ROLL BACK MALARIA

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Mathematical Modelling to Support Malaria Control and Elimination

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ACRONYMS AND ABBREVIATIONS

ACT	*Artemisinin-based combination therapy*
DDT	*Dichlorodiphenyltrichloroethane*
EPI	*Expanded Programme on Immunization*
IRS	*Indoor residual spraying*
IPTp	*Intermittent preventive treatment for pregnant women*
ITN	*Insecticide-treated mosquito net*
LLIN	*Long-lasting insecticide-treated net*
MACEPA	*Malaria Control and Evaluation Partnership in Africa*
MalERA	*Malaria Eradication Research Agenda*
MVI	*Malaria Vaccine Initiative*
MV	*Mass vaccination*
MMV	*Medicines for Malaria Venture*
PK/PD	*Pharmacokinetic/pharmacodynamic*
RBM	*Roll Back Malaria*
SIRS	*Susceptible-infected-recovered-susceptible*
WHO	*World Health Organization*

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PREAMBLE

Global control of malaria inherently involves consideration of a vast matrix of variables, each with its own set of complexities, values, and uncertainties. The malaria situation may not be any simpler at the national level, for example in countries with heavy malaria burden that are bordered by similar neighbors. As countries progress with deploying proven interventions, they are striving to maintain and improve on gains already made: there may be a sense that adding more (or new) interventions, possibly in new combinations, can further the gains on reducing infection and disease. But research identifying the optimal mix of interventions in different settings is not readily at the hands of decision-makers.

In Africa today many countries are attaining higher coverage of their population with insecticide treated mosquito nets (ITNs), intermittent preventive treatment in pregnant women (IPTp), and prompt diagnosis and appropriate treatment for malaria. Some countries are adding indoor residual spraying (IRS) in certain areas and expanding this if they can afford it. Others are considering adding larviciding to their intervention mix, or more aggressive efforts to find infected people and treat them quickly so that they are not able to transmit parasites on to other mosquitoes. Additionally, many countries are anticipating a vaccine becoming available in coming years and will need to consider how best to use it. There are some countries that now have declining numbers of malaria cases and deaths and they recognize the need for alternative means of improvement. Urgent questions emerge from this remarkable progress, such as:

- When, where, and to what levels should countries introduce IRS when they already have ITNs?
- Could countries stop using IPTp if malaria transmission intensity were considered low enough?
- When does it make sense to go into communities to identify all malaria-infected persons and treat them in order to further reduce malaria transmission intensity?
- In what age groups or risk populations should a vaccine be introduced to further control malaria disease or transmission?

- Under what transmission circumstances does it make sense to introduce larviciding—or does that even work?

- What would be required to successfully eliminate malaria transmission in a formerly endemic setting?

- At what level of artemisinin-based combination therapy (ACT) drug resistance should a change to a different drug combination be made?

- At what level of insecticide resistance should a change to a different insecticide be made—and then rotated to a third insecticide (or back to the original one)?

Developing models to inform responses to these questions can assist WHO in setting global malaria policy and malaria endemic countries in adapting and implementing those policies.

This is a time of rapid, positive change: in developments of new malaria control technologies and improvements in existing ones, the epidemiological profile/burden of malaria disease, and funding available for and commitment to fighting the disease. All this, when cast against a backdrop of a highly adaptable parasite, shifting national and global priorities, and decision-makers who are eager for guidance on what to do next, makes it clear that mathematical modelling can play a critical role in navigating complex public health decisions. In this context, this report was developed to provide background to the malaria community and public health decision-makers on mathematical modelling and to expand the dialogue on priority decision-making and when and how modelling can help.

INTRODUCTION

Mathematical modelling involves the use of mathematics to describe, explain, or predict behaviour or phenomena in the real world. It can be particularly useful in investigating questions or testing ideas within complex systems. A mathematical model is an abstraction of a physical system that uses precise language to describe the system's behaviour. The model is then analysed, solved, or simulated on a computer. The results can be interpreted in physical terms to aid understanding of the underlying system or to point to parts of the system that might be targeted for change.

Any strategy to solve a problem is based on some kind of model. If a problem has a simple solution, the model can be purely conceptual and it is sensible to implement the strategy (such as removing the handle of a particular water pump to prevent cholera) without wasting time on calculations. This can apply to disease eradication. Given the high efficacy, low cost and universal applicability of vaccination against smallpox, the eradication of smallpox proceeded with minimal mathematical underpinnings.

Global malaria control and eradication efforts, however, require massive changes to a complex web of interconnected biological systems. Deciding the best way forward is complicated by the potential for parasites and vectors to evolve, the waxing and waning of human immunity, behavioural changes in human and vector populations, and interactions among large numbers of heterogeneous sub-populations of the organisms involved. The range of conditions that favour malaria transmission is so diverse that responses cannot be based solely on the evidence acquired in randomized trials in just a few settings. Furthermore, many questions cannot be answered by field trials as they may be either too expensive or unethical.

Yet the uncertainties should not stall responses. Choices must be made and incorporated into preliminary strategies to be implemented at various levels. These must be constantly re-evaluated using the latest surveillance, monitoring, and technical innovations. A conceptual model devised during planning will need to consider the many potential sources of uncertainty. If a model is to be rational and quantitative, it must be formalized and will inevitably involve mathematics. Mathematical models enable knowledge to be extrapolated and synthesized in a rational way, providing critical quantitative insights not possible otherwise.

As countries achieve scale-up and reach high coverage targets for malaria control interventions, they are faced with the question of what they should do next *(1)*. The strategy for maintaining and enhancing the achieved reductions in transmission is not obvious. It is not clear if maintaining current coverage levels of interventions would continue to reduce transmission, stabilize transmission at a new level, or slowly give way to an increase in transmission. Field trials to understand these effects are only possible in a limited number of settings and do not provide information on long-term dynamics. Modelling can build on available data, test multiple scenarios and combinations

of intervention strategies, and make verifiable predictions on what can be expected from these strategies.

For example, regions that have achieved high coverage of ITNs need to decide whether there is an additional benefit to be gained from adding IRS as a second vector control intervention (additional examples of applying mathematical modelling to malaria control can be found in Box 1). The answer is likely to be that it depends on the situation, and modelling can help to determine the expected benefit in different situations.

Furthermore, targets, both for coverage levels of malaria control interventions and for desired reductions in disease and transmission, are often dictated by finances, and set with little theoretical underpinning. However, recent advances in mathematical modelling of malaria can determine whether desired reductions in disease and transmission are realistically achievable or not, and help to define intervention coverage levels required for those reductions.

There are many examples where modelling can be useful to malaria control planning. This report is designed in two sections; the first provides a summary overview of the mathematical models of malaria, their history and role in the fight against the disease, and their potential in planning for malaria control and elimination. The second section provides a Technical Annex that includes a glossary and examples of extensions to the basic malaria model. As a whole, this report demonstrates how and where mathematical modelling can be useful to malaria control, where it should be central to planning, and the limits to which modelling can reasonably provide answers or inform strategies. This report follows recent related publications *(2)*, and the Malaria Eradication Research Agenda (MalERA) report on modelling that focuses on modelling for malaria elimination *(3)*.

While there are four types of human malaria, most malaria models have focused on *Plasmodium falciparum* because it is more prevalent, more dangerous, and simpler to model. Consequently, this report focuses on *P. falciparum* malaria but refers to other species where appropriate.

The report starts with a brief overview of the some of the techniques of modelling and types of models. It provides an outline of the history of mathematical epidemiology, with an emphasis on developments in malaria control and modelling. It explains some of the more important concepts of malaria modelling and surveys the different models in use today, their advantages and disadvantages, and some of the challenges ahead. It also discusses the place of modelling in the global malaria control infrastructure and its future direction.

Box 1: Three examples of how mathematical modelling can be applied in country settings

Example 1. Building a model to understand the potential implications of combining ITNs and IRS

Several African countries have achieved high coverage of ITNs and are now considering the potential benefit (in terms of reducing disease burden or interrupting transmission) of adding IRS as an additional means of vector control. Different mathematical models are required in order to produce outputs that would reasonably inform understanding about this issue. The models need to:

- accurately describe the malaria transmission cycle including malaria infections in humans and mosquitoes;
- account for the effects of malaria infection in humans on clinical disease, morbidity, and mortality;
- include the effects of the health system on malaria transmission and disease;
- account for the effects of ITNs and IRS on the malaria transmission cycle;
- use available data in model inputs (such as pre-intervention transmission level, predominant vector species, population age structure, first line treatment drug for malaria) and outputs (such as incidence of infection, age-prevalence of parasitemia, age-incidence of mortality) to estimate parameter values for the model;
- use additional data for model outputs to ensure that it can reproduce data that it has not been fit to;
- include a set coverage level of ITNs to see the corresponding disease burden;
- add various coverage levels of IRS to see the effects on disease burden and transmission;
- compare different insecticides to see what is most appropriate to the situation, especially when insecticide resistance is taken into account;
- use cost data to determine the cost-effectiveness of adding IRS.

Adding a model for the evolution of resistance would allow for the testing of resistance management strategies with the combination of ITNs and IRS.

Example 2. Building a model to understand the potential role of active surveillance

Countries already having achieved high coverage levels of one or more vector control interventions may want to know whether active surveillance can additionally reduce disease burden or lead to interruption of transmission. To find out, several models are required that need to:

- include vector control interventions as described in Example 1;
- use available data on the effectiveness of active surveillance in detecting and treating malaria infections;
- when combined, demonstrate the effects of different coverage levels of active surveillance at various degrees of efficiency in reducing disease burden;
- demonstrate in what situations active surveillance can reduce transmission to zero;
- include data on imported cases to see if active surveillance can maintain elimination (but only if active surveillance is found to lead to interruption of transmission);
- apply cost data to determine cost-effectiveness of active surveillance (if active surveillance does not lead to interruption of transmission).

Example 3. Introducing malaria vaccines

A reasonably effective malaria vaccine could be an important tool in malaria control. Policymakers, researchers, health ministries, donors and others are now considering two critical questions:

1. **What are the transmission settings and deployment strategies that can potentially make a given vaccine most useful?**
2. **What properties would a new vaccine need to have to be worth developing?**

To begin answering both questions, two models are needed:

- a full model with vector control interventions as described in Example 1;
- a model for the effects of a vaccine on the parasite and on human immunity.

To answer the first question about transmission settings and deployment strategies, the models must:

- use data to estimate parameter values for the given vaccine;
- have the ability to analyse or simulate the effects on disease burden and transmission of introducing the vaccine in different transmission settings; with different deployment strategies (Extended Programme on Immunization [EPI], mass vaccination [MV], EPI+MV); and at different coverage levels).

In combination, these models will make it possible to determine under what conditions the vaccine might be most effective in reducing disease burden or interrupting transmission.

To answer the second question about properties that would make a vaccine worth developing, the models must have capacity to:

- analyse or simulate the effects on disease burden and transmission caused by
  - i) different kinds of vaccines (pre-erythrocytic, blood-stage, mosquito-stage transmission blocking)
  - ii) vaccines with different efficacies
  - iii) vaccines with different half-lives
  - iv) vaccines in different transmission settings
  - v) vaccines with different deployment strategies (EPI, MV, EPI+MV)
  - vi) vaccines at different coverage levels;
- determine what vaccine (or combination of vaccines), and under what setting, has the desired effect in reducing disease burden and transmission;
- incorporate cost data to determine whether the desired effort of the vaccine is worth the cost of developing and deploying the vaccine.


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OVERVIEW OF MATHEMATICAL TECHNIQUES AND TYPES OF MODELS

Mathematics is the logical study of quantity, arrangement, form, and space. Statistics is the science of collecting and interpreting quantitative data. While mathematical analysis focuses on the underlying processes that drive a system and does not necessarily deal with data, statistical analysis starts with data and works backwards to infer cause. In modelling malaria, as with other diseases or systems, statistics and mathematics are frequently combined: statistical analysis is used to estimate the parameters of mathematical models by comparing model predictions with data.

Models are commonly classified as *deterministic* or *stochastic*. Deterministic models assume the system follows a fixed and defined rule with no random variation or noise; stochastic models assume that randomness or noise is present. Most modelled systems include complexities that are not understood and cannot be represented, and are treated as random noise. Stochastic models assume this randomness is important and explicitly include it in the behaviour of the system. Deterministic models assume the randomness has a negligible effect and consider only the average or mean behaviour of the system.

Stochastic models are essential to evaluate interventions designed to reduce malaria deaths because deaths are an important and relatively rare event. Similarly, in malaria elimination, stochastic models will be important to analysing the risks of reintroducing malaria in receptive areas, as such risks are often related to the behaviour of individuals, rather than populations.

Another important distinction is between *static* and *dynamic* models. Static models assume the system has reached a steady state solution that does not change with time and study the properties of the system at equilibrium; dynamic models, on the other hand, study the evolution of a system over time. Similar to the contrast between deterministic and stochastic models, static models are simpler to formulate and analyse, while dynamic models, though more difficult to formulate, allow for more analysis and the inclusion of those aspects of the physical system that are interdependent. Dynamic models

can be either deterministic or stochastic, and dynamic models may lead to static analysis of equilibrium points.

Dynamic models may treat time as discrete units, leading to difference equations, or they may consider continuous time, leading to differential equations. Much of the history of mathematical modelling of malaria, and mathematical modelling in general, has consisted of population-level differential equations and (to a lesser extent) difference equations. While differential equations are often easier to analyse, difference equations are frequently easier to simulate on a computer. The choice between the two depends on whether the dynamics of the system are better approximated with continuous or discrete time, and also on the questions asked of the model.

Traditionally, most models have tended to be population-based, treating all individuals within a population as identical. With the rise in computing power, the past two decades have brought strong growth in individual-based models that simulate individuals (or communities of individuals) and their interactions within a population. Since the models include interaction at an individual level, they can incorporate a high level of detail and complexity, making them more realistic than traditional population-level difference equation or differential equation models. They can also answer questions that are difficult or not feasible with population-level equations, such as the effects of changes in human behaviour in response to epidemics. But they are also more difficult to analyse or fit to data, requiring substantial computing resources.

In many fields of physics, where a few simple rules largely govern the behaviour of many systems, analytical models have been able to make reliable quantitative predictions. However, in modelling of malaria (and other infectious diseases), where there are many unknown and seemingly stochastic variables, analytical models have been more useful to better understand the underlying processes and factors that drive malaria transmission. Detailed individual-based models can provide quantitative evaluations and predictions of the effects of interventions on the levels of malaria transmission, morbidity and mortality, though they do not always give general rules. Both paradigms of models are useful and have their place in our understanding of malaria and in planning for malaria control.

HISTORY OF MALARIA MODELLING AND MATHEMATICAL EPIDEMIOLOGY

The first modern example of mathematical modelling influencing public health policy was Daniel Bernoulli's 18th century investigation of improved life expectancy from inoculation against smallpox. In 1760, Bernoulli used a mathematical model to show that the benefits of inoculation outweighed the negative consequences of artificial smallpox and its subsequent spread. This work, published in 1766, was the first to mathematically describe the proportion of susceptible individuals at equilibrium of an endemic infection in terms of the force of infection and average life expectancy *(4–6)*.

In the late 19th century, Ronald Ross discovered that mosquitoes transmit malaria parasites. He went on to develop the first mathematical model for malaria transmission. He started by relating mosquito flight distances and densities to larval control *(7)*. After overseeing malaria control activities in Mauritius, he published his first transmission model for malaria *(8)*, before publishing his more famous differential equation model *(9)*. Ross introduced the idea of a threshold condition in epidemiology, a *critical density of mosquitoes*, below which the malaria parasite would die out. Ross's mathematical models drove the first few decades of malaria control when efforts focused on larviciding and destruction of larval breeding sites.

In the late 19th and early 20th centuries, there was significant progress in mathematical epidemiology, including the first epidemic model by En'ko to fit measles data *(10, 11)*. The seminal model by Kermack and McKendrick *(12)* in 1927 and its subsequent extensions have driven, and continue to drive, much of mathematical epidemiology today. Dietz *(13)* and Brauer *(14)* have surveyed the history of mathematical epidemiology and the importance of these early contributions.

As surveyed by Heesterbeek and Dietz *(15)*, Heesterbeek *(16)*, and Nishiura et al *(17, 18)*, the concept of the basic reproductive number (R0) slowly emerged from the end of the 18th century through to the early 20th century, eventually accepted in epidemiology as, "the expected number of secondary cases produced by one typical infected individual during its entire infectious period, in a population of only susceptible individuals".

Mathematical modelling started to play a more important role after the World Health Assembly voted in 1955 to eradicate malaria, and the World Health Organization (WHO) coordinated a Global Malaria Eradication Programme based largely on IRS with DDT. In the early 1950s, George Macdonald took the first steps towards testing Ross's theory with epidemiological *(19)* and entomological *(20)* field data. Field trials with DDT in the early 1950s had demonstrated that it was an effective way to interrupt malaria transmission. Macdonald's analysis helped to explain that DDT and other residual anti-imago insecticides worked because they greatly reduced the number of mosquitoes that would live long enough to survive sporogony and transmit malaria *(21)*.

One of Macdonald's biggest contributions to malaria theory was his emphasis on defining and measuring parameters, such as the basic reproductive number and the stability index, that were operationally relevant for eradication. During the Global Malaria Eradication Programme, mathematical models were also used for other purposes, such as establishing realistic response timelines for interruption of transmission *(22)*.

In the 1970s, a large-scale malaria control project was launched in Garki, Nigeria, to evaluate whether malaria could be controlled in an African context with multiple, combined interventions. In planning the Garki project, an innovative new difference equation mathematical model was developed *(23)* that improved the model for superinfection, considered the development of immunity in two stages, and considered a type of transmission-blocking immunity (individuals were infectious only if they were non-immune and recently infected). The Garki model was able to reproduce, at least qualitatively, the age-specific patterns in malaria prevalence.

There have been numerous surveys on the mathematical modelling of malaria and infectious disease that summarize these developments and explore model extensions *(24–30)*, some of which are explored in Chapter 4.

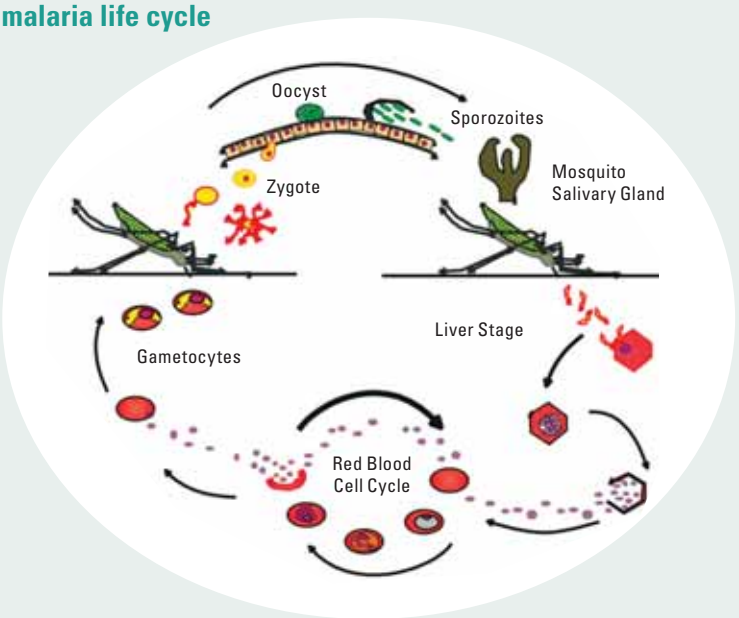
CURRENT MALARIA MODELS: MAIN CONCEPTUAL DEVELOPMENTS

In the three and a half decades since the publication of the Garki model, there have been many scientific and technological developments that have directly and indirectly driven malaria modelling. Foremost among these have been advances in computers that have made once prohibitively expensive computations and simulations commonplace. Great progress has been made in our understanding of the biology of the disease, from the population level of transmission to the molecular level of the interaction of the parasite's surface proteins with the human immune system. There have also been significant advances in the mathematical and statistical methods used to model and analyse physical and biological systems, including: the development of network theory, the progress in statistical methodologies and the creation of spatial statistics, and the development of individual-based models. These changes have led to new modelling techniques and types of models, and improvements to existing ones. Malaria modelling has continued in several directions, with models exploring different facets of biology and natural history, and the effects of interventions and their evolutionary consequences.

Box 2: The *Plasmodium* life cycle and vector feeding cycle

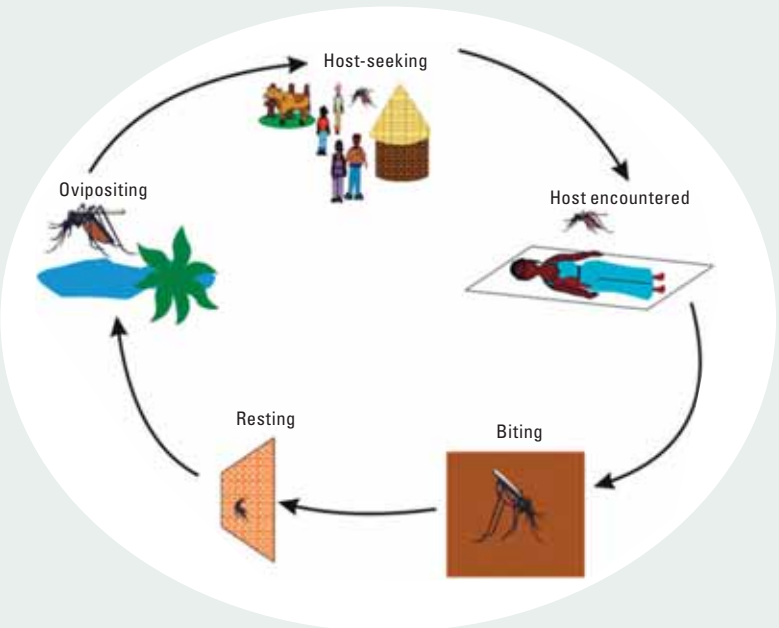
The Ross–Macdonald model is a basic quantitative description of the *Plasmodium* life cycle (Fig. 4.1) and the vector feeding cycle (Fig. 4.2). The parasite enters the mosquito during a blood meal and the mosquito becomes infectious 10–16 days later, after the parasite develops into sporozoites. In the meantime, the mosquito will have fed several times and most infected mosquitoes will die before they become infectious. Mosquitoes that survive to become infectious can then give several infectious bites before they die.

Figure 4.1
The malaria life cycle



Human infections begin during the mosquito blood meal when sporozoites enter the skin. Parasites are not obvious in the blood until about 11 days later. A human with a *P. falciparum* infection is not infectious until a fraction of the blood-stage parasites become gametocytes and then mature, 8–10 days later. Untreated or improperly treated infections last about 200 days on average, though some infections can last more 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 at which parasites develop, and the longevity of the mosquitoes.

Figure 4.2
The feeding (or gonotrophic) cycle of the female mosquito vector



Source: Modified from Chitnis et al *(31)*.

Foremost among the concepts used to describe malaria transmission is the basic reproductive number, R0. It is often used as a measure of the severity of disease transmission and the possibility or ease of disease elimination. While each model for malaria transmission would lead to its own definition of R0, the details of R0 from the Ross–Macdonald model are described here. R0 summarizes transmission providing a quantitative answer to the question, "How many infectious humans could be expected from a single infectious human after just one generation of the parasite, assuming all other humans and mosquitoes are susceptible?" Box 3 shows the division of this question into six simpler questions and their answers in terms of basic malaria parameters. R0 is the product of those six answers.

Box 3: Basic reproductive number for the Ross–Macdonald model

The seven basic parameters that describe malaria transmission, with their mathematical expressions in parentheses, are:

- **Number of female mosquitoes per human host (m)**
- **Number of bites per mosquito per day (a)**
- **Probability of transmitting infection from infectious mosquitoes to humans per bite (b)**
- **Probability of transmission of infection from infectious humans to mosquitoes per bite (c)**
- **Recovery rate of humans (γ)**
- **Death rate of mosquitoes (μ)**
- **Extrinsic incubation period (τ)**

The questions that can be answered for R0 in terms of the above malaria parameters are:

- **How long does a person remain infectious? ($1/\gamma$)**
- **How many times is a person bitten by vectors each day? (ma)**
- **What fraction of mosquitoes becomes infected after feeding on an infectious human? (c)**
- **What fraction of mosquitoes survives sporogony? ($e^{-\mu\tau}$)**
- **How many human blood meals does a vector take over its lifetime? (a/μ)**
- **What fraction of blood meals taken by infectious mosquitoes cause an infection in humans? (b)**

Multiplying the six terms together, the basic reproductive number is $R_0 = \frac{ma^2bce^{-\mu\tau}}{\gamma\mu}$

The Ross–Macdonald model describes changes in the fraction of infected humans and the fraction of infectious mosquitoes (i.e. the sporozoite rate) over time as infections are acquired and cleared. If R0 is greater than 1, then a single infectious human would tend to leave more infectious humans and as a consequence, the parasite rate would increase until it reached a steady state in which new infections were balanced by cleared infections.

Mathematical models can provide a good qualitative description of malaria, even if there is uncertainty about the underlying quantities. Despite the uncertainty and quantitative differences among models, R0 often provides a unifying concept. When indexed to parasite rate or other routinely collected malaria measurement indices in a credible way, R0 provides practical guidance on the extent to which transmission would have to be reduced to eliminate malaria. It is important to note, though, that when models include seasonality or demographic heterogeneity (in humans or mosquitoes), R0 may not necessarily correspond to its initial definition of "the expected number of cases arising from one index case in a fully susceptible population", but rather, provide a threshold for whether or not an introduced case would lead to the disease persisting in the population.

Some extensions to the basic malaria model include:

- superinfection, within-host dynamics and immunity;
- heterogeneity;
- human demography;
- mosquito population dynamics;
- seasonality;
- interventions;
- migration: reintroduction risk (vulnerability) and outbreak risk given reintroduction (receptivity);
- mapping malaria;
- drug and insecticide resistance.

Detailed explanations of these extensions can be found in the Technical Annex.

CHAPTER V

ROLE OF MODELLING IN MALARIA CONTROL

To aid decision-making, models can be structured so that inputs and outputs are relevant to the needs of the clients. In malaria control, these clients comprise a broad range of decision-makers with responsibility at global and local levels, acting in both the public and private sectors. Clients include those developing new interventions, field researchers analysing interventions, and those dealing with global and national coordination and prioritizing control and elimination efforts.

The research and development process for any range of products has its own scientific agenda, and is likely to make use of models to help optimize product performance. These include strategic models that analyse the underlying dynamics of the system and provide a framework for understanding how an intervention might work and which elements may be susceptible to modification. Product profiles also need to be developed with the likely public-health effects in mind, and this requires tactical models that aim to quantify the real-world impact.

Once an intervention is available, tactical models are needed to help decide how best to deploy it, if at all. These models need to provide decision-makers with comparative information on the likely costs and health effects over time. Model predictions should be adjusted to the local setting, taking into account both the epidemiological and health systems.

Health policy decision-makers need to decide whether their focus is malaria control, elimination or eradication because each has different modelling requirements. If the focus is on control, decision-makers might aim to maximize cost-effectiveness in different geographical regions. Eradication demands a single, flexible global strategy that must also consider the ways in which different regions interact (through human migration, for example).

The RBM Partnership has set the following targets —for 2010, 2015, and beyond—to control malaria through universal intervention coverage *(32)*.

By 2010:

- 80% of people at risk from malaria use locally appropriate vector control methods such as long-lasting insecticidal nets (LLINs), IRS, and, in some settings, other environmental and biological measures.

- 80% of malaria patients are diagnosed and treated with effective anti-malarial treatments.

- In areas of high transmission, 100% of pregnant women receive IPTp.

- The global malaria burden is reduced by 50% from 2000 levels to less than 175–250 million cases and 500 000 deaths annually from malaria.

By 2015:

- Universal coverage continues with effective interventions.

- Global and national mortality is near zero for all preventable deaths.

- Global incidence is reduced by 75% from 2000 levels to less than 85–125 million cases per year.

- Achievement of the malaria-related Millennium Development Goal—halting and beginning to reverse the incidence of malaria by 2015.

- At least 8–10 countries currently in the elimination stage achieve zero incidence of locally transmitted infection.

Beyond 2015:

- Global and national mortality stays near zero for all preventable deaths.

- Universal coverage (which translates to ~80% utilization) is maintained for all populations at risk until local field research suggests that coverage can gradually be targeted to high-risk areas and seasons only, without risk of a generalized resurgence.

- Countries currently in the pre-elimination stage achieve elimination.

In meeting these targets, the questions that mathematical modelling can help to answer are central to all levels of malaria control. The seven constituents of the RBM Partnership, (endemic countries, bilateral government partners, private foundations, industry, academia, nongovernmental organizations, and international organizations) can each be placed, to varying extents, in at least one of five functional categories:

- malaria control policy-makers at global and regional levels

- malaria control planners at country and local levels

- academic researchers

- product research and development planners and implementers

- donors.

These functional categories can each benefit in unique ways from mathematical modelling of malaria to inform policies, strategies, and plans, as explained below.

Malaria control policy-makers at global and regional levels

The leading policy-making body at the global level is WHO, which issues, as one of its core missions, evidence-based, objective guidelines. Other international organizations, such as the World Bank; the Global Fund to Fight AIDS, Tuberculosis and Malaria; the US President's Malaria Initiative; and the Bill & Melinda Gates Foundation, have substantial resources to invest in malaria control and may have influence on how guidance is adapted and implemented at country level. For all of these organizations, modelling can fill an important gap by integrating epidemiological and health systems dimensions, and examining all major malaria interventions in a single framework.

The most valuable modelling information for policy-makers is on the effectiveness and cost-effectiveness of malaria interventions and their combinations in different settings, in reducing transmission, morbidity and mortality, and in potentially interrupting transmission. Modelling

can generalize the results of randomized controlled field trials and programme data to a wide variety of situations. Modelling can help to determine optimal combinations and intervention strategies.

Given the targets for 2010 and beyond described above, modelling can help to answer such questions as:

- Do the goals that describe reductions in burden follow naturally from the target intervention coverage levels?
- Is it beneficial to add a second vector control intervention to a population with already high coverage of one intervention? If so, under which circumstances? Would an alternative intervention be more effective?
- What combination of interventions would best reduce the development of resistance (to drugs, insecticides, vaccines, or even in terms of changes in mosquito behaviour)?
- As transmission reduces, at what point can certain interventions, such as IPTp or even ITNs or IRS, be scaled back or withdrawn?
- In low-transmission settings, what combination of interventions or changes can help to interrupt transmission?
- In areas where elimination has been achieved, what level of intervention coverage or surveillance is necessary to prevent the return of malaria?

Malaria control planners at local and country levels

Malaria control planners usually work in national control programmes at a central level, though also sometimes at the decentralized level, such as at a regional, provincial, or district level. With few exceptions, they use resources from donors and national and local government, though malaria control planning may also be planned and funded by mining and plantation companies, and by bilateral, non-governmental and humanitarian organizations.

National level policy-makers often need to translate general WHO recommendations to more specific guidelines. Where WHO may have to use generalized language because of the variability of malaria, national-level policy-makers must set precise criteria, creating a transition from policy-making to planning. And, malaria control planning is often initially done in a simplified way, assuming that a set of standard interventions will lead to an internationally agreed-upon goal, such as halving the malaria burden by 2010. As progress occurs, there is an increasing need for programmes to improve and focus their work and to make evidence-based projections on the impact of the investments. Modelling can help provide such an evidence base and the accompanying assessment of the effectiveness of the intervention package.

Academic researchers

Mathematical modelling of malaria largely falls within the domain of academia. It is conducted at the intersection of mathematics, epidemiology, and public health research, and there is considerable potential for interaction between different facets of academia. Modelling is driven by results from malaria field research and to some extent from health systems and biomedical research. In turn, it can help to drive new research in these areas by identifying gaps in knowledge and priority areas. Within academia, modelling is also useful to teach and train academics and staff who will work in malaria control.

Product research and development planners

Those involved in developing new products for malaria control include scientists (overlapping with malaria researchers), manufacturers, traditional foundations such as the Wellcome Trust, and public-private ventures, such as the Medicines for Malaria Venture (MMV) and the Malaria Vaccine Initiative (MVI). Modelling can help to devise target product profiles for new interventions, for example the required minimum efficacy and half-life to make a new vaccine worth developing. Modelling can also determine the effects of changes (mainly incremental) in product characteristics (such as the durability of an insecticide, doses of an antimalarial medicine, sensitivity of a diagnostic test) on the level of malaria transmission, morbidity and mortality. Modelling can also address the cost-effectiveness of these changes. Another important role for modelling is to help devise strategies for product development and deployment to mitigate and delay parasite and vector resistance.

Donors

Donor organizations such as the World Bank, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the US President's Malaria Initative may sometimes undertake specific analyses for their own purposes because they control considerable funds and must report on the use of those funds to their constituents. The World Bank, for example, focuses on economic development and may need to examine the economic consequences of malaria control at the country level. Modelling can assist their efforts in these analyses and allow them to extend individual country analysis to multiple countries. Additionally, donors can use information from modelling to balance needs in research and product development, and to assess the merits of investing in malaria control against investments in other public and global endeavours.

CHAPTER VI

EXAMPLES OF ADDRESSING KNOWLEDGE GAPS IN MODELLING MALARIA

While great progress has been made over the past century in modelling malaria, many challenges remain. There are still many gaps in our knowledge and models of malaria biology and ecology, some of which are addressed here.

Within-host dynamics of parasite species

Improved knowledge and models of the development of parasite species and their dynamics in their human and vector hosts are needed. Better quantification of the features of the parasite's life cycle is important for understanding transmission and improving control. In particular, better data and models are needed to understand and quantify the relapse in *P. vivax* and other unique aspects of non-*falciparum* parasites, and the nature of interactions between all species.

Human infectious reservoir

Models need to capture the infectious reservoir across a range of transmission intensities. Poorly understood factors contribute to the variability in the transition rates of parasites from the asexual blood stage onwards through each subsequent stage of the transmission cycle to, and in, the mosquito. Even if, for operational purposes, those with measurable parasites are considered to be infected and, therefore, not distinguished from gametocyte carriers, it is important to capture the relative infectiousness of different population groups.

Stimulation and decay of human immunity

Natural immunity to malaria that partially protects against the disease or reduces transmission is a particular challenge for epidemiological models. A better understanding of the stimulation, duration, and effects of acquired immunity needs to be incorporated into models.

Morbidity and mortality

Models are needed to accurately describe the relationship between the within-host dynamics of the parasite and the consequent direct and indirect morbidity and mortality in humans. Although the global objective has moved to elimination, there is a public health need to model malaria morbidity and mortality.

Vector ecology

The seasonal and ecological determinants of mosquito densities and the dynamics of larval stages and their effect on adult fitness and density are poorly understood. In addition to field studies, models are needed to consider the effects of seasonality, dry-season refuges, mosquito dispersal patterns, the potential of larval control, and optimal larval control strategies. The effects of infection and environment on adult mosquito behaviour, infectivity, and survival also need to be considered in field research and modelling efforts.

Heterogeneities in hosts, parasites and vectors

Correlated heterogeneities in the range of biological and population behavioural mechanisms are not comprehensively addressed in current malaria models. There are substantive problems in measuring levels of heterogeneity and incorporating their effects in models that need to be overcome. This is likely to have a greater impact on model results as transmission is reduced.

Parasite and host movement

As transmission is reduced, the effects of the parasite's geographical movement—resulting from both vector and human movements—will dominate the dynamics. The relative role of movement versus refuge in maintaining the infectious reservoir during the dry season in epidemic settings remains poorly understood but will be crucial to devising a strategy to achieve elimination and hold the line. Human movement, in particular, is difficult to quantify based on current data. Spatially explicit models that can track parasite movement and link spatially distinct populations need to be developed.

Effects of (new) interventions

Models of drug dynamics (pharmacokinetics and pharmacodynamics, dosing regimen) and vaccine dynamics (in particular, transmission-blocking varieties) need to be developed. Similarly, models are needed describing the ecology of genetically modified mosquitoes and of variations in the susceptibility of the vector and the potential impact on malaria.

The scope of these models needs to be expanded to consider the overall effects of the health system, taking into account the capabilities of pre-existing health system infrastructures. These expansions include the effects of combinations of interventions/tools, the effects of scheduling interventions, and supporting the optimization of target product profiles and their alignment with existing packages of interventions. All these components need to be supported by micro-economic appraisal.

Resistance to interventions

Intervention resistance is defined broadly to include any behavioural and heritable changes that reduce the effectiveness of drugs, pesticides, vaccines, and other interventions. Target product profiles will need to consider model-based analyses of the likely evolution of resistance. Modelling needs to be developed that integrates population genetics and direct intervention effects, particularly: PK/PD data for drug resistance, behavioural and physiological changes in response to vector control, and molecular epidemiology for vaccine escape variants. Crucial for this evolution is a better characterization of the biological cost of resistance. As new tools are developed, it will be important to plan deployment strategies with an awareness of the effects they will have on the evolution of resistance.

Uncertainty analysis and communication of uncertainty

Models of any aspect of malaria inherently contain uncertainty and it is important to communicate this when presenting results. There is a need to further develop and apply techniques to interpret the effects of uncertainties in both model formulation and available data. There is a need also for operational research on how best to communicate the effects of this uncertainty to user groups who may not be familiar with the details of uncertainty analysis. This is an essential step in translating model results into policy.

CHAPTER VII

CONCLUSION

Modelling may seem a long way removed from day-to-day activities in malaria control, especially if control is seen largely as being about illness and death. When control efforts embrace the concept of transmission reduction (in the renewed discussion on elimination and eradication, for example), modelling takes a more prominent role. Although mathematical modelling has played a significant role throughout the history of malaria control, as it has for a number of other diseases (27), including onchocerciasis (33) and foot and mouth disease (34), it should in the future play a stronger part in informing policy development.

Modelling can help devise realistic targets for interventions. While such targets have usually been set without modelling inputs, tools are now available to help define goals from desired coverage levels. Furthermore, models can provide more information on the longer-term impacts of interventions than is possible through field trials or programme data.

It is important to note, however, that mathematical models are created with underlying assumptions and driven by data that inherently contain measurement errors; they have their limitations. While models can help decision-makers understand disease dynamics and devise control strategies, if the models are applied beyond feasible assumptions or after using unreliable data, the results can be meaningless at best, dangerous at worst.

A good example of this is climate and weather models. They respect reliability bounds but are still used as powerful predictive tools. Few people would expect a weather forecast to say whether it is going to rain at a particular place at a particular time. However, they would mostly trust the forecast to tell them whether to take an umbrella. The weather forecast gives people a general idea of what to expect but not a full and complete prediction. Similarly, models can play a beneficial role in malaria control provided users know how to interpret results and at what level they are useful.

Another facet of weather models that the malaria modelling community can learn from is the comparison of multiple independently derived models as a way of arriving at a more robust set of predictions. As emphasized by the Malaria Eradication Research Agenda report *(3)*,

comparing multiple models leads to higher confidence where the results of the different models agree, and point to uncertainty and need for more attention where the results do not. This step is essential in successfully translating model results into useful and reliable policy recommendations.

Models can mean all things to all people, and consequently are often tailored to a given set of questions. Implementing models, therefore, should be done in partnership between technical experts in mathematical modelling, and decision-makers who need their guidance. A lack of communication and understanding between these groups is usually where criticisms of modelling start *(35)*.

Good communication is essential between health policy decision-makers, those with expertise in field and laboratory malaria, and those with expertise in mathematics, so that models are formulated with important biological realities in mind and their results interpreted with care. In addition, training endemic-country scientists to develop modelling skills is essential to ensuring the local sustainability of modelling efforts. Throughout much of its history, mathematical modelling has had an important symbiotic relationship with physics. It is hoped that the same can happen with epidemiology in general, and malaria epidemiology in particular, driving both fields and leading to improved malaria control and elimination.

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TECHNICAL ANNEX 1. Glossary

Modelling terms

System: A set or arrangement of items so related or connected, they form an integrated whole: the malaria infection and illness system, for example, where the malaria parasite, mosquito vector, human host and their determinants and interactions establish the pattern of malaria infection and illness in the population.

Mathematical model: An abstraction of a physical system that uses precise language to describe its behaviour.

Statistics: A branch of science concerned with the collection and interpretation of quantitative data.

Deterministic system: No randomness is present and any given starting state at a given point in time always leads to the same consecutive states.

Stochastic system: Includes randomness or noise.

Differential equations: A system based on continuous values of time.

Difference equations: A system based on discrete values of time.

Agent-based/individual-based model: A simulation or computational model composed of more than one agent or individual that interacts (usually stochastically) within a network.

Measurements of malaria

Parasite rate (PR): The prevalence of malaria in a population; it is the proportion of the population with asexual blood-stage parasites. In a stable malarious area, this proportion varies with age. People are rarely born infected but parasite rate rises with age until it reaches a plateau in older children. By age 10, some immunity begins to develop and parasite rate 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 *(1)*. As immunity rises in older children and adults, parasite densities decline. This measured decline in parasite rate is partly attributable to the inability to detect parasites. There may also be some real declines in parasite rate because of immunity and other factors. The parasite rate in children aged more than two but less than 10 is called the standard parasite rate.

Entomological inoculation rate (EIR): The expected number of infectious bites, per person, per unit time (usually a year). The EIR is the product of the sporozoite rate (the proportion of mosquitoes with sporozoites in their salivary glands) and the human biting rate (the number of mosquito bites 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 rate at which humans are infected. The force of infection is closely related to the EIR, at least conceptually. While 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 to estimate the force of infection is to plot the prevalence of an immune marker in the blood serum, or seroprevalence, against age and look at the slope in young children. Such methods

provide a sensitive study of malaria transmission in low-intensity settings.

Annual parasite incidence (API): Designed to measure the number of malaria fevers per year, per thousand people. The proportion of the population examined is called the human blood examination rate (HBER). Suspicious fevers are examined for parasites and the proportion of parasite positive slides is called the slide positivity rate (SPR). API is defined as the product of the two (API = HBER × SPR). Most API data come from clinics where suspected fevers are examined for the presence of parasites but are often supplemented by active case detection. When malaria becomes rare, it becomes increasingly difficult to detect transmission using PR *(2)*. API can be a reliable method for reporting new malaria infections in low-intensity settings. API data are difficult to interpret as a measure of malaria intensity. API has low value in places where PR is high enough to measure but it may be the only way to measure progress towards elimination when malaria transmission is lowered *(2)*.

Vectorial capacity: The expected number of infectious bites arising from all the mosquitoes that bite a single infectious person on a single day *(3)*. Vectorial capacity measures the potential of the mosquito population to transmit malaria, not the actual level of malaria transmission in a given location.

Basic reproductive number (R0): The number of infected humans that would arise from a single infected human in an otherwise fully susceptible population, 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.

Controlled reproductive number (RC): While R0 describes maximum potential transmission, RC describes maximum potential transmission in a population with malaria control. R0 measures the intrinsic potential for epidemics in a population with no immunity, while RC measures the potential for epidemics after taking into account all of the measures that have been put in place to slow transmission.

Elimination terms

Control: Reduction of disease incidence, prevalence, morbidity and mortality to a locally acceptable level as a result of deliberate efforts. Continued intervention measures are required to maintain the reduction.

Elimination: Reduction to zero incidence as a result of deliberate prevention efforts of locally transmitted infection caused by the four *Plasmodium* species that infect humans in a defined geographical area. Continued intervention measures are required to prevent reintroduction.

Receptivity (outbreak risk): In an area where elimination has been achieved, receptivity is a measure of the presence of vector anopheles mosquitoes and the existence of other ecological and climatic factors favouring malaria transmission. Receptivity is a reflection of vectorial capacity of the local anopheles mosquito population during the season most favourable for malaria transmission *(4)*.

Vulnerability (reintroduction risk): In an area where elimination has been achieved, vulnerability is a measure of the influx of humans or mosquitoes infected with malaria. It includes: the proximity to malarious areas or liability to the frequent influx of humans and vectors; the level of malaria awareness of the population; and the level of sophistication of the health authorities *(4)*.

Eradication: Permanent reduction to zero as a result of deliberate prevention efforts of the global incidence of infection caused by the four species of *Plasmodium* that infect humans. Intervention measures are no longer needed.

TECHNICAL ANNEX 2. Examples of Extensions to the basic malaria model

Superinfection, within-host dynamics and immunity

Superinfection is the notion that additional infection in an already infected or infectious individual has an effect and may not be ignored. This is typical in macroparasites, especially in helminthes where the severity of infection depends on the number of incoming infections as most worms do not reproduce in the body. While the asexual blood stages of the malaria parasite freely reproduce within the human body, additional infections can affect the onset of clinical symptoms and the time it takes to clear infection.

The dynamics of the malaria parasite, especially *P. falciparum*, in the human body are complicated and show multiple fluctuations, leading to episodes of clinical disease and high infectivity. These infections lead to naturally acquired immunity that, in turn, regulates the dynamics of the parasite. While immunity is not fully understood, it is assumed that repeated infections provide protection against clinical disease, and possibly against new infections, and that this protection may wane over an extended infection-free period.

The original Ross–Macdonald model assumed that new infections made no difference (and were therefore ignored) and that the dynamics of the malaria parasite were similar to that of a virus. Walton was the first to describe a formula for superinfection *(5)*. A few years later, Macdonald developed a model for simulating complex infections *(6)* but while the written description of his assumptions was consistent with Walton's model, the equations corresponded to a different set of assumptions *(7)*. Bailey described a "queuing model" that described dynamical changes in the number of different parasite types using the same assumptions as Walton *(8)*. This queuing model motivated the development of a much simpler formula in the Garki model *(9)*. The queuing model was later extended and generalized by Nasell to describe superinfection with a finite number of types *(10)*, and by Dietz to consider density dependence *(11)*.

Macdonald had assumed that there was no naturally acquired immunity. The Garki model *(9)* allowed for a proportion of infected humans to subsequently become immune and no longer transmit malaria. The Garki model was criticized for making assumptions about immunity that were severe and not consistent with data. For example, in an area where malaria prevalence was more than 90% in children, and where immunity in adults would tend to be quite high, adults did, in fact, transmit malaria to mosquitoes, albeit at lower rates *(12)*.

Following the Garki model, Aron and May *(13)* introduced a model (further explored by Aron *(14)*) that combined the infected but non-infectious classes to create a susceptible-infected-recovered-susceptible (SIRS) compart-mental model, with dynamics such as viral diseases. The assumption in the Garki model that made these SIRS models relevant was that only non-immune individuals who had been recently infected were infectious. In response to the critique of the Garki model that adults also transmit malaria, some SIRS models were modified to allow semi-immune individuals to remain infectious to mosquitoes but to transmit malaria with lower efficiency *(15, 16)*. However, recent evidence *(17)* suggests that naturally acquired immunity only affects parasite densities and clinical incidence but not duration of infection, which is contrary to the assumptions of SIRS models. Furthermore, though adaptations of SIRS models can capture

the effects of superinfection, most SIRS models of malaria have failed to do so.

The Garki model has also been extended to consider the transmission dynamics and epidemiology of serial infection and immunity to infection with multiple parasite "strains" *(18, 19)*. There have also been subsequent developments in models of the malaria parasite within the human body and its interaction with the immune system *(20–23)*, which can be included in individual-based models.

Individual-based models, such as by Smith et al *(24, 25)* allow each infection to run its own course within the human body, qualitatively reproducing available data on within-host dynamics of malaria. They also allow superinfection, where multiple infections can enter the body and run their own course, interacting with each other only through the immune system, which grows in response to the infections, modulates their dynamics and potentially decays if there are no new infections.

Heterogeneity

An implicit assumption of the Ross–Macdonald and basic SIR models is homogeneity: all humans (and all mosquitoes) are identical and may be treated as such. Each human has the same probability of being bitten by a mosquito, consequently developing malaria if the bite was infective and passing the infection back to mosquitoes. In reality, humans and mosquitoes are heterogeneous: some people are more likely to be bitten, to develop clinical malaria, to have access to interventions and treatment and to infect mosquitoes.

During the 1980s, motivated in part by the outcome of the Garki project but also by studies of sexually transmitted diseases, attention focused on the biting behaviour of mosquitoes and its consequences for disease transmission, and in particular, on the importance of heterogeneous biting *(26, 27)*. Mathematical modelling suggested that heterogeneous biting would amplify transmission, raising R0 proportionately to the squared coefficient of variation in human biting rates.

Recent individual-based models *(24, 25, 28, 29)* have included heterogeneities at several levels, such as: mosquito biting behaviour and survival; the development of immunity in humans; and the within-host dynamics of the parasite.

Human demography

A special form of heterogeneity is age structure and demography. In humans, most facets of malaria heterogeneity discussed above, such as the likelihood of being bitten, development of clinical malaria, development of immunity, and mortality rates, and non-malaria heterogeneities, such as non-malaria mortality rates, vary with age. Furthermore, as human age is relatively easy to measure and quantify, many measures of malaria transmission, such as prevalence and incidence, can be denoted as a function of age. Models that include age not only allow us to better understand malaria but also provide self-evaluation through comparison of their output to age-prevalence and age-incidence data.

Lotka, who also analysed malaria, developed a model of human age distribution in 1922 *(30)* but it was not until 1950 that Macdonald included age structure in a model for malaria transmission *(31)*. Though Macdonald did not explicitly include age in his model, he fitted his parameters for different age groups to age stratified data. Since then, numerous models have included age structure, either in the form of differential equations *(32)* or in individual-based models that assign an age to each individual in the population.

Mosquito population dynamics

The level of malaria transmission is closely linked to the density and longevity of adult female mosquitoes, which, in turn, are determined by climate and larval dynamics in breeding sites. For example, in many places it is likely that the number of eggs laid is much greater than that

which the breeding sites can support and the emergence of new adults is regulated by density-dependent mortality in larvae. However, if the adult density were significantly reduced (for example, through vector control interventions), the emergence of new adults would depend more on the number of eggs laid. There is also evidence that the fitness (and correspondingly, longevity) of adult mosquitoes depends on larval density *(33)*.

Dye *(34)* modelled the dynamics of Aedes aegypti with difference and differential equations, while Otera et al *(35)* used a stochastic model. Depinay et al *(36)* modelled the dynamics of anopheles mosquitoes with an individual-based model.

Seasonality

In most parts of the world, malaria transmission is not constant but varies seasonally over the year. The emergence of mosquitoes depends on the availability of larval habitats, which depends on rainfall and temperature. The development time of the parasite within the mosquito and the human-biting rate of mosquitoes depend on the ambient temperature. As temperature and rainfall vary seasonally, malaria transmission also tends to vary seasonally in most locations, leading to some months when there is a peak of intense transmission and other months that are relatively free of malaria. This affects the planning of time-limited interventions, such as IRS.

Macdonald first explored modelling epidemics in 1953 *(37)*. Since then, most models that include seasonality assume a periodic function for the number of mosquitoes, starting from Aron and May *(13)* to more recent models *(38)*, though Hoshen and Morse linked a model of climate to a model of malaria transmission *(39)*.

Interventions

The Ross–Macdonald model was able to make valuable statements about which parameters had the biggest effect on the basic reproductive number: increasing the adult death rate had the strongest effect on lowering malaria transmission. Since then, many models have been developed to either explicitly include the effects of interventions or include specific details of the malaria life cycle that can be targeted by the interventions.

Saul et al *(40)* developed a model of mosquito and malaria transmission dynamics that has since been extended to model several vector control interventions, including zooprophylaxis *(41)*, ITNs *(42–45)* and combinations of ITNs with IRS *(46)*. Okell et al developed a compartmental model to investigate the effects of artemisinin-based combination therapies (ACTs) on transmission *(47)*, and simpler Ross–Macdonald models have been adapted to look at transmission at low intensity and the added value of primaquine *(48)*. An individual-based model has been used to investigate the effects of intermittent preventive treatment in infants *(49)* and vaccines *(50–52)*. Other models have been developed to consider the effects of releasing transgenetically modified mosquitoes and what is required to establish them in the mosquito population *(53, 54)*.

Migration: Reintroduction risk (vulnerability) and outbreak risk given reintroduction (receptivity)

Any modelling to plan for malaria elimination and eradication will need to include the effects of migration and movement of infected humans (or mosquitoes) into areas that have eliminated malaria. If the malaria control efforts have ceased after elimination and receptivity has increased, introduced infections could trigger epidemics and/or lead to the reestablishment of endemic malaria in that location. This requires spatially explicit models. It is only recently that these issues have begun to be addressed by models *(55–57)*.

Mapping malaria

Geospatial statistical models are a different quantitative approach to malaria that do not necessarily model the underlying processes of malaria but that relate environmental and sometimes intervention data to transmission or prevalence data from survey sites to produce transmission, prevalence or disease maps across broad geographical sites *(58–61)* (see Fig. A2.1 and A2.2). There has also been some work on mapping the distribution of malaria vectors across the world *(62–64)*.

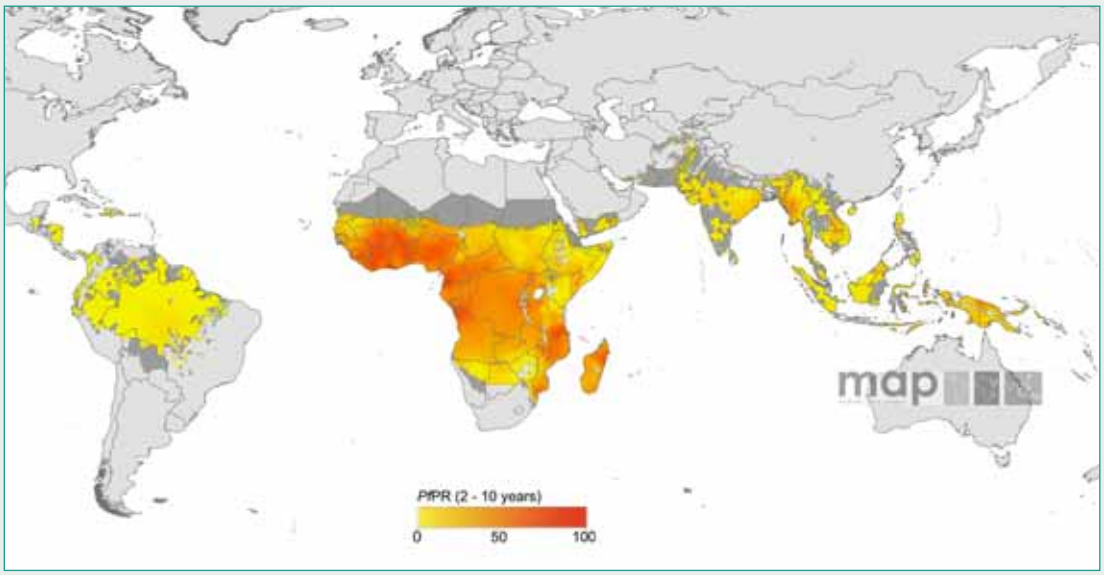
Drug and insecticide resistance

A significant hurdle in Global Malaria Eradication Programme was the evolution of drug resistance to chloroquine in parasites and insecticide resistance to DDT in mosquitoes. Resistance continues to be a key consideration in malaria control, with reports of the falling effectiveness of ACTs on the Thai-Cambodia border *(65)* and of the failure of pyrethroids to control mosquito populations *(66)*. Models have looked at the evolution of drug resistance and its effects *(67–69)*, to justify the use of combination therapies *(70)*, to evaluate the likely effects of a global subsidy for ACTs *(71)*, and weigh the effects of multiple first-line therapies *(72, 73)* though there has been little work on modelling insecticide resistance from public health use, and its impact on public health, except for statistical analysis *(74)*.

Figure A2.1

***Plasmodium falciparum* malaria global endemicity**

This figure shows the intensity of the *Plasmodium falciparum* parasite prevalence rates (PPR) in children aged 2–10 years.



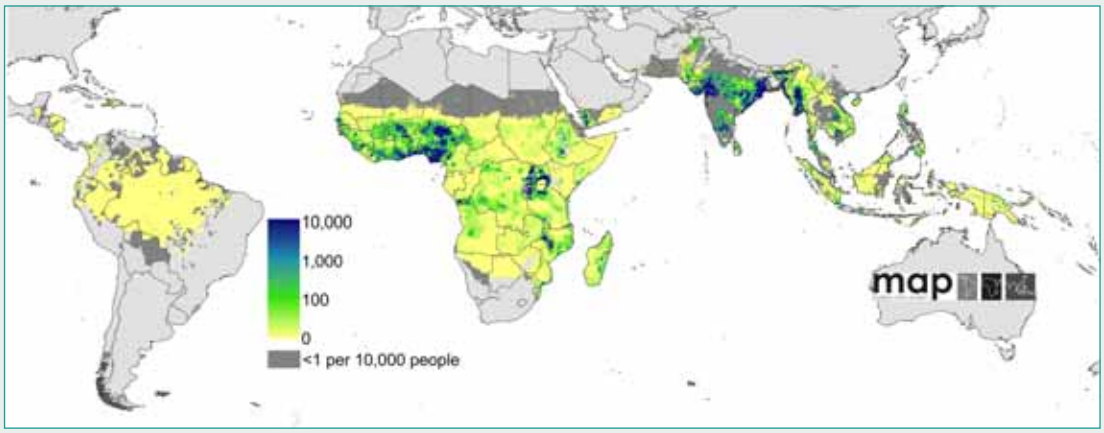
Source: Malaria Atlas Project *(60)*.

Note: The lighter colour shows low intensity and the darker colour shows the highest intensity of malaria transmission (dark grey = epidemic malaria; light grey = no malaria transmission). The dotted line represents approximately the Line of Control in Jammu and Kashmir agreed upon by India and Pakistan. The final status of Jammu and Kashmir has not yet been agreed upon by the parties.

Figure A2.2

Global clinical burden of malaria

This figure shows the intensity of clinical burden of malaria, that is, the number of clinical cases of malaria per 10,000 people per year.



Source: Malaria Atlas Project *(61).*

Note: The lighter colour shows low intensity and the darker colour shows the highest intensity of malaria transmission (grey = no malaria transmission). The dotted line represents approximately the Line of Control in Jammu and Kashmir agreed upon by India and Pakistan. The final status of Jammu and Kashmir has not yet been agreed upon by the parties.

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