Outbreak Risk

Outbreak risk, also known as receptivity, is essentially a measure of potential transmissibility that takes into account the two components described below:

1. the intrinsic potential for malaria transmission, as determined by the vectors and by geographic, environmental, and social factors (Chapter 7)
2. the interventions that reduce potential transmission from this baseline, including IRS, long-lasting insecticide-treated nets (LLINs), and well-developed health systems that treat malaria promptly with effective antimalarial drugs such as ACTs

The MEG recommends assessing intrinsic potential for malaria transmission to determine the need for maintaining interventions that lower outbreak risk.

Assessing potential transmission is important because many places in the world have suitable vectors and a history of malaria transmission. Some long-term changes in the intrinsic potential for transmission come about naturally as a consequence of socioeconomic growth, environmental modification, and climate change (Table 3.2).

The effect on malaria transmission of interventions to achieve elimination is discussed in Chapter 7. In planning for elimination, it is important to evaluate whether it will be necessary to sustain high coverage levels of nets and spraying

Table 3.2 | Factors affecting outbreak risk

Factors increasing outbreak risk	Factors decreasing outbreak risk
Evolution of vector resistance to insecticides or parasite resistance to antimalarial drugs	Economic development
Increased poverty and deteriorating living conditions	High-quality housing, screened windows
Increased agriculture or other land-cover/land-use changes (which may also decrease potential)	Paved streets, with gutters to improve drainage
Civil strife	Increased urbanization

even after reaching zero. Given that such operations will likely have been vital to the success of interrupting transmission, maintaining them should create an environment hostile to reemergence.

In countries where baseline outbreak risk is low, it will not be necessary to continue specific interventions to reduce outbreak risk further. The decision to maintain intervention coverage will depend upon the overall malariogenic potential: if baseline suitability for transmission or importation risk (or both) is high, reducing outbreak risk will be necessary to diminish reemergence risk to an acceptable level (Figure 3.2). At present, it is difficult to prescribe precisely what level of outbreak risk is "acceptable."

Outbreak-risk-reducing activities in a post-elimination region may involve regular and targeted vector control in previously persistent transmission foci identified during the elimination campaign:

- Regions in which final cases persisted before elimination are very likely to be the same regions in which risk of resurgent malaria is highest.
- New transmission foci may be identified by factors such as the influx of a large population of migrant workers or changes in the environment and geography.

In some cases, distribution of insecticide-treated nets (ITNs) may be warranted to ensure that outbreak risk does not return to baseline levels, while in other cases, larviciding and/or environmental management may be appropriate to control key vector breeding sites (Chapter 9).

In cases where analysis of outbreak risk and importation risk indicate the need to continue activities that lower outbreak risk, the MEG recommends that

such interventions should be conducted in a spatially targeted way that concentrates on previously identified foci.

Some countries have eliminated or come close to eliminating locally important anopheline vectors as part of their malaria campaigns, but the persistence of suitable breeding habitats and failure of malaria vigilance systems have allowed vectors to reestablish and create a suitable environment for malaria to reemerge. In some cases, the vectors have returned decades after malaria transmission was first interrupted. Countries where malaria parasites have been eradicated but where competent mosquito vectors remain—such as Australia,[15] France,[6] Italy,[5] Mauritius,[16] Réunion,[17] and Singapore (and nearly every eliminating country shown in Figure 1.1)[18]—can be said to exist in a state of "anophelism without malaria." Rather than attempt to further diminish outbreak risk, such countries have focused largely on ensuring that importation risk is minimized. Due to the proven resiliency of anopheline species, only in special circumstances should complete elimination of the vector be considered. In other areas, sustainable mosquito control measures may succeed in reducing anopheline levels and thus decreasing outbreak risk.

3.5 Surveillance: From Case Detection to Case Investigation and Response

Effective surveillance, efficient contact tracing, and aggressive response may be able to compensate for some weaknesses in other programs that reduce importation risk and outbreak risk. Surveillance for malaria in a region where malaria has been eliminated for a considerable time is somewhat facilitated by the loss of immunity in the population, because infections are more likely to manifest clinically, rather than remain asymptomatic. There is some hope of controlling outbreaks, even in areas with high outbreak risk, because of the length of time required for parasites to develop in the mosquito and in the human.

Even in the case of a country where the probability of local transmission is low, a strong and effective surveillance system (Figure 3.6) will be essential for ensuring the continued sustainability of malaria elimination, as long as humans and mosquitoes continue to cross borders freely:

Passive case detection Surveillance begins by examining a high fraction of people with suspicious fevers who show up at the clinic, either with microscopy or RDTs.

Active case detection Some transmission may have already occurred, whether or not the person in question was the index case; serological

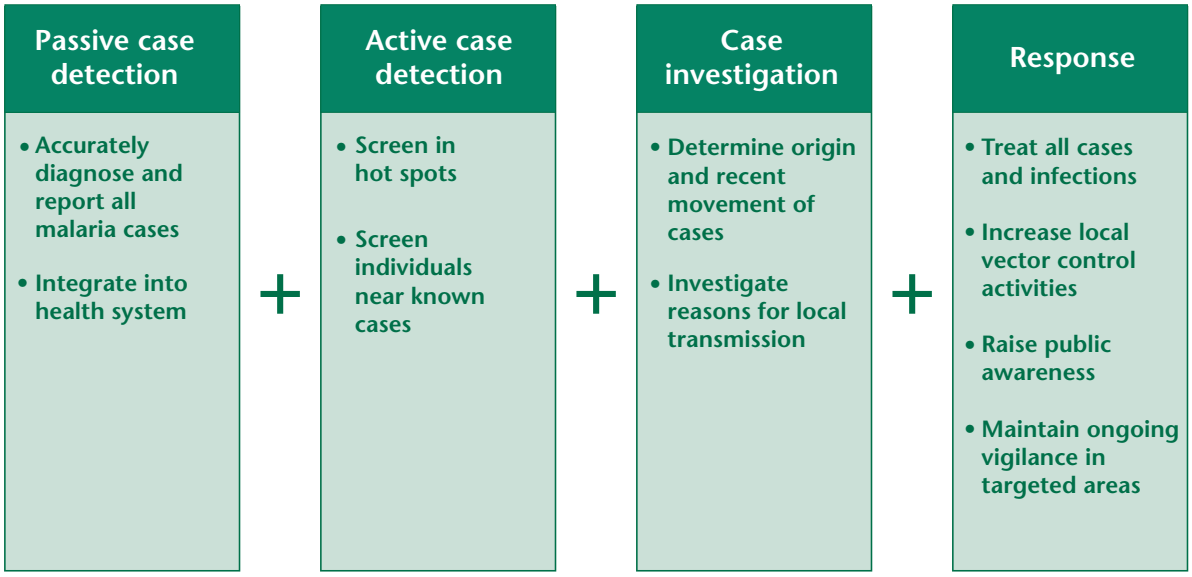

FIGURE 3.6 | Components of the surveillance and response safety net. Most surveillance activities should be integrated into the public health system.

sampling of individuals in the surrounding area can help define the history of infection, and increased testing for malaria in incident fevers may identify other malaria infections.

Case investigation When malaria is detected inside a country, follow-up procedures should be established. A history of travel should be taken to ascertain the source of the case—did the person travel to a malaria-endemic country? A travel history can also help to identify other places where malaria may have spread.

Response If there is any evidence of transmission, mass spraying with insecticides can help to reduce the reservoir of malaria in the adult vector population and reduce the level of immediate risk; identification and focal elimination of local breeding sites may also prove useful. Enhanced vigilance for malaria should continue for several months.

Surveillance for very rare occurrences of malaria is unlikely to succeed if it is conducted as a vertical system. Preventing isolated malaria cases from flaring into epidemics or endemic transmission requires identifying cases as they occur and ensuring that further transmission is prevented. In Oman, for example, strong interaction with the community encourages reporting of malaria cases even among illegal immigrants who might generally fear contact with

BOX 3.6 | Post-elimination Surveillance in Action

In the United States, around 1,000 to 1,500 cases of malaria are reported to the Centers for Disease Control and Prevention (CDC) annually, the great majority of which are imported cases among travelers and visitors from malaria-endemic regions. Although the United States received certification of malaria eradication in 1969, there have been 20 cases of probable local transmission reported to the CDC since 1992. The CDC's National Malaria Surveillance System collects information on cases reported by state health departments, laboratories, and health care providers, using a standardized form, and the CDC maintains a hotline to assist health departments in confirming malaria diagnoses with microscopy, serology, or PCR. Following identification of malaria cases in 2003, there were 300,000 residents living in the same county as identified cases who were urged to use prevention measures through telephoned warnings, while other residents were warned through mailing of informational postcards and posting of flyers. Additionally, enhanced mosquito spraying was implemented within a 3-mile radius of the homes of the malaria patients.

government agencies. Those cases can then be investigated. Case investigation is likely to be a cornerstone of post-elimination malaria programs, since maintaining a strong surveillance and treatment system is essential for containing infections before they can spark epidemics. Countries should be prepared to respond to imported malaria, regardless of the precautions taken to prevent it.

The MEG recommends that malaria surveillance needs to be integrated into the public health system for it to succeed.

It is also recommended that, until malaria is finally eradicated, every country should develop a case response plan with appropriate human capital and resource capacity to hold the line.

Following identification of malaria cases, screening of people in the surrounding area should be paired with rapid, targeted vector control to diminish the probability of local transmission. Because any infected individuals must be treated promptly, it is essential to maintain sufficient stockpiles of effective ACTs. These ACT stocks must be monitored, old drugs must be replaced as they expire, and an appropriate mix of pediatric and adult dosages must remain on hand.

3.6 | Conclusion

As long as malaria exists, countries free of transmission must be prepared to hold the line against reintroduction. Every country will have its own set of challenges to overcome in order to do so. This risk of reemergence must be

weighed against a country's surveillance and outbreak response capabilities. Assessing reemergence risk will require a careful assessment of importation risk and outbreak risk; ideally, an initial assessment should be conducted as a part of planning for malaria elimination. National malaria elimination programs should also develop surveillance to collect data about outbreak risk and importation risk, including historical patterns of endemicity and a record of imported malaria cases that have been investigated. Countries should weigh the value of reducing outbreak risk or importation risk. As a general rule, wherever the intrinsic potential for transmission is high, a combination of the following will be required to reduce the malariogenic potential:

- border screening to reduce importation risk
- ongoing malaria control to reduce outbreak risk
- rapid and robust response to identified cases

As malaria control succeeds in surrounding countries, importation risk will decline, but the need for vigilance will remain until malaria has been eradicated.

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4 | FINANCING ELIMINATION

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4.1 | Introduction

This chapter returns to the discussion of the economics and financing of malaria elimination that was introduced in Chapter 1. Elimination lies at one end of a continuum that spans intensive control of highly endemic malaria and goes through sustained control of modest levels of malaria to elimination (and sustaining elimination) of local transmission. Control of highly endemic malaria can bring major health gains with modest cost and, indeed, is among the most cost-effective of all available health intervention areas.[1] The objectives of moving from sustained control to elimination include, but also go well beyond, further reduction of morbidity and mortality. Chapter 1 discussed this broader range of objectives, which include improving the climate for foreign direct investment and tourism, contributing to the regional and global malaria elimination agenda, creating a sense of national accomplishment from closing the books on a major health problem, and engaging in a process that will in all likelihood strengthen both the public health and clinical care systems of a country.

In this chapter, we turn to two related and more specific issues concern-

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BOX 4.1 | Main Messages

- Countries considering elimination may wish to estimate carefully and compare the long-term costs of sustaining high levels of control versus eliminating. Elimination costs will likely be high during the drive to stop transmission; they may then become substantially lower during the subsequent period of holding the line at zero local transmission.
- In some countries, perhaps in a majority, the annual cost of sustained control will exceed the annual cost of sustaining elimination. This chapter presents a simple approach to allow such countries to estimate an approximate internal rate of return (IRR) for elimination efforts. If the IRR exceeds 3%, elimination is almost certainly something a country should seriously consider independently of other benefits, which may themselves be substantial.
- In order to ensure sustained funding after elimination and to avoid resurgence, donors will need to work with endemic countries to develop innovative financing mechanisms that ensure long-term funding and restrict the use of these funds to malaria. Endemic countries may also benefit from collaborating to seek funding for activities that are implemented across borders or regionally.
- A systematic evidence base on elimination economics should be developed: actual costs and financing should be formally documented in settings where elimination is now being undertaken or has recently been accomplished. This will increase data for elimination planning, and it may identify ways to reduce elimination costs, making it more economically attractive and sustainable.

ing the financing of elimination. The chapter correspondingly divides into two parts. The first part of the chapter explores the case where maintaining elimination may actually cost less than sustaining control and, therefore, be in some sense self-financing. The second part addresses standard issues of financing: where will the money come from, and how should particular problems associated with elimination, such as its long-term characteristics and frequent cross-border interrelations, affect the design of financial mechanisms and institutions?

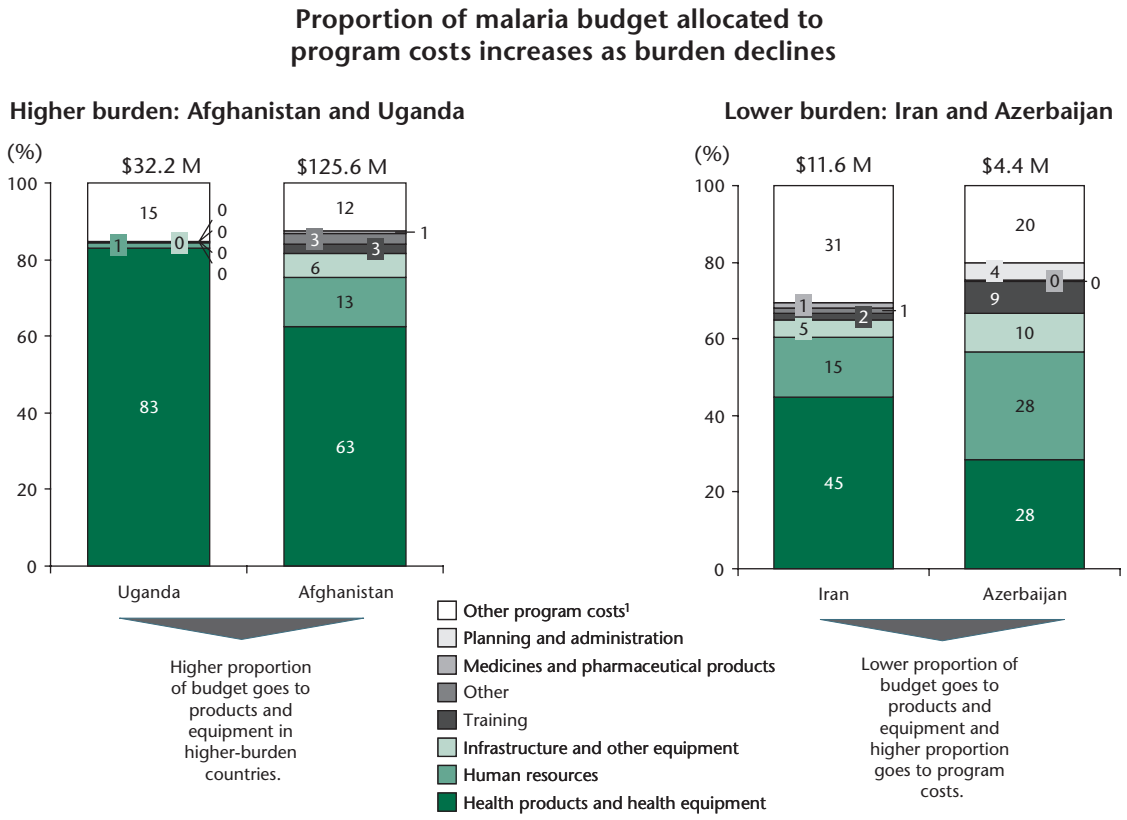
To explore the idea that elimination may be self-financing in some cases, we analyzed plans for malaria elimination efforts in the Jiangsu and Hainan provinces of China, and in Swaziland. For these locales we estimated current malaria control spending, the anticipated costs of elimination, and the savings from reduced malaria control activities that are expected to accrue after

elimination. The reader may reasonably question the general relevance of the examples from China and Swaziland. We use them in this chapter because they are the only detailed comparisons between the cost of elimination and the cost of sustained control that we have available at this time. However, similar detailed costing exercises are being worked on in a variety of other settings, including Mauritius, Morocco, and the Philippines. We will learn much from these cost comparisons, as they take place in very different epidemiological and ecological settings. This information will be posted on the MEG Web site as soon as it is available. Meanwhile, Section 4.2 presents results that we feel span a reasonable range of the circumstances likely to be encountered.

During an elimination campaign, when malaria transmission no longer poses a serious threat, donors or national treasuries may lose interest or redirect their funds to other pressing issues. This reduction in support may lead to a significant risk of resurgent malaria. Thus, financing mechanisms to ensure sustainability require two key features: stability and predictability. In Section 4.3 we explore financing mechanisms to help ensure an effective long-term strategy to prevent reemergence once malaria has been eliminated. Stable control efforts are essential to avoid backsliding, and thus to yield optimal health and financial dividends. The potential net savings referred to above and analyzed below require that malaria-elimination-related activities be sustained over years and decades, by definition in the absence of local malaria cases. The understandable tendency to redirect funds to more obvious health needs will need to be resisted. This challenge suggests the requirement for financial strategies that effectively isolate and protect funds for maintenance of malaria elimination. We explore four potential funding mechanisms, consider evidence of their use from other global health funding, and describe the pros and cons of each for sustained malaria elimination. First, however, we explore the possibility that malaria elimination may be cost-reducing and hence potentially self-financing.

4.2 When Will Elimination Be Cost-Reducing?

We review the anticipated costs of malaria control and elimination and then present more specific analyses of the anticipated costs and savings associated with malaria elimination in two provinces in China, and then in Swaziland. While these three case studies are unique, they highlight the sorts of analyses that individual countries and regions could conduct when contemplating a strategy of elimination.



1. Includes technical assistance, procurement and supply chain costs, communication materials, monitoring and evaluation, and overhead. Program costs are not directly related to commodities but to general support of malaria program. Adapted from: Global Fund applications.

FIGURE 4.1 | Malaria budget allocations of higher- and lower-burden countries

COSTS OF MALARIA CONTROL

Roll Back Malaria's Global Malaria Action Plan provides estimates of the long-term costs for the control and elimination of malaria. Over the near future, control costs are likely to total $6 to $7 billion per year. Figure 4.1 illustrates the types of resources required for both control and elimination programs. In higher-burden countries, the bulk of spending is dedicated to commodities (health products in the figure) such as bed nets, insecticides, and drugs. In lower-burden settings, the balance shifts toward human resources, as Azerbaijan's allocation shows. During and after elimination, surveillance and response costs will dominate. As discussed below, long-term costs are likely to decline due to decreasing need in many environments. This is because there will be only imported cases, a few relapsing and lingering infections, and lower and more-geographically-constrained risk. There may also be efficiencies associated with integration into national health services.

The costs of malaria elimination are less studied. Estimates from the Global Malaria Eradication Program in the 1950s and 1960s suggest a cost ranging between $0.50 and $2.00 per person per year, or $3 to $13 per person per year in today's dollars. More reliable and up-to-date are the estimated costs for elimination in countries or regions that are currently embarked on elimination and have made detailed Global Fund proposals (generally 5 years in length) to support their costs, though it is not assured that elimination will occur within the period of the proposal. Six such estimates are available:

- For Hainan Island, China, the annual costs of elimination are estimated to be $0.25 per person for the whole population of Hainan, and $2 per person at risk.
- For Sao Tome and Principe, the annual costs of elimination are estimated to be $11 per person.
- For the Solomon Islands and Vanuatu, the annual costs of elimination are estimated to be $18 and $25 per person, respectively.
- For Sri Lanka, the annual costs of elimination are estimated to be $1 per person for all Sri Lankans, and $5 per Sri Lankan at risk.
- For Swaziland, the annual costs of elimination are estimated to be $3 per person for all Swazis, and $7 per person at risk.

An important caveat about these cost data is that they relate to the costs of achieving elimination, rather than the costs of maintaining it once achieved. We know very little about the latter topic, and the collection of better cost data, both pre-elimination and post-elimination, is a high priority for operational research.

Caution is also needed in interpreting elimination cost differences among countries, since the costing exercises do not all include the same activities. For example, the costs for the Solomon Islands and Vanuatu include significant support for the malaria component of the routine health services and external management and technical assistance, both provided by the Pacific Malaria Initiative Support Centre in Brisbane. The costs for Swaziland, by contrast, include neither routine health service contributions to malaria elimination nor technical support from partner organizations.

Costs also vary widely depending on local circumstances. The high costs in the Solomon Islands and Vanuatu are linked to the logistic challenges of providing sustained services to small populations on remote islands. Differences in cost structures, particularly in the labor markets, between the different

BOX 4.2 | Projected Cost Savings from Malaria Elimination in Jiangsu, China

The MEG obtained data on current control and anticipated incremental elimination costs from Jiangsu health officials, based on ministry of health expenditures and budgets (national, provincial, and local), as well as Global Fund proposals. The current and projected elimination costs are divided functionally, allowing us to understand spending in four broad categories that we believe will respond differently to successful elimination efforts: surveillance, treatment, prevention, and program management. The analysis explores the costs of elimination versus sustained control over 20 years, accounting for future savings due to reduced malaria control costs. It includes an examination of the implications of imported malaria cases for potential reductions in control costs.

Jiangsu is a central province considering elimination. In 2007, there were 940 reported malaria cases, all *Plasmodum vivax*, in a population of 73 million (0.129 per 10,000). Underreporting is estimated at 4.5-fold, suggesting 4,230 actual cases per year. These internal cases include those that are imported. Jiangsu would expect to achieve elimination by 8 years from the formal beginning of its program. This goal is reflected in our longitudinal analysis.

In the longitudinal analysis, we tried two approaches to estimate savings in malaria control costs. First, we relied on the expert opinion of officials we interviewed regarding the scale of efforts required to achieve sustained control in the long term. Second, we used an algorithmic approach. We assumed that malaria control cost savings (e.g., decreased need for prevention) reflect the reduction in cases and that different types of costs may be differentially sensitive to these case reductions. For example, a 90% reduction in cases might correspond to a 90% reduction in treatment costs. The model allowed us to explore the effect on results of different quantitative values for assumptions. The two analysis methods yield very different results for Jiangsu (although rather similar estimates for Hainan).

Imported malaria cases are important to overall costs and to potential savings. To explore the effect of imported cases, we incorporated two parameters in the analysis. First, we specified a 0-to-1 scale that represents the severity of the border problem. In this scale, 0 designates no border cases and 1 designates a very severe border problem. Roughly, the score reflects the proportion of current cases due to border crossing. Second, we specified how the border problem affects the sensitivity of control costs to the reduction in cases. For example, a value of 0.3 for surveillance means that a border problem of a severity equal to 1 results in an added 30% surveillance cost (as compared with the start of the elimination phase); border problems of lesser severity lead to proportionally lower additions to costs. The model allows the effect on results of different input values to be explored.

The over-time analysis explores how elimination might affect total malaria control costs over 20 years. We compare current ongoing costs (i.e., ongoing sustained control) with the added costs and subsequent savings from elimination. This presents a more inclusive, and thus likely more realistic, assessment of the net costs of elimination than a shorter-term analysis.

For Jiangsu, the longitudinal result appears attractive. The reason is that the anticipated incre-

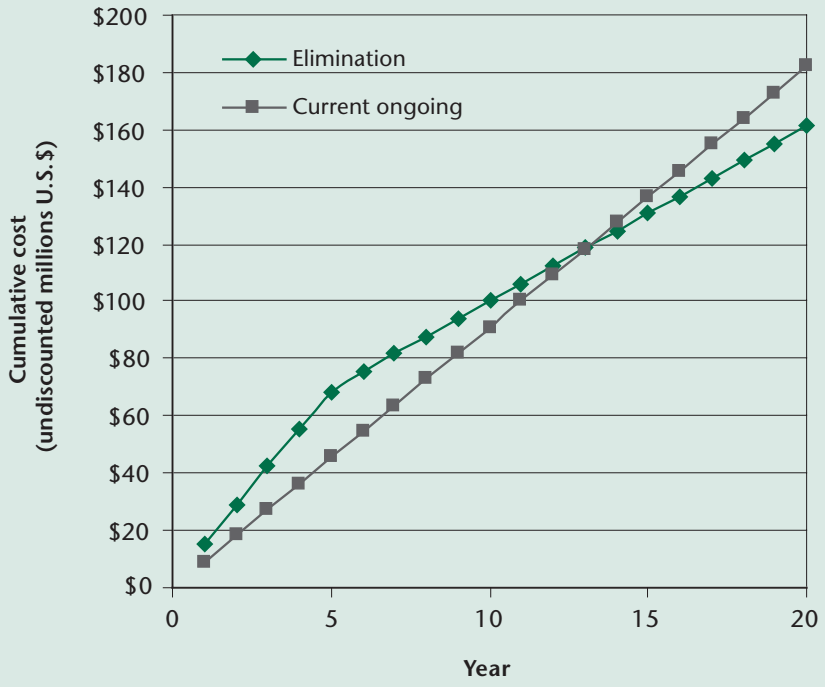


FIGURE 4.2 | Cumulative costs over time, elimination versus sustained control, for Jiangsu, China (algorithmic approach) (adapted from Kahn et al.[2])

mental cost of elimination is small in relation to current control costs. Jiangsu officials estimate $6.5 million in annual incremental elimination costs, as compared with $9.1 million in annual sustained-control costs (71% more).

After year 5, we assume that the sensitivity of each cost category decreases. For example, with no border effects, we assume that treatment costs are 100% sensitive (1.0) to case counts and that prevention is fairly (80%) sensitive to case counts after 5 years once elimination is nearly achieved (0.8).

The extent of importation risk affects this sensitivity. If migrants largely originate from nonendemic areas, as is the case on Hainan Island, we would assume that importation risk is low at 0.05. On the other hand, Jiangsu is a mainland province that borders the higher-endemic province of Anhui. With this greater importation risk for Jiangsu, we use a value of 0.25 so the final sensitivities are lower.

The result for Jiangsu is presented in Figure 4.2. The undiscounted cumulative costs for elimination are $161 million over 20 years, versus $182 million for sustained control. The undiscounted cost lines cross at 14 years, a short period for reaching total cost savings. If control costs following elimination are $4 million, as discussed by Jiangsu officials (lower than our algorithm-based estimate of $6.2 million), then the lines cross after only 9.5 years.

The scale of the border problem affects the internal rate of return for Jiangsu. If we increase the border problem scale from 0.25 to 0.4, based on the estimate that 40% of current cases are being imported, the lines cross at 18 years. If we decrease the border problem scale from 0.25 to 0.05, based on a sharp reduction in imported cases, the lines cross at only 11 years.

economies will also have a large effect on elimination costs. We return later to more detail on Hainan and Swaziland costs.

ELIMINATION AS A POTENTIALLY COST-REDUCING INVESTMENT

While prevention and treatment costs in highly endemic areas are generally very cost-effective, elimination presents different economic issues. First, elimination is contemplated only in situations with relatively few malaria cases. Thus, new strategies are likely to yield relatively few malaria cases or deaths averted when compared with the same strategies in high-burden settings. On the other hand, elimination offers the prospect of significant savings in future malaria control costs. Successful elimination would reduce treatment costs, as only imported cases would require treatment. Elimination would also potentially lead to a large reduction in prevention-related costs, as intervention measures are confined to restricted geographic areas such as entry ports and border zones. In some cases, therefore, pursuing elimination may "pay for itself."

We conducted a preliminary analysis of planned malaria elimination in Jiangsu and Hainan provinces, China, and in the southern African country of Swaziland. Our goal was to explore long-term costs versus savings, focusing on a 20-year time horizon.[2] To provide a sense of the data sources available for these studies, and the nature of the results, Box 4.2 summarizes the MEG's case study for Jiangsu, China.

THE INTERNAL RATE OF RETURN ON ELIMINATION INVESTMENTS

Box 4.2 provides a flavor of the complex considerations that underpin cost projections either of sustaining control or of moving toward elimination. A background paper for the *Prospectus*[2] provides more detail on that example from Jiangsu, China, and on additional examples from Hainan, China, and Swaziland. The next step involves calculating internal rates of return (IRRs) to provide an argument in favor of investment in elimination when the long-term annual costs of sustained control exceed the long-term annual costs of elimination.

The three cost flows and two ratios that are essential to understanding the financial attractiveness of elimination are shown in Table 4.1. The table also provides estimated values of these numbers for Hainan, Jiangsu, and Swaziland. The flows include the cost of maintaining the status quo (C), the cost of the transition to interrupted transmission (T), and the cost of maintaining elimination (E). The table defines these terms and expresses the values in millions of

TABLE 4.1 | Estimated costs of eliminating malaria in three locales

Cost parameter	Hainan Island, China	Jiangsu Province, China	Swaziland
C = cost of sustaining high level of control (U.S. $ millions per year)	2.9	9.1	0.7
T = transition cost of getting to zero (U.S. $ millions per year for 5 years, averaged)	5.8	13.9	2.4
E = annual cost of sustaining elimination (holding the line) (U.S. $ millions per year)	2.4	6.13	1.25
e = elimination cost ratio, i.e., cost of elimination phase as a fraction of sustaining control = T / C	2.0	1.53	3.43
s = annual cost savings as a fraction of cost of sustained control (cost savings ratio) = (C – E) / C	0.17	0.33	–0.79[a]

[a](i.e., increasing by 79%)

U.S. dollars per year for the three cost streams. Two ratios that are defined give annual elimination costs (e) as a fraction of sustained control costs, $e = T / C$, and long-term annual cost savings (s) also as a fraction of sustained control costs, $s = (C – E) / C$. Here e provides a sense of the cost of the elimination investment, and s provides a sense of its financial returns. The case of Swaziland is instructive here: the planned long-term costs of elimination exceed those of control, and hence s, the savings, is negative. To reiterate a point made in Chapter 1 and earlier in this chapter, a negative s in no way suggests that elimination is not worthwhile. However, it does imply that the full range of benefits must be assessed and that the effort may not be "cost-reducing" over time.

Given e, elimination costs, and s, the savings, and then using the methods outlined in Box 4.3, a calculation of an internal rate of return shows an ultimately cost-saving elimination investment. Figure 4.3 presents IRRs for a range of values of e and s. It shows, as would be expected, that IRR values will increase for a given cost (e) as the value of the cost savings (s) increases. The figure also places Hainan and Jiangsu results into the larger range of possibilities. This figure serves as a working tool for others to use in estimating IRRs.

In conclusion, we observe that Hainan, Jiangsu, and Swaziland span the continuum of possible outcomes for assessing whether elimination is self-financing: For Swaziland, the result is clearly negative. For Jiangsu, the IRR (at 10%) is sufficiently high to justify elimination by itself. For Hainan, elimination is ultimately cost-reducing, but the relatively low IRR of 3% suggests the need for careful assessment of the benefits to Hainan before a decision is made

BOX 4.3 | The Simple Algebra of Rate of Return

Investments entail giving up resources now to attain more resources later. An investment of $100 that yields $200 in 10 years is said to have a rate of return of 7.2% because $100 invested with 7.2% per year compound interest will yield $200 after 10 years. Alternatively phrased, the "present value" of $200 ten years from now at 7.2% per year is $100. The concept generalizes to circumstances when costs and benefits are spread over multiple years. Investing in malaria elimination will sometimes yield financial savings, in the sense that the annual costs of maintaining sustained control can exceed the annual costs of maintaining elimination. During the transition period of getting local transmission to zero, costs will exceed those of sustained control. The present value of these excess costs over a period of years, assumed for purposes of this example to be 5 years, can be viewed as an investment. If the ongoing cost of holding the line (maintaining elimination) falls below that of sustained control (after the 5-year investment period), then there will be a return on the investment that is equal to the difference between those numbers each year. Again, there will be a present value of benefits that is the sum of the present values in each year.

The present values of costs and benefits vary with the interest rate. A common figure of merit for investments is the IRR, that is, the interest rate that equalizes the present value of costs and of benefits. In these calculations we assume that the benefits continue unchanged over an extended period. In reality, because of changes in economic levels, the level of malaria in neighbors, or the effectiveness of available control measures, both costs and benefits will change with time. If the numbers are known, the change is easy to incorporate into the analysis. The results presented in this *Prospectus,* however, should be viewed as a first approximation, as suggestive rather than definitive.

With this as background, the following equations yield the results we have used for this *Prospectus*.

Let

PVC(r) = present value of costs, given an interest rate of r

PVB(r) = present value of benefits, given an interest rate of r

C = annual costs of sustained control

T = annual costs of transition to elimination

E = annual costs of maintaining elimination

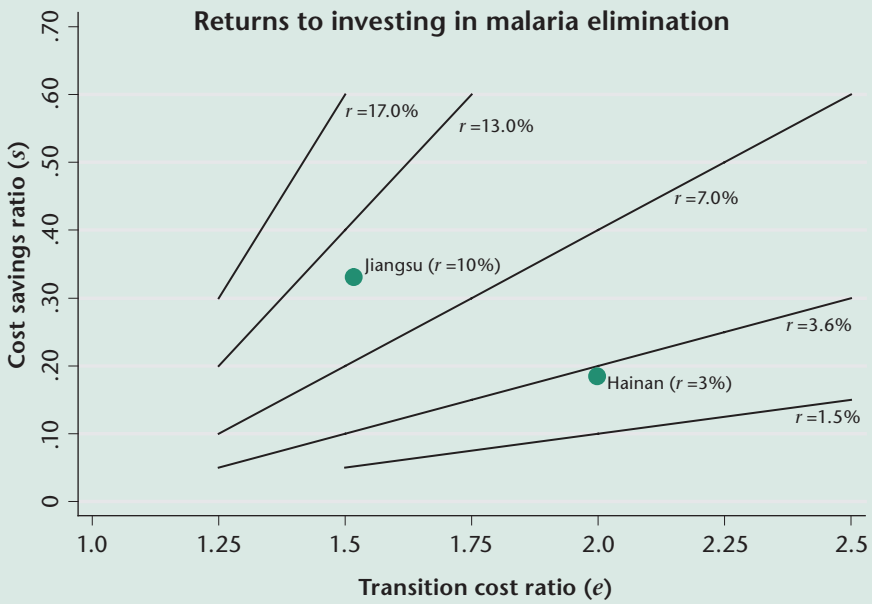


FIGURE 4.3 | Internal rates of return for investing in malaria elimination (from Kahn et al. background paper[2])

NOTE: These are cost estimates prepared for planning purposes and, as such, do not directly reflect historical experience with costs. The background paper by Kahn et al.[2] describes sources and makes estimates of the sensitivity of the results to the underlying assumptions.

Then the present value formula gives the following:

(1) $PVC(r) = \sum_{t=0}^{4} (T-C)/(1+r)^t$

(2) $PVB(r) = \sum_{t=5}^{t=100} (C-E)/(1+r)^t$

Equation (1) assumes costs remain constant for the first 5 years, and equation (2) assumes benefits last until year 100. (The results vary little whether the assumption is 100 or 60 or 40.) Table 4.1 gives values—based on planning exercises—for T, E, and C for Hainan, Jiangsu, and Swaziland.

Given T, E, and C for a country, it is possible to calculate the IRR for the elimination investment by solving for the value of r that makes equation (1) equal equation (2). As discussed in the text, for example, Hainan Island's IRR is about 3.6%.

to undertake elimination. Once these analyses have been done, financing is the next logical need to discuss.

4.3 Financing Malaria Elimination

INTRODUCTION—THE NEED FOR SUSTAINED FINANCING

Once the costs have been established pertaining to sustained control or pursuing elimination, finding sustainable funding for the long term is the next challenge. First we will look at historical patterns of country-level, international health financing. Then, current opportunities for regional malaria initiatives will be explored.

Continuing control efforts for a disease that no longer causes significant morbidity or mortality is a challenge in that such efforts may lead to fatigue, lapsed funding, and then attenuation of control efforts. In addition, the effectiveness and cost of sustaining elimination within a country often depend on actions taken beyond its borders. These issues are essential to take into account when thinking about long-term and international financing. Figure 4.4 provides concrete examples of the volatility of donor support to health, an essential component of malaria funding for low-income countries considering elimination. The volatility is perhaps more important today than during previous elimination efforts, as many of the countries that are considering elimination today are largely dependent on official development assistance (ODA) for health sector spending. The specific implications of this deserve further study and attention, as halting elimination efforts after they begin could result in significant rebounds in morbidity and mortality.

Successful malaria elimination programs can thus have a downside: reduced incidence results in diminishing awareness and, potentially, a corresponding loss of funding to sustain control efforts. Ongoing, high-volume control efforts likewise lead to decreased political salience. Resurgence of malaria in previously low-transmission areas is often blamed on such factors as insecticide resistance or supply shortages, yet many of these proximal causes may ultimately stem from decreases in funding and attention for malaria programs. In the past, rising donor fatigue within the international community led to a reduction in commitment at the same time that countries, impatient with lengthy elimination or eradication processes, reduced funding or shifted it to other programs. In many countries, indoor residual spraying (IRS) activities were the first item to be scaled back; there is a direct link found between donor fatigue and demise of the IRS program.[3] In India, the resurgence of

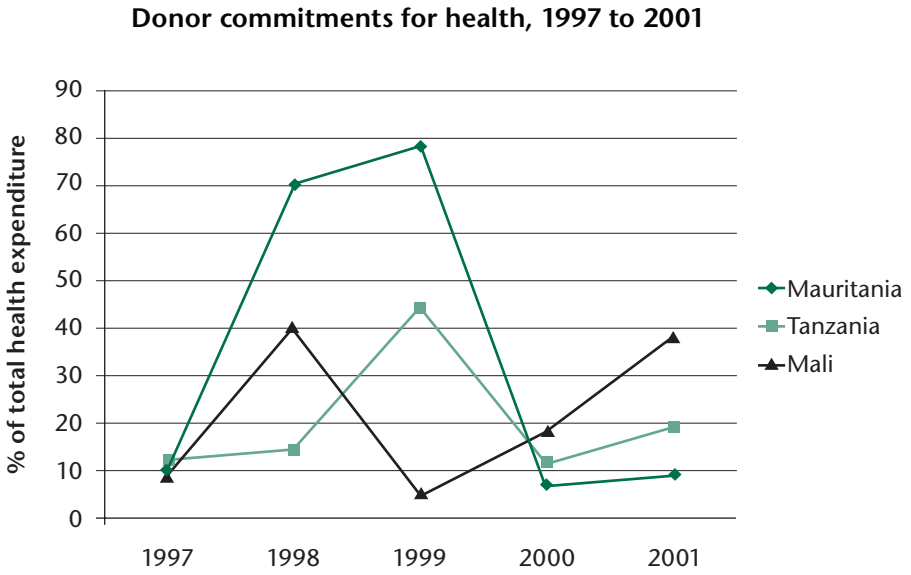


FIGURE 4.4 | Funding for health in three countries, 1997-2001 (from Gottret and Schieber[3])

malaria in the late 1960s may have been the result of this deterioration of vector control.

Governments with limited health budgets also shifted funds away from drug supplies and surveillance activities, resulting in poor detection and treatment in addition to weak program management and supervision.[4] Failing financial support contributed to staffing shortages in India: key positions were left unstaffed, creating a shortage of technical and operational guidance. At the same time, urban municipalities endured gaps in financing, leading to an increase in urban cases and the creation of urban foci of transmission that may have paved the way for the resurgence.[5] The continuation of funding and support might have ensured proper control and management, thereby preventing or minimizing the resurgence experienced by many countries. Large-scale morbidity and mortality might have been prevented.

Research support for development of new insecticides and drugs was likewise limited after 1963 when international funding was dwindling. This downward trend discouraged young scientists from pursuing studies on malaria, and as a result, research and development stagnated.[5] With the deterioration of financial support of these essential efforts in the fight against malaria, the momentum generated by the elimination and eradication campaigns quickly ground to a halt. Meeting the challenge of sustaining financing thus remains a priority for countries considering elimination. The lessons from the Global

Malaria Eradication Program relay the importance of sustaining financing over the long term to prevent the climate for a resurgence of the disease and the resulting morbidity and mortality.

Considering this history of fluctuating support, it is important to recognize that lower income countries will require external assistance for elimination that has a long-term and consistent commitment. This funding must be maintained even after malaria is eliminated and the focus moves toward preventing reintroduction. Yet, as we have seen, donor support can fluctuate in ways that complicate and even paralyze the management of a long-term intervention. This is a particular risk when working with diffuse and hypothetical benefits, as with malaria elimination: The risk of bounce-back is significant. Financing for elimination that is sustained over the long term is the only way to ensure that the benefits of elimination will evolve, and these methods are explored in more detail below.

Consistent financing is also important for regional elimination efforts, and different financing options are available to partners of this type of strategy. First, in a small number of cases, a country on one side of the border will be relatively high-income and could, if it chose, finance cross-border control efforts for both countries out of its own budget. Second, neighboring countries can receive donor funding individually and then collaborate across their borders. A third option is for countries to form a regional consortium and apply together to the Global Fund or other sources of international financing. For example, the four eliminating countries in southern Africa could join forces, create links with their northern neighbors (the E8 countries), and write a regional application to strengthen the necessary structures to ensure cross-country coordination and effective implementation on the border areas. Typically this would also include some elimination work within their borders. Whether funds are sought regionally or nationally, strong multi-country and cross-border collaboration and coordination will greatly facilitate elimination in continental countries with malarious neighbors. To date, it has been relatively difficult to find donor resources for regional or cross-border efforts, as most health ODA channels consider the country the basic unit of lending or granting.

FINANCIAL MECHANISMS

Financing mechanisms to ensure sustainability require two key features: a secure source of funds and the ability to restrict use of those funds to ongoing malaria control. By secure we mean stable and predictable, not subject to wide fluctuations. Table 4.2 summarizes several mechanisms that have the potential to meet these requirements. These are then further discussed below.

TABLE 4.2 | Four examples of long-term funding mechanisms for elimination

Mechanism (source)	Pros	Cons
Very long-term external assistance (from standard donors such as bilateral and multilateral agencies, foundations)	• Funder is committed to specified purpose; funds are not lost to local competing priorities. • Funding is flexible and can support cross-border efforts and adjust amount or structure as needed.	• Funds rely on external funder (are not internally sustaining). • Funder may face competing priorities for other diseases/countries. • Funds are time limited.
Domestic earmarked tax (tapping national tax base)	• Funds are substantial if based on large transaction base. • Income can be retained in earmarked funds.	• Taxed parties resist. • Earmarked funds may be reassigned due to competing priorities.
Trust fund (from standard donors, foundations, domestic taxes for middle-income countries)	• Funds are very substantial if they tap global capital markets. • Spending can be tightly restricted by charter. • Funds can support cross-border efforts.	• If funds are from bonds, donors must commit to repayment. • Funds are inflexible if conditions change.
Endowment (from private or public sources)	• Annual funds are predictable if endowment is stable. • Spending can be tightly restricted by charter.	• Annual spending is limited, does not tap principal. • Funds may be inflexible if conditions change. • Donor comfort level with endowments is often low.

Long-Term Official Development Assistance ODA can entail the prospective commitment for one or more decades of foreign aid dedicated to a specific purpose. This approach is similar to current health assistance efforts, and it differs fundamentally only in duration. A well-known and successful example is the Onchocerciasis Control Program (OCP), which was launched in 1974 and, at its peak, covered 30 million people in 11 countries. Funding was planned for 20 years and was divided into 6-year phases. Continuation was conditional on performance.[6] Another example is substantial funding by the Bill and Melinda Gates Foundation for the Global Alliance for Vaccines and Immunization (GAVI). These long-term commitments allow time for rollout of ambitious health initiatives and can be tailored to them. However, they may be more appropriate for activities with an anticipated end date than for post-elimination malaria control of uncertain duration. They may also be subject to competing priorities at the funder level.

Long-term ODA may be a very suitable option for regionally implemented programs.

Earmarked Taxes Earmarked taxes are special taxes, often levied on a single type of transaction, to generate funds for a designated public purpose. They are designed to be simple to administer in that they are added on to an existing tax mechanism. By being proportionally very small, they do not substantially distort commercial transactions, yet they are substantial in magnitude through application to a large transaction base. In the United States, a "black lung" tax on private companies funds medical care for pneumoconiosis. Another recent successful example is the Solidarity Tax on aircraft tickets used to support UNITAID, which purchases drugs for the developing world.[7-10] Funds can be retained in special funds. Challenges include potential opposition from taxed parties and a fund's vulnerability to competing priorities if earmarking does not fully shield it. However, general taxes used for health are typically more vulnerable than earmarked taxes.[11]

Trust Funds and Endowments Trust funds are financial reserves dedicated to a specific purpose, both present and future. They are funded mainly up-front with initial investments, rather than pay-as-you-go taxes. Funding can derive from taxes but can also tap into other mechanisms, such as international capital markets. A very successful recent example is the International Finance Facility for Immunisation (IFFIm). IFFIm sells bonds on capital markets, with the repayment obligation falling to participating European bilateral donors.[12] Bhutan provides another example of a health trust fund to which government and donors contribute. Ethiopia has also taken a trust fund approach, using a Millennium Development Goals Trust Fund to secure multi-donor commitments to procure essential health commodities, including malaria control commodities. This mechanism permits initial investments, such as would be required to achieve malaria elimination, and also protects a portion of funds as needed for future activities. If chartered appropriately, the trust fund can protect funds for specific uses.

Endowments are similar to trust funds, except that annual spending is often limited to interest on the principal. The stock market crash of 2008, however, underscored the vulnerability of endowments to asset price fluctuations unless funds have been very conservatively invested.

Private Sector Dedicated Funds Corporate initiatives can assist with malaria elimination in two separate ways. An excellent example is (PRODUCT)^{RED}, which has generated over $120 million for the Global Fund through regular contributions from sales of participating products. A related philanthropic approach is the use of credit cards for which a small percentage of all billing is contributed to a public fund, as with the American Express RED card.

BOX 4.4 | Corporate Financing of Malaria Control Foci in Ghana and South Africa

In low-income countries, where a domestic program budget is likely to be insufficient for elimination and where donor funding may prove unreliable, industries such as mining and tourism provide examples of supplemental private funding sources that provide mutual benefit to a company and the local population. Two examples come from Ghana and South Africa.

In 2004 and 2005, malaria was considered to be the "most significant health threat" to the operations of AngloGold Ashanti Limited in the Obuasi gold mine in the southwest of Ghana.[13] The workforce suffered a prevalence rate of over 20%, leading to between 2,600 and 3,900 sick days annually. Available domestic resources were not sufficient to make a difference, and productivity declined. In response, AngloGold Ashanti initiated an integrated malaria control program in 2006 that included scientific studies as well as IRS, larviciding, case management, and surveillance. Costs for the first year were an estimated $1.7 million, with an annual budget of $1.3 million in the following years. This program yielded a 73% decline in reported cases in less than 2 years, drastically reducing absenteeism and increasing productivity in the mine. AngloGold Ashanti plans to expand the malaria program into three other mines in the southwest of Ghana, in addition to programs in Guinea, Mali, and Tanzania. Their commitment to malaria provides a model for private sector participation when the national budget is unable to foot the bill.

The tourism industry is also directly affected by malaria. In South Africa, tourism brings an estimated 8.45 billion international dollars every year into the country.[14] In the Lubombo region, a popular destination for international tourists, malaria is "identified as the primary impediment to the effective development of the high potential Lubombo tourism area." In response, the Business Trust, the government of South Africa, the Global Fund, and other donors co-funded a regional malaria control program, the Lubombo Spatial Development Initiative, or LSDI, in 1999.[15] Seventy percent of funding for LSDI is from the private sector (Chapter 2).

The results of the intervention are substantial: in the 1999-2000 season, when incidence reached 42,395 cases in the KwaZulu Natal province alone, 89% of tourism operators felt that malaria was a detriment to the industry, and 53% had cancellations because of malaria concerns.[16] In contrast, from 2002 to 2003, only 42% of operators believed malaria to be a detriment to their profits and 9% recorded cancellations due to malaria. In the interests of tourism, private companies have worked with government programs to control malaria, driving down transmission rates and increasing revenue in the region.

A separate motivation for corporate involvement reflects the importance of malaria control for conducting business. Box 4.4 describes two successful cases of private sector involvement in implementation of control efforts, as well as their financing. While corporate interest offers no promise for carrying a major fraction of the financial burden, in some circumstances such contributions will be significant. Further, if corporations execute their investments efficiently, they can provide a useful model for other companies (Box 4.4). In this way, there are potential mechanisms to create long-term financial structures for malaria elimination. Donor support is available for low-income countries, but knowledge of the funding volatility over the years can make a good idea seem precarious. A thorough investigation and evaluation of the funding sources and methods to secure funding (listed above) is essential before getting down to the business of elimination.

4.4 Conclusions

1. Estimating three categories of costs can help inform the elimination decision. The categories comprise the following:
   - annual costs of sustaining control at a high level
   - the investment (or transition) cost of going from sustained control to zero local transmission
   - the annual costs of holding the line at zero local transmission

   The *Prospectus* presents three sets of estimates of planned costs in these categories, and the MEG has initiated case studies to expand the knowledge base.
2. For two of the three costing case studies reported in this *Prospectus*—from Hainan and Jiangsu, China—long-term elimination costs lie below those of sustained control. These cases lead to the calculation of an internal rate of return of elimination as a cost-reducing investment. Even if long-term costs of elimination exceed those of sustained control, as they did for our case study from Swaziland, benefits may well exceed costs for elimination. The value of rate-of-return assessments, however, lies in findings of rates of return sufficiently high—greater than 3%, say—to justify elimination even in the absence of assessed benefits.

3. Financing elimination has two unusual challenges:
    - The time horizon may exceed a quarter of a century, leading to "elimination fatigue" on the part of voters and donors.
    - Cross-border externalities and global public good point to the need for coordinated multi-country financing.
4. To address these particular financing problems, several less-frequently used financial instruments should be considered to complement general revenue taxes and standard forms of foreign aid:
    - very long-term ODA (conditional on performance)
    - earmarked taxes
    - trust funds
    - endowments
5. Alongside exploring financial solutions to the elimination efforts, it would also be useful to concurrently explore political solutions. Most elimination financing is likely to come from traditional channels, and long-term political commitment—at donor and endemic country level—may be the most powerful driver of all.

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5 | UNDERSTANDING MALARIA

Michelle S. Hsiang,[a] Claire Panosian,[b] and Grant Dorsey[c]

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

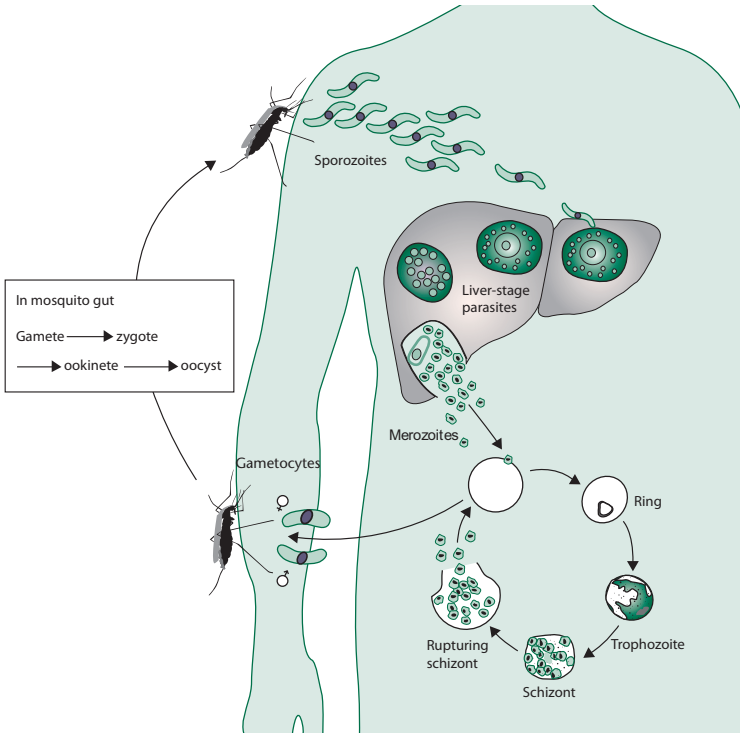

FIGURE 5.1 | Life cycle of the malaria parasite between mosquito vector and human host (Reprinted from *The Lancet,* 365 (2005): 1487-1498. Greenwood, B.M., Bojang, K., Whitty, C.J.M., & Targett, G.A.T. Malaria. With permission from Elsevier.[4])

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

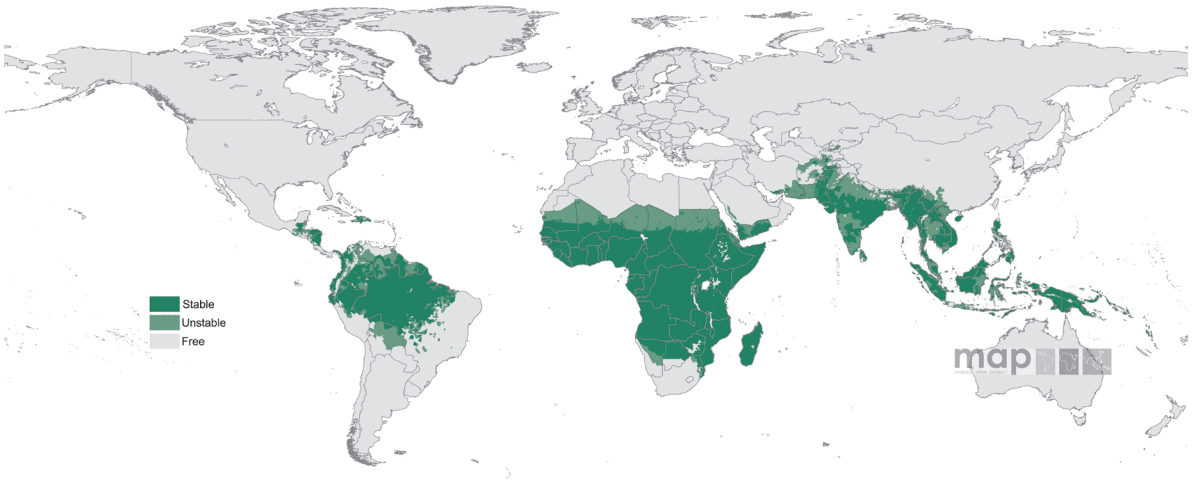

FIGURE 5.2 | Global distribution of *P. falciparum*. Areas are defined as stable (dark green areas, where *P. falciparum* annual parasite incidence, or *Pf*API, ≥ 0.1/1,000 persons per year), unstable (light green areas, where *Pf*API < 0.1/1,000 persons per year), or no risk (light gray). This distribution 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.

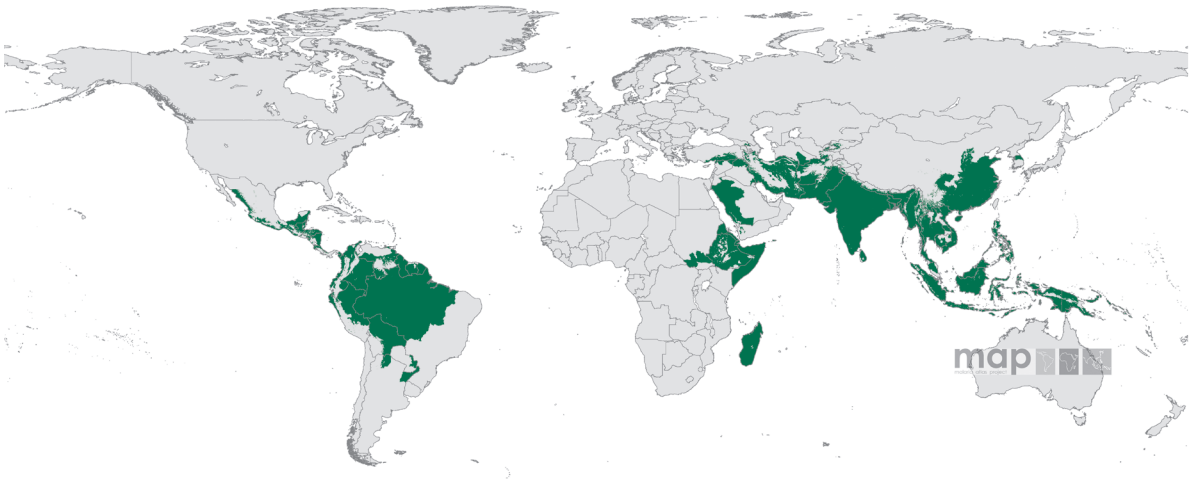

FIGURE 5.3 | Global distribution of *P. vivax* (from Guerra et al.[12, 13])

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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6 | LEARNING FROM HISTORY

Walther Wernsdorfer,[a] Simon I. Hay,[b] and
G. Dennis Shanks[c]

6.1 | Introduction to Malaria Elimination: Lessons from Yesterday for Today and Tomorrow

Malaria has accompanied mankind since the origin of *Homo sapiens*. The cause of malaria, parasites of the genus *Plasmodium*, and the mechanism of transmission by mosquitoes were discovered before the end of the 19th century, followed by the development of the armamentarium of malaria control, namely, methods of personal protection, advances in the discovery of therapeutic and prophylactic drugs, and methods of vector control directed against larval breeding sites and adult mosquitoes. These developments set the scene for attempts to eliminate malaria through the Global Malaria Eradication Program (GMEP), which considered elimination feasible in countries with malaria of low or intermediate stability. However, after only 14 years, WHO downgraded the GMEP to malaria control because many countries had experienced difficulties in initiating or sustaining national programs, often because of inadequate national commitment. Nevertheless, several countries successfully eliminated malaria, demonstrating that this goal remains a feasible option for other malaria-endemic countries. This chapter analyzes the lessons learned from both successful and unsuccessful attempts to eliminate malaria, as well as

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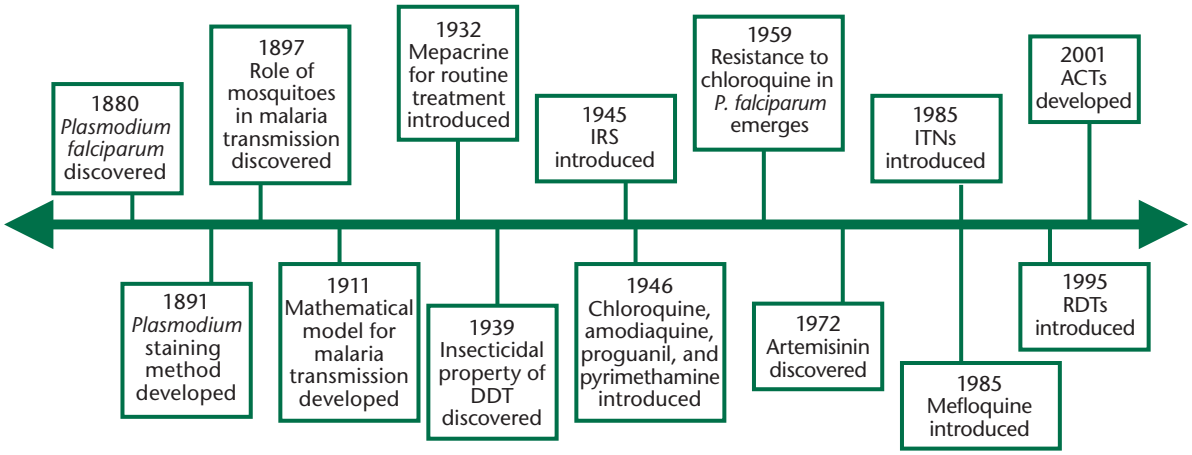

FIGURE 6.1 | Timeline of the development of the malaria armamentarium

factors that have contributed to a constant shrinking of the malaria map from 1955 to today.

6.2 | Chronology: Development of Tools for Malaria Control

Since *Plasmodium falciparum* was first discovered in 1880, many important discoveries have been made, and tools have been developed that enable endemic countries to control and/or eliminate malaria. A timeline of major discoveries and the development of technologies in use for diagnosis of malaria and for parasite and vector control is given in Figure 6.1.

Drugs that today are essential for the treatment of malaria (quinine and artemisinins) were first used in their native form for treatment of periodic fevers long before the malaria parasites were discovered in the 19th and early 20th centuries.[1, 2, 3] The demonstration of the natural mode of transmission through anopheline mosquitoes around the same time led to the development of vector control measures against the larval and adult stages.[4]

6.3 | History of Conceptual Changes: Malaria Control to Elimination

The concept of eradicating malaria was first proposed by Fredrick L. Hoffmann in 1916 in his "plea for malaria eradication in the Western Hemisphere."[5] At

that time, however, controlling malaria was the priority, and eradication was not yet considered a feasible goal.

New tools such as indoor residual spraying (IRS), chloroquine, amodiaquine, proguanil, and pyrimethamine were developed at the end of World War II and radically improved the prospects for intensifying malaria control. International attention directed toward control of malaria became stronger, as demonstrated by the establishment of disease control institutions such as the Centers for Disease Control and Prevention (CDC) in the United States in 1946, which was founded to limit the impact of malaria and which eventually achieved elimination of the disease in 1952 in the 13 states where malaria was still endemic.

Devastating postwar malaria epidemics in southern Europe highlighted the need to design and implement effective malaria control programs. Cyprus, Greece, and Italy strengthened their health systems to cope with diagnosis and radical treatment of malaria, with transmission controlled by residual spraying of DDT. After the Greek government suspended DDT spraying, the expected resurgence of malaria did not occur, indicating that in similar eco-epidemiological settings, *P. falciparum* and *P. vivax* can be eliminated if transmission is fully suppressed for 4 years for *P. falciparum* and 5 years for *P. vivax*.

Successful elimination campaigns such as those in Greece and Italy gave hope for a malaria-free world. The GMEP was launched at the eighth World Health Assembly in 1955, when the following announcement was made: "The World Health Organization should take the initiative, provide technical advice, and encourage research and coordination of resources in the implementation of a program having as its ultimate objective the worldwide eradication of malaria."[6, 7]

This new strategy was heavily dependent on employing long-lasting pesticides, primarily DDT, to kill adult vectors and interrupt malaria transmission. The countries and regions where elimination seemed feasible were initially targeted, which at the time included the Americas, Europe, the Mediterranean countries, western and eastern Asia, and the western Pacific and Australia. Malaria elimination in sub-Saharan Africa and New Guinea was not considered feasible with available tools and means, a perception that remained fundamentally unchanged until recently, despite the fact that very large swaths of both regions experienced low endemicity.[8]

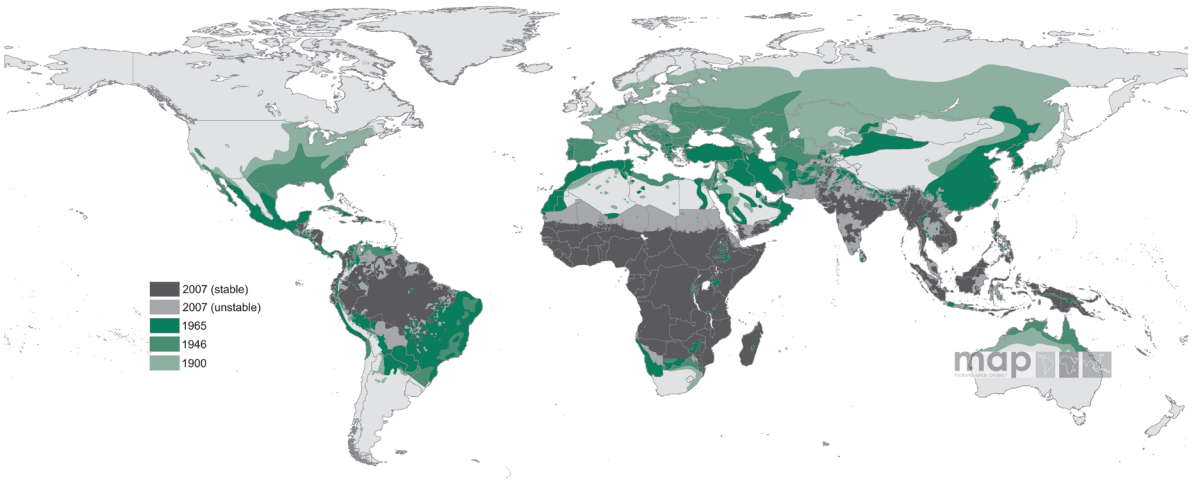

FIGURE 6.2 | Geographical distribution of all-cause malaria 1900, 1946, and 1965 (modified from Hay et al.[9]) with the overlay of the 2007 spatial limits of *P. falciparum* malaria transmission (modified from Guerra et al.[8]). The 2007 bounded areas were defined as stable (dark gray areas, where *P. falciparum* annual parasite index, or *Pf*API, ≥ 0.1 per 1,000 per year) or unstable (lighter gray areas, where *Pf*API < 0.1 per 1,000 per year).

6.4 | Shrinking the Map: Geographical and Chronological Progression of Malaria Elimination

The geographical and chronological progression of malaria elimination between 1900 and 2007 is shown in Figure 6.2 and summarized in Table 6.1.

Practically all malaria-endemic countries in the Americas joined the GMEP, and most endemic countries in Europe continued to move toward elimination. In tropical Africa, only two offshore islands declared national malaria eradication programs. Australia, the Solomon Islands, and Vanuatu joined the program, as did the majority of southern Asian countries, from Turkey in the west to Taiwan in the east.

In the Americas, 22 countries achieved malaria elimination from 1950 to 1978, among them the majority of Caribbean countries. With the exception of the United States and Chile, none of the malaria-endemic continental countries in the Americas reached this goal. In the European region, 37 of the remaining 43 malarious countries became malaria free during the same time period. Small foci, or limited areas of continued transmission, persisted in Greece beyond 1970, but malaria was eliminated in the late 1970s. Australia, Japan, and Singapore all succeeded in eliminating malaria by 1978. Brunei, Israel, and Réunion followed suit soon after.

Table 6.1 | Malaria status of countries and territories 1900, 1949, 1978, and 2009 by WHO regions

Parameter	Africa	Americas	S.E. Asia	Europe	E. Med.	W. Pacific	Total
Total number of countries	48	45	10	58	20	27	**208**
Malaria free in 1900	1	2	0	3	1	13	**21**
Malaria free 1900-1949	0	0	0	9	0	0	**9**
Malaria free 1950-1978	2	22	0	37	4	4	**68**
Malaria free 1979-2009	1	1	1	1	6	0	**10**
Total malaria free	4	25	1	50	11	17	**108**

Sources: Wernsdorfer,[10] WHO,[11] Packard,[12] Bruce-Chwatt and Zulueta,[13] and "Malaria in the Southwest Pacific"[14]

Although mortality and morbidity from malaria decreased significantly in most countries during the GMEP, the initiative failed to reach the ultimate goal of eradication. Consequently, in 1969, the WHO General Assembly reexamined the strategy[15] and recommended a reversion to malaria control for the countries that were clearly unable to achieve elimination within the foreseeable future; however, it failed to provide guidelines and recommendations for a systematic strategy to achieve control. After 1972, the malaria situation worsened as a result of political factors, insufficient national support, and withdrawal of external assistance. This was marked by a substantial increase in the number of autochthonous malaria cases recorded in areas under surveillance between 1972 and 1976 (Figure 6.3).

Nevertheless, several countries continued on the path to the elimination of malaria, as shown in Table 6.1, and ten countries achieved elimination between 1979 and 2009, among them six Eastern Mediterranean countries, including Bahrain, Morocco, Oman, Syria, Tunisia, and the United Arab Emirates. Kazakhstan, Maldives, and Seychelles were also successful.

Remarkable success in spatially progressive elimination in large parts of endemic countries has been achieved in Argentina, Brazil, China, Paraguay, the Philippines, and Thailand. By the year 2000, an estimated 60% of the world's population resided in malaria-free areas, a great increase from 20% in 1950. In 2007, 35% of the world's population lived in areas still endemic for malaria,[8] with about 66% of those protected by some form of organized malaria control. Tropical Africa and the island of New Guinea are still considered the last epicenters of endemic stable malaria.

The decision taken by the World Health Assembly in 1969 reflected the

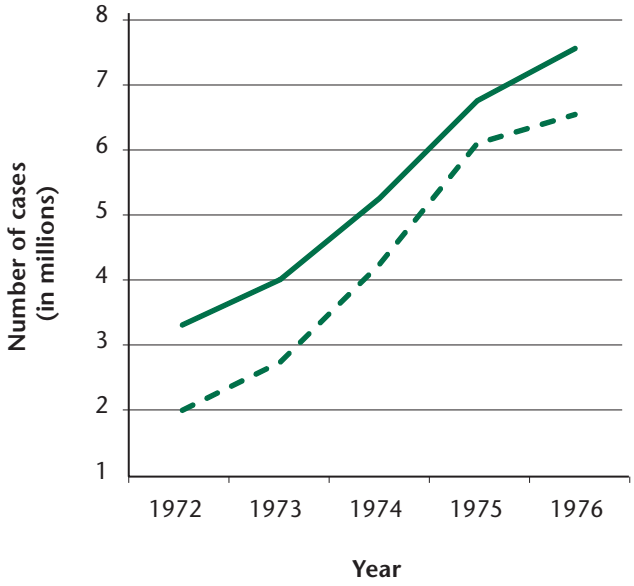

FIGURE 6.3 | Number of autochthonous malaria cases (in millions) in areas under surveillance outside tropical Africa (solid line) and in Southeast Asia (broken line), 1972-1976 (from Wernsdorfer[10])

opinion of three separate groups. Those groups were countries not yet able to embark on malaria control or elimination, those that declared the intention of eliminating malaria but failed to implement and sustain efficient programs, and several malaria-free countries that financially supported others in the elimination effort and intended to end these obligations.

6.5 | Yesterday's Approach in Malaria Elimination

In countries that successfully eliminated malaria, the disease was predominantly hypo- and mesoendemic, and transmission was of low or intermediate stability. Some countries, including Tunisia and the United Arab Emirates, had hyperendemic areas characterized by intermediate stability.

Before the adoption of WHO's malaria eradication policy in 1955, malaria elimination in the United States relied on vector control to interrupt transmission and reduce the malaria reservoir, organized detection and treatment of residual cases, and complementary focal antivectorial measures that were continued until complete elimination of malaria had been achieved. This model was subsequently adopted by the GMEP. In European countries such as Cyprus, Greece, and Italy, malaria was reduced to low incidence by systematic diagnosis and radical treatment of individual cases before effective

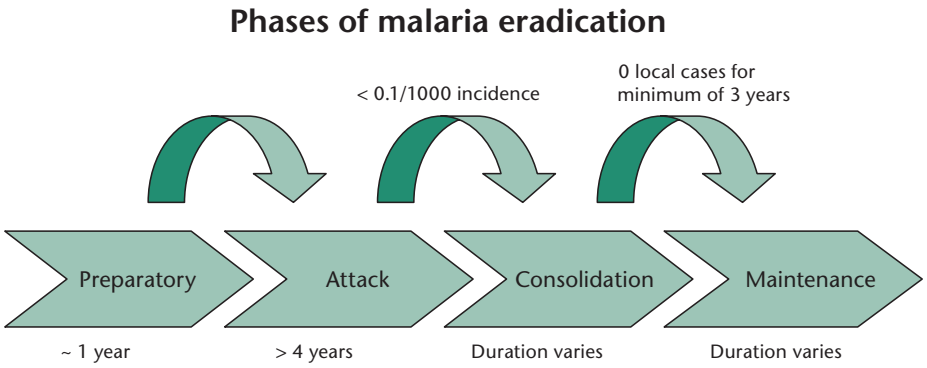

FIGURE 6.4 | Phases of the Global Malaria Eradication Program (adapted from Pampana[16] and Hay et al.[17])

vector control became feasible. In Europe, the vector control measures interrupted any residual malaria transmission, and case management through the general health system was responsible for eliminating the remaining malaria reservoir.

The majority of countries that established national malaria elimination programs from 1955 adopted a vertical organizational structure and followed a standard chronological sequence of four phases: preparatory, attack, consolidation, and maintenance (Figure 6.4).[16, 17]

PREPARATORY PHASE

The preparatory phase usually lasted a year and did the following:

- established or improved organizational infrastructure
- trained personnel
- established physical facilities for running operations
- carried out geographical reconnaissance and census
- conducted epidemiological and entomological baseline assessment

ATTACK PHASE

The attack phase usually lasted 4 or more years and did the following:

- applied attack measures, usually antivectorial intervention
- regularly monitored the impact of the attack measures
- from the second year, established full-scale epidemiological surveillance

- from the second year, conducted active and passive case detection, effective treatment and case follow-up, epidemiological investigation and follow-up of cases and foci, and application of remedial measures

CONSOLIDATION PHASE

The consolidation phase could start when the surveillance mechanisms, including the general health care system, were functioning smoothly with complete coverage in space and time, and when the malaria incidence had been reduced to a very low level (approximately < 0.1 positive slides per 1,000 population per year). In this phase, antivectorial measures were usually restricted to foci of malaria transmission and particularly receptive areas. The duration of the consolidation phase varied depending on how long it took to reach the qualification for moving into the maintenance phase.

MAINTENANCE PHASE

The maintenance phase could start when no autochthonous transmission had occurred for a minimum of 3 years, provided there was a strong surveillance system. Surveillance continued in the form of vigilance through a strong health system, which maintained a designated operational group to monitor outbreak risk and importation risk and to cope with problematic events such as the reintroduction of malaria.

Although the concept of the GMEP may appear rigid, it did allow considerable leeway in the selection of appropriate tools to be applied in the attack phase. Generally, this required the deployment of vector control measures, namely IRS and/or any of the many forms of larvicidal measures or source reduction. Decisions regarding the selection of intervention methods needed to be based on sound preoperational epidemiological and entomological stratification, an essential task in the preparatory phase, subject to continuous updating throughout the intervention phase.

Activities outlined in the consolidation and maintenance phases should have a firm place in any program aimed at eliminating malaria. When analyzing the GMEP, it is important to remember that it is useless to adhere to a national uniform operational plan unless the entire country shows homogeneous epidemiological features—a rare situation, even in tropical Africa. Malaria control usually requires different approaches in urban, peri-urban, and rural environments. Updated recommendations for interrupting transmission and preventing reintroduction of malaria are the subjects of Chapters 2 and 3.

Table 6.2 | Common denominators from the Global Malaria Eradication Program

Common denominators from successful elimination programs	Common denominators from failed elimination programs
Political stability and absence of internal and/or external conflicts	Political instability, civil unrest, internal and/or external armed conflicts
Firm political and financial commitment to the elimination of malaria	Lack of or fluctuating political and financial commitment
Minor dependence on external financing	Donor fatigue
Good organizational and technical infrastructure	Poor monitoring of operational activities and the epidemiological situation, failure to update the plan of operations, insufficient understanding of the benefits of eliminating malaria
High quality of training and personnel	Inadequate human resources; poor quality of training, staff, and operations; high staff turnover
Fully developed and functional general health system	Weak general health system
Enlightened public that understood and supported the program	Poor public understanding and support of the program
Absence of major cross-border movement from adjacent malarious countries	Major cross-border movement from adjacent malarious countries
Originally unstable or intermediately stable malaria	Originally stable malaria or malaria of high intermediate stability

6.6 | Lessons Learned from Past Elimination Programs

Although many factors that assist and enable elimination programs today have changed and improved on those available during earlier global and national programs, it is important to evaluate the lessons learned from the GMEP (Table 6.2) in order to determine the factors that made the difference between success and failure.

EXAMPLES FROM COUNTRIES THAT SUCCESSFULLY ELIMINATED MALARIA

Australia, 1960 Malaria was endemic in the tropical part of Australia, affecting the Northern Territory and Queensland. It was predominantly hypo- and mesoendemic malaria, unstable or with low intermediate stability, with several hyperendemic areas in northern Queensland. Systematic malaria control operations started soon after World War II, with IRS, source reduction, and

water management in the sugar plantations as well as case detection and treatment within the framework of the well-developed general health care system. Malaria was eliminated from continental Australia in the 1960s. In the Torres Strait Islands, an integral part of Australia and subject to the introduction of malaria from nearby Papua New Guinea, it took longer to eliminate malaria and to establish effective mechanisms to prevent reintroduction. Nevertheless, malaria was eliminated there in 1978.

Taiwan, 1965 Taiwan provides an example of an outstanding success of island elimination. Following a DDT spray program starting in 1952, over 20 residual foci of transmission were eventually eliminated with intensive IRS, and courses of chloroquine/primaquine were used for mass drug administration (MDA) in the entire population in each focus of transmission. In Taiwan, MDA was ancillary to the use of insecticides.[18] Finding and eliminating the residual foci was a massive effort of malaria surveillance involving over 5 million blood slides taken from July 1958 to December 1964, which identified and treated 1,023 malaria infections. Taiwan was certified malaria free in November of 1965. The elimination program spanned over 20 years and involved over 7,000 staff and a full research institute, as well as a large logistical establishment.[18]

The United Arab Emirates, 2007 Until the mid-1950s, malaria was meso- or hyperendemic in most areas in the country, generally with low-grade intermediate stability and an almost equal incidence of *P. falciparum* and *P. vivax*. In the 1960s, the country embarked on malaria elimination, initially using source reduction and IRS. Case detection and treatment were introduced at an early stage, making full use of the strong general health care system in the public and private sectors. During this program, the United Arab Emirates pioneered the use of local larvivorous fish in the main mosquito breeding sites—*Tilapia* for deep wells, and *Aphanius dispar* for shallow wells, irrigation heads, and natural water courses. Despite the annual importation of 2,000 to 3,000 malaria cases from malarious countries, especially Bangladesh, India, Pakistan, and Sudan, transmission was completely interrupted as of 1997, and the country was certified as malaria free in 2007.

EXAMPLES FROM COUNTRIES THAT FAILED TO ELIMINATE MALARIA

Colombia, since the Late 1950s Malaria was originally mesoendemic with some hyperendemic zones and low-grade intermediate stability. After initial success and near elimination, the program became increasingly affected by civil strife

and illicit activities, thus barring access to large malarious areas. These conditions continue to persist, with little likelihood of change in the near future.

Sri Lanka, Mid-1960s Malaria was originally mesoendemic with some hyperendemic areas and an incidence of 2.8 million cases in 1946. Malaria was generally of low-grade intermediate stability. The malaria program had well-trained, highly motivated, and competent staff. The program ran smoothly through the consolidation phase in the mid-1960s. In 1966, the number of autochthonous cases had decreased to 18 at which time parliament and government decided to disband the entire malaria program and to transfer its activities to the general health services, which were unprepared for this task. Following 3 years of moderately rising incidence of malaria, the country was struck by a major and widespread malaria epidemic, resulting in a half million cases widely distributed throughout the island.[19]

Among the countries that declared a policy of malaria elimination but failed to implement or achieve it, the most important adverse factors have been lack of political will, inadequate and unsustained financial commitment, infrastructural deficiencies, insufficient availability and appreciation of epidemiological information, and administrative rigidity. In some countries, bureaucratic procedures repeatedly delayed the timely allocation of public funds for malaria elimination, delaying the performance of seasonal IRS beyond the limits of usefulness. Similarly, the allocation of external financial assistance was often delayed, resulting in the late arrival of essential commodities, such as insecticides for IRS. Also, as is occurring today, some countries declared the goal of malaria elimination apparently without true evaluation of their readiness or any serious intention of implementing such a program.

6.7 Recommendations: Eliminating Malaria Today and Tomorrow

As 39 countries pursue malaria elimination, with strong indications that many, if not all, will achieve their goal, it is appropriate to take note of a passage from the Second General Report of the Malaria Commission of the League of Nations, a statement that is as valid today as it was when it was issued in 1927: "The Commission has always insisted that the fight against malaria must be waged not as a separate and isolated task but as part of a general social, economic and sanitary campaign by an enlightened public health service which is

able to obtain assistance from other Government departments and from unofficial agencies, and to secure continuity of action and unity of purpose."[20]

Observing which countries have achieved and maintained their elimination of malaria supports the Commission's statement. Equally, it was inadvertent or intentional disregard of the Commission's views that was responsible for failure in the countries with national malaria elimination programs that did not reach the elimination goal.

Whenever a country considers eliminating malaria, it should carefully examine the lessons learned from past successes and failures, and it should take preemptive remedial action to eliminate any weaknesses. For instance, it is futile to attempt malaria elimination if the country has an active military conflict on a substantial part of its territory or lacks stable political or financial commitment.

Retrospectively, innovative research suffered during the malaria eradication program. Moreover, the unresolved issue of malaria in tropical Africa was overlooked. The pharmaceutical industry was unwilling to invest in developing drugs principally to address the problems of largely insolvent economies. Continued research and development of innovative tools must always be a priority to sustain a program through the inevitable challenges inherent in any process as complex as malaria elimination.

Nevertheless, the comparison of the geographical distribution of malaria in the years 1900, 1946, 1965, and 2007 (Figure 6.2) indicates remarkable success in the fight against malaria, even if the stated goal of malaria eradication was not achieved. Moreover, many countries have a considerable potential for eliminating malaria in the near future.

6.8 Conclusion

With over 3 billion people still at risk for malaria, much needs to be done to control and eliminate malaria from the areas still affected by the disease, and we are still facing the most difficult part of the campaign. As today's spatially progressive elimination program continues to shrink the global malaria map, we must remember the many important lessons learned from the GMEP and past attempts to eliminate malaria, yet look forward with new hope and commitment to reach a malaria-free world.

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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

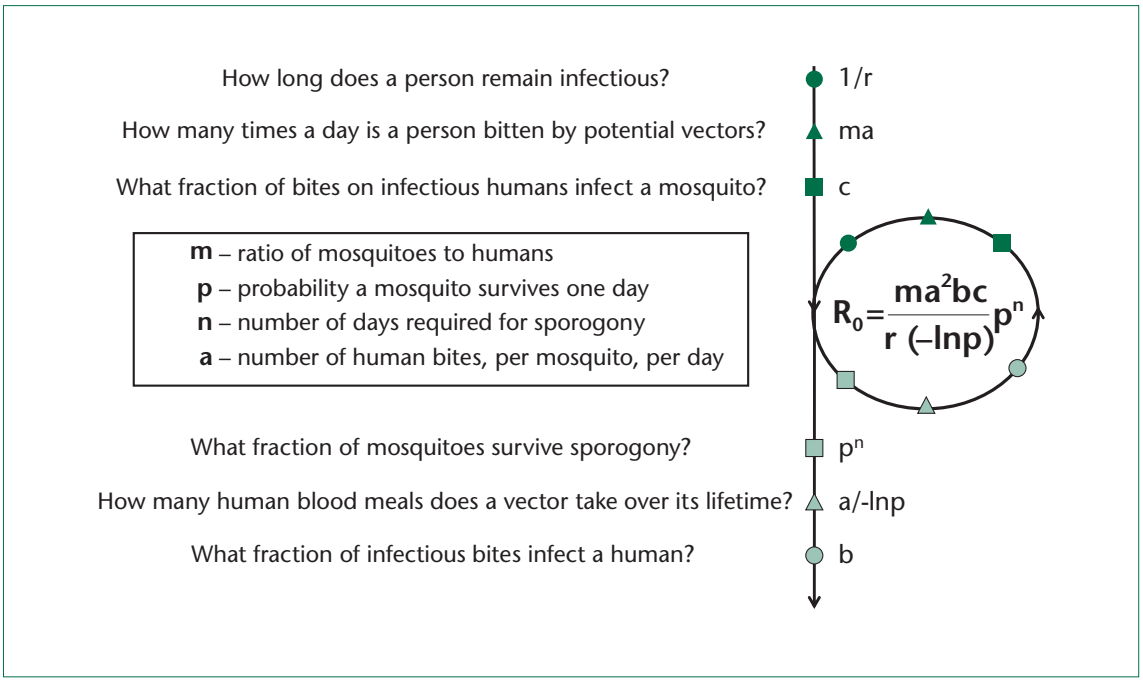

FIGURE 7.1 | Measuring R_0

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-

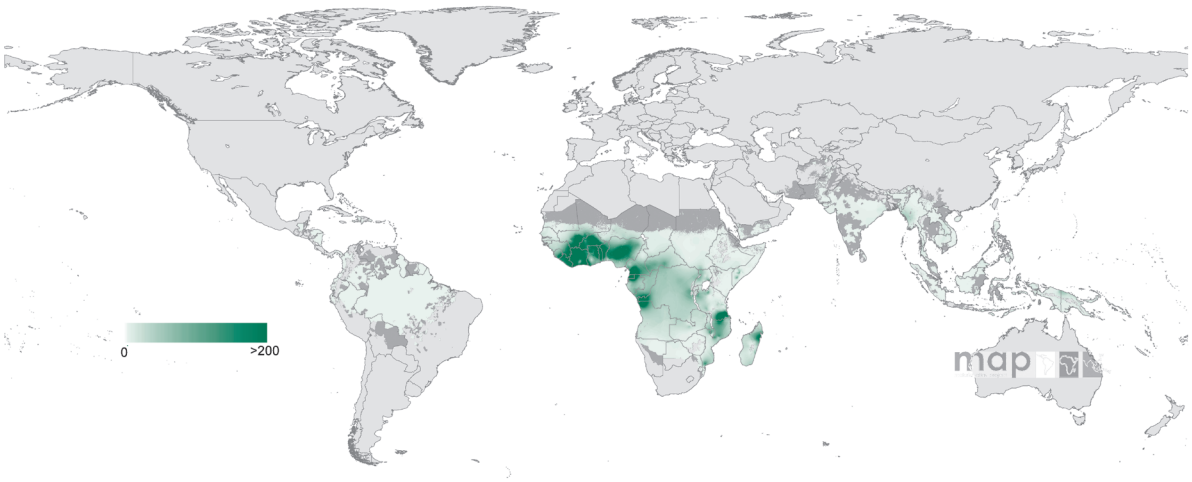

FIGURE 7.2 | The spatial distribution of the estimated basic reproductive number of *P. falciparum* malaria at present levels of control (R_C)

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

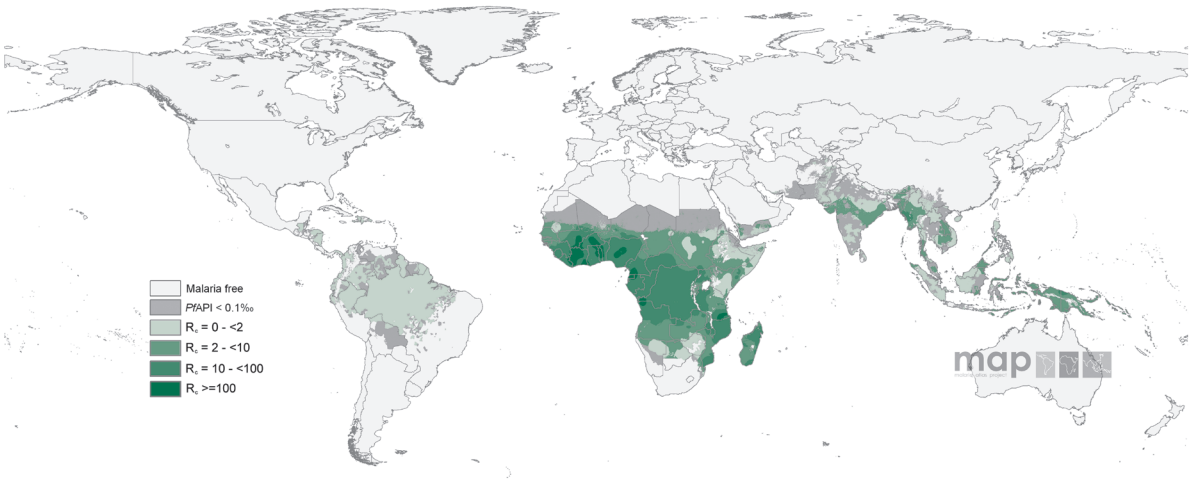

FIGURE 7.3 The spatial distribution of the estimated basic reproductive number of *P. falciparum* malaria at present levels of control (R_C) stratified according to the ease of the additional control required to interrupt *P. falciparum* malaria transmission

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.

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8 | KILLING THE PARASITE

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8.1 | Introduction

The pattern of malaria transmission around the world is highly variable and covers a broad spectrum of epidemiological situations ranging from areas with a high population at risk, high mortality, and high transmission (predominantly *Plasmodium falciparum* malaria) to the other extreme of low population at risk, low mortality, and low mixed-species transmission. As we have seen, a very different approach is needed to achieve elimination of the parasite from low-transmission settings than is required for the attack on disease in high-transmission settings. A conceptual and operational shift must be made, from prevention and treatment of disease in individuals across entire or broad areas of the country, to community-focused strategies aimed at ending transmission and eliminating residual foci of infection. Strategies for elimination must be based on accurate case reporting and precise assessments of the epidemiology and the populations at risk (Chapter 2). It will be necessary for an elimination program to constantly monitor the shifting character of malaria and adapt intervention strategies appropriately to these changes as they occur, as an aggressive intervention program will change the pattern of malaria over time.

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BOX 8.1 | Main Messages

- Strategies developed for malaria elimination should be planned to detect all infections and not just those that are responsible for clinical malaria.
- The progress of a malaria elimination initiative should be monitored regularly, as the epidemiology will change and measures used for parasite killing (and vector control) may need to be modified. It is important to obtain accurate estimates of the numbers of infections persisting in the community.
- Clinical diagnosis is inappropriate for an elimination program and should be replaced by malaria-parasite-specific diagnosis, by either rapid diagnostic tests (RDTs) or microscopy of blood films. Reference facilities, with personnel to provide quality assurance for microscopy and RDTs, are needed.
- Diagnostic measures should assume that all *Plasmodium* species can persist as both subclinical and mixed infections.
- Trials of drug combinations that include a drug capable of killing gametocytes (or stages developing in the mosquito) should be undertaken for both treatment and mass drug administration (MDA). Safety should be a priority, particularly when drugs are likely to be given to a large number of people who are not infected.
- An assessment should be made of the appropriateness of using either MDA or mass screening and treatment (MST) in order to find and kill the last parasites.
- There needs to be greater focus on *P. vivax*, as the number of infections and the severity of the disease are commonly underestimated.
- *P. vivax* and *P. ovale* present particularly challenging problems because they can persist undetected in the liver for 3 to 5 years. A detection and treatment strategy should assume that new blood infections can occur in an individual over several years without exposure to infectious mosquito bites.

8.2 | Non-*falciparum* Malaria: A Challenge to Elimination

PLASMODIUM VIVAX

The focus of malaria control programs has, to date, been largely on *P. falciparum* because this parasite is the major cause of mortality and severe clinical malaria, especially in tropical Africa, although there is recent evidence that the burden of *P. falciparum* infection in Southeast Asia may have been underestimated.[1,2] However, once elimination becomes the target, *P. vivax* needs to

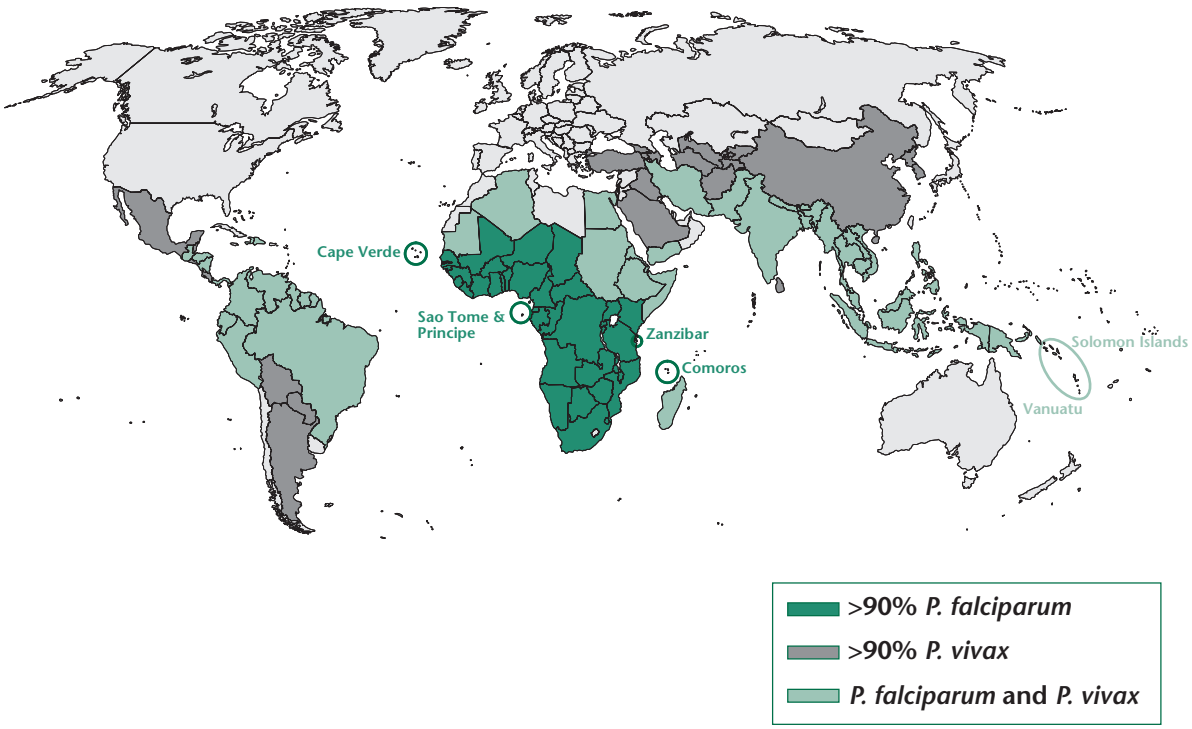

FIGURE 8.1 | The distribution of *P. falciparum* and *P. vivax* by country

be given much more attention. As discussed in Chapter 5, the proportion of the 3.6 billion people who were living at risk of malaria in 2005 was higher for *P. vivax* than for *P. falciparum*.[3] As many as 250 million infections may be due to *P. vivax* each year.[4] In many places outside Africa, such as in some countries of Central and South America, *P. vivax* is the dominant malaria problem.[5] As shown in Figure 8.1, *P. vivax* and *P. falciparum* coexist in many countries around the world.

Issues such as underdiagnosis, relapse from dormant liver stages, a poor understanding of mechanisms of acquisition of immunity, and interspecies interaction complicate any malaria control intervention in areas where *P. vivax* infection predominates and will block achievement of the goal of eradication unless taken into account.[6]

The low priority given to *P. vivax* infections by policy makers, funders, and researchers stems in part from the historical under-recognition of the scale of the problem, an issue which is now being acknowledged. Even more of an obstacle has been the definition of *P. vivax* malaria as "benign" malaria, implying that it does not present as serious an infection and can be ignored until the *P. falciparum* malaria problem is controlled. This perception is being seriously

challenged by a growing number of case studies that indicate that *P. vivax* can cause severe malaria.[7] Two recent studies on the island of New Guinea, from both the Papua, Indonesian, side and the Papua New Guinean (PNG) side, have shown that *P. vivax* can cause severe disease.[8, 9] In the PNG study of almost 10,000 children, mainly under 5 years old, the proportion of cases with a WHO definition of severe malaria caused by *P. falciparum* was 11.7%, while *P. vivax* followed closely behind at a substantial 8.8%.

Although there is increasing recognition that *P. vivax* contributes significantly to the global malaria burden, the number of infections persisting in the community is probably still being massively underestimated. This has significant implications for those countries where *P. vivax* malaria is endemic and that are already setting an elimination goal, for example, Vanuatu and the Solomon Islands. The extent of this underestimation has been revealed by the use of sensitive methods based on polymerase chain reaction (PCR) for diagnosis of blood-stage infections in large community studies in areas of PNG where the four human malaria species are co-transmitted.[10, 11] Increases in the estimated prevalence of *P. vivax* by 2- to 3.5-fold were observed, and even greater increases in the prevalence of *P. malariae* and *P. ovale* were seen.[12] The number of estimated mixed infections increased by orders of magnitude when these sensitive detection methods were used. We should note that the same problem of underestimation of prevalence can occur with *P. falciparum* in apparently low-endemicity areas, unless the sensitive diagnostic methods are employed.[13]

One of the big obstacles to stopping transmission of *P. vivax,* and one of its major distinctions from *P. falciparum*, is the ability of *P. vivax* to relapse after cure of the original bloodstream infection. A proportion of sporozoites remain dormant as hypnozoites for periods as short as a few weeks or as long as 5 years before emerging to cause a clinical, blood-stage infection (Chapter 5). The dormant stages are not detectable, and the ability to relapse will hinder elimination of this parasite. In order to interrupt transmission completely, it will be necessary to kill the hypnozoites.

MIXED INFECTIONS

PCR-based studies such as those discussed above have shown that there is a much larger pool of mixed infections than suspected, which raises another difficulty for elimination. In areas where transmission of more than one malaria species is common, a malaria-infected person is very likely to be co-infected with more than one species of *Plasmodium*. In such circumstances, there may be interspecies interactions that are modified by interventions that alter the bal-

ance between species, as has been seen in the highlands of Papua New Guinea.[14, 15] The question remains open as to whether the simultaneous presence of non-*falciparum* malaria can reduce the clinical impact of infection with *P. falciparum*. Good examples can be found in the literature arguing either way, although a recent meta-analysis of all available studies fell on the side of a significant negative association between mixed infection and clinical disease.[16] Most of these earlier studies are, however, colored by the underestimation inherent in the use of non-PCR-based techniques for diagnosis, and more research is needed to determine how the pattern of malaria might be altered in areas where infection with multiple species is common as a program moves toward elimination.

8.3 Malaria Immunity and Elimination

People who live in malaria-endemic areas show an age-structured burden of clinical disease, with older children and adults having resistance to severe morbidity and death due to the acquisition of natural immunity, although the nature of the immunological changes that are involved is still not fully understood.[17] Once control programs have reached the stage at which elimination in a particular community is a possibility, it is likely that there will have been a reduction in the level of naturally acquired immunity in that community, though it may be a number of years before there is a substantial loss in the community as a whole. This progressive change may have a significant impact on the final attempts to achieve elimination. Some examples of the changes that may be encountered are considered below.

Reduction in naturally acquired immunity in a community may result in a change in the age pattern of the few clinical infections that continue to occur, with more cases being seen, first in older children and then in adults, than had been the case previously. This necessitates a change in treatment programs with, for example, an increased focus on older schoolchildren.

There is strong evidence that in malaria-endemic areas where some level of drug resistance is present, treatment success is often enhanced by naturally acquired immunity. As control improves and elimination becomes a feasible target, highly effective drug combinations will be needed that can achieve cure without any help from naturally acquired immunity.

Reduction in the community level of acquired immunity as a result of successful control programs over a period of years will also increase the risk of an epidemic resurgence of the infection, as seen in the highlands of Madagascar[18] and on the island of Mauritius (Chapter 10) when control programs failed after a lengthy period of success. Much still needs to be understood about the impor-

tant and dynamic interplay between immunity and exposure before we can be confident in predicting the effect of interventions and can formulate strategies to minimize adverse impact.

8.4 Finding and Killing the Last Parasites

In an elimination program, treatment of a sufficient number of infected subjects in a community, whether they are symptomatic or asymptomatic, to interrupt transmission becomes the primary goal. Two possible approaches to this objective can be adopted—detection and treatment of infected individuals capable of transmitting the infection, or MDA given to as large a proportion of the population as possible on the grounds that this will cover a high proportion of those infected. As naturally acquired immunity wanes, the proportion of symptomatic individuals increases, making it easier to detect them as they are more likely to seek treatment. However, as we have seen, even in areas of relatively low transmission, asymptomatic individuals are still detected, and they need to be treated in order to interrupt transmission. The availability of a sensitive method for diagnosing malaria is essential for this strategy of malaria elimination.

DIAGNOSIS OF MALARIA INFECTION

When killing the last remaining parasites becomes the goal, an ability to identify all parasites becomes increasingly important. Good-quality microscopy conducted by skilled technicians with capacity to manage appropriate quality control, and currently available RDTs, whose effective use requires less training than microscopy, are generally adequate for diagnosis in persons who are acutely ill with malaria. However, there are particular issues to be addressed with both procedures. Ensuring the quality of microscopy used for routine diagnosis has often proved difficult, as the sensitivity and specificity of routine microscopy is significantly lower when compared with that of qualified microscopists based in central reference laboratories. This underlines the need for good training in microscopy for staff in primary health centers, coupled with the provision of reliable, well-maintained equipment and regular monitoring and quality control (Chapter 2).

There is a wide range of commercially available RDTs. Each one incorporates a monoclonal antibody that detects one of three well-characterized proteins of the malaria parasites. Though cost is a problem, they are becoming widely used. Among the many tests being manufactured, there is considerable vari-

ability in quality, however, so it is important to establish quality assurance programs for quality of manufacture, plus measures of their stability and performance over time.[19, 20] Some RDTs detect only *P. falciparum*, but others can distinguish between *P. falciparum* and non-*falciparum* malarias, although RDTs are generally less sensitive at detecting non-*falciparum* infections.[21]

When compared against each other, microscopy and RDTs detect a similar minimum threshold density of parasites (about 50 parasites per microliter of blood). Thus, the choice for routine use is this: use microscopy, which is technically more difficult but is better for species identification (especially non-*falciparum* species) and for estimating parasite densities, or diagnose with the user-friendly RDT, which gives a positive or negative result (but not a measure of the density of parasites) and is not as good for detecting *P. vivax* and the other non-*falciparum* parasites.

Since most elimination efforts will need to deal with both low-density parasitemias and non-*falciparum* species, diagnosis becomes a major challenge for elimination programs. More-sensitive methods of diagnosis than microscopy and RDTs are likely to be needed, including those that can detect small numbers of gametocytes. Although the propensity of a gametocyte carrier to transmit infection is related to the density of gametocytemia, individuals with very low gametocyte numbers can still transmit infection and can be an important part of the reservoir of infection. Thus, if an elimination program is to be based on detection and treatment of all potential transmitters of infection, much more sensitive detection tests will be needed.

PCR assays provide the sensitivity needed to detect low parasitemias, including low-level gametocyte infections. Studies in Kenya and Tanzania using the QT-NASBA real time PCR assay have shown that this increases the number of gametocyte carriers detected in the population 40-fold over the number detected by microscopy. LAMP assays may prove to be equally sensitive.[22] Developing tests with the sensitivity of these assays that can be employed in field situations is a key priority for the operational research agenda (Chapter 10) in elimination.

Serology, which employs relatively crude assays such as the measurement of antibodies against the whole parasite by fluorescence, was occasionally used during previous eradication programs to monitor their impact, but serology has, until recently, been a largely neglected aspect of malaria research. In China, immunofluorescence assays are being used in schools at the end of malaria transmission seasons to measure how much *P. vivax* transmission has occurred, and it is used as a guide to whether any control interventions are needed. New studies using antibody assays to defined malaria antigens, particularly MSP-1,

have shown that serology can play an important role in assessing malaria endemicity, and it could therefore make an important contribution to elimination programs. It is unlikely to be used to detect infection in individual subjects, but it may prove to be very useful in monitoring the progress of elimination efforts and for detecting foci where transmission is still continuing, and where extra control efforts are needed.

DRUGS TO KILL THE LAST PARASITES

Treatment of malaria in the context of elimination necessitates achieving a complete parasitological cure, including killing of the parasites in their sexual stages, either in the blood of the infected subject or in the midgut of any vector mosquito that ingests them. Artemisinin-based combination therapies (ACTs), now the first-line treatment for *P. falciparum* malaria in nearly all countries, have an advantage over many other antimalarials used for treatment—they have some effect on gametocytes, thus reducing the potential for transmission. The introduction of ACTs may have contributed to the marked reduction in the incidence of *P. falciparum* malaria seen on the Thailand-Myanmar border[23] and, more recently, in some countries in Africa, such as South Africa[24] and Zanzibar. However, the effect of artemisinins on gametocytes of *P. falciparum* is not complete, and patients treated with artemisinins can still transmit malaria infection.[25] In fact, the mature gametocytes of *P. falciparum* are resistant to most of the antimalarial drugs that affect the asexual stages, and they develop much more slowly than gametocytes of the other three species. Currently, the only licensed drug that can ensure complete killing of *P. falciparum* gametocytes is the 8-aminoquinoline drug primaquine, which is very effective at preventing transmission when given as a single treatment. Thus, in the context of elimination, any patient treated for *P. falciparum* malaria should also receive primaquine in addition to the primary treatment unless he or she is glucose-6-phosphate dehydrogenase (G6PD) deficient and thus at risk from hemolysis.[26] Within the context of an active case detection program, the inclusion of screening for G6PD deficiency is recommended, but the tests available are not readily applicable, and testing becomes increasingly difficult for mass treatment programs. Development of simple, cheap, field-friendly tests for G6PD deficiency (Chapter 10) would greatly facilitate the elimination agenda, particularly because there are different forms of G6PD deficiency, some of them relatively mild and therefore perhaps not presenting such a serious risk to the treated patient.

There are many factors that can lead to an increase in the number of game-

tocytes of *P. falciparum* circulating in the blood and hence capable of increasing transmission to vector mosquitoes. Most of these are not well defined, but the numbers can increase during the course of a long infection (being higher at the end of a season of transmission than at the beginning), when the patient is anemic, and as a consequence of the development of drug resistance. This last effect is particularly important as the increased transmissibility contributes to the spread of resistance. Increase in gametocyte numbers has been identified as the first indication that a drug is beginning to fail and emphasizes the need for treatment to include drugs that will kill the sexual stages—what has been called "prevention by treatment."[19, 27]

Gametocytes of *P. vivax, P. ovale*, and *P. malariae* appear in the circulation at the same time as the asexual stages and, unlike the gametocytes of *P. falciparum*, are killed by the antimalarial drugs that are effective against the asexual blood stages. *P. vivax* transmits well at very low parasite densities, so transmission can already have occurred before a patient has become symptomatic and sought treatment.[19]

Obtaining a complete cure of *P. vivax* or *P. ovale* malaria is a more complex procedure than is the case for *P. falciparum* infections, as it involves not only killing sexual and asexual blood-stage parasites but also eliminating residual inactive parasites in the liver (hypnozoites). Currently, primaquine is the only licensed drug that can do this.[28] As mentioned above, primaquine can cause hemolysis when given to subjects who are G6PD deficient, and this complication is more likely to occur when the drug is used to eliminate hypnozoites, as opposed to killing gametocytes, as a much more prolonged course of treatment is needed—for example, a 14-day course.[26] Tafenoquine is a new 8-aminoquinoline under development that has the advantage over primaquine that a much shorter course of treatment is needed.[29] However, it still has a propensity to cause hemolysis in G6PD-deficient subjects, and development of a safer treatment for killing *P. vivax* hypnozoites is a high research priority that is now being addressed by organizations such as the Medicines for Malaria Venture (MMV).

8.5 | Mass Drug Administration and Elimination

MDA has a mixed reputation and is not recommended by WHO. Part of the antagonism comes from a form of MDA that involved use of salt fortified with chloroquine or pyrimethamine (the Pinotti method) that, predictably, led to the rapid development of resistance. However, other forms of targeted MDA have been much more successful, for example, intermittent preventive treatment

(IPT) in infants and children[30] (though IPT is not appropriate in low-endemic settings). Many large community-based studies of MDA, such as those undertaken in Nicaragua and Garki, Nigeria, have shown that community-based MDA can be highly effective in reducing parasite prevalence to a very low level but that parasitemia soon rebounds to its previous level once MDA is stopped.[31] Thus, this form of MDA has no role in disease control programs, except during epidemics. However, MDA could play a key role in the final stages of an elimination program as an alternative to an active case detection program, once the level of infection has been reduced to a low level.[27] Although a difficult and labor-intensive process, MDA may be easier and more effective than mass screening and treatment, and previous studies have shown that a high level of coverage can be achieved for a limited number of treatment rounds, provided there is full involvement of the community. MDA probably played an important role in the elimination of *P. falciparum* and *P. vivax* malaria from Aneityum, Vanuatu.[32]

Drugs used for MDA should ideally be active against sexual-stage parasites (and hypnozoites, if used in an area where *P. vivax* or *P. ovale* infections are present), and they must be very safe, as a high proportion of the subjects treated are likely to be uninfected. Any serious adverse event that could clearly be linked to the medication would end a community's participation, no matter what the long-term risk-benefit equation indicated. Whether it would be safe to use primaquine for MDA in large populations where G6PD deficiency prevalence is high without screening is uncertain; a safer drug, or drug combination, for MDA is urgently needed.[28]

8.6 Vaccines

This *Prospectus* focuses on the tools available to eliminate malaria today and/or in the near future, and it therefore pays little attention to malaria vaccines. This is because it is unlikely that a malaria vaccine that is effective enough to play a significant role in malaria elimination will become available in the next few years. However, in the longer term, malaria vaccines may have a very important role to play in malaria elimination programs, especially in areas where the infection is otherwise difficult to control.

Any malaria vaccine that is highly effective at preventing infection, regardless of whether it acts at the pre-erythrocytic or erythrocytic stage of parasite development, will have an impact on transmission. However, in areas of mod-

erate or high transmission, modeling indicates that for a significant effect to be achieved, efficacy will need to be very high, probably as high as 95%.

Thus, as elimination becomes an increasingly realistic prospect, there has been renewed interest in the development of vaccines which are targeted specifically at preventing transmission either by inducing an immune response that destroys gametocytes or interferes with the development of the parasite in the mosquito. A move to elimination has raised the development of transmission blocking vaccines higher up the malaria research agenda than in the past and a number of candidates are now reaching the stage of early clinical trials.[33] For transmission blocking vaccines to be most effective they will need to be given to as large a proportion of the population as possible, and probably delivered through mass campaigns in a manner analogous to that used to deliver drugs in MDA programs.

8.7 | Conclusion

Elimination of malaria involves a paradigm shift away from treating patients with malaria toward killing the last few malaria parasites. Relapsing malaria such as *P. vivax* will become increasingly important as current measures limit transmission of *P. falciparum* malaria. Improved means to detect asymptomatic persons with low parasitemia will be crucial to malaria elimination. Effective chemotherapy is and will remain a primary means of achieving malaria control and eventually elimination. Mass screening (active case detection) and MDA are alternative approaches toward this goal, but both are hindered by the lack of a safe and effective drug that is highly effective at killing both the sexual stages of all the main human malaria parasites and the resting stages of the relapsing malaria infections.

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9 | SUPPRESSING THE VECTOR

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9.1 | Introduction

Vector control is the main attack weapon for reducing malaria transmission.[1] It is a lead intervention in the Roll Back Malaria (RBM) Global Malaria Action Plan. It is the only tool that is capable of bringing intense or moderate transmission down to the low levels where elimination is within reach. It can also play an important role in knocking out the last foci of transmission in the later stages of elimination. In this chapter, we provide an overview of available vector control tools and a summary of the essential characteristics of the various methods. We then consider how these methods fit within an elimination context and their respective roles at each stage of the process. Finally, we consider a few examples of operational issues in implementation and some critical constraints to the effectiveness of vector control.

9.2 | Introduction to the *Anopheles* Vector Species

Malaria is transmitted by female mosquitoes of the genus *Anopheles*. About 70 species of *Anopheles* transmit human malaria, but only about 30 of these are of major importance as vectors. In any given area, just a few *Anopheles* species will be responsible for most malaria transmission. Individual species

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BOX 9.1 | Main Messages

- Vector control is a vital attack weapon of elimination. It is the only intervention capable of reducing transmission in the early stages of elimination.
- In the later stages of elimination, the role of vector control is to knock out the remaining foci of transmission; post-elimination, its role is reducing outbreak risk and as a defense against reinvasion.
- The deployment of vector control must be carefully adapted both to the biology of the local species of vector mosquitoes and to the local epidemiology of malaria.
- Although some countries have kept up intensive and successful vector control operations for several decades, many others have encountered serious technical and operational obstacles to sustainability, including insecticide resistance in the mosquitoes and gradual declines in both the technical quality of spraying operations and acceptance by target communities.
- If transmission is suppressed by vector control for a long period and this suppression is then withdrawn suddenly, rapid resurgence of malaria can sometimes lead to catastrophic epidemics with substantial loss of life.
- Without a substantial expansion in training, the scarcity of specialized expertise in vector control will be a growing practical constraint on the delivery and effectiveness of vector control programs.

vary widely in their breeding and biting behavior. The main characteristics that determine whether an *Anopheles* mosquito is a major vector of malaria are its blood feeding preferences (predominantly animal or human) and longevity. The range and type of breeding place can be highly variable for different mosquito species.

Anopheles mosquitoes occur throughout the world, with the exception of the Polynesian and Micronesian islands of the Pacific Ocean and most arctic regions. Following is a list of some examples of biological and behavioral differences.

IN AFRICA

The principal vectors in sub-Saharan Africa belong to the *A. gambiae* or *A. funestus* groups of species. The vector species within these groups feed and rest indoors at night (i.e., are endophagic and endophilic), so insecticide-treated nets (ITNs) and indoor residual spraying (IRS) are effective against them.

The relative efficiency of these African species as vectors, compared with

their equivalents in other continents, is one of the main reasons that 90% of the world's malaria mortality occurs in Africa.

These species do not breed well in man-made containers or in water with organic pollution, so they tend to be excluded by the process of urbanization; for this reason, the intensity of transmission in Africa tends to be much lower in urban areas.

IN INDIA

Conversely, India is the only part of the world where malaria transmission is often more intense in town than in the surrounding countryside. This is because one of the main Indian vectors, *A. stephensi*, is the only important malaria vector that has adapted to breeding in man-made containers, such as rooftop water tanks. Transmission in the rural areas is sustained by members of the *A. culicifacies* complex, another very effective vector.

IN SOUTHEAST ASIA

The most efficient vectors in Southeast Asia, *A. dirus* and *A. minimus*, are strongly associated with forests. Hence, malaria transmission tends to be most intense in forested areas, many of which are in remote mountainous regions, often on the borders between countries.

The African and Indian vectors tend to bite and rest indoors and so are well controlled by indoor spraying. By contrast, the forest vectors of Southeast Asia, and the equivalent species in the Amazon basin, such as *A. darlingi*, are all much less likely to rest indoors and so are less well controlled by spraying.

9.3 | The Vector Control Menu

IRS—INDOOR RESIDUAL SPRAYING

In terms of its immediate impact, IRS remains the most powerful vector control technology to reduce and interrupt malaria transmission.[2] This reflects two critical aspects of the biology of the vector. The first concerns the biting habits of anopheline mosquitoes. Tropical *Anopheles* mosquitoes feed repeatedly, every 2 or 3 days, and most of the important vector species tend to bite humans indoors and then rest on the walls of the bedrooms. This means that they risk being killed every time they feed indoors. The other key biological fact is that it takes malaria parasites approximately 11 to 14 days to mature inside the mosquito before they are ready to be passed on to the next human host, and in the tropics, only a small minority of *Anopheles* females live that

long. The critical advantage of IRS is that it not only reduces the abundance of mosquitoes but, more importantly, reduces their lifespan. This makes a big difference; even a marginal reduction in longevity will produce a dramatic reduction in transmission.[3]

The advent of house spraying in the 1950s made effective malaria prevention feasible for the first time in scattered rural populations. The impressive initial achievements of large-scale IRS led to the creation of the first global malaria eradication campaign, and the eventual failure of this campaign was also attributable in part to vector control problems that were anticipated but underestimated. First, a long series of pilot IRS trials failed to demonstrate that the highly intense transmission in tropical Africa could be interrupted, even by careful deployment of a combination of the most powerful malaria control weapons.[4, 5] Meanwhile, in much of Asia, progress had slowed down or stalled because of problems related to logistics, reduced compliance from target populations, insecticide resistance, and vector behavior.[6] Eventually, the world reluctantly concluded that global eradication was "technically unfeasible."

The same caveats that applied to the first eradication campaign can be applied to elimination campaigns today. IRS is a logistically demanding intervention: it is easy to do badly and is then ineffective. Proper infrastructure that can sustain coverage in a targeted area must be in place, including a system for selecting the right insecticide, adequate supervision of the program, enforced safety measures for sprayers, reliable and up-to-date spray equipment, frequent monitoring of progress, and careful evaluations of the program. The local epidemiological, entomological, and transmission patterns of the targeted areas must be understood and carefully monitored throughout the program. Furthermore, as IRS must be deployed on the insides of homes, community acceptance of IRS must be obtained to ensure that targeted populations understand and will consent to the spray program.

For elimination, IRS may have to be intense, thorough, and prolonged; the problem is that this may also intensify selection for resistance. The speed at which resistance is selected is unpredictable. The crucial point is that there are only four classes of insecticide recommended for IRS, so running out of effective compounds is possible. This means that there may be a limit to the period over which very intensive IRS can be sustained.

Insecticide choice may be further constrained by available formulations. Current IRS insecticide formulations last from 2 to 6 months, and this is a major constraint on its effectiveness. Formulations have improved recently, but with the exception of DDT, which is intrinsically stable, most IRS formulations last less than 4 months, so there is room for considerable further improvement.

BOX 9.2 | Is a Combination of Both ITNs and IRS More Effective than Either Alone?

So far, there is insufficient operational data to answer this question, which is important for the purposes of elimination at the geographical margins of malaria. From the point of view of disease control, however, we must not forget that the majority of children in Africa (who suffer about 85% of the global burden of disease) so far have no access to either of these interventions. For the moment, therefore, the public health priority at the regional level must be to extend coverage with either IRS or ITNs, whichever is more convenient locally.

ITNs—INSECTICIDE-TREATED NETS

Insecticide-treated nets have become the most widely used form of vector control, not because they are more powerful than IRS, but because they are usually less demanding logistically and coverage is easier to sustain. Ordinary ITNs need to be retreated every year or so, but this is not so with long-lasting insecticide nets (LLINs), which are designed so that the insecticide lasts as long as the net. ITNs work in two ways: first, they protect the individual user against biting, and second, they can kill some of the mosquitoes that try to bite. Like IRS, use of ITNs can produce a community-wide reduction in transmission.[7] Untreated nets give valuable protection against malaria, and their public health utility should not be underestimated, but the addition of the insecticide approximately doubles this protection.

ITNs (including LLINs) can be distributed in large-scale campaigns or through routine health contacts such as antenatal care and childhood immunization services. When the aim is disease control in high-transmission settings, they may be targeted to young children and pregnant women. In an elimination program, they should be provided to every sleeping place, as a means of general transmission control.

Community acceptance of ITNs, as with IRS, is essential if the targeted population is to use the nets properly. For example, some communities have a long tradition of net use, with well-established preferences for shape, size, color, and fabric. In places with a lot of nighttime nuisance biting by mosquitoes, most people who are not otherwise protected are happy to use a net, but it is often important to emphasize the need to use ITNs even when levels of nuisance biting are low. Engaging the community in the decision-making

process is important, as are information, education, and communication (IEC) campaigns.

ATTACKS ON BREEDING SITES—SOURCE REDUCTION, ENVIRONMENTAL CONTROL, AND LARVICIDING

Before the advent of DDT, destroying the larvae of mosquitoes was the only available form of vector control.[8] However, if the aim is to interrupt disease transmission, attacking the larvae tends to be less effective and efficient than attacking the adults. Larval control is not effective unless it is extremely thorough, and this is difficult to achieve. Most malaria vector *Anopheles* species prefer breeding sites that are small, numerous, scattered, and shifting. The critical obstacle is not how to kill the larvae in the known breeding sites but how to find and routinely treat all the sites. Each species has its own idiosyncratic preferences, so detailed knowledge of the specific kinds of water exploited by the local vectors is needed: some vectors breed in freshly formed puddles, others in rice fields or in established pools or marshland. The larval control has to be deployed and constantly sustained over a large area; tropical malaria vectors take only a week to complete their larval development and can easily fly 4 or 5 kilometers. For all these reasons, effective larval control requires highly specialized expertise, substantial investment, and constant effort.

There are opportunities for effective larval control when breeding sites are few, fixed, and easy to identify. Most of the famous examples of successful larval control have occurred in circumstances where, for one reason or another, breeding sites were clearly identifiable and confined to locations that were well defined and fixed.[9] Such situations are not common, but experience shows that when they occur, there are sometimes opportunities to knock out all the sites with just one economical intervention. The key rule is "don't make things worse." In many places, a substantial proportion of the local breeding sites are man-made, typically as an inadvertent side effect of some otherwise beneficial activity. Often these problems are a consequence of ignorance and misinformation about mosquitoes and how they breed.

9.4 Comparing the Impact of Alternative Vector Control Methods on Transmission

Eliminating the vector is not possible; our current methods of vector control are not normally capable of reducing vector numbers to zero over a large area. As we have seen, some methods of vector control (such as attacks on breed-

BOX 9.3 | Genetic Control

At present, the use of genetically modified mosquitoes is an area of intense research. Such methods might eventually be useful for elimination purposes, but there is no genetic control technology that is likely to be practical for application against malaria vectors in the next few years.

ing sites) act simply by reducing mosquito numbers and reduce transmission in simple direct proportion to their effect on vector population size. Other methods (such as IRS) have a larger impact on transmission by reducing not only the size of the vector population but also its capacity to transmit malaria.

The intensity of malaria transmission varies across a remarkably large range. For example, in areas with moderately intense transmission, people are typically exposed to an average of 10 to 100 bites from infectious mosquitoes per person per year. At the other end of the scale are locations that have reached the threshold between the pre-elimination and the elimination phases of the process, a point that is defined by the World Health Organization in terms of an observed incidence of 0.1 cases per 1,000 persons per year. A difference of about 100,000-fold separates these two situations. Converting any given location from the former condition into the latter is beyond the capacity of control methods that reduce mosquito population size but have no other effect on vectorial capacity. In the future, this might become feasible if researchers succeed in developing methods, almost certainly involving genetic modification of the mosquitoes, that can eliminate the ability of local vector populations to transmit malaria altogether. At present, this essential first giant step in the elimination process can only be done with methods such as IRS and ITNs, which work by reducing vector longevity as well as vector population size.

9.5 | How the Role of Vector Control Evolves Through Phases of Elimination

Because of the characteristics reviewed above, the relative roles of these different forms of vector control evolve—before, during, and after elimination is achieved. These changes are summarized in Table 9.1. Various terms have been suggested for the successive stages of the elimination process (Chapter 3); here we use our own functional classification, which focuses on the role of different vector control methods during each phase.

PREPARATORY PHASE

Planning is the key to effective vector control.[10, 11] Accurate information is needed on the biology and behavior of the vector mosquito species and on the geography and epidemiology of the malaria foci to be attacked. This informa-

TABLE 9.1 | Allocation of malaria suppression measures to different phases of an elimination program

	Attack phase	Elimination stages	Consolidation	Maintenance
Rationale and role	• General reduction in transmission • Maximum intensity and complete coverage throughout, with aim to interrupt transmission completely	• Intensive attacks on remaining foci (predictable) and outbreaks (unpredictable) • Maximum targeting and responsiveness as malaria becomes increasingly unstable, with essential vector control and drugs	• Rapid (fire brigade) emergency responses around cases • Long-term background measures to reduce outbreak risk	• Background long-term measures to reduce outbreak risk, perhaps now with reduced scale and intensity
Weapons	• IRS and 100% coverage with ITNs (LLINs) for maximum impact	• Good epidemiology, key for targeting, and IRS for shifting targets	• Nets (including untreated) for outbreak risk, and IRS (and ITNs) for fire brigade	• Nets, with environmental measures in selected places
Vulnerabilities, threats, possible reasons for failure	• Very high-intensity transmission in equatorial Africa • Mobile populations, open houses, exophilic vectors, and inaccessible shifting foci of forest malaria in Southeast Asia and Amazon • Insecticide resistance • Conflict and complex emergencies	• Failing to follow the shifting target • Conflict and complex emergencies	• Sluggish or ineffective emergency response • Neglect of background measures • Conflict and complex emergencies	• Complacency • Conflict and complex emergencies

tion should be used to formulate a plan of action for vector control activities within the malaria elimination strategy. Another important technical aspect of the preparatory phase is mapping of the main sources of infection in the country in order to allow targeting of interventions at individual malaria foci.[12]

ATTACK PHASE

The aim of the attack phase is to interrupt transmission completely for a period long enough to allow the reservoir of infection to die out, or else to suppress the transmission to such low levels that drug-based interventions can finish the job. The attack phase starts with the selection of vector control measures and then formulation and implementation of a plan of action, which must consider the following criteria: efficacy, cost, ecological acceptability, acceptability by the local population, operational feasibility, and administrative suitability, including availability of infrastructure, trained personnel, financing, transportation, legislative support, technical direction, public information, and community participation and sustainability. For present purposes, we should stress that these issues must not be underestimated; they require investment in human, operational, and technical resources, and meticulous attention to detail.

ELIMINATION STAGES—ROOTING OUT THE LAST FOCI OF LOCAL TRANSMISSION

Sooner or later, as the general suppression of transmission proceeds, it will become clear that local transmission is no longer occurring in many places but still continues in a few remaining foci. When the target locations have been identified, vector control must be directed with great intensity, and since the targets are likely to be shifting from year to year, vector control must be capable of tracking this moving target. There are three key operational issues to evaluate:

1. How can we find and track the moving target as the foci of transmission shift and recede? This requires an excellent surveillance system, one that is active and effective even in places where other parts of the health system are weak. Creating or reinforcing such a system is a critical preparation for this phase, and its importance must not be underestimated.
2. Having detected the foci, intensive vector control must be deployed, much as in the attack phase, but there is little evidence to guide the difficult operational decisions about the extent and manner of this deployment.

3. We need to know if there is a particular reason why transmission is persisting in some places but not others. Sometimes these remnant foci reflect operational or other problems in the deployment or public acceptance of vector control, resulting in less-effective coverage in these areas. In other cases, there may be a different vector (with different behavior or with insecticide resistance) or differences in human behavior (e.g., migration patterns), so an alternative or supplementary method of vector control (e.g., adding ITNs to IRS) may be needed.

CONSOLIDATION PHASE

This is a lengthy endgame in which vigilance against reintroduction of malaria is required. At the start of this phase, the program must anticipate the possibility of reinvasion outbreaks and possible epidemics. This means remaining vigilant and being ready to respond, even after a long period of zero local cases. A robust surveillance system is needed, covering the whole population, especially the hardest-to-reach areas where outbreaks are most likely (Chapter 3). When an outbreak is detected, the response must be rapid, determined, and thorough. This is classical epidemic control, and the necessary systems and methods are essentially similar to those used to control unstable and epidemic malaria. For this purpose, IRS has particular advantages that ITNs do not share.[13]

MAINTENANCE PHASE

During this phase, the desirable characteristics of vector control activities are low intensity, with high long-term coverage, and low cost. The key concept is outbreak risk reduction. For example, the routine use of untreated nets is to be greatly encouraged: It is already a social norm in much of Southeast Asia, the Americas, Madagascar, and large areas of West Africa, and such nets give approximately half the protection of a treated net.[14] Other effective means of personal protection, such as the use of window screening, should also be encouraged. Vector control interventions that are too weak to be useful in the attack phase, such as larviciding and environmental management and especially avoidance of the creation of man-made mosquito breeding sites, may be useful to reduce the risk of reinvasion.

Perhaps the most powerful and neglected factors influencing outbreak risk are the social, economic, and environmental developments that have indirect and unintended effects on malaria transmission. For example, recent decades have seen a massive transformation in housing materials in Africa. Twenty

BOX 9.4 | How Quickly Will Malaria Return If Elimination Is Not Successful and Vector Control Stops?

The answer to this question depends on background vectorial capacity, the period for which transmission has been suppressed, the quality and capacity of the surveillance and response program, and the immune status of the human population. In Africa, where background vectorial capacity is high, the withdrawal of spraying after 3 to 5 years of intensive control led to different results in different places. In the Pare-Taveta project, malaria came back over several years, eventually reaching the original levels of endemicity, but without any excess of disease.[15] This may have been because the spraying was with the insecticide dieldrin, which has a very long active life span. After another spray trial in Kisumu, Kenya, which used the very short-acting insecticide fenitrothion, malaria is said to have returned much more quickly, with abnormally high levels of morbidity and mortality in the young children who had grown up in the sprayed area and had little immunity. A human population that has been unexposed to malaria for a substantial number of years will have little or no immunity to malaria, and reinvasion can then produce sudden epidemics that are explosive and catastrophic. This is not just a theoretical threat: Disastrous epidemics, sometimes causing hundreds of thousands of deaths, occurred after various intervals following the withdrawal of spraying in Ethiopia, Madagascar, and Sri Lanka.[16]

years ago in northern Tanzania, almost all rural houses were thatched, and corrugated iron was a luxury; now metal is becoming as common as thatch in many areas. This has a profound impact on mosquito entry and biting numbers in houses.[17, 18] The same is likely to apply to other house construction features that are spreading rapidly (e.g., ceiling boards, window shutters, concrete brick walls, cement flooring). More effort is needed to study the impact of these changes on malaria risk at the household level, and their contribution to observed trends in malaria statistics at the population level.

9.6 | Operational and Technical Constraints on Vector Control

This is a selective list of issues that are either frequently encountered or strategically important and limit the present and future usefulness of vector control.

PROCUREMENT

The procurement of insecticides for IRS or the bulk purchase of LLINs is not complicated, but it is time-consuming. In the case of IRS, the amount of

insecticide needed can be calculated based on previous years' consumption, with a small percentage increase to take into account new structures that may have been built. The tendering process involves a great deal of decision making and needs to be started early. Timing is critical: IRS must be performed at or just before the onset of the transmission season, and any delay greatly reduces its effectiveness. The manufacturers only start making the product after the order has been placed, and this means that lead times can be very long. Underestimation of the need to plan well in advance and order early is a common source of problems in practical vector control programs.

COMMUNITY RESISTANCE

Community involvement and acceptance of vector control measures, particularly IRS, have been cited as very important. Sometimes they are difficult to obtain, and the response may depend on the insecticide that is used. Modern house construction may offer protection against transmission, but their inhabitants often have the most resistance to spraying, especially of DDT.

FOREST MALARIA

In large forested areas of Southeast Asia, Africa, and South America, vector control is less effective than elsewhere. This is partly because of vector behavior: Vectors of forest malaria mainly rest outdoors and not in houses protected by IRS. Some tend to bite outdoors, or early in the evening, reducing the effectiveness of ITNs. Human behavior is also an important part of the challenge; often forest communities are mobile, practice shifting cultivation, move to stay in distant farms during part of the rainy season, and may be wary of outreach efforts. In many areas, the people live in houses with incomplete walls and sleep in hammocks, not beds. Forests also attract many temporary visitors. All this makes it very difficult to deliver vector control in a way that is effective.[19]

INSECTICIDE RESISTANCE—ESPECIALLY, PYRETHROID RESISTANCE

Insecticide resistance is often a key constraint limiting the sustainability of intensive insecticide-based vector control operations.[20] Experience in the 1960s and 1970s, in the first malaria eradication campaign, showed that resistance is not the most frequently encountered obstacle to effective vector control, but it is one of the most difficult to overcome.[1]

Resistance is a particularly urgent and decisive threat for ITNs because, so far, we have only one class of insecticides, the pyrethroids, that combine a safety profile suitable for use on fabric next to the skin with a rapid mode of

action that kills or repels the insect before the person sleeping under the net is bitten. One form of a pyrethroid-resistant gene, *kdr*, is already widespread in West African vectors and present to a lesser extent in East Africa.[21,22] Some studies have claimed that ITNs and even IRS can still be effective despite high frequencies of this resistance gene in the local vectors,[23] but the gene is spreading rapidly and hence must confer some advantage on the insects that carry it. Even more worrying is the evidence that more-powerful metabolic mechanisms have appeared in some localities in South and West Africa.[24, 25, 26] It is hard to overestimate the strategic implications of a resistance gene that can undermine or eliminate the effectiveness of IRS and ITNs.

There are only four classes of insecticide suitable for IRS. Resistance management can be practiced using rotations or mosaics of insecticides, but a basic understanding of the underlying resistance mechanisms and the cross-resistances they produce is necessary.[27, 28] Theoretical models suggest that the most effective form of resistance management would be the use of combinations of insecticides for IRS, but this would require a great deal of development research (Chapter 10), as well as a policy change as great as that needed to establish combination drug therapies as the standard for treatment of malaria.

None of this can be managed properly without better monitoring of resistance. There has been a great deal of technical progress developing simplified methods for monitoring resistance, but these are not used nearly as widely as they should be.[20]

HUMAN RESOURCES

It was said that the Global Malaria Eradication Program "failed to eradicate malaria, but nearly succeeded in eradicating malariologists," and this is especially true for malaria entomologists. The facts are simple: global expenditure on malaria vector control is at an all-time high, but the supply of people with knowledge and skills in vector biology and control has declined steadily for the past 25 years. This has happened at all levels, from the most advanced experts to the most basic field-workers and technicians. The knowledge and skills needed for effective vector control are not especially difficult or demanding, but they are specialized, and they are no longer included in most modern courses in epidemiology, infectious disease, or tropical public health. The scarcity of these skills has emerged as one of the most important constraints on current efforts to scale up vector control, and unless the problem is tackled, it will remain a key constraint on efforts at elimination.

9.7 Conclusion

Vector control is indispensable for getting to zero transmission. Although vector control is the make-or-break intervention, there is still much to be done to maximize its effectiveness. Many forms of vector control are especially sensitive to coverage; there can be a great deal of difference between the effectiveness of 70% and 95% coverage. For elimination, the target is zero transmission, and completeness is therefore even more important than in a control setting. For the moment at least, effective technologies and the finances to pay for them are available, and the critical limiting factors are often infrastructural weakness, inadequate organizational capacity, and a scarcity of the skilled personnel needed to use these resources most effectively. The issues highlighted in this chapter illustrate the need for detailed analysis of the technical and operational obstacles to 100% coverage and effectiveness of available vector control interventions. In the longer term, there remain critical threats to the sustainability of vector control that are not yet being adequately addressed.

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10 | IDENTIFYING THE GAPS—WHAT WE NEED TO KNOW

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10.1 | Introduction

The preceding chapters have set a detailed agenda for countries considering or pursuing an elimination goal, and they discuss the multiple components of the decision-making process that leads from a state of improved control to the new strategy of elimination. The process by which countries assess elimination of malaria as a strategy will have a complex, challenging, and, for some, long-term agenda requiring the resolution of a substantial number of unknowns. Country or regional resolution of these unknowns will be key to the success of the programs. There is no single strategy for countries to follow. This immediately requires them to adopt an integrated approach that evaluates and investigates the operational requirements of health systems structures and functions. They must consider stakeholders (public, private, nongovernment organizations, and charity), program management, financial feasibility, and related issues, plus assessment of technical needs, to determine what is going to be the most effective way forward.

The Roll Back Malaria (RBM) Global Malaria Action Plan[1] calls for research of three kinds to help lead us toward the eventual goal of global malaria eradication:

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- research and development for new tools, including vaccines, better drugs, more vector control options, and more effective diagnostics
- research to inform policy, both international and national
- operational and implementation research, to better guide detailed strategies and action plans in individual countries and ensure the optimal use of the correct set of interventions and tools

MalERA (the Malaria Eradication Research Agenda) has been established by the Bill and Melinda Gates Foundation to elaborate an agreed research and development (R&D) agenda related to successful malaria elimination and eradication. This complements the Global Malaria Action Plan by detailing R&D needs for each step. This work is a short-term activity leading to a long-term R&D enterprise of the utmost importance. Specifying the need for a better drug or a better diagnostic tool needs to be done now, although the products of R&D that result will probably not be available for widespread use for another 10 years. This gestation time could be even longer, for example, with vaccine development.

The operational research agenda that the MEG is interested in for elimination is primarily focused on the second and third areas of research defined by the Global Malaria Action Plan. In other words, it is research that is directed towards policy and operations and which has a short-term time horizon. The MEG is particularly interested in operational research that can help the blue elimination countries (Figure 1.1) improve their work and reach elimination within the next 5 to 10 years.

The purpose of this chapter is to highlight these more pragmatic operational research needs in order to assist countries to move on to an elimination strategy in the short term or to sustain their ongoing elimination programs. In addition to the chapter's three authors, others have contributed content in their areas of expertise. These include Scott Barrett, Chris Drakeley, Erin Eckert, Michelle S. Hsiang, Oliver Sabot, David L. Smith, and Jim Tulloch.

The chapter is organized as a series of key questions leading to research priorities. The questions are arranged in a tabular form that is intended to guide planning of operational research investigations relevant to getting to zero and holding the line. It is not possible here to do more than highlight important research areas and admit that in some of these areas, very major questions have to be addressed in a progressive manner. They are of fundamental importance to consideration, adoption, and achievement of an elimi-

nation strategy. Predictive modeling of the complex questions may assist in decision making.

10.2 Case Studies

There is a diverse literature on the history of malaria elimination from the countries where it was achieved. Outlines of two of the successful programs, Mauritius and Morocco, are presented.

However, details of activities that were the core of elimination programs are often not available. A selection of the key questions that need to be asked about each program is set out below to serve as a guide to countries embarking on or contemplating elimination. Some of these are very substantial questions:

- How was the decision to pursue elimination made?
- What intervention strategies were used, and why were they selected?
- How was the effectiveness of interventions measured?
- How long was it necessary to employ each of the interventions?
- What were the financial and economic costs of each activity?
- How was the national elimination budget managed?
- How was the program financed?
- If outside funding was required, how was long-term and dependable financing ensured?
- What human resources were required to pursue elimination?
- How did the government program interact with nongovernmental and private sector stakeholders?
- What are the annual costs of preventing reintroduction of infection?
- How did personnel priorities change as transmission decreased?
- How are vigilant, trained staff retained to deal with outbreaks?
- Was there a political and legal framework that enabled elimination and prevention of reimportation?
- What were the major challenges of the elimination program, and how were these overcome?

The MEG will investigate case studies of countries that achieved elimination or came close to doing so, and these will be made available on the MEG Web site.

BOX 10.1 | Elimination Case Study: Mauritius

Mauritius was originally malaria free.[2] The first malaria case was detected in 1864 after anopheline vectors were imported through shipping. In 1948, with the support of the British colonial authorities, the malaria eradication program was initiated. Mandated DDT spraying resulted in decreased transmission and the elimination of *Anopheles funestus*. In 1960, WHO assisted in setting up an active malaria detection system, and 6 years later targeted DDT spraying replaced the previous strategy.[3]

Mauritius was certified malaria free in 1973. However, after a cyclone event led to an outbreak of malaria in 1982, Mauritius established a plan of action with support from WHO.[3] Household spraying with DDT was reinstituted in all active foci for a 3-year period, in addition to large-scale environmental sanitation work, fogging and larviciding, and the implementation of a malaria detection system. Blood slides and treatment of all malaria cases began, and staff training was increased. During this time, funding was primarily used to purchase spray, fogging equipment, entomology and laboratory equipment, insecticide, and drugs.

By 1998 the country was once again considered malaria free. Since then, there has been key political support for malaria activities, and government services now carry out most preventive measures. The port and airport unit disinfects airplanes, screens incoming passengers, registers those originating from or transiting malarious areas, and refers them to regional offices for follow-up blood slides. Early diagnosis through microscopy, including through the private sector, and free treatment and follow-up are provided for all cases. A government laboratory tests all blood slides and cross-checks private laboratory slides. Protocols are established for each of these activities. Entomological surveillance is ongoing, and vector control requires port and airport DDT spraying every 6 months, larviciding, and health education to eliminate breeding areas. Free malaria prophylaxis is provided for nationals traveling abroad.

10.3 | Checklist for Health Systems

This section is based on the health systems structure and functions as proposed by WHO.[4] Health systems as defined here include both public and private stakeholders. Those from within the private sector may include private-for-profit, NGO, and charity stakeholders.

ACCESS TO DIAGNOSIS AND TREATMENT

Accepting that malaria elimination requires an integrated and systemic approach, the key questions are around determinants of different health system functioning that need to be addressed. This entails understanding (1) which comparative analyses are required to evaluate health systems performance in

BOX 10.2 | Elimination Case Study: Morocco[5]

By the mid-1990s, Morocco had made substantial progress in reducing malaria transmission. This was brought about by classifying geographical areas according to their degree of risk of transmission. Once a risk area was classified, an appropriate surveillance and control strategy was implemented to target its specific needs.

In 1999, Morocco implemented the Autochthonous Malaria Elimination Strategy (AMES) with a goal to eliminate malaria by 2002. The program included case detection and treatment, vector control, entomological surveillance, and larval control.

AMES was followed by a 5-year consolidation phase to prevent the reintroduction of malaria. To sustain the elimination effort, training and retraining of essential staff (such as microscopists and entomology technicians) specific to the program was implemented and fully supported. Information and education campaigns were conducted throughout Morocco to raise awareness about the elimination process. To reduce the number of imported cases of malaria, border health control staff were also retrained, and travel agency and airline executives were engaged to help promote more understanding among persons traveling to or from malaria-endemic countries. Morocco reported zero locally acquired cases of malaria.

Through these various elimination efforts and continued vigilance to prevent reintroduction of malaria, Morocco provides an excellent example for many other lower-middle-income countries that wish to be malaria free.

the delivery of diagnosis and treatment, (2) which health system factors are most important to ensure access to preventative interventions and cure, and (3) what are the basic requirements for individual and community diagnosis and the diagnostic tools/strategies that will enhance health systems performance.

Key linked questions include the following:

- How do you improve the reliability of supply of good-quality diagnostics and treatment through public sector delivery channels?
- How do you ensure that access is assured across the whole health system, including public and private (private-for-profit, NGO, charity) providers?

- How can diagnosis reach the remotest and poorest populations, who often have the residue of infection?
- What is required to integrate public and private sector access to ensure effective treatment in an equitable and economic way?
- How can poor treatment practices, including use of poor-quality drugs and monotherapies, be eliminated?
- How do you ensure adequate detection and treatment of *P. vivax* (and *P. ovale*) where this is relevant?
- How can vertical antimalarial diagnostic and treatment programs be integrated within the existing health care systems?
- How can new and introduced cases be diagnosed and treated within existing health care systems?
- Are there novel, effective, and equitable strategies to deliver treatment and prevention in a given sociocultural, economic, and political setting?
- In which circumstances is syndromic treatment (e.g., home or community-based management) appropriate and effective?
- What systems of training, incentives, regulation, and consumer education will ensure a good outcome, especially regarding the informal and private sector system?

ORGANIZING THE MAJOR NONCLINICAL FUNCTIONS IN MALARIA ELIMINATION

In what ways (roles, responsibilities, and contractual relationships) can NGOs contribute to elimination programs at national and subnational levels, specifically the following:

- indoor residual spraying (IRS) implementation and/or promotion and distribution of insecticide-treated nets (ITNs) in relation to the stages of expansion and maintenance of coverage
- maintaining community involvement in malaria elimination, including the promotion of early diagnosis and treatment, such as use of mass media
- linking with private facilities
- training the required human resources
- integrating malaria vector control into a broader vector-borne disease program following elimination

THE RELATIONSHIP BETWEEN THE NATIONAL MALARIA CONTROL PROGRAM AND THE REST OF THE MINISTRY OF HEALTH AND OTHER GOVERNMENTAL DEPARTMENTS

- How can the necessary focus and vigilance in preventing the reintroduction and resurgence of malaria be ensured?
- How do we ensure that the investments and scale-up necessary to achieve and maintain malaria elimination are of maximum benefit for the overall health system?
- How do we make the best use of strengthened monitoring and evaluation (M&E), surveillance, and laboratory systems to bring broad benefits to the health system?
- What are the key determinants to move from pilot studies to nationwide or regional initiatives?
- What structures and processes are required to ensure coordination and cooperation between different governmental and nongovernmental partners?

10.4 | Checklist for Finance and Economics

An elimination strategy presents financial and economic challenges at least equal to the technical issues that have to be resolved.[6] Elimination of malaria will require substantial financial investment. The effectiveness and sustainability of different financing mechanisms need to be explored (Chapter 4).

COST COMPARISONS

A fundamentally important question is the cost of an elimination program and how this might compare with the counterfactual of sustained control. Requirements include the following:

- a standardized analytical approach to compare costs and cost structure between different countries and settings
- direct and recurrent costs of interventions, costs of support at the district level, and costs of necessary health system strengthening
- a monitoring system to obtain standardized comparative information on the coverage required and on the intervention mix needed

COST BENEFITS

Comparisons of the strategies of elimination and sustained control should address the benefits that can accrue to the people and the economy:

- Costs and benefits of elimination should be compared with those of sustained control, specifically the incremental cost and benefits derived from moving from low-level malaria to no malaria.
- Costs of elimination and control should be calculated for a period of 20 to 25 years. If elimination is cost-reducing, further calculation of the cost benefits of elimination is not essential.
- Where elimination costs do not come out lower, a full cost-benefit analysis is necessary.
- Benefits to be costed will include the following:
  - labor supply, productivity, and agricultural output through reduction in malaria-related morbidity and mortality
  - reduced treatment and other health sector costs
  - improved foreign investment
  - increased tourism
  - long-term cost reductions
- Assigning a monetary value to these benefits and comparison with costs of elimination provides a cost-benefit ratio.
- Decisions are required on how to deal with benefits that cannot be given monetary values, for example, educational attainment and natural satisfaction.
- New approaches should be explored to health planning at national and subnational levels for the elimination strategy. Such approaches should be based on both burden of infection and cost benefit.
- Regional benefits, which should be regionally financed, and internationally financed global benefits should be considered.
- Who benefits most from elimination (relative to control)?

COST-EFFECTIVENESS

Consideration of cost effectiveness should be based on technical efficiency and can be assessed by cost-effectiveness analysis (CEA) of the health returns of different elimination strategies and interventions.

The CEA technical efficiency measures are relevant for a diverse range of interventions, such as the following:

- selection of diagnostic procedures to be used peripherally and centrally
- combinations of interventions—additive or synergistic
- interventions used as transmission changes over time
- active case detection
- extending the reach of malaria interventions, especially to isolated, lowest-quintile populations

10.5 Checklist for Surveillance

The single objective of a surveillance program is to prevent transmission. Countries need to consider individually and regionally what procedures are required to reduce transmission to zero, how to prevent importation of infections, and if there is transmission, how to detect cases rapidly in order to stop an outbreak.

FOCI OF INFECTION

As transmission is driven down to very low levels, it is likely to become restricted to small foci.

The key questions are these:

- What determines the heterogenicity of transmission?
- How much local transmission is there, and can intense local control eliminate it?
- What strategies and practical procedures have to be established for dealing with new foci of infection?

FINDING ALL PARASITES

Elimination is only achievable if all infections are detected and treated. The challenge is to develop and integrate strategies, both passive and active, that will achieve this. As transmission reaches low levels, infections that do occur are more likely to be symptomatic, but even in low-transmission settings, there remains a significant number of carriers of asymptomatic infections.[7]

There is an equally urgent need to ensure that only those with a confirmed malaria infection are treated.[8] It is necessary to devise means of finding the individuals who generally have little or no contact with the public health sector and assess the effectiveness of different types of surveillance and diagnostic procedures to cover these under operational conditions.

Key questions include the following:

- What surveillance systems are required, particularly for subpopulations at special risk?
- How can robust malaria surveillance be effectively conducted within a weak health system, including through use of new technology?
- What system of active case detection is required to detect, treat, and investigate all new cases and to contain new foci of infection?
- What is the cost-effectiveness of varying approaches to active case detection?
- In which settings is mass treatment or mass screening and treatment effective for removing remaining cases of infection?
- What approaches and systems are needed to find asymptomatic infections?
- How can malaria infections be identified best among those with acute febrile illness?
- What systems are needed for reporting and integrating data on malaria detected outside the public health system?
- What central and peripheral routine systems are most effective for detection and prevention of cross-border importation of infections?

COMMUNITY INVOLVEMENT

- How can advocacy campaigns and community-led initiatives be developed, used, and sustained in a given health and social system?
- Can village health workers be used for frontline surveillance?
- What incentives are required to maintain community involvement?
- How can IT (including GPRS or cell phones) best be used for community and public health reporting of infections?

10.6 | Monitoring and Evaluation

A strategy of the scope and duration required for elimination needs an M&E plan to identify the steps necessary to achieve the endpoint over a given time frame and then to maintain it.

The procedures required to deal with small numbers of cases that remain to be detected and treated in the process of getting to zero are similar to those that must be employed, or in readiness, to prevent importation and an outbreak.

GETTING TO ZERO

Once transmission has been reduced to a point where elimination can be planned, specific changes in emphasis and capacity must be made before pursuit of complete elimination. The M&E research areas to be addressed include the following:

- How is parasite (including gametocyte) prevalence monitored in at-risk populations?
- How is the quality of clinical and laboratory services monitored?
- How is the accuracy of diagnosis and response systems to ensure effective use of resources monitored and evaluated?
- How can equity of access to prevention and cure be monitored?
- How is the effectiveness of vector control interventions evaluated?
- What systems are needed for monitoring drug quality and drug and insecticide resistance?
- How can all monitoring systems permit effective reporting and near-real-time analysis?

HOLDING THE LINE

The key M&E issues to research are the following:

- effective detection and response to outbreaks, including determination of the species and origins of the parasites (imported or local)
- comparison of the position and role of the centralized laboratory facilities used for confirmation of diagnosis and determination of origin of parasites, versus the role and responsibility of the peripheral facilities, including reporting systems
- monitoring of vector control measures used in focal areas and assessing development of resistance to insecticides or larvicides

MEASURES OF EXPOSURE

Antibodies are produced in response to a first infection, and a memory response can be induced that can persist for decades. The likelihood of being antibody positive depends on the age of the individual and the frequency with which he or she is exposed to infection. Simple antibody prevalence rates can be used to define malaria endemicity, and a more detailed examination of age-specific antibody positive rates can be used to monitor changes in transmission.

Developments using standardized recombinant antigens of different immunogenicities, from both *P. falciparum* and *P. vivax* (and potentially other species), allow a detailed assessment of malaria exposure.[9] Analytical and modeling advances will allow antibody levels, in addition to prevalence, to be used to monitor the progress of an elimination program. Antibodies can be detected in blood from a small finger prick, and samples can be assayed in large numbers quickly, making this approach readily accessible and suitable for monitoring elimination efforts.

The key question is this:

- How can existing and new sero-epidemiological strategies be used to measure success in elimination of transmission or, conversely, to obtain evidence of reexposure?

POPULATION MOVEMENTS/MIGRATION

What are the technical and systems needs for monitoring population movements within a country to prevent reintroduction of infections into a malaria-free area? Specific questions include the following:

- How can we capture the heterogeneity of moving populations with regard to finding the clusters of infected people (imported cases)?
- How can reintroduction of malaria by cross-border population movement best be prevented?

INDICATORS

The key issue for impact is monitoring of rapid completion of case reports and immediate reporting to a local rather than a central response network.

The key issue for outcome and output is to ensure local responsibility for achieving high coverage, with systems to track diagnosis, ensure prompt, effective treatment, and monitor drug efficacy.

The key issue for input and process is to ensure that financing systems are in place so that there are no problems with outputs and outcomes, or with stock-outs.

10.7 Checklist for Diagnosis

Making the best use of currently available diagnostic tests and advancing the introduction of new highly sensitive and specific tests are crucial to the success of an elimination strategy.

Clinical diagnosis of malaria is widely used as the basis for treatment in areas of moderate to high transmission, but it is not appropriate for an elimination strategy[8] (or for sustained control). The preferred alternatives available are rapid diagnostic tests (RDTs) that detect parasite-specific antigen in the blood.[10] Currently available RDTs have the improved benefits of ease of use and of speed, detect the majority of malaria cases (*P. falciparum* more effectively than *P. vivax*), and are specific enough to guide treatment. RDTs should be widely deployed in order to identify malaria infections within the context of management of fevers.[11] Medical staff and the community as a whole need to be educated to accept the results of diagnosis (particularly negative results).[12] This requires that malaria diagnosis should be an integral part of a health facility capable of managing the major causes of fever.

There are increasing reports that all species of *Plasmodium* can persist as subpatent blood-stage infections mostly below the level of detection possible by microscopy or RDTs. Progress is being made in the development and application of more-sensitive PCR-based diagnostic tests. There is no way of detecting hypnozoites of *P. vivax* or *P. ovale* until they give rise to blood-stage forms.

Mixed infections are not uncommon,[13] and where two, three, or four species occur together, it is important to target all of them for elimination (Chapter 8).

The key questions are the following:

- How can the use of RDTs or microscopy be optimized to avoid fever mismanagement and overdiagnosis of malaria?

- What system of quality assurance of RDTs is required?
- How should more-sensitive diagnostic techniques (PCR and related tests) be tested and introduced for point-of-care, screening of subpatent infections, and/or regional reference center diagnosis?
- How can long-term persistence of *P. vivax*, *P. ovale*, and *P. malariae* be monitored?
- What strategies are needed to improve acceptance of diagnostic tests and their results by health workers and patients?

10.8 | Checklist for Drugs

There are some very substantial operational questions to be addressed regarding use of the drugs that are currently available. Maintaining fully effective drugs for treatment is a very high priority for both control and elimination programs. The approach identified as "prevention by treatment"[14] requires use of drug combinations that prevent transmission through effects on gametocytes or mosquito stages (Chapter 8).

DRUGS FOR TREATMENT

- What drug combinations should be used for treatment in an elimination strategy?
- Can rotating first-line treatment be used to delay the evolution of drug resistance?
- How is the access to drugs ensured in a given elimination program?
- What systems for rapid deployment of treatment are needed?

GAMETOCYTICIDAL DRUGS

Gametocytes of *P. vivax*, *P. malariae*, and *P. ovale* are generally sensitive to the drugs that kill the asexual forms,[15] but the effectiveness of currently available drug combinations, especially artemisinin-based combination therapies (ACTs), needs to be established, as they are likely to be used more frequently once chloroquine ceases to be effective against *P. vivax*.

- Can primaquine (or other 8-aminoquinolines) be deployed in combination with ACTs?

MASS DRUG ADMINISTRATION OR MASS SCREENING AND TREATMENT

Mass drug administration (MDA) could be considered for elimination (Chapter 8), for example, for removal of small residual foci of infection or reintroduced foci. For MDA, the general guidelines would be to use drugs in combination, but not those required as first- or second-line treatment, to include a drug effective against gametocytes or mosquito stages of the parasite, and to ensure that the drugs are safe to use.

An alternative to MDA for clearing residual foci and, more appropriately, for dealing with the reintroduction of infections is mass screening and treatment (MST). Operational questions that must be considered in comparing the two approaches are the following:

- Which approach is more appropriate, and which drugs should be used?
- What pilot study designs are required?
- What level of coverage is needed?
- How might these interventions be sustained and for what period?
- How cost-effective are these interventions?

Hemolytic episodes in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency is a risk factor when they are treated with primaquine. There are many different forms of this deficiency, many of them mild, and it is likely that a single dose of primaquine combined with ACT treatment would be sufficient to reduce substantially the numbers of circulating gametocytes. Trials of the ACT-primaquine combinations (and with ACT plus a single dose of tafenoquine) are needed.

Key questions include the following:

- What are the tests to use to identify G6PD deficiency in MDA programs and allow the use of primaquine (or other 8-aminoquinolines) in MDA or MST?
- Is there an effective dosage or delivery system for primaquine (and possibly tafenoquine) that can be given safely and easily to large populations without screening for G6PD deficiency? For example, a skin patch designed to deliver a graduated amount of drug slowly over a week or month could lessen the likelihood of hemolytic events by avoiding the peak blood concentration seen after oral use.

P. VIVAX AND *P. OVALE* HYPNOZOITES

The only licensed treatment capable of radical cure of *P. vivax*, by killing hypnozoites, is a 14-day regime with primaquine. The safety concerns in G6PD-deficient patients are more serious with this long treatment schedule. Without this radical cure, relapses can occur for 3 to 5 years without exposure to any additional mosquito bites. A 14-day regimen would not be feasible for MDA in most settings.

Other long-acting 8-aminoquinolines such as tafenoquine also induce the same hemolytic episodes but require fewer doses than primaquine[16] and should be investigated further as an alternative. The key question is how primaquine (or other 8-aminoquinolines) can be used safely and effectively?

MONITORING FOR RESISTANCE

The development of antimalarial resistance needs to be monitored carefully, as it can have a marked effect on transmissibility as well as reducing the clinical impact of treatment. A reduction in drug efficacy is marked by an increase in gametocytemia (Chapter 8) and therefore infectivity of the population. The failure of treatment will increase the likelihood of recrudescence and gametocyte carriage with resistant infections. Recent evidence of tolerance to artemisinin has emerged from the Thai-Cambodia border where decreased efficacy of artemisinins is manifesting as prolonged parasite clearance times.[17] This is a global crisis, as the worsening and spread of artemisinin resistance threatens the efficacy of most of the ACTs on which treatment of malaria depends. The capacity for monitoring drug resistance needs to be strengthened. Particular focus should be paid to monitoring the efficacy of artemisinins. A network for collecting, analyzing, and sharing data is currently being established under the umbrella of the World Antimalarial Resistance Network.

- What strategies are needed to contain or eliminate the spread of artemisinin-resistant infections through alleviating drug pressure and isolating and removing foci of resistant infections?

10.9 | Checklist for Vector Control

Vector control, or more precisely the reduction in the ability of mosquitoes to acquire, incubate, and transmit malaria parasites, is an essential part of an elimination strategy (Chapter 9). Elimination of the mosquito vector of malaria is only rarely optional for elimination.

FOCI OF INFECTION

Mosquitoes in particular determine the outbreak risk, and the breeding habits and behavioral characteristics of different *Anopheles* species determine the range of measures that can be used to reduce or prevent malaria transmission.

There may be human behavioral factors that include, on the one hand, creation of breeding sites for the mosquitoes and, on the other, a reluctance to accept ongoing vector control measures such as IRS. The persistence of foci and the factors that make such foci receptive to reintroduction of transmission depend on vectorial capacity. This in turn depends on mosquito species and density, biting habits, the egg-laying cycle, survival, and duration of development of parasites within the mosquito. Other factors are included below, and once the characteristics of a focus of infection have been established, an intensive and appropriate package of vector control measures must be implemented.

Special transmission settings are of particular importance. Forest malaria is maintained by communities living within the forest areas and may make up a high proportion of malaria cases. Forest malaria is difficult to control, especially because vectors are outdoor-resting early biters that are largely unaffected by IRS and ITNs. These are populations where alternative vector control measures such as use of repellents should be investigated. Malaria within the fringe areas may be dramatically changed by activities such as deforestation, which can change the whole vector ecology and the mosquito species transmitting infections.

Key questions include the following:

- What are the specific entomological and epidemiological features of foci of transmission?
- What vector control interventions are most effective?
- How do vector-specific characteristics determine outbreak risks?
- How can importation from forest to nonforest areas be monitored and managed?
- How does changing ecology affect transmission?

INSECTICIDE RESISTANCE

Insecticide resistance poses some difficult questions. On the one hand, a range of mechanisms of resistance to the different classes of insecticides being used has been identified, and resistance could therefore reduce the efficacy of the insecticides (Chapter 9).[18] However, the operational impact that different resistance mechanisms have is far from clear. Further investigation is required, in

the context of what insecticides are used and the resistance status of regional anopheline species.

Key questions include the following:

- How can insecticide resistance be monitored routinely?
- What strategy can increase and sustain IRS or ITN effectiveness, and to what extent are rotation and mosaic use of insecticides important in a given epidemiological setting?

REPELLENTS

Many mosquito vectors are exophilic (outdoor resting), dawn or dusk biting, exophagic (outdoor feeding), and not exclusively or even predominantly anthropophilic (human blood feeding). Consequently, ITNs and/or IRS may be of limited effectiveness, and supplementary or alternative methods may be required. Combining repellents with ITN use has been shown to be highly effective,[19] and cluster randomized trials of this combination should be considered. Issues will include effectiveness, safety, acceptability, and sustainability.

The key question is this:

- How can repellents be used beneficially either alone or in combination with ITNs or IRS?

BREEDING SITES

Larval control is generally less effective than attacking adult mosquitoes, and there must be good coverage when it is used. Many species of *Anopheles* (notably *A. gambiae*) have breeding sites that are difficult to identify because they are not fixed bodies of water. However, finding sites, especially those linked to foci of infection, along with intensive vector control (Chapter 9) that includes antilarval measures can be effective. Many of the identifiable breeding sites are man-made, and investigations into mosquito source reduction should include environmental management and community involvement to prevent creation of such sites.

Key questions include the following:

- Which are the epidemiological settings where larval control is feasible and has a high potential effectiveness? In epidemiologically suitable sites, how can transmission be contained by reducing natural and man-made mosquito breeding sites?

- How and under what circumstances can community involvement be used to prevent creation of man-made breeding sites for vectors?
- Can larval control be scaled up in a cost-effective way for vector species that are not adequately controlled by use of IRS and ITNs because of their resting and biting habits?

COMBINING VECTOR CONTROL INTERVENTIONS

Interventions need to be combined as packages. Research into the best ways to deliver existing tools should be continued. In many countries, scaling up provision of ITNs, and especially LLINs (long-lasting ITNs), is a high priority. Other interventions will be required, and trials must be designed to assess the incremental effect of adding any intervention against the background of high use of nets in different epidemiological settings.

There are a few examples of where the benefits of combining different vector control measures have been investigated, but much more needs to be known about the value of using combined interventions.

Integrated vector management (IVM) is defined as "a rational decision-making process for the optimal use of resources for vector control," and it is recommended for national malaria control programs especially as they elect to move from sustained control to elimination. IVM goes beyond vector control measures alone because IVM is employed as part of intersectoral collaboration and incorporates social mobilization, advocacy, legislation, and capacity development.[20]

All interventions should be reviewed in an ongoing way to ensure that they remain fully effective and cost-effective. This is particularly important when the elimination strategy is well advanced or when maintenance of a malaria-free state is the objective. For example, IRS is a very demanding vector control measure, requires repeated application, is costly to maintain, and often becomes progressively more unpopular with the populations required to accept it. It also leads to insecticide resistance.

Key questions include the following:

- What are the additive or synergistic benefits of combining different antivector measures?
- When would it be appropriate to consider withdrawing or replacing a vector control intervention tool within the course of an elimination program?
- What is required for integrated vector management?

10.10 Conclusion

The much broader R&D agenda that embraces both basic research needs and the multidisciplinary global agenda needed to make the long-term goal of eradication feasible is not addressed here but is the remit of the recently established MalERA project. This consists of an intensive 12-month program of consultation and definition culminating in the production of an agenda (or white paper) designed to strengthen the links between different research areas and to gain consensus among research institutions and sponsors on directions for malaria R&D toward the ultimate long-term goal of eradication.

This chapter is intended to flag the issues that need to be considered for the planning and implementation of malaria elimination programs in order to make them feasible and effective. The checklists presented point to both operational requirements and operational research needs.

Consequently, any national plan aiming at elimination may find these checklists helpful when completing their operational plans, identifying where in a given setting specific operational research is required, and/or identifying where the program could draw from evidence generated in comparable settings. We feel that this approach will assist countries and regions to establish a relevant operational research agenda that can be presented to national and international partners for support and implementation.

Finally, the research agenda outlined in this chapter can be improved and more fully adapted to the various epidemiological settings in which elimination programs are undertaken by an interactive process between national/regional programs, WHO, and other technical experts and MEG members. In this way, questions can be refined and/or adapted to specific settings and stages of elimination. We particularly welcome input based on practical experience from areas that have already moved into implementation of an elimination program or are holding the line.

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GLOSSARY

The following definitions apply specifically to malaria.

Active case detection Proactive screening of a defined portion of the population for malaria parasites.

Acquired immunity Immunity acquired over time in people residing in malaria-endemic areas through continued exposure to malaria parasites. Although full immunity is not obtained, and low-level parasite infections may still occur, it does generally protect against severe malaria.

Administrative feasibility The possibility of creating a national administrative infrastructure that can carry out a malaria elimination program with a strong long-term governmental commitment and a conducive legal environment for elimination.

Annual blood examination rate (ABER) The number of blood slides examined for malaria parasites as a proportion of the total population in areas at risk of transmission.

Annual parasite index (API) A measure of the number of confirmed malaria cases per thousand people per year in a defined geographical area.

Autochthonous (indigenous, local) Transmission acquired locally in an area where malaria regularly occurs.

Basic reproductive number (R_0) The number of potentially infected humans that would arise from a single infected human, or the number of potentially 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.

Case, imported A case whose origin can be traced to a known malarious area outside the area in which the case was diagnosed.

Case, indigenous A malaria case likely to have occurred through local transmission.

Controlled reproductive number (R_C) The same as the basic reproductive number (R_O) but takes into account all of the malaria control measures that have been put into place to slow transmission. It is also a measure of potential for outbreaks.

Cost-benefit Ratio of costs to benefits, considering the financial value of a wide range of health benefits, economic benefits, and social benefits.

Cost-effectiveness Ratio of the net cost divided by the number of disability-adjusted life years (DALY) averted, or some other metric of morbidity or mortality averted.

Elimination The interruption of local mosquito-borne malaria transmission in a defined geographical area, creating a zero incidence of locally contracted cases.

Endemic Applies to a malarious area when a sustained measurable incidence of cases and mosquito-borne transmission occur over a succession of years.

Entomological inoculation rate (EIR) The expected number of infectious bites per person per year.

Epidemic Occurrence of many cases of infection that substantially exceeds the expected number in a given place and time period.

Eradication The permanent reduction to zero of the worldwide incidence of malaria infection. Intervention measures are no longer needed once eradication has been achieved.

Financial feasibility The ability to establish and sustain the necessary funding to achieve and maintain elimination on a long-term and reliable basis from domestic and international sources, given other demands on health sector expenditure.

Focus (foci) A defined and circumscribed locality situated in a current or former malarious area that contains the continuous or intermittent epidemiological factors necessary for malaria transmission.

Force of infection Rate per year at which susceptible individuals become infected by malaria.

Gametocyte The sexual stage of malaria parasites, present in the host red blood cells, that are infective to the anopheline vector mosquito.

Gametocyte carrier Person who has malaria gametocytes in his or her peripheral blood, making the person a potential source of infection.

Holoendemic Permanent intense transmission with a high parasite rate among infants and a well-developed immunity in older children and adults.

Horizontal program An effort to provide the population with access to all health services and interventions through an integrated health delivery system.

Human biting rate The number of mosquito bites per person per year.

Hyperendemic An area with high transmission, frequently seasonal, with infants being the most susceptible.

Hypoendemic An area with little malaria incidence and a parasite rate of less than 10% in children aged 2-9 years.

Importation risk (also known as vulnerability) The probability of malaria reintroduction based on an area's proximity to other malarious areas and the movement of infected humans or infected *Anopheles* mosquitoes.

Internal rate of return (IRR) The percentage rate of interest that represents the economic return on an investment in malaria elimination; it is calculated from the incremental annual costs of an elimination strategy over the baseline costs of a strategy of sustained control over time.

Malariogenic potential Combination of a region's outbreak risk and importation risk.

Mass drug administration (MDA) Presumptive treatment of a defined population with a therapeutic dose of an antimalarial drug or drugs.

Merozoites Parasites released into the host bloodstream when a hepatic or erthrocytic schizont bursts, initiating a new cycle of development within the red blood cells.

Mesoendemic An area of intermediate malaria incidence and a parasite rate of up to 50% in children aged 2-9 years.

Operational feasibility The ability to establish and sustain the systems and capacity to effectively implement all the activities needed to achieve and maintain elimination.

Outbreak A case or number of cases of locally transmitted infection greater than would be expected at a particular time and place.

Outbreak risk (also known as receptivity) A measure of the potential of an area or focus to allow transmission to occur, or once elimination has been achieved, the propensity for reintroduced malaria to give rise to malaria outbreaks.

Parasite rate (PR) Prevalence of asexual blood-stage parasites.

Parasitemia Percentage of malaria infected red blood cells.

Passive case detection Detection of malaria cases among patients who on their own initiative went to a health post to get treatment, usually for a febrile disease.

Positive predictive value (PV^+) The probability that infection is truly present, given a positive diagnostic test result.

Pre-elimination phase Malaria control program reorientation during the period between sustained-control and elimination, in which emphasis on surveillance, reporting, and information systems increases.

Private sector All health facilities outside of the government's health system, and all potential malaria contributors that are outside government.

Reintroduction risk The risk following elimination that endemic malaria will be reestablished once surveillance shows a reduction to zero of all locally acquired cases (i.e., not including imported cases), when malaria can be reintroduced to the local environment.

Sensitivity (of a test) The percentage of true positives correctly identified by diagnostic test results.

Serology The diagnostic identification of immunoglobulins/antibodies in the serum.

Slide positivity rate (SPR) The proportion of blood slides found positive among all slides examined.

Spatial analysis A general ability to manipulate spatial data (e.g., maps) into different forms and extract additional meaning (e.g., high-risk areas) as a result.

Specificity (of a test) The percentage of true negatives correctly identified by diagnostic test results.

Sporozoite rate The proportion of mosquitoes with sporozoites in their salivary glands.

Surveillance The part of the program aimed at the discovery, investigation, and elimination of continuing transmission; the prevention and cure of infections, and the substantiation of claimed elimination.

Sustained control Period during which malaria control measures are stabilized and universal coverage is maintained by continued strengthening of health systems.

Technical feasibility The probability that malaria transmission can be reduced to zero in a given area and that zero transmission can be maintained in that area once elimination has been achieved using currently available control tools.

Transmission foci Areas in which malaria transmission is concentrated.

Transmission, stable Constant, year-round malaria transmission that is relatively insensitive to environmental changes.

Transmission, unstable Malaria transmission with marked fluctuations in intensity due to changing environmental conditions.

Vectorial capacity The expected number of infectious bites that will arise from all the mosquitoes that bite a single person in one day.

Vertical program A nonintegrated (e.g., stand-alone) health program, often aimed at a single disease, group of diseases, or target population.

ABBREVIATIONS AND ACRONYMS

ABER	annual blood examination rate
ACT	artemisinin-based combination therapy
API	annual parasite index
CDC	Centers for Disease Control and Prevention
DALY	disability-adjusted life year
DNA	deoxyribonucleic acid
EIR	entomological inoculation rate
E8	Elimination 8 (Angola, Botswana, Mozambique, Namibia, South Africa, Swaziland, Zambia, Zimbabwe)
GIS	geographic information system
GMAP	Global Malaria Action Plan
GMEP	Global Malaria Eradication Program
GPRS	General Packet Radio Service
G6PD	glucose-6-phosphate dehydrogenase
HBER	human blood examination rate
IEC	information, education, and communication
ITNs	insecticide-treated nets
IPT	intermittent presumptive treatment
IRR	internal rate of return
IRS	indoor residual spraying
LAMP	loop-mediated isothermal PCR
LLINs	long-lasting insecticide-treated nets

LSDI	Lubombo Spatial Development Initiative
M&E	monitoring and evaluation
MDA	mass drug administration
MEG	Malaria Elimination Group
MSP-1	merozoite surface protein 1
MST	mass screening and treatment
NGO	nongovernmental organization
NMCP	National Malaria Control Program
ODA	official development assistance
PCR	polymerase chain reaction
PR	parasite rate
PV^+	positive predictive value
QT-NASBA	quantitative nucleic acid sequence-based assay
RBM	Roll Back Malaria
R_C	controlled reproductive number
RDT	rapid diagnostic test
R_0	basic reproductive number
R&D	research and development
SADC	Southern African Development Community
SPR	slide positivity rate
WHA	World Health Assembly
WHO	World Health Organization

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