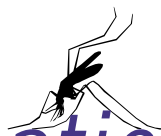


# *Malaria elimination*



GUIDE FOR PARTICIPANTS



World Health  
Organization



# Malaria elimination



GUIDE FOR **PARTICIPANTS**

WHO Library Cataloguing-in-Publication Data

Malaria elimination.

2 v.

Contents: Guide for tutors – Guide for participants

1.Malaria - prevention and control. 2.Disease Eradication. 3.Case Management. 4.Endemic Diseases – prevention and control. 5.Population Surveillance. 6.Teaching Materials. I.World Health Organization.

ISBN 978 92 4 154943 1 (Guide for tutors)

(NLM classification: WC 765)

ISBN 978 92 4 154942 4 (Guide for participants)

***Preparation of this document was made possible through a grant from the Russian Federation for strengthening human resource capacity for the control and elimination of malaria.***

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Cover Design par Paprika-Annecy.com

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# Foreword

Malaria is a major global public health problem and a leading cause of morbidity and mortality in many countries. It caused an estimated 198 million cases (range, 124–283 million) and 584 000 deaths (range, 367 000–755 000 deaths) in 2013. Approximately 80% of the cases and 90% of the deaths occurred in Africa and the remaining cases and deaths mainly in the South-East Asia and Eastern Mediterranean Regions.<sup>1</sup> For the most recent figures on burden of malaria, see the *World malaria report*, available on the WHO Global Malaria Programme website (<http://www.who.int/malaria/en/>).

The new WHO *Global technical strategy for malaria 2016–2030* provides a comprehensive framework to guide countries in accelerating progress towards malaria elimination. The strategy sets the targets of reducing global malaria incidence and mortality rates by 2030 by at least 90% from the rates in 2015 and eliminating malaria from 10 countries in 2020, 20 countries in 2025 and 30 countries in 2030.

Elimination of malaria is defined as the reduction to 0 of the incidence of locally acquired infection from human malaria parasites in a defined geographical area as a result of deliberate efforts. Elimination programmes require more technical expertise than standard malaria control programmes, including national expertise in malaria epidemiology and entomology. Since 2007, three countries (Armenia, Morocco and Turkmenistan) have been certified malaria-free. As of December 2014, 12 countries (Argentina, Armenia, Azerbaijan, Georgia, Iraq, Kyrgyzstan, Morocco, Oman, Paraguay, Sri Lanka, Turkmenistan and Uzbekistan) reported 0 indigenous cases. In addition, 19 countries were in pre-elimination or elimination stages.<sup>1</sup>

The progression to malaria elimination builds on successful, sustained malaria control, which requires appropriately planned, targeted diagnostic testing of all suspected malaria cases and prompt treatment with effective artemisinin-based combination therapy (ACT), intermittent preventive treatment of pregnant women and infants where appropriate and seasonal malaria chemoprevention in children, appropriate vector control interventions, particularly long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS), and effective surveillance.

This training module has been prepared to support health professionals in planning, managing, monitoring and evaluating malaria elimination programmes. The aims are to improve capacity in critical synthesis and analysis of determinants of malaria transmission in low-endemic settings; increase understanding of health system components in order to assess the feasibility of national or sub-national malaria elimination; and plan strategies and approaches for sustained malaria elimination.

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<sup>1</sup> World malaria report 2014. Geneva, World Health Organization; 2014 ([http://www.who.int/malaria/publications/world\\_malaria\\_report\\_2014/en/](http://www.who.int/malaria/publications/world_malaria_report_2014/en/), accessed 14 September 2015).

## Abbreviations

ACT	artemisinin-based combination therapy
bw	bodyweight
ESP	elimination scenario planning
G6PD	glucose-6-phosphate dehydrogenase
GIS	geographical information system
GMP	Global Malaria Programme
IRS	indoor residual spraying
ITN	insecticide-treated net
LLIN	long-lasting insecticide-treated net
PCR	polymerase chain reaction
pLDH	parasite lactic dehydrogenase
RDT	rapid diagnostic test
WHOPES	WHO Pesticide Evaluation Scheme



# Acknowledgements

This module was produced by the WHO Global Malaria Programme (GMP), with the participation of current and former staff from WHO headquarters and regional offices. WHO gratefully acknowledges the following experts who contributed to preparation of this document.

Dr A.E. Beljaev prepared the first draft of the content, and Dr A.A.A. Adeel transformed the training material into guides for learners and tutors.

The technical experts who reviewed and updated this module are: A.A.A. Adeel (King Saud University, Saudi Arabia), M.S. Al-Zedjali (Malaria Epidemiology, Ministry of Health, Oman), A. Kondrashin (former WHO staff, Russian Federation), B. Ayivi (National University Hospital, Benin), C. Hugo (ACT Malaria Foundation Inc., Philippines), A. Baranova (Martzinovsky Institute of Medical Parasitology and Tropical Medicine, Russian Federation), P.F. Beales (former WHO staff, United Kingdom), A.E. Beljaev (Russian Medical Academy for Moscow, Russian Federation), S. Elbushra (University of Gezira, Sudan), K. Kolaczinski (Malaria Consortium Africa, Uganda), S. Lutalo (Harare Central Hospital, Zimbabwe), R. Majdzadeh (Tehran University of Medical Sciences, Islamic Republic of Iran), E.M. Malik (Federal Ministry of Health, Sudan), P.S. Mapunda (Centre for Enhancement of Effective Malaria Interventions, United Republic of Tanzania), R. Mintcheva (Centre of Infectious and Parasitic Diseases, Bulgaria), O. Mokuolu (University of Ilorin Teaching Hospital, Nigeria), E. Morozov (Martzinovsky Institute of Medical Parasitology and Tropical Medicine, Russian Federation), A. Mwakilasa (consultant, United Republic of Tanzania), J.B. Ouedraogo (Direction Regionale de l'Ouest, Burkina Faso), V. Sergiev (Martzinovsky Institute of Medical Parasitology and Tropical Medicine, Russian Federation) and H. Vatandoost (Tehran University of Medical Sciences, Islamic Republic of Iran).

Dr A. Schapira reviewed the content of the module, led field testing of the package in several courses and incorporated feedback from facilitators and participants.

WHO staff who contributed to the technical content of the module are H.Y. Atta, A. Bosman, K. Carter, M. Lynch, K. Mendis, A. Rietveld, M. Warsame and G. Zamani.

WHO also thanks the participants, tutors and facilitators of several national and international courses for their comments and suggestions during the field testing, which led to improvements in the module.

Revision was coordinated by M. Warsame.

The preparation of this document was made possible through a Russian Federation grant for strengthening human resource capacity for the control and elimination of malaria, and revision of the module was made possible through a Russian Federation grant for malaria capacity development in Africa.

## Development of the module

The content of the module is based on current WHO guidelines and other evidence-based technical documents. The following manuals and technical documents served as the main references and resources: *Malaria elimination: a field manual for low and moderate endemic countries*, 2007; *Global malaria control and elimination—report of a technical review*, 2008; *Guidelines for the treatment of malaria*, 3<sup>rd</sup> edition; *Malaria microscopy quality assurance manual*, version 1, 2009; *Disease surveillance for malaria elimination: an operational manual*, 2012 and *World malaria report 2014*.

The training module was prepared by WHO/GMP in collaboration with the WHO regional offices for the Eastern Mediterranean and Europe. Several technical experts from malaria training and academic institutions, malaria researchers, country programme managers and WHO contributed to the content of the module. The process comprised the following steps:

- ▶ Three WHO consultations of technical experts (7–9 April 2008, 14–16 October 2008 and 15–17 April 2009) were held to review existing WHO technical documents on malaria elimination and to identify relevant materials for development of a training package for malaria elimination. The content of the training module was then prepared and agreed upon.
- ▶ Technical experts were commissioned to write the content of specific sections of the training module on the basis of the agreed outline.
- ▶ The revised module was then reviewed for content and completeness by WHO technical staff and additional external experts.
- ▶ The updated module was field-tested in four international training courses, held in Egypt in 2012, the Philippines in 2014, Zimbabwe in 2014 and Tunisia in 2014.
- ▶ Feedback from participants and facilitators in these training courses and input from technical experts and WHO/GMP secretariat were used to finalize the text for publication.

# Introduction

This module is designed to provide trainees with the necessary skills and knowledge to assess the feasibility of malaria elimination in a given area and to prepare a national or sub-national plan for an elimination programme, with particular emphasis on the surveillance component. The module is made up of two books, the *Guide for participants* and the *Guide for tutors*. This *Guide for participants* contains information and guidance on issues of malaria elimination associated with specific learning objectives. It is to be used with two other WHO guidelines, *Malaria elimination. A field manual for low and moderate endemic countries* (2007; <http://www.who.int/malaria/publications/atoz/9789241596084/en/>, accessed 12 September 2015) and *Disease surveillance for malaria elimination—an operational manual* (2012; <http://www.who.int/malaria/publications/atoz/9789241503334/en/>, accessed 12 September 2015) and a few other materials, including spreadsheet and presentation files, which are parts of exercises (see Table 1). The *Guide for tutors* provides additional guidance on training, on preparing to teach each unit and on evaluating the course.

## Potential users of the training module

The training module is designed for health professionals who have, or will have, some responsibility for programme planning and for malaria elimination. They include national malaria programme managers and their team members, health professionals in other government departments and partner organizations with malaria elimination programmes. Participants are expected to have high-school-level knowledge of mathematics, to be well acquainted with malaria and its control and to have practical public health experience, including planning.

## Objectives

At the end of a training programme with this module, participants should have acquired the knowledge, skills, competence and confidence to do the following.

- ▶ Give an account of the history of malaria control, eradication and elimination, including lessons learnt and the current concept of malaria elimination.
- ▶ Describe the epidemiological basis for malaria control and elimination.
- ▶ Describe the basic principles for setting up or modifying a national programme to eliminate malaria in a particular area.
- ▶ Select interventions appropriate to the local situation, and design approaches (strategies) to achieve the objectives.
- ▶ Assess a malaria surveillance system, and identify any changes necessary for making it adequate for an elimination programme
- ▶ Conduct a feasibility assessment to weigh the different antimalaria programme options, including malaria elimination.
- ▶ Write a plan for malaria elimination, with emphasis on any necessary modifications to the surveillance system, including priorities, activities, operational targets and indicators.
- ▶ Describe the process of WHO certification of malaria elimination

## Content

This *Guide for participants* is designed to help users achieve these objectives. It is divided into learning units, each of which has specific objectives. The units will be considered in sequence, as they follow a logical process and are interdependent. To benefit fully from the training, participants should achieve the learning objectives of each unit before starting on subsequent units.

The detailed objectives of each of the nine units of the course are listed in Table 1.

**Table 1. Modular units, objectives and resources for the training programme**

Number of unit and title	Objectives	Reading materials and exercises in addition to the field manual and surveillance manual
1. Introduction to malaria elimination	<ul style="list-style-type: none"> <li>• Define malaria control, elimination and eradication.</li> <li>• Explain the concept of malaria elimination and the control–elimination continuum.</li> <li>• Specify key differences between malaria control and elimination approaches.</li> <li>• Explain the concepts, achievements and shortcomings of the 1960s Global Malaria Eradication Programme, including lessons learnt.</li> <li>• Place the “elimination debate” in the context of historical and recent developments and the current world malaria situation.</li> </ul>	<p>WHO. <i>World malaria report</i>, latest edition</p> <p>WHO. <i>Global malaria control and elimination—report of a technical review</i>. 2008.</p> <p>WHO. <i>Malaria elimination. A field manual for low and moderate endemic countries</i>.</p>
2. Basic malaria epidemiology, including transmission dynamics	<ul style="list-style-type: none"> <li>• Specify the biological and epidemiological features of <i>P. vivax</i> and <i>P. falciparum</i> that favour or hinder elimination.</li> <li>• Specify the factors related to vectors that influence malaria elimination.</li> <li>• Specify the factors related to human hosts that influence malaria elimination.</li> <li>• Specify the eco-geographical factors that influence malaria elimination.</li> <li>• Define the major parameters of transmission intensity used in malaria epidemiology.</li> <li>• Identify the relations between vectorial capacity, basic reproduction number, entomological inoculation rate and incidence and prevalence of malaria infection.</li> </ul>	Exercises 2.2–2.4.xls
3. Road map to elimination: from advanced control to the prevention of reintroduction	<ul style="list-style-type: none"> <li>• Describe the continuum of malaria control to elimination.</li> <li>• Explain the objectives of each programme phase.</li> <li>• Describe the major programme reorientations and approaches from malaria control to elimination to prevention of reintroduction.</li> <li>• Identify major programme transition milestones, interpret them, and discuss their limitations.</li> </ul>	WHO. <i>Malaria elimination. A field manual for low and moderate endemic countries</i> .
4. Approaches and interventions in pre-elimination, elimination and prevention of re-establishment	<ul style="list-style-type: none"> <li>• List the objectives of malaria treatment in elimination programmes.</li> <li>• Describe antimalarial treatment strategies for <i>P. falciparum</i> and <i>P. vivax</i> in malaria elimination programmes.</li> <li>• Describe the indications and objectives of mass drug administration.</li> <li>• List the different vector control methods and their role in malaria elimination.</li> <li>• Describe the technical and operational issues in vector control measures.</li> <li>• Review the interventions that can be used from pre-elimination to the prevention of reintroduction.</li> <li>• Describe the four approaches (strategic elements) that define a malaria elimination programme.</li> </ul>	<p>WHO. <i>Malaria elimination. A field manual for low and moderate endemic countries</i>.</p> <p>WHO. <i>Guidelines for the treatment of malaria</i>, latest edition</p> <p>WHO. <i>Guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets</i></p> <p>WHO. <i>Global plan for insecticide resistance management in malaria</i></p>

Number of unit and title	Objectives	Reading materials and exercises in addition to the field manual and surveillance manual
5. Surveillance, including laboratory methods	<ul style="list-style-type: none"> <li>• Describe the role of surveillance in different phases of malaria elimination.</li> <li>• Describe the role of different diagnostic techniques in malaria elimination.</li> <li>• Interpret laboratory reports.</li> <li>• Describe key issues in the establishment and maintenance of quality assurance for microscopy.</li> <li>• Describe the place of a geographical information system in malaria elimination.</li> <li>• Explain the role of meteorological data in relation to malaria transmission (including Moshkovsky's method for certain areas).</li> <li>• Organize case detection activities.</li> <li>• Conduct an investigation of a malaria case.</li> <li>• Classify cases of malaria.</li> <li>• Classify foci of malaria.</li> <li>• Explain the epidemiological indicators used in surveillance.</li> <li>• Establish a surveillance system for malaria elimination.</li> </ul>	<p>WHO. <i>Disease surveillance for malaria elimination. An operational manual.</i></p> <p>WHO. <i>Malaria microscopy quality assurance manual</i>, version 1. Annex 1. Key issues in quality assurance for malaria microscopy in the elimination phase</p> <p>Exercise 5.5.pptx</p>
6. Prevention of reintroduction	<ul style="list-style-type: none"> <li>• Explain the relations between receptivity, vulnerability and the likelihood of re-establishment of malaria.</li> <li>• Define vigilance, and describe patterns of vigilance required to prevent re-establishment of transmission in different settings.</li> <li>• Explain the required capabilities and organization of health services in countries that have recently been freed from malaria transmission.</li> <li>• Determine the training needs for adequate malaria vigilance in different settings.</li> </ul>	<p>WHO. <i>Malaria elimination. A field manual for low and moderate endemic countries.</i></p>
7. Health systems and inter-sectoral and cross-border collaboration	<ul style="list-style-type: none"> <li>• Explain how the different components of health systems are related to effective malaria control and elimination.</li> <li>• Give examples of common weaknesses in health systems that jeopardize malaria elimination, and identify ways to overcome those weaknesses.</li> <li>• Describe measures for reorienting health systems towards the requirements for malaria elimination.</li> <li>• Determine the roles of the private sector, the community, other sectors and inter-country collaboration.</li> <li>• Identify suitable topics for operational research related to elimination.</li> </ul>	<p>Case studies: Cape Verde, Turkmenistan</p>
8. Feasibility of malaria elimination	<ul style="list-style-type: none"> <li>• Describe the purpose of a feasibility assessment.</li> <li>• Describe the technical, operational and financial factors that should be considered in assessing the feasibility of malaria elimination.</li> <li>• Define a clear problem for a feasibility assessment in your own country.</li> <li>• Analyse feasibility using technical and operational data from your own country.</li> <li>• For African countries, apply the simplified “elimination scenario planning” method to assess feasibility, including timetables for reducing the <i>P. falciparum</i> burden to a very low level.</li> <li>• Formulate interim targets for malaria elimination from the analysis.</li> <li>• Analyse financial feasibility for a given area, and explain how the cost-effectiveness of elimination and control can be compared.</li> </ul>	<p>Unit 8. ESP worksheets.xls</p>

Number of unit and title	Objectives	Reading materials and exercises in addition to the field manual and surveillance manual
9. Certification	<ul style="list-style-type: none"> <li>• Explain the concept of burden of proof in the context of malaria elimination.</li> <li>• Describe the steps in certification of malaria elimination.</li> <li>• Explain the reporting requirements for countries that have been certified malaria-free.</li> </ul>	WHO. <i>Malaria elimination. A field manual for low and moderate endemic countries.</i>  Case studies: Turkmenistan, United Arab Emirates

Unit 1 presents the history of the current concept of elimination. Unit 2 provides an overview of basic malariology, with emphasis on the aspects that are relevant for malaria elimination, and then the classical model for transmission dynamics. As learners often find this model challenging, the mathematics has been reduced to the essentials, with easy spreadsheet exercises that bring the topic to life. Apart from the mathematical model, units 1 and 2 are designed for self-study, with limited time set aside for group work.

Units 3 and 4 clarify how progress in elimination can be achieved with appropriate strategies and tools; they should be fairly easy to follow.

Unit 5 on malaria surveillance includes much material and should be given ample time and attention. As surveillance is the critical intervention for achieving elimination, participants should work through all the exercises in groups and in plenary. In this unit, Moshkovsky's method for assessing the temperature suitable for transmission will be explained only briefly, as it is relevant only for areas in highlands and northern and southern fringes of malaria transmission areas. Participants with a particular interest in this method should ask for additional reading and training material from the facilitators. In the group work for unit 5, participants will start the planning exercise, focusing on surveillance, which is central to the course.

Units 6 and 7, on preventing reintroduction and health system strengthening requirements in the different phases of malaria elimination, should not provide major challenges. Unit 8, dealing with technical, operational and financial feasibility, contains a good deal of theory as well as practical applications. It resumes the modelling concepts from unit 2 and all the technical and strategic elements of units 3–7. It introduces participants to the use of the “elimination scenario planning method” (ESP method), which is suitable mainly for tropical Africa.

Unit 9, on WHO certification, is fairly straightforward.

In general, the exercises are presented as the last section of each learning unit, but many of them should be done by individual participants while reading the unit. Relevant points in the text at which readers are invited to stop and do a particular exercise are marked by ►.

## The course

To facilitate learning by all participants, the tutor will encourage them to learn from each other as well as from the facilitators, particularly in group discussions. Each participant will therefore be expected to participate actively throughout the course. In working through the learning units, there will be opportunities to put what has been learnt into practice, individually or collectively.

The tutor has overall responsibility for the planning and management of the course. He or she is assisted by a number of facilitators who will work with the participants to achieve the objectives

listed above. The facilitators will lead discussions and provide general help to individuals and to small groups. The tutor may introduce all the learning units or delegate some of them to facilitators.

### **The Guide for tutors**

During the course, the *Guide for tutors* will be available only to the tutor and facilitators. Upon completion of the course or module, participants will receive the *Guide for tutors* so that they can use it for training and further reference.

### **Evaluation**

Judging whether or not the course was successful involves answering the following questions:

- ▶ *How well did the participants learn?*
- ▶ *How did the participants view the training?*

#### *Evaluation of the participants*

Progress and achievements are evaluated by the tutor, the facilitators, and by the participants themselves. As well as general assessment during the group activities, a number of quizzes and problems solve are used. The evaluation is intended to provide a helpful opportunity for participants to measure their progress, and as a contribution to the learning process.

Whether this module is used for group training or individual learning, assessment of progress made by the trainee in gaining skills and competence in the subject matter is essential. This can be accomplished by means of a pre-test and a post-test, using a multiple-choice questionnaire (MCQ). The pre-test will be given before the trainee reads the Guide for Participants. The posttest will be administered after all the Learning Units have been completed. In MCQ tests, each question is provided with a list of possible answers from which one must be selected (i.e. considered to be correct). At the end of these sessions the tutor will analyse the results to identify topics that were not fully understood. The tutor may also explain to individual participants where mistakes were made and areas where improvement is needed.

The evaluation of the participant's progress also includes assessment of classroom, practical and field activities, degree of group participation, etc. including how the group work was presented in plenary sessions, and the degree of clarity.

#### *Evaluation of the training by the participants*

The entire training activity, including the organization and content of the course, the suitability of the learning methods, the quality of the teaching and training materials, and the competence of the tutors and facilitators will be assessed by the participants. This will be done through administration of a questionnaire, and at a plenary session after the post-test questionnaires have been completed. This evaluation will take place at the end of the training period in order to provide as much feedback from the participants as possible. All participants are encouraged to make suggestions for improvement on the part of the tutor and facilitators as well as in the content of the course and the training facilities. The objective of the plenary session is to ascertain whether an issue(s) raised by one or more persons has the consensus of the whole group, and to judge the importance of the issue(s) raised. Feedback provided through this exercise allows the tutor to assess how well the training has been received and to propose modifications that seem necessary for improving future programmes.





# LEARNING UNIT 1

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## Introduction to malaria elimination

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### Learning objectives

By the end of this unit, the participants should be able to:

- Define malaria control, elimination and eradication
- Explain the concept of malaria elimination and the control–elimination continuum
- Specify key differences between malaria control and elimination approaches
- Explain the concepts, achievements and shortcomings of the 1955–1969 Global Malaria Eradication Programme, including lessons learnt
- Place the “elimination debate” in the context of historical and recent developments and the current situation of malaria in the world

## Reading material

*Malaria elimination. A field manual for low and moderate endemic countries.* Geneva: World Health Organization; 2007. Foreword and introduction (<http://www.who.int/malaria/publications/atoz/9789241596084/en/index.html>, accessed 12 September 2015).

*World malaria report 2014.* Geneva: World Health Organization. Latest version, section on elimination (<http://www.who.int/malaria/areas/en/>, accessed 12 September 2015).

*Global malaria control and elimination—report of a technical review.* Geneva: World Health Organization; 2008. Executive summary and recommendations (<http://www.who.int/malaria/publications/atoz/9789241596756/en/>, accessed 12 September 2015).

### 1.1 History, with emphasis on the Global Malaria Eradication Programme

Until the mid-nineteenth century, malaria was endemic in most countries; an estimated 90% of the world's population lived in malarious areas. In the late nineteenth century, large areas of northern and central Europe and North America became malaria-free, probably mainly as a result of changes in land use, which affected the larval habitats of local vectors, improved housing and wide-scale use of quinine. The identification of the malaria parasite in 1880 and its mode of transmission in 1897 led to the development of techniques that helped some countries in Europe to eliminate malaria before the Second World War, while the burden in southern Europe and the USA was greatly reduced. In the 1940s and early 1950s, the adoption of indoor residual spraying (IRS) with DDT (and soon after also other long-acting insecticides) led to spectacular successes in parts of South Africa, the Americas, India, southern Europe and the former USSR. In 1954, the Pan-American Sanitary Conference adopted a programme for malaria eradication for the Americas, and, 1 year later, with the endorsement of the World Health Assembly, WHO launched the Global Malaria Eradication Programme as its second eradication initiative.<sup>2</sup>

The 10-year, time-limited campaign, which was designed technically by the WHO Expert Committee on Malaria, started in 1957. As it was considered uncertain that existing tools would result in “eradication” in tropical Africa, a series of pilot projects was set up in a number of countries. The Malaria Eradication Special Account, managed by WHO, was created in 1957, and, over the next 7 years, 44 countries contributed a total of US\$ 20.3 million, 85% of which was from the USA. The number of WHO staff employed in malaria eradication worldwide increased substantially to 444 in 1967.<sup>3</sup> The population covered by the Programme peaked at 1.4 billion in 1969.

The aim of the Global Programme was “the ending of the transmission of malaria and the elimination of the reservoir of infective cases, in a campaign limited in time and carried out to such a degree of perfection that, when it comes to an end, there is no resumption of transmission”. The strategy was to target malaria in adults with large-scale IRS operations, conduct intensive surveillance and treat the cases detected. Gradually, it came to be recognized that health

<sup>2</sup> A yaws eradication programme was launched at almost the same time. It received much less attention and resources than malaria; incredibly, from a modern perspective, it was a pure intervention programme without surveillance. It ended in failure. Smallpox eradication, which started a few years later, combining standardized application of a single intervention with operational flexibility and strong surveillance, was successful.

<sup>3</sup> Najera JA. Malaria control: achievements, problems and strategies. *Parasitologia* 2001;43:1–89.

services had to be improved to provide treatment and better surveillance data. In some areas where accessibility was a problem, salt medicated with chloroquine was tested and added to the armamentarium.

Since its inception, the strategy was a stepwise approach, with four phases: preparation, attack, consolidation and maintenance; the maintenance phase involved preventing reintroduction of malaria and consequent resumption of transmission.<sup>4</sup> Once eradication was achieved, governments would request WHO certification of elimination by a team of independent experts. The team's findings would be subject to confirmation by the WHO Expert Committee on Malaria and added to *The official register of areas where malaria eradication has been achieved*, published in the *Weekly Epidemiological Record*.

Part of the justification for a time-limited global programme for malaria eradication was a perceived window of opportunity: a race against insecticide resistance. This race came up against the requirements for planning based on understanding of local epidemiological, ecological and social conditions and for efficient organization to carry out the Programme, which were beyond the capabilities of many endemic countries. Acceleration of global interventions led to oversimplification and standardization, which conflicted with efforts to improve local knowledge and validate approaches. The limitations of the eradication tools in practice emerged at an early stage, and eradication was not achieved in many countries.

Although many achieved success in the “attack” phase, the “consolidation” and “maintenance” phases proved more difficult, as decision-makers shifted financial resources to other health programmes when the number of malaria cases fell. In 1969, the World Health Assembly concluded that “due to various administrative, financial and technical reasons, the goal of global eradication could not be achieved at the present time.”

During the campaign, malaria was eliminated from most areas of socioeconomic stability in temperate and subtropical zones of the Americas, Asia and Europe. Of the 143 countries that were endemic for malaria in 1950, 37 were free from malaria by 1978, including 27 in the Americas and Europe, and the burden of malaria was greatly reduced in other countries. In India, the annual number of malaria cases declined from an *estimated* 110 million in 1955 to about 100 000 *reported* cases in 1965, while the *reported* number of deaths from malaria dropped to 0; furthermore, large tracts of land that had been unproductive due to the presence of malaria were reclaimed. In countries where vectors depend on marshy areas for larval development, drainage and reclamation of fields for agriculture decreased the number of vector breeding places, thus reducing the transmission of malaria. The incidence of malaria in Sri Lanka was reduced from an estimated 2.8 million cases in 1946 to 18 reported cases in 1966. Failure to sustain the programme, however, led to a resurgence of malaria in many countries, and, in 1969, the goal of malaria eradication in many countries was abandoned in favour of control.

Figure 2.5 in learning unit 2 shows the distribution of malaria in the mid-nineteenth century and in 2005: by 1945, malaria had been eliminated from Sweden and large parts of North America, and by 1977 an additional 37 countries had been freed from malaria. Over the next 30 years, however, the geographical distribution of malaria changed little, and, by 2007, elimination had been achieved only in Maldives, Tunisia and the United Arab Emirates. Some areas that

<sup>4</sup> Pampana E. A textbook of malaria eradication. London: Oxford University Press; 1963.

eliminated malaria during the Global Eradication Programme have since seen resurgences, especially in the 1990s after the dissolution of the Soviet Union. In recent years, most of these areas have again become malaria-free or almost malaria-free. Other countries have been certified as malaria-free—Armenia, Morocco, Turkmenistan—and a number of countries, mainly in the WHO Eastern Mediterranean and European regions, have interrupted local transmission (see the latest *World malaria report* at <http://www.who.int/malaria/areas/en/>).

After termination of the Global Eradication Programme, WHO recommended that national governments evaluate their malaria programmes to determine whether they could achieve “eradication” in the short term, or, otherwise, to consider them as “control” programmes. Both international and national financial support was greatly reduced as the burden dropped and malaria was considered a lower priority. With reduced investment in control and surveillance and the progressive disappearance of skilled epidemiologists, malaria returned, often as epidemics, to some of the countries in which the incidence had been reduced to a low level. By 1970, “malaria experts” were experienced in conducting standard large-scale operations, but there were few who knew how to conduct epidemiological assessments and field research. For WHO, the focus shifted to a search for new tools. In 1975, the Special Programme for Research and Training in Tropical Diseases was established by WHO, the United Nations Children’s Fund (UNICEF), the United Nations Development Programme (UNDP) and the World Bank to promote scientific collaboration, research training and product development.

In the 1980s, malaria control went into further decline in many countries as a result of increasing resistance of the parasites to chloroquine and sulfadoxine–pyrimethamine and resistance of mosquitoes to DDT. The incidence of malaria increased in most parts of the world, as did the rate of childhood deaths from malaria in Africa. In sub-Saharan Africa, the few, limited organized malaria programmes were *de facto* abandoned, and malaria was again considered an inevitable evil.

In the early 1990s, the tide started turning. A global malaria control strategy was prepared by WHO in 1992, adopted by the Ministerial Conference on Malaria in Amsterdam in 1992 and endorsed by the World Health Assembly in 1993. The launch of the Roll Back Malaria initiative in 1998 and the establishment of the Roll Back Malaria programme in 1998 by WHO, UNICEF, UNDP and the World Bank attracted greater financial investment in malaria control, which was further stimulated by the adoption of new tools, such as insecticide-treated nets (ITNs) and ACT. However, it was only after the start of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002 that funding for malaria control began to be commensurate with the needs of national programmes. The Roll Back Malaria initiative was established mainly to reduce the intolerable malaria burden in Africa and did not initially address malaria elimination.

## 1.2 Contemporary terminology

After a series of publications and international consultations, WHO published conceptually rigorous definitions of control, elimination and eradication of disease and infection in 1998:<sup>5,6</sup>

- ▶ *Control*: The reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction. Example: diarrhoeal diseases.
- ▶ *Elimination of disease*: Reduction to 0 of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts. Continued intervention measures are required. Example: neonatal tetanus.
- ▶ *Elimination of infections*: Reduction to 0 of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required. Examples: measles, poliomyelitis.
- ▶ *Eradication*: Permanent reduction to 0 of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed. Example: smallpox.
- ▶ *Extinction*: The specific infectious agent no longer exists in nature or in the laboratory. Example: none.

The current WHO definitions in relation to malaria control, elimination and eradication are listed in Box 1.1.

<sup>5</sup> Dowdle WR. The principles of disease eradication and elimination. Bull World Health Organ 1998;76(Suppl 2):22

<sup>6</sup> Malaria elimination. A field manual for low and moderate endemic countries. Geneva: World Health Organization; 2007 (<http://www.who.int/malaria/publications/atoz/9789241596084/en/>, accessed 12 September 2015).

### Box 1.1. Current WHO definitions of malaria control, elimination and eradication

#### *Malaria control*

Reducing the malaria disease burden to a level at which it is no longer a public health problem.<sup>7</sup>

#### *Malaria elimination*

The interruption of local mosquito-borne malaria transmission; reduction to 0 of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required.<sup>8</sup>

#### *Certification of malaria elimination*

The official recognition of malaria-free status granted by WHO after it has been proven beyond reasonable doubt that the chain of local human malaria transmission by *Anopheles* mosquitoes has been fully interrupted in an entire country for at least 3 consecutive years and there is evidence that the elimination can be maintained.

#### *Malaria eradication*

Permanent reduction to 0 of the worldwide incidence of infection caused by a particular malaria parasite species. Intervention measures are no longer needed once eradication has been achieved.

#### *Criteria of re-establishment of transmission*

The occurrence of at least three or more introduced and/or indigenous malaria infections in the same geographical focus for 2 consecutive years for *P. falciparum* and for 3 consecutive years for *P. vivax*.

Malaria elimination is a relatively new term. Until the late 1990s, “eradication” of malaria was used in a broad sense for global, regional, national or even sub-national initiatives. In present-day terminology, the global malaria eradication campaign of 1955–1969 might be seen as a series of national elimination initiatives. The distinction was not, unfortunately, realized or not made explicit at the outset. The idea of “a campaign limited in time and carried out to such a degree of perfection that, when it comes to an end, there is no resumption of transmission” would be perfectly rational in relation to global eradication, if technically feasible, because, at the end of it, there would be no parasite reservoir anywhere in the world (except possibly in laboratories). The world learnt the hard way that maintenance of elimination (in a country or another geographical region) requires continued effort.

Many countries that have achieved elimination and are maintaining their malaria-free status occasionally experience small outbreaks of secondary cases that are contracted from primary

<sup>7</sup> For disease control in general, the term “to a locally acceptable level” has been proposed instead of “to a level at which it is no longer a public health problem” (above). Although this definition includes local variation, it may be more useful, because it corresponds to a general principle in public health, that a given programme should be funded up to the point at which an alternative use of the available resources would provide greater returns (health effects).

<sup>8</sup> Malaria elimination does not require complete elimination of disease vectors or a complete absence of reported malaria cases in a country: imported malaria cases will continue to occur due to international travel.

imported cases. WHO has addressed this issue by defining an operational criterion for re-establishment of transmission (see Box 1.1).

### 1.3 Concepts related to malaria elimination

A number of variants of standard national malaria elimination programmes or closely related programmes are currently proposed or pursued.

#### *Pre-elimination*

Pre-elimination refers to a phase of programme reorientation from malaria control to elimination. It is characterized by building the local and national capacity necessary for elimination. A programme may be reoriented to elimination when a feasibility analysis has shown that elimination is a realistic objective in a specific area of the country.

#### *Containment of resistance*

Containment was first attempted in India in the 1980s, with the goal of preventing the spread of chloroquine-resistant *P. falciparum*. Since 2008, WHO has coordinated inter-country efforts to contain artemisinin-resistant *P. falciparum* in the Greater Mekong sub-region, with the intention of preventing the spread of artemisinin-resistant falciparum parasites from the foci. It has been found recently, however, that artemisinin-resistant falciparum parasites in the area continue to spread and to emerge de novo, suggesting that the containment approach might not not been effective in the current context. Further, evidence of full resistance to ACT in the region (resistance to both artemisinin and the partner drug) will effectively make falciparum malaria an untreatable disease. For this reason, a malaria elimination approach is now advised.

#### *Species-specific elimination*

Presently, WHO certifies malaria elimination in a country only when all species that cause human malaria have been eliminated. WHO does, however, consider (global) eradication of a single malaria parasite species as eradication (Box 2, page 21 of Malaria elimination. *A malaria elimination field manual for low and moderate endemic countries*. Geneva: World Health Organization; 2007). A country may well decide to plan elimination of one species first, an achievement that would still be a major milestone. In the past, a number of countries achieved *P. falciparum* elimination unintentionally while fighting malaria “in general”, whereas they failed to interrupt *P. vivax* transmission or did so years later.

#### *Subnational elimination*

Current definitions of elimination do not exclude the possibility of malaria elimination at subnational level; however, such elimination is not certified by WHO. Countries in which national elimination cannot be envisaged at present but where elimination appears to be feasible in significant, well-delimited areas could consider establishing national regulations for certification.

#### *Prevention of reintroduction*

In many countries and areas, it might be possible to interrupt transmission of malaria, but, because of high receptivity in some areas, it would be impossible or extremely costly to prevent the occurrence of small outbreaks completely. In this scenario, interruption of transmission

can still be considered a major achievement, as long as the outbreaks are rapidly and effectively controlled so that malaria does not become re-established as an endemic disease.

## 1.4 Recent malaria elimination efforts and the present situation

Countries in the WHO Eastern Mediterranean and European regions were the first to attempt malaria elimination, from the 1990s onwards, starting with individual countries and progressing to blocks of neighbouring countries. In 1991, Oman launched an elimination programme (despite being discouraged by WHO). In 1997, the five countries of North African (Algeria, Egypt, Libya, Morocco and Tunisia) launched a subregional malaria elimination programme. Tunisia had already achieved interruption of malaria transmission in 1979, and local transmission in Africa north of the Sahara was limited to Algeria by 2006. At a conference on malaria elimination organized by the WHO regional offices for the Eastern Mediterranean and Europe, held in Rabat, Morocco, in 2002, it was concluded that sustainable elimination of malaria is feasible in selected countries.

On the Arabian Peninsula, the United Arab Emirates was certified by WHO as malaria-free in 2007—the first such certification since 1973. In Oman, sporadic transmission of *P. falciparum* and *P. vivax* was reported until 2003 and again during 2007, when several small outbreaks occurred due to subsequent international importation of parasites. Saudi Arabia and other Gulf countries are assisting Yemen to eliminate malaria from the Peninsula. Iraq has not reported any indigenous cases since 2009. The Syrian Arab Republic also made significant progress towards elimination, but recent political developments have jeopardized the programme. The Islamic Republic of Iran is progressively freeing its territory of falciparum malaria transmission. For the most recent figures on the burden of malaria, see the *World malaria report* on the WHO/GMP website (<http://www.who.int/malaria/en/>).

The WHO European Region, which includes Central Asia, the Caucasus and Turkey, overcame resurgences of malaria in the 1990s, the number of locally acquired cases falling from 90 000 in 1992 to < 1000 in 2007. In 2005, the Region adopted a joint strategy of malaria elimination (Tashkent Initiative). The current trend in each of the WHO regions is described in the *World malaria report 2014*. It should be noted that the boundaries of the WHO regions bear no relation to the distribution of determinants of malaria risk, such as migration, biogeography and ecology. For continued progress in elimination, it will therefore be important to work across these regions.

## 1.5 Main distinctive features of malaria elimination programmes as compared with control programmes

One fundamental difference between malaria elimination and control is that:

- ▶ a malaria control programme is concerned with reducing the burden of malarial *disease*, whereas
- ▶ malaria elimination is concerned with reducing malaria *infections* to 0.

During the control phase, malaria control tools such as LLINs, IRS, diagnosis and treatment, seasonal malaria chemoprevention and intermittent preventive treatment (for infants and pregnant women) are provided on a wide scale to the target populations. Interventions in elimination programmes are based on the concept of a malaria focus, assuming that transmission is localized. A focus is a defined, circumscribed locality situated in a currently or formerly malarious area



and containing the continuous or intermittent epidemiological factors necessary for malaria transmission. Examples are a town, village or other defined geographical area in which there are vector breeding, feeding and resting sites at which people are exposed to biting.

The objective of malaria elimination is total sustained ending of local malaria transmission in all transmission foci within a defined time.

- ▶ It should be *total*, which means that no local (autochthonous) case due to recent transmission is present in the area.
- ▶ It should be *sustained*, which means that all cases acquired outside the area (imported cases) are detected and treated very early, to prevent them from infecting local mosquitoes. If one step in local transmission does occur (introduced cases), action should be so swift and effective that no further transmission (indigenous cases) becomes possible.
- ▶ In an elimination programme, the objective of ending malaria transmission must be *time-bound*. The statement that elimination is the “ultimate goal” in any malaria-endemic country is reasonable and can even be seen as an ethical imperative, but an elimination programme must be guided by commitment to a time-bound objective. If it is not, resources may be wasted, the objective may never be achieved, and fatigue and frustration may take their toll. If malaria-free status is not achieved on or before the target date, a timely review should be conducted to determine whether elimination should be pursued with a different timetable and how the programme should be changed.

It is often assumed that elimination is much better control, because, once malaria-free status has been achieved, the cost of the malaria programme is dramatically reduced. It is reasonable to expect a dividend, as large-scale operations should no longer be needed. The difference between a situation of low malaria endemicity and “controlled non-endemic malaria” and malaria-free status may not, however, be great, because in both situations most expenditure is usually for malaria surveillance.

## Unit 1 exercises

### Exercise 1.1

Review the latest *World malaria report* at <http://www.who.int/malaria/en/>, and answer the following:

1. Which countries have been certified as malaria-free?
2. Locate these countries and endemic countries on the world map.
3. What are latest additions to this list (in the previous year)?
4. What do you conclude from the spatial distribution and trend of countries in which malaria has been eliminated?

### Exercise 1.2

Why was elimination distinguished from eradication in the 1990s? Does the distinction have any practical implications?

### Exercise 1.3

Review what happened in the era of the Global Malaria Eradication Programme in your country. What are the lessons for the present? In each group, select the one country that appears to have the most interesting story.

### Exercise 1.4

Do you think that malaria elimination efforts now would have a better chance of success than the previous failed “eradication” attempts? Justify your answer.

### Exercise 1.5

Compare malaria control and malaria elimination by filling in Table 1.1.

**Table 1.1 Differences between malaria control and elimination programmes**

Aspect	Control programme	Elimination programme
Objective		
Area of operations		
Minimum acceptable standard of operations		
Duration of operations		
Economic aspects		
Integration with other health programmes		
Case-finding		
Imported cases		
Epidemiological investigation of individual cases		
Epidemiological evaluation and analysis		
Unit of intervention		
Administration of the programme		

# LEARNING UNIT 2

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## Basic malaria epidemiology, including transmission dynamics

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### Learning objectives

By the end of this unit, the participants should be able to:

- Specify the biological and epidemiological features of *P. vivax* and *P. falciparum* that favour or hinder elimination
- Specify the factors related to vectors that influence malaria elimination
- Specify the factors related to human hosts that influence malaria elimination
- Specify eco-geographical factors that influence malaria elimination
- Define the major parameters of transmission intensity used in malaria epidemiology
- Identify the relations between vectorial capacity, basic reproduction rate, entomological inoculation rate and the incidence and prevalence of malaria infection

This learning unit covers topics in the biology and epidemiology of malaria. It is assumed that most participants are familiar with the biology of malaria parasites, but, to ensure that the basics are well understood, the pertinent details are covered. Attention should be given to the incubation periods and other intervals listed in Table 2.2 in this learning unit. These should be well known to people working in malaria elimination. Learning unit 2 also covers the ecology of malaria and transmission dynamics, with a minimum of mathematical detail, which will take a little intellectual effort to absorb. Participants should find their effort well rewarded when they use the Excel file distributed with this learning unit to vary entomological and other parameters and observe the effects on measures of malaria risk. This learning unit covers the theoretical basis of malaria elimination. Therefore, participants should feel that they are on firm ground when assessing feasibility and estimating “what it will take” to achieve elimination—if possible—in different scenarios.

## 2.1 Biological aspects of parasites, vectors and human hosts

### 2.1.1 Aspects of parasites

#### *Malaria species*

Malaria parasites belong to the group Protozoa. Human malaria is caused by four species of the genus *Plasmodium*:

- ▶ *Plasmodium falciparum*
- ▶ *Plasmodium vivax*
- ▶ *Plasmodium malariae*
- ▶ *Plasmodium ovale*

Of these, *P. falciparum* and *P. vivax* are the most important; *P. falciparum* is responsible for most cases of severe illness and death due to malaria.

Occasionally, humans contract simian malarial parasites, such as *P. knowlesi* and *P. cynomolgi*. While *P. knowlesi* is now suspected to be transmitted from human to human in Malaysia, this is still hypothetical. At present, WHO does not consider that simian malaria is directly relevant to malaria elimination or eradication.

#### *Life cycles of malaria parasites*

Malaria parasites are transmitted by female mosquitoes belonging to the genus *Anopheles*. The development of malaria parasites in the vector, called *sporogony*, includes a number of stages in different organs of the insect. Detailed descriptions are unnecessary for the purpose of this module; however, the following facts should be retained:

- ▶ At their entry point, male and female gametocytes are ingested by a mosquito as part of a blood-meal.
- ▶ At the exit point, sporozoites accumulate in salivary glands during their maturation and are injected with the mosquito’s saliva. Note that sporozoites may be injected even during probing; thus, ingestion of blood is not critical for infectivity.

- ▶ Potentially, several thousand sporozoites may emerge from one pair of gametocytes.
- ▶ Mosquitoes that emerge from hiding places after hibernation are not infected.
- ▶ The speed of development of malaria parasites in the vector, called sporogony, depends on the temperature (see details below).

In primates, including humans:

1. Sporozoites injected by a mosquito enter the host's blood circulation and migrate to the liver, where they invade hepatocytes. Those that do not reach the liver within 30 minutes perish.
2. After entering hepatocytes, *P. falciparum* and *P. malariae* immediately undergo exo-erythrocytic schizogony, whereby the parasite nucleus divides repeatedly over several days; at the end, the schizont bursts, giving rise to thousands of merozoites. This process is uni-directional, not cyclical. *P. vivax* and *P. ovale* either start exo-erythrocytic schizogony in the same way or become dormant as *hypnozoites*.
3. At the end of the period of dormancy, the hypnozoites undergo exo-erythrocytic schizogony. At the end of exo-erythrocytic schizogony, merozoites are released into the bloodstream, where they invade red blood cells and begin to multiply again, undergoing repeated cycles of growth, rupture, release and re-invasion of fresh red cells. All clinical manifestations of malaria are due to the processes of erythrocytic schizogony.
4. Gametocytogenesis is the process of formation of male and female gametocytes. On entering red blood cells, some of the merozoites grow and mature without division to become gametocytes. They continue their development only in mosquitoes; otherwise, they die out. Gametocytes do not cause clinical manifestations.

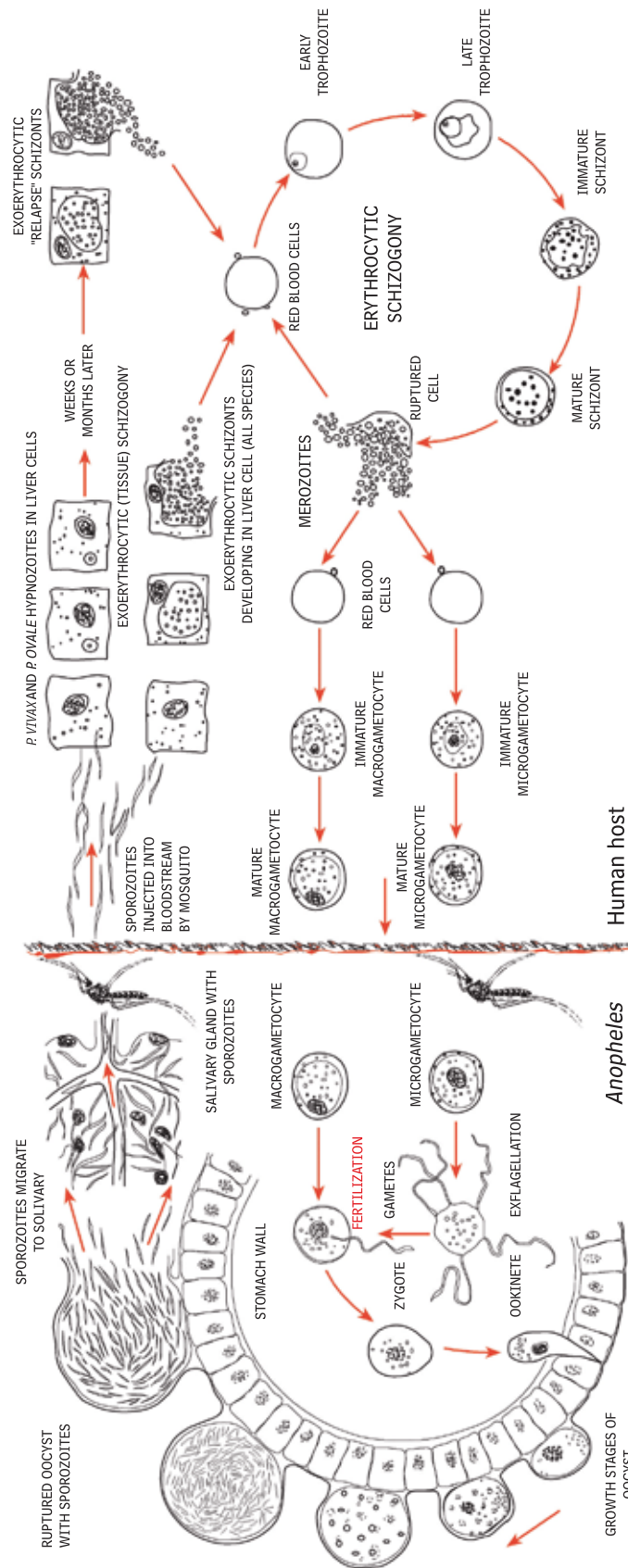
The four processes and their durations are presented in Table 2.1. A flowchart of the parasite life-cycle is shown in Fig. 2.1.

**Table 2.1 The four processes of the malaria parasite life cycle and their durations**

Process	Host organ	Host cell	Stages involved	Duration
Dormancy (for certain species of plasmodia)	Liver	Hepatocyte	Hypnozoite	Usually 5–18 months <sup>a</sup>
Exo-erythrocytic schizogony	Liver	Hepatocyte	Exo-erythrocytic schizont → merozoite	6–15 days, depending on the species
Erythrocytic schizogony	Blood	Red blood cell	Merozoite → trophozoite → schizont → merozoite → etc.	A number of cycles, each of 2 or 3 days' duration
Gametocytogenesis	Blood	Red blood cell	Merozoite → gametocytes (male and female)	See text

<sup>a</sup> As little as 3 weeks in tropical *vivax* strains

Figure 2.1. Life-cycle of *Plasmodium* species in human and mosquito hosts



### Comparison of species

Malaria attained its widest worldwide distribution in the mid-nineteenth century. Since then, the area of distribution of malaria has continued to contract. The area of distribution of human species has changed. *P. malariae* has become a rare species almost everywhere; the area of distribution of *P. ovale* has remained restricted, and it is common only in sub-Saharan Africa; only *P. falciparum* and *P. vivax* remain widespread, with a marked predominance of the former (about 90% of the total worldwide). We therefore consider mainly the latter two.

The critical intervals that may be observed do not correspond to the duration of these elementary processes (e.g. the length of incubation is the duration of exo-erythrocytic schizogony plus the time required for building up parasite densities above the pyrogenic threshold, which may take one or more cycles of erythrocytic schizogony). The durations of the observable intervals are shown in Table 2.2.

**Table 2.2. Durations of critical, observable intervals for the two main species of human malaria parasite**

Characteristic	<i>P. falciparum</i>	<i>P. vivax</i>
Prepatency period <sup>a</sup>	5.5 days	8 days
Incubation period <sup>b</sup> : short	9–14 days	12–17 days
Incubation period: long	Not applicable	5–18 months
Time of appearance of mature gametocytes <sup>c</sup>	8–15 days	0 days
Time of disappearance of circulating gametocytes <sup>d</sup>	8 weeks	< 1 day
Asexual cycle in the blood	48 h	48 h
Maximum duration of untreated infection <sup>e</sup>	1–2 years*	1–2 years (exceptionally, ≤ 5 years)

<sup>a</sup> From infection to the appearance of detectable parasitaemia

<sup>b</sup> From infection to the appearance of symptoms

<sup>c</sup> After the appearance of parasitaemia

<sup>d</sup> After treatment with blood schizontocides

<sup>e</sup> Assuming uncomplicated infection

### ► Do exercise 2.1.

#### 2.1.2 Aspects of vectors

##### *Life-cycle of anopheline mosquitoes*

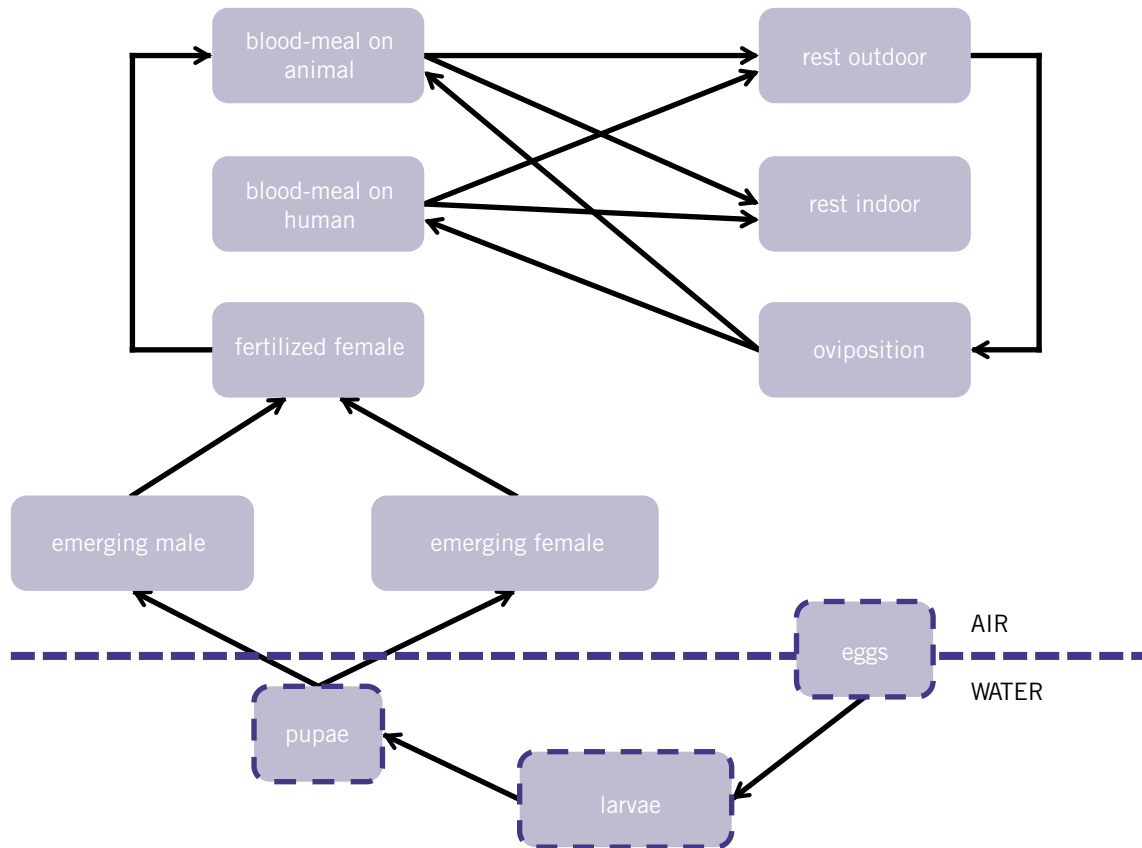
The life-cycle of the mosquito has four distinct stages: egg, larva, pupa and adult (Fig. 2.2). The development periods of the various stages depend on the ambient temperature, relative humidity and nutritional factors and are shorter at higher temperatures.

A blood-meal is necessary for maturation of a mosquito's eggs. Several batches of eggs are produced during a mosquito's lifetime, one after each blood-meal, providing several opportunities for mature females to feed on humans and thus transmit malaria.

There are about 490 species of *Anopheles* mosquitoes, including sibling species. Approximately 60–70 species worldwide can transmit malaria; of these, about 30 are vectors of major importance.

The list of known species of *Anopheles* never stops growing, with the identification of new sibling species (two species that are morphologically identical but genetically distinctly different).

Figure 2.2. Schematic representation of the malaria vector's life-cycle



### *Vector bionomics and its relation to epidemiology*

The following features are important for understanding malaria epidemiology:

- ▶ A batch of eggs develops in a female only after a blood-meal; therefore, female mosquitoes regularly move between feeding (e.g. human or animal), resting (e.g. house or vegetation) and breeding places (e.g. ponds or lake edges).
- ▶ A female mosquito moves by odour attractants to the location of the last feeding. The probability that a mosquito will return after an oviposition to the same house depends on multiple factors that are not fully understood, including distance from the breeding places and density of houses or shelters with suitable sources (human or animal) of a blood-meal.
- ▶ The time from one egg-laying to the next (the gonotrophic period) is typically 2–3 days, which is much shorter than the time required for maturation of sporozoites (about 12 days at comparable temperatures). Therefore, a female must make three or four journeys between feeding and breeding places before it becomes able to infect humans. Thus, during sporogony, a mosquito may travel a much longer distance than it does in a single gonotrophic cycle, perhaps several kilometres.



The main properties of mosquitoes that influence their efficiency (ability to transmit malaria), are (in order of importance):

- ▶ their susceptibility to malaria parasites: A mosquito with poor susceptibility cannot be a good vector, whatever its density or ability to feed on humans; some vectors transmit all plasmodial species equally well, while others are somewhat specific.
- ▶ their longevity, expressed as the probability that a mosquito will survive through 1 day (strictly speaking, 24 h): Species with a short life span and which die out before maturation of sporozoites are not vectors. The daily survival rate depends not only on the species but also on environmental conditions (e.g. predators, (micro-)climate). Under natural conditions, the daily survival rate is 75–95%, so that 5–30% survive to a potentially infective status at the ideal temperature for sporogony.
- ▶ anthropophily, defined as the preference of mosquitoes for human blood: Genetic factors influence the preference to feed on human, even when mosquitoes are subjected to the availability of other animal hosts.
- ▶ population density: Mosquitoes that can use extended surfaces for breeding, like rice fields (e.g. *An. pulcherrimus*), tend to build up high densities and may be important vectors even though they are not very efficient; in contrast, mosquitoes that use specialized breeding places, like tree holes, as is the case for *An. plumbeus*, are never very numerous.

Some species combine characteristics that are conducive to high vectorial capacity. *An. gambiae* and *An. funestus* in sub-Saharan Africa combine high susceptibility to parasites, high survival rates, anthropophily and the ability to exploit many different types of breeding places. At the other end of the spectrum is the northern European *An. messeae*, which has a short life span, is easily attracted by cattle and depends on specific larval habitats. Many rice-field breeders in South-East Asia, such as *An. philippinensis* and *An. jeyporiensis*, have a short life-span and are therefore poor vectors, despite their high densities and the favourable climate.

When there are several vector species in the same area, they often work in tandem: when environmental conditions become unfavourable for one species, another takes over, thus extending the period of transmission. An example is the pair on the Indian subcontinent, *An. culicifacies*, which prefers small, shallow water bodies and thrives during droughts, and *An. fluviatilis*, which prefers running water and proliferates during the monsoon.

Some mosquitoes have selective susceptibility to *P. falciparum* from certain areas. Thus, Palearctic vectors, which occur in Europe, North Africa and parts of western and northern Asia are refractory to Afrotropical and Indo-Malay *P. falciparum*. Therefore, elimination of *P. falciparum* is relatively easy to sustain in Europe, where the local *P. falciparum* has been exterminated, despite continuing importation of this species from other continents. It is not clear whether there are similar biogeographical barriers for *P. falciparum* in other parts of the world. Apparently, *P. vivax* from any part of the world can be transmitted by vectors in all world regions.

The following vector properties are important for vector control:

- ▶ exo- or endophagy, i.e. tendency to feed outside or inside houses;

- ▶ exo- or endophily, i.e. tendency to rest outside or within houses during blood digestion; these two characteristics may combine in different ways, yet exophagic vectors tend also to be exophilic (e.g. *An. dirus*, *An. arabiensis*);
- ▶ anthropophily or zoophily, i.e. preference for taking blood-meals on human or animal hosts; usually, zoophilic vectors tend to be exophagic also;
- ▶ biting time; and
- ▶ predilection to rest at a particular height on a wall.

These properties depend, again, on species and may be different in individual sibling species, even between populations of the same species. Generally, endophilic and endophagic mosquitoes are better controlled by IRS and to some extent also by ITNs.

Another important factor is the way vectors survive unfavourable periods of year. The mechanisms of overwintering have been studied extensively in European, North Asian and North American vectors. Most of them overwinter as adults resting inside houses. These mechanisms have been poorly studied for tropical species, which may brave long periods of droughts and low temperatures at high altitudes. Some of them overwinter as larvae.

### 2.1.3 Aspects of the human host

Malaria exercises a strong evolutionary pressure on human populations. A number of hereditary factors may mitigate the course of malaria; however, all humans are susceptible, except those with no Duffy antigen on red blood cell surfaces, who are refractory to *P. vivax*. This genotype is widespread among Africans, especially in the western part of the continent. Although there are susceptible individuals in tropical Africa, there are too few to form a sufficiently large pool to allow stable transmission of this parasite. South of the Sahara, *P. vivax* is commonly transmitted only in the Horn and some parts of southern Africa.

A number of haemoglobinopathies are balanced polymorphisms that provide some protection against malaria while having negative health effects in people not infected by malaria parasites. These include haemoglobin S, the cause of sickle-cell disease, the thalassaemias and ovalocytosis. Likewise, glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-borne trait, confers some protection against severe malaria, but it is associated with an increased risk for haemolysis in response to certain substances, including primaquine and some other medicines.

## 2.2 Geographical factors

### 2.2.1 Temperature

Temperature is the major influence on the development of mosquitoes and the malaria parasites within them. Mosquitoes are less sensitive to low temperatures than parasites: in northern Eurasia, anophelines can breed at water temperatures above 10 °C and may survive at a daily temperature of 7 °C (*An. messeae*), whereas the lower threshold for the development of parasites in the vector is much higher, i.e. 16 °C for *P. vivax* and 19 °C for *P. falciparum*. When the temperature is slightly above the threshold, the development of parasites in mosquitoes is so slow that only a few of them survive up to the infective stage. For example, at an average daily temperature of 18 °C, the development of *P. vivax* sporozoites takes about 30 days, which is well beyond the usual life

span of mosquitoes. In this case, malaria transmission is possible but only at a very low level. Extremely high ambient temperatures are deleterious to both vectors and parasites.

About 20 temperature indicators are used by meteorologists. Of these, only the average daily temperature should be retained, as the relation between this variable and the speed of development of *Plasmodia* of different species is well known.

### 2.2.2 Rainfall

Rainfall defines the availability of breeding places for many malaria vectors, which depend on the availability of collections of rainwater. These mosquito species are therefore known as “rainwater breeders”. Heavy rains may increase the proliferation of species that breed in running water and suppress those that prefer stagnant water and small pools. In semi-arid and arid areas, heavy rainfall may be followed 3–4 weeks later by epidemics.

Not only the overall amount of precipitation is important but also its rate. A heavy rain within a few hours may flush out breeding places, whereas the same amount spread over a few days is beneficial for breeding. Rainfall should therefore be monitored daily, and the total rainfall and the number of rainy days may be used as indicators.

Low rainfall by itself is not critical for malaria if there are permanent springs or rivers, wells or cisterns. Typically, malaria is present in oases in deserts, where, by definition, the amount of rainfall is < 200 mm per year. In some North African countries, oases were the last foci of malaria transmission when the rest of the countries’ territory had been freed from the disease.

In arid areas, an important indicator is the level of water in rivers. Its rise due to rainfall hundreds of kilometres away, in the highlands of Ethiopia, has been associated with epidemics in Somalia and Sudan.

### 2.2.3 Altitude

One of the most important indicators of malaria is altitude above sea level. Its relation with malaria is indirect, acting mostly through temperature. The rate at which temperature decreases with elevation is, on average, 6.5 °C per 1000 m. Use of altitude as an indicator is simpler than using meteorological records, as data on altitude are available for any geographical point and may be read from topographic maps, global positioning systems (GPS) or the Internet. Data on temperatures in a particular locality are less exact, as they are the result of interpolation of measurements from meteorological stations.

For antimalaria programmes in mountainous areas, a cut-off altitude must be identified above which there is no regular transmission of malaria. The cut-off higher altitudes for *P. vivax* in South Asia, at about 3000 m. In areas where *P. falciparum* predominates, near the equator in Africa, the cut-off is approximately 2500 m. The cut-off decreases in the direction of the poles, e.g. 2000 m in Ethiopia and Yemen, 900–1200 m in Zimbabwe and only 400 m in South Africa. When there is an unusual increase in temperature, malaria may appear even above this line, with devastating effects on non-immune populations. Furthermore, microclimatic variations may lead to quite large deviations from these approximations. Global warming appears to be associated with (so far modest) increases in the malaria risk at high altitude, as observed in Africa.

Altitude determines not only the temperature but also some other factors that may be related to malaria, such as rainfall pattern and type of breeding places. Thus, the altitude above sea level should be retained as an obligatory characteristic of any focus.

In mountainous countries, a focus may occupy a gradient of a few hundred metres, which could imply an elevated malaria risk in lower parts and a low or null risk in the upper parts of the same village, if it is located near the cut-off. Disparities also occur when villages are on top of hills and the agricultural land in fertile valleys 200–300 m below (as in Burundi and Rwanda). The malaria risk may thus be low for people who stay at home but high for those who work and spend nights on the land. Besides more rapid development in mosquitoes at lower altitude, increased exposure also plays a role, as field sheds are usually of poor quality, open to the entry of mosquitoes and often remain unsprayed.

In tropical conditions, hilly areas 200–600 m above sea level (e.g. in the Indian subcontinent, Oman and Viet Nam) are often much more malarious than the adjoining lowlands because the temperatures and rainfall are more suitable, especially when the main vectors prefer streams (“foothill malaria”).

#### 2.2.4 Hydrology, including water supply

The presence, type and distribution of water bodies are important indicators of malaria. The significance of a particular type of water body varies from one part of the world to another, depending on the vector species. By the time malaria control reaches the stage of elimination of foci, there is usually abundant information about local vector species and their bionomics, including preferred breeding places.

For example, rice fields are major breeding places for malaria vectors in Central Asian plains but are of a limited importance in the plains along the eastern coast of the Indian peninsula, where they produce mostly culicine mosquitoes and inefficient malaria vectors. The link between malaria and swamps in southern Europe has been known since Antiquity; yet, in sub-Saharan Africa, swamps usually do not play a more important role than savannah areas.

The distribution of water bodies in relation to the locality and the geographical distribution of human settlements is of great importance. When there is a large area of breeding places at some distance from a locality, cases tend to be scattered, because, as mentioned above (see “Aspects of vectors”), a mosquito that became infective is unlikely to return to the spot at which it was infected. The number of cases tends to be higher in the parts of the locality that are nearest to the breeding place.

When many small breeding places are dispersed within a locality, mosquitoes need make only short-distance trips for feeding and are more likely to return to the place they started from. Secondary cases are likely to be concentrated near the source of infection. There is a mosaic of cases: several in some households but none in many. In such cases, foci have a marked microfocal structure. This happens when there is no organized water supply, and people have to store rain- and surface water that accumulates in spring during the summer. The provision of piped water might solve the problem. Likewise, better maintenance of wells by cementing reduces moisture due to spillage and removes breeding places from villages (as in the case of *An. culicifacies* on the Indian subcontinent).

The number and maintenance status of overhead water tanks are important indicators of urban malaria on the Indian subcontinent but do not contribute to malaria transmission elsewhere, because *An. stephensi* is one of the few malaria vectors that can breed in closed spaces with neither light nor vegetation.

Many potential breeding places may be by-products of construction, irrigation and other human activities, again depending on the bionomics of local vectors.

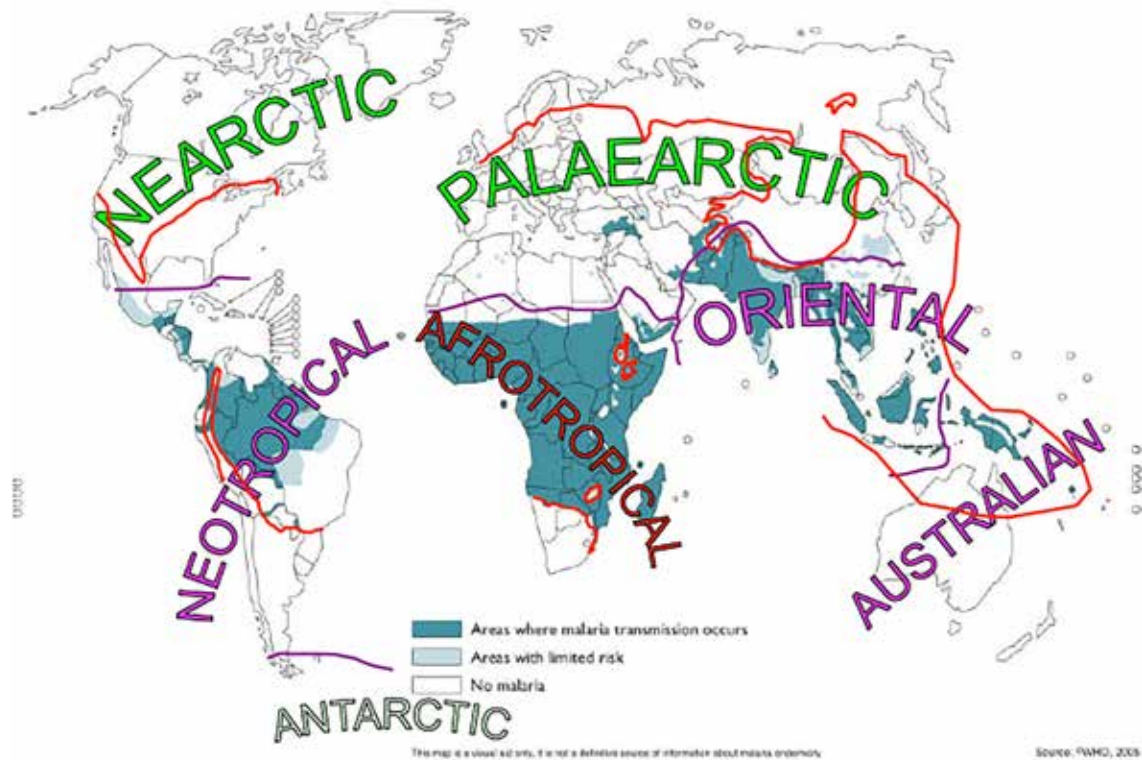
### 2.3 Ecosystems and zoogeography

The factors described above are never isolated: they play in concert, in such a way that factors related to non-living matter (abiotic factors) are integrated with those related to living creatures (biotic factors). Together, they form a unity or an ecosystem. Ecosystems are built up in a hierarchical way, so that several ecosystems at the lowest level form one ecosystem at a higher level, and so on. In other words, an ocean and a drop of water are both ecosystems, at different levels.

The ecosystem at the highest level is the biosphere as a whole. The next lower level, for fauna (including malaria vectors), is a zoogeographical region, an entity of continental or sub-continental scale, of which there are six, excluding Antarctica. These regions result from interactions among geographical barriers, physiography and evolution over millions of years, which have allowed certain genera and species to spread and adapt to varying ecological conditions within certain geographical confines. Differences among zoogeographical regions are evident. The Afrotropical region, for example, harbours a number of species of large mammals that do not exist elsewhere. This is also the case for smaller mammals, birds, insects and even helminths and parasitic Protozoa. Among the malaria vectors that do not occur outside the Afrotropical region are mosquitoes belonging to the *An. gambiae* complex (except when inadvertently introduced by humans, as happened twice in the twentieth century). In many cases, certain species occupy specific ecological niches within a zoogeographical region so effectively that species from other regions have little chance of establishing themselves if introduced. Thus, it is thought that the risk that Afrotropical malaria vectors will become established in tropical Asia is low, while the ease with which this took place in South America in the 1920s can be explained by the scarcity of local vectors occupying the same niches.

There are also similarities among zoogeographical regions, resulting from parallel evolution: the characteristics of malaria in South American rainforests are strikingly similar to those in Southeast Asia, both presenting with marked exophily of the main malaria vectors. In contrast, the vectors in forest areas of Africa are not highly exophilic; higher levels of exophily are found in the West African savannah. The observed interaction between the biogeographical regions and ecological conditions within the regions have led to the definition of malaria ecotypes.

Figure 2.3. Zoogeographical regions and malaria



Source: adapted from the map on world malaria distribution in 2007<sup>9</sup> and from the Lysenko and Semashko map<sup>10</sup> by A. Beljaev.

In Fig. 2.3, the historical limits of malaria are shown as red lines. These limits were reached by malaria in the late nineteenth century in Europe and North America and by the mid-twentieth century in Australia, the former USSR and South America. The following features of the global distribution of malaria should be retained:

- ▶ The northern limits of the historical area of distribution of malaria are further from the Equator than the southern limits, due mostly to the fact that the Southern hemisphere is colder than the Northern hemisphere.
- ▶ The lacunae are due to the absence of malaria at high altitudes and/or in arid areas.
- ▶ The spread of malaria to the north is limited by low temperatures and not by the absence of vectors: anophelines occur in some areas beyond the Arctic circle.
- ▶ The northern limit of the area of distribution is nearer to the pole in continental Eurasia than in western Europe because malaria depends on the temperatures in the hottest months of the year rather than on the average yearly temperature.
- ▶ The eastern part of Oceania is malaria-free, despite a favourable climate, because of the absence of anopheline mosquitoes that failed to reach those islands. The limit of their distribution in Oceania is called the “Buxton line”.

<sup>9</sup> Global malaria control and elimination - Report of a technical review, page 19. Geneva: World health Organization, 2008 (<http://www.who.int/malaria/publications/atoz/9789241596756/en/>)

<sup>10</sup> Lysenko AY and Semashko IN. Geography of malaria. Medical Geography 1968. Pages 25-146 (<http://www.who.int/malaria/publications/atoz/lysenko/en/>)

The patterns of malaria in the six zoogeographical regions are different, even in similar climates. More important for the issue of malaria elimination is that malaria in some zoogeographical regions is much more tenacious than in the others. This is evident in countries crossed by biogeographical boundaries: malaria prevails in the south-eastern part of the Islamic Republic of Iran, which belongs to the Oriental region, but not in the rest of the country. The same applies to the Afrotropical southwest of Saudi Arabia but not in other areas of the same country. In the Afrotropical region, the overall limits of malaria did not change much during the twentieth century, although the structure of the area of distribution did. Because of different degrees of resilience of malaria vectors to control measures, the prospects for elimination are very different (Table 2.3).

**Table 2.3. Zoogeographical regions of the world and technical feasibility of malaria elimination**

Zoogeographical region	Malaria species present and technical feasibility of elimination
Palaeartic and Nearctic	Only <i>P. vivax</i> at present: elimination is feasible everywhere.
Neotropical and Oriental	<i>P. vivax</i> and <i>P. falciparum</i> roughly at par: elimination is feasible in some areas but will be very difficult in forested areas in much of South-East Asia and South America and urban areas on the Indian subcontinent.
Australasia	Elimination was achieved in Australia but will be very difficult in areas with favourable ecological conditions and multiple, efficient vectors, as in Papua New Guinea.
Afrotropical	<i>P. falciparum</i> overwhelmingly predominant: Elimination is not feasible with existing tools, except on some islands, in mountain and desert fringe areas, at the southern fringe and in some urban areas.

► Do exercises 2.2 and 2.3.

## 2.4 Dynamics of malaria transmission: a simple mathematic model

What is measured by standard epidemiological methods is not always proportional to the intrinsic variables that govern malaria transmission. For example, an increase in the intensity of transmission (as measured by the number of infective mosquito bites) does not often lead to a proportional increase of incidence or prevalence, because there is a state of saturation, when additional infective bites are received mostly by people who are already infected. The main objective of elimination is to interrupt transmission; to determine what is required, it is therefore necessary to evaluate measures and determinants of malaria transmission that are not directly observable.

### 2.4.1 Basic assumptions

A number of mathematical models of malaria have been proposed, starting from the first, published by Ross in 1910. So far, no model fully describes the interaction of all the factors that determine malaria transmission, because of the extreme complexity and diversity of the parasitic system. Here, we present the model of transmission dynamics developed by Macdonald in the 1950s<sup>11</sup>, because it demonstrates the influence of several important entomological and parasitological determinants. The simplifications and assumptions must be well understood; otherwise, the conclusions from modelling will be misleading. In this particular model, the following assumptions are made.

<sup>11</sup> Macdonald G. 1956. Epidemiological basis of malaria control. Bull World Health Organ 1956;15: 613–626

- ▶ Within a given area, there is a system of interacting populations of malaria parasites, vectors and humans, each belonging to only one species.
- ▶ There are no migrations in and out of the area.
- ▶ The uninfected or infected status of each person can be ascertained.
- ▶ All humans have the same susceptibility to infection.
- ▶ The behaviour of the vectors in relation to hosts, resting places and breeding sites is uniform, with no seasonal variation.
- ▶ The mortality of the vectors does not depend on their age (the probability of dying within 1 day is constant over the animal's life span).
- ▶ The presence of parasites in the mosquitoes does not influence their mortality or behaviour.
- ▶ An infected person becomes infective to mosquitoes as soon as symptoms start.
- ▶ Infected people get rid of parasites at a constant rate that does not depend on the duration of the infection.

All these assumptions are simplifications. Still, a model based on these assumptions greatly helps in understanding malaria transmission, how it depends on entomological variables and how different vector control interventions affect transmission. The basic model can be improved by introducing more realistic assumptions, such as heterogeneity and access to treatment, but it then becomes more complex.

## 2.4.2 Variables

### *Entomological inoculation rate*

In the epidemiology of infectious diseases, the variable that determines all the observable phenomena is the force of infection. The exact interrelation between the force of infection and epidemiological parameters depends on the natural history of the particular infection, e.g. susceptibility of humans and vectors, longevity of the parasite and immunity.

The best measure of the force of infection in malaria is the entomological inoculation rate: the number of mosquito bites containing sporozoites (inoculations) received by the population in a given time. It is often expressed as the number of infective bites per person per day or per year. Although this rate can be measured, the measured value differs from the true value because of factors such as errors of sampling and the heterogeneity of humans and vectors. In the past, the entomological inoculation rate was measured by human landing catches. This method is no longer considered ethical on a large scale and has been replaced by various trapping methods, which add considerable uncertainty to the measurements. In areas of low transmission, the number of infected vectors and mosquito densities may be so low that it becomes practically impossible to measure the rate with adequate precision.

### *Vectorial capacity*

Vectorial capacity is defined as the potential number of secondary cases originating from one primary case in 1 day, assuming that the human population is, and remains, fully susceptible



(no immunity). The term refers to the effectiveness of a local mosquito population<sup>12</sup> to transmit malaria and not to the amount of malaria (or malaria transmission) in a population, although the human host is the beginning and end of the sequence of events leading to transmission.

Understanding the concept of vectorial capacity helps to understand the factors that determine malaria transmission and is therefore important for planning malaria control strategies.

The definition of vectorial capacity presented here includes the word “potential”. If a malaria patient is present in the area, vectorial capacity is the number of cases that could potentially originate from that person per day. *It is a characteristic of the population of vectors in an area; parasites are not necessarily present.* In other words, vectorial capacity can be calculated for regions in which there are anopheline vector mosquitoes but no malaria. It is a measure of the entomological dimension of *malaria risk* but not malaria transmission (although a high vectorial capacity is a precondition for intense transmission). Vectorial capacity is an entomological measure but is strongly influenced by human ecology: it is lower than it would otherwise be, for example, if people live in screened houses and/or at a distance from mosquito breeding sites.

### Basic reproduction rate

The basic reproduction rate is the number of secondary cases that could potentially originate from one primary case throughout a patient’s infectivity, assuming that the community is, and remains, fully susceptible to malaria infection, in the absence of deliberate control measures. Note that the basic reproduction rate is the potential number of new infections in a fully susceptible population and not the actual expected number at any time (which will be much lower when the population is not fully susceptible).

### Relation between vectorial capacity and basic reproduction rate

According to the definitions:

$$R_0 = C \times D$$

where  $R_0$  is the basic reproduction rate,  $C$  is vectorial capacity, and  $D$  is the number of days an infected person can transmit the disease (is infective to mosquitoes).

The duration of infectivity is in fact highly variable. Mathematically, this measure is best handled as the inverse of a patient’s recovery rate for the infective status ( $D = 1/r$ ), where  $r$  is the proportion of infective people who become non-infective per day (or lose infectivity per day). This is based on the assumption that  $r$  is constant over the lifetime of an infection and that recovery is irreversible. The concept of recovery rate is clear in the case of *P. falciparum*, where parasites are present in the blood from the beginning to the end of the infection, but not for *P. vivax* where parasites are not present in the blood most of the time but are dormant in the liver as hypnozoites.

As  $D = 1/r$ , the formula above can be written as:

$$R_0 = C \times \frac{1}{r} \text{ or } R_0 = \frac{C}{r}$$

The assumptions about recovery rates are approximations for untreated infections. A few studies of recovery rates in untreated cases indicate that the natural recovery rate from falciparum malaria

<sup>12</sup> Note that vectorial capacity refers to effectiveness of the mosquito population present in a given area at a given time, in contrast to vector efficiency, which refers to the suitability of a particular vector species to transmit malaria, irrespective of its density. A highly efficient species may be associated with high vectorial capacity even at low density.

is 0.05 per day, corresponding to a duration of infection of 200 days. If *all* cases are symptomatic and are *effectively* treated soon after the appearance of symptoms, the duration of infectivity (see Table 2.1) is obviously much shorter.

*Example:*

If a malaria case carries gametocytes in the blood (i.e. is infective) for only 14 days and directly adds five new cases to the community every day, the case would add  $14 \times 5 = 70$  new cases. In this example, the vectorial capacity is 5 per day and the basic reproduction rate is 70. If the duration of infectivity is reduced by treatment to an average of 0.5 days,  $R_0$  will be only 2.5. Note that the basic reproduction rate reflects only about one generation of cases. According to the model, each of those cases will cause just as many secondary cases, as long as the great majority of people are susceptible and not infected.

*Derivation of vectorial capacity and basic reproduction rate*

*Factors composing vectorial capacity:*

The formula for vectorial capacity illustrates the relation between the factors involved in transmission, which can be described as the following stages:

- ▶ Stage 1: The primary, infective case is bitten by a certain number of vectors per day.
- ▶ Stage 2: A fraction of these vectors acquire the infection. Not all mosquitoes will become infected by sucking blood from an infective patient. Many variables affect this process, resulting in a probability for transmission of infection to the insect of  $< 100\%$ .
- ▶ Stage 3: Some of the mosquitoes that have sucked blood survive the extrinsic incubation period (the time it takes the parasite to develop into sporozoites in the mosquito) and become infective.
- ▶ Stage 4: The infective mosquitoes will live for a certain time, during which they will bite a constant number of humans per day.
- ▶ Stage 5: A fraction of bitten humans acquire the infection and become secondary cases of malaria. As for the mosquitoes, the probability that the infections will be transmitted from mosquito to human is  $< 100\%$ .

*Creating a formula for vectorial capacity:*

- ▶ Stage 1: The mosquito–human contact can be defined as the “human-biting rate”. The number of female mosquitoes that bite humans daily depends on the number of available female mosquitoes per person (vector intensity),  $m$ , and the human-biting rate,  $a$ , which is the number of humans bitten per mosquito per night. The human-biting rate is thus the product  $ma$ :

$$ma = \text{number of bites per human per night by available vectors.}$$

- ▶ Stage 2: The probability that infection will pass from an infectious human to a mosquito when it bites the human is denoted by  $c$ , which is  $< 1$ .
- ▶ Stage 3: The probability that a vector will survive sporogony is the number of mosquitoes that have sucked blood and live long enough to complete the sporogonic cycle, which depends on (1) the mortality rate of mosquitoes,  $g$ , which, like the recovery rate of humans, is the reciprocal

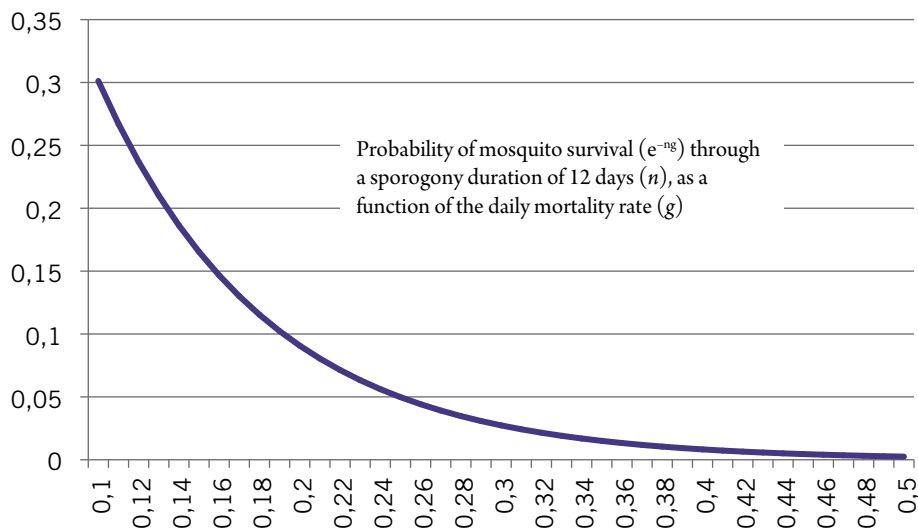
of the expected duration of a mosquito's life; and (2) the duration of the extrinsic incubation period,  $n$ .

The probability that a mosquito will survive the extrinsic incubation period is then:

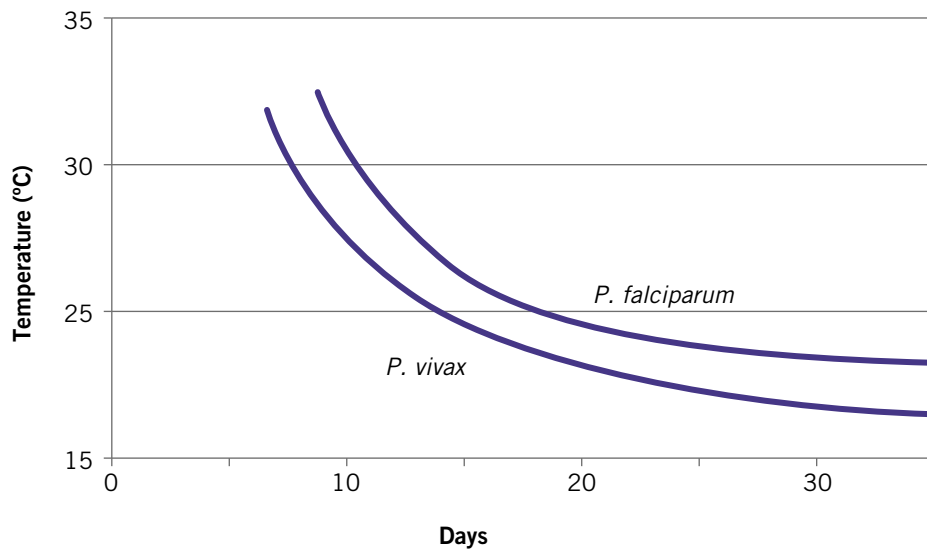
$$e^{-ng}$$

where  $e$  is the base of the natural logarithm (2.718... often written as  $\ln$ ), as it is assumed that mosquitoes die at a constant exponential rate for a duration of  $n$ . In Excel software, as formulae have to be written in one line, the above expression would be  $\exp(-ng)$ . Note that  $n$  and  $g$  must have the same units of time (for example, days). The longer the extrinsic incubation period and the higher the mosquito's mortality rate, the lower the probability that it will survive long enough to transmit. Fig. 2.4 shows an Excel-generated curve, with the probability of survival =  $e^{-12g}$  as a function of  $g$ .

Figure 2.4. Excel-generated curve with the probability of survival =  $e^{-12g}$  as a function of  $g$



- ▶ Stage 4: The expected number of bites from infectious mosquitoes is the product of the expected lifespan of infectious mosquitoes and the biting rate of mosquitoes. The expected life span of any mosquito (irrespective of its age) is the inverse of the mortality rate,  $1/g$ , as described earlier. Additionally, “the number of blood-sucking events on humans per mosquito per day”,  $a$ , is added to the formula *for the second time*, as the expected number of bites on humans by an infectious mosquito is  $a/g$ .
- ▶ Stage 5: The probability that infection will pass from an infectious mosquito to a human when it bites the human is denoted by  $b$ , which is  $< 1$ .



Insert 1.  $n$  as a function of temperature<sup>9</sup>

We can now present each stage mathematically:

Stage 1:  $m \times a = ma$

Stage 2:  $c$

Stage 3:  $e^{-ng}$

Stage 4:  $a/g$

Stage 5:  $b$

and derive  $C$  as the product of all these:

$$C = \frac{ma^2bce^{-ng}}{g}$$

or, in Excel notation,  $C = m^*a^2*b*c*\exp(-n*g)/g$ .

In the notation used by Macdonald<sup>9</sup> and Garrett-Jones<sup>13</sup>, the vectorial capacity was represented as,

$$C = \frac{ma^2bcp^n}{-\log_e p}$$

where  $p$  is probability of a mosquito surviving 1 day. The two formulae are equivalent, with the change of variables  $p = e^{-g}$ .

<sup>13</sup> Garrett-Jones C. Prognosis for interruption of malaria transmission through assessment of mosquito's vectorial capacity. Nature 1964; 1173-1175.

### Derivation of the formula for “basic reproduction rate”

The basic reproduction rate, it is recalled, is the vectorial capacity multiplied by the duration, in days, of a malaria patient’s infectivity, equal to the vectorial capacity divided by the daily recovery rate,  $r$ , of infectivity:

$$R_0 = \frac{C}{r} = \frac{ma^2bce^{-gn}}{gr}$$

Note that the unit of both  $C$  and  $r$  is  $\text{day}^{-1}$ , while  $R_0$  is dimensionless.

Macdonald<sup>14</sup> devised the following explanation of the basic reproduction rate:

One may imagine an individual suffering from falciparum infection, who is infective to all the mosquitoes which feed on him during 80 days (or half of those that feed on him for 160). If 10 bite each day he originally infects 800 mosquitoes. These might have a probability of survival during one day of 0.9; if the temperature were such that the extrinsic cycle lasted 12 days, 28 per cent of these would survive to the development of sporozoites and they would have a subsequent expectation of life of 10 days. If the mosquito were entirely anthropophilic, feeding once every two days on man, the survivors would on the average each convey the infection to five people. Through this mechanism 1,120 infections might be distributed in the population from the primary case.

Note that, even for *An. gambiae*, the daily survival rate and the human-biting habit are unusually (though not unrealistically) high.

### Vectorial capacity, basic reproduction rate and control of transmission

The following control measures can affect the components of vectorial capacity:

- ▶ IRS, which reduces  $m$  and  $1/g$  (increases  $g$ ) and may also reduce  $a$  if the insecticide has a repellent effect;
- ▶ space spraying, source reduction and larviciding, which reduce  $m$ ;
- ▶ reduction of human–vector contact, which reduces  $a$ ;
- ▶ impregnated mosquito nets, which reduce  $m$ ,  $a$  and  $1/g$  (increases  $g$ ); and
- ▶ treatment of cases, which increases  $r$  (decreases  $D$ ).

The magnitude of the basic reproductive ratio is affected by variation in the different factors listed above, as follows:

- ▶ reduction of  $m$  reduces  $C$  (or  $R_0$ ) in the same proportion;
- ▶ reduction of  $1/r$  reduces  $R_0$  in the same proportion;
- ▶ reduction of  $a$  is amplified by squaring  $a$  in the formula; and
- ▶ the increase of  $g$  is amplified much more by the exponential form of the survival of the mosquito through the extrinsic incubation period ( $e^{-gn}$ ), with  $n = 8$  or 10 for *P. falciparum* at high temperature, in addition to the reduction in longevity,  $1/g$ .

<sup>14</sup> Pampana E. A textbook of malaria eradication. London: Oxford University Press; 1963.

The actual reductions in the relative efficacy of different control measures depends on the values of all the parameters in the formulae above; however, analysing the expression for  $C$  and  $R_0$  provides more general information. For example, most parameters appear linearly in the equations; so, reducing the mosquito-to-human ratio ( $m$ ) by a factor of 2 reduces the vectorial capacity (and the basic reproduction rate) by a factor of 2. But the mosquito biting habit,  $a$ , appears as a square; so, reducing  $a$  by a factor of 2 reduces the vectorial capacity by a factor of 4. The mosquito mortality rate,  $g$ , appears in the denominator and in the exponential; so, increasing  $g$  by a factor of 2 can decrease the vectorial capacity by a factor far greater than 2, depending on the value of  $n$ . Therefore, interventions that reduce contact between humans and mosquitoes or kill adult mosquitoes are much more effective than interventions that reduce only the number of mosquitoes.

*Typical values of the parameters used in calculation of vectorial capacity:*

$m$ : 0 to several hundred

$a$ : the product of the daily human-biting rate, which may vary from 0.2 to 0.5 (higher at high ambient temperatures) and the human blood index, which may vary from 0 (complete zoophily) to 1 (complete anthropophily)

$b$  and  $c$ : difficult to measure and usually set to 1; however, some studies suggest that  $b$  is much lower; this is one reason that these calculations should not be used to make predictions but to understand malaria transmission.

$g$ : see Table 3 in Kiszewski et al. (2004),<sup>15</sup> which gives daily survival rates of 0.7–0.9, corresponding to values of  $g$  from 0.1 to 0.3.

$n$ : may vary from 12 to 20 days depending on the parasite species and temperature (see insert 1).

### 2.4.3 Inference

*Limitations of the model*

Some of the assumptions underlying the model can be analysed qualitatively as follows:

- ▶ *Heterogeneity*: Malaria transmission is not homogeneous. Some people are intrinsically more attractive to mosquitoes and thereby more susceptible to malaria or more infectious to mosquitoes. Some mosquitoes are more robust and survive longer than others, and others are more susceptible to malaria. Breeding sites and human settlements are not distributed uniformly. When interventions with < 100% coverage are targeted carefully, to “hotspots”, in a heterogeneous environment, they are more effective than they would be if spread evenly. Therefore, heterogeneity can be used advantageously in prevention, if detailed data on malaria distribution are available.
- ▶ *Seasonality*: Almost everywhere, malaria transmission varies seasonally because of variations in rainfall and temperature. The appropriate timing of interventions can greatly increase their effectiveness. As a general rule in the tropics, IRS with insecticides that are effective for only a few months should be conducted just before the start of the rainy season so that the population is protected throughout the period when mosquito densities would otherwise be highest. In temperate areas, IRS is most effective when carried out just before the onset of

<sup>15</sup> Kiszewski A, Mellinger A, Spielman A, Malaney P, Sachs SE, Sachs J. A global index representing the stability of malaria transmission. *Am J Trop Med Hyg* 2004;70:486–98.

the season of effective temperatures (See learning unit 5). Mass drug administration should be conducted when the mosquito density (or malaria burden in mosquitoes) is at its lowest.

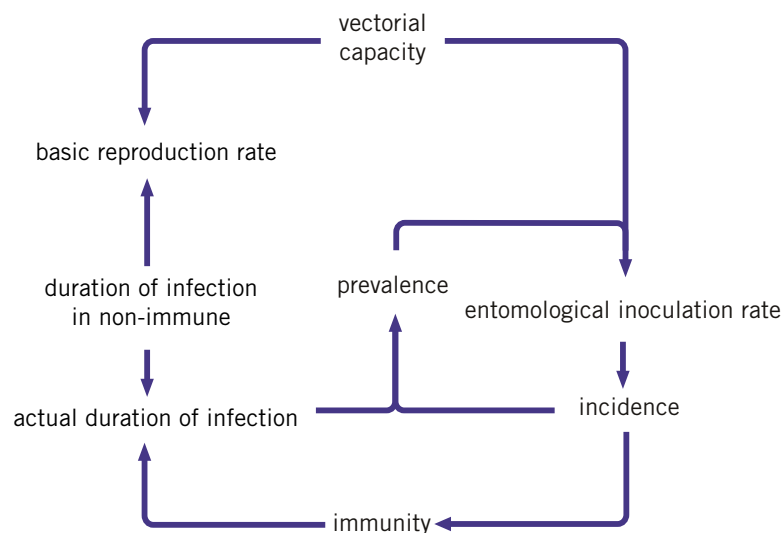
- *Migration*: In high-transmission settings, the movement of people or of mosquitoes with malaria is usually small relative to the malaria burden in the population. In planning for elimination, the importation of new cases becomes increasingly important. See learning units 6 and 8.

Furthermore, the *effectiveness* of interventions in controlling or eliminating malaria depends on multiple biological and operational factors, which are discussed in learning unit 8.

### *Qualitative relations among the dimensions of intensity of malarial infection and its transmission*

The vectorial capacity and the prevalence together determine the entomological inoculation rate. This determines the incidence rate, which in turn determines the level of immunity in humans. Immunity, together with the basic (non-immune) recovery rate and treatment, determine the actual recovery rate (i.e. the actual duration of infection). The incidence rate and the actual recovery rate together determine the prevalence rate, while the vectorial capacity and the duration of infectivity in non-immune people together define the basic reproduction rate (Fig. 2.5).

**Figure 2.5.** Relations among measures of intensity



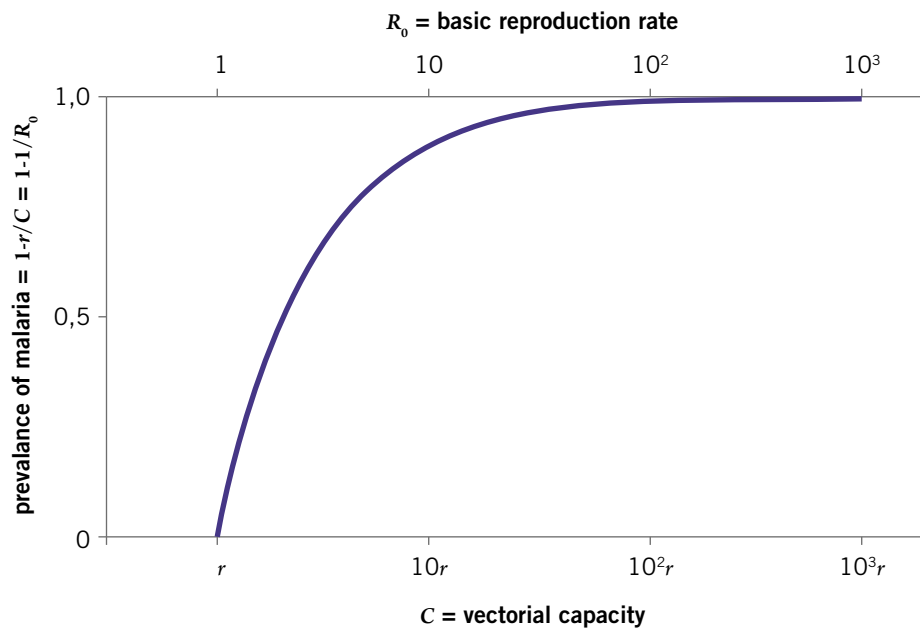
One out of this dizzying array of relations deserves to be highlighted. From a model originally developed by Ross, it is possible to show that, at steady state, the prevalence of malaria,  $y$ , has a simple relation to vectorial capacity and basic reproduction rate:

$$y = 1 - r/C, \text{ or}$$

$$y = 1 - 1/R_0,$$

using the same terms as above. The graph of these equations is shown in Fig. 2.6. Those interested can request documentation on the derivation from the tutor.

Figure 2.6. Relations between prevalence and basic reproduction rate, vectorial capacity and recovery rate<sup>16</sup>



As seen in Fig. 2.6, a rise in vectorial capacity leads to an increase in prevalence, to a maximum value close to 100%. Immunity is not considered and, in fact, at very intense transmission, prevalence tends to be lower in adults. The non-linear relation helps to understand the role of vectorial capacity. If the biological, human and ecological determinants favour a high vectorial capacity in an area, it is always at the plateau part of the curve. Here, a modest change of vectorial capacity in either direction due to control or weather will not significantly change the prevalence. Malaria is stable. At low-to-moderate vectorial capacity, however, when the slope of the curve is sharp,  $y$  is highly sensitive to changes in vectorial capacity. Malaria is unstable, more controllable but also more prone to epidemics.

In recent years, malaria-endemic areas with high prevalence rates are often said to be characterized by “high stable transmission”. This term is typically applied to rural malaria in Africa and what is meant is probably that transmission is stable. This term, however, blurs the conceptual specificity of Macdonald’s notion of stability. Not only is transmission intense in stable malaria but also the vectorial capacity is so high that there is oversaturation of the human hosts with frequent superinfections, so that a major reduction in vectorial capacity will be required before there is a change in prevalence, although morbidity and mortality may be reduced, for example by use of ITNs. The concept of malaria stability was much used in the Global Malaria Eradication Programme, but it has several weaknesses. First, it is hard to link decision-making to the broad range of intermediate stability; secondly, important determinants of the resilience of malaria transmission, such as exophily of the vector and population movement, are not captured.

Another important element of the graph is the point of intersection with the vectorial capacity axis. This is the point where  $C$  is equal to  $r$ . The fact that vectorial capacity is not equal to 0 at the point of intersection implies that, in order to eliminate malaria in a region, vectorial capacity

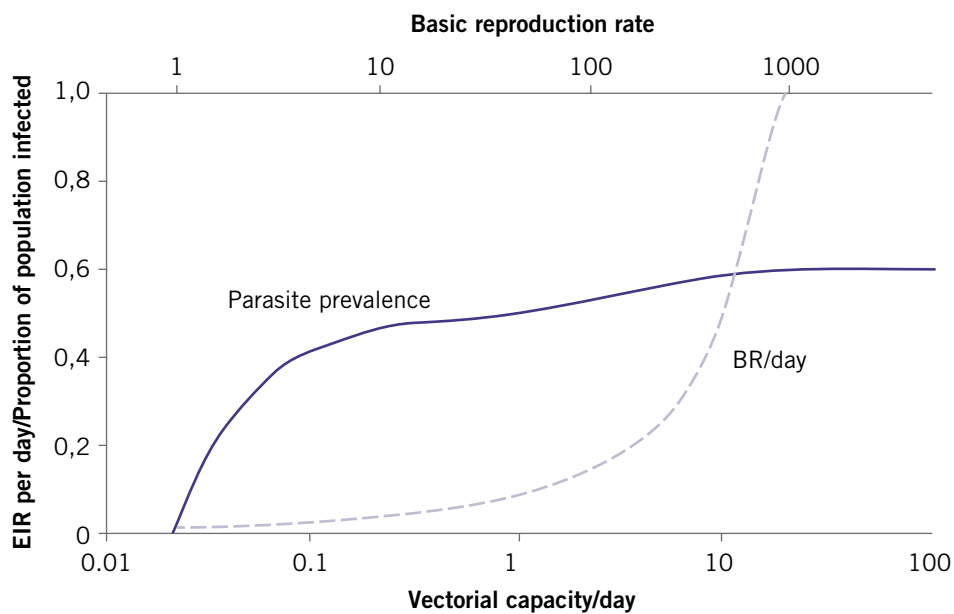
<sup>16</sup> Molineaux L. The epidemiology of human malaria as an explanation of its distribution, including some implications for its control. Chapter 35 In: Wernsdorfer WH, McGregor I. Malaria. Principles and practice of malariology, vol. 2. Edinburgh: Churchill Livingstone; 1988.



does not necessarily have to reach 0. In other words, elimination of malaria in a region does not depend on complete elimination of the vector. This critical value of vectorial capacity below which transmission is interrupted is traditionally represented by  $C^*$ . Malaria transmission occurs as long as  $r$  is smaller than  $C$ . If  $r$  is  $\geq C$ , the disease will disappear.

Fig. 2.7 shows again prevalence as a function of vectorial capacity but on the basis of a more comprehensive model, which also allows demonstration of the entomological inoculation rate as a function of vectorial capacity.<sup>17</sup> It is seen that, at low-intensity transmission, the entomological inoculation rate is not sensitive to changes in vectorial capacity; the opposite is the case at high levels of vectorial capacity.

**Figure 2.7.** Relations between vectorial capacity, basic reproductive rate, entomological inoculation rate per day and prevalence of patent parasitaemia<sup>18</sup>



<sup>17</sup> Dietz K. A malaria model tested in the Africa savannah. *Bull World Health Organ* 1974; 50:347-57.

<sup>18</sup> Molineaux L. The epidemiology of human malaria as an explanation of its distribution, including some implications for its control. Chapter 35. In: Wernsdorfer WH, McGregor I. *Malaria. Principles and practice of malariology*, vol. 2. Edinburgh: Churchill Livingstone; 1988.

### Box 2.1. Conclusions on transmission dynamics

- ▶ There is a non-zero critical value of vectorial capacity below which malaria cannot maintain itself in an area ( $C^*$ ). This implies that malaria can disappear without the elimination of all vectors.
- ▶ The relation between the prevalence of malaria and vectorial capacity is not linear. Near the critical value, minor changes in vectorial capacity lead to major changes in prevalence, i.e. malaria is unstable; but, at higher levels of vectorial capacity, even large changes in vectorial capacity will not affect the high prevalence, i.e. malaria is stable. Prevalence alone does not predict whether malaria is stable, because high prevalence may be compatible with moderate or high vectorial capacity. Stable malaria is present if vectorial capacity is high, which is the case when the climate is favourable for malaria and vectors are long-lived, with a high human-biting habit.
- ▶ In the absence of population movement, a risk for epidemics is present near the critical value at which malaria is unstable. It is near this critical value, however, that vector control has a significant effect and elimination is likely to be possible.
- ▶ The critical value for vectorial capacity, represented by  $C^*$ , occurs when the vectorial capacity and recovery rate  $r$  are equal. Thus, the critical vectorial capacity below which the transmission cycle is interrupted is lower for *P. vivax* than for *P. falciparum*. It is more difficult to eliminate *P. vivax* than *P. falciparum*, everything else being equal.
- ▶ At low levels of transmission, the entomological inoculation rate is an insensitive measure of transmission intensity—apart from being difficult to measure with precision. Malaria prevalence is much more sensitive, although, for practical reasons, malaria incidence becomes more useful when the prevalence falls below 5%. At high levels of transmission (stable malaria), the opposite is the case: the entomological inoculation rate reflects changes in vectorial capacity well, while prevalence is insensitive.

## Unit 2 exercises

### Exercise 2.1

*Comparing the natural history and epidemiology of two species of malaria*

Analyse the biological traits of vivax and falciparum malaria that are responsible for major distinctions in their natural history and epidemiology. Organize the information in tabular form using the template below (one row has been filled as an example).

**Template for comparison of two species**

Trait	<i>P. falciparum</i>	<i>P. vivax</i>	Inference
1. Presence of hypnozoites	Always absent	Usually present	Long latency in <i>P. vivax</i> , with phenomena of long incubation and true (exo-erythrocytic) relapses (Add epidemiological features that follow from the long latency)
2.			
3.			
4.			
5.			
6.			
7.			
8.			

Summarize the data, and describe the main features of vivax and falciparum malaria epidemiology. Group those that are similar in the two species and those that are divergent.

Which species is easier to eliminate in your area? Discuss your findings in plenary.

**Exercise 2.2**

*Factors that determine transmission of malaria*

Identify the factors in the area in which you work that are most important in the local epidemiology of malaria. Consider human, parasitological, entomological, environmental and health system factors. It may be a good idea to present a map, as the main determinants may vary geographically.

**Exercise 2.3**

*Geography of malaria*

Examine the map (Fig. 2.3). Compare the red line, representing the limits of the distribution of malaria during the time of its maximum extent, with its present distribution (blue shading).

*Questions for discussion*

- ▶ Enumerate the geographical and ecological factors that limit the area of distribution of malaria.
- ▶ Why did the area of distribution of malaria contract to different degrees on different continents?
- ▶ Describe the patterns of malaria encountered in the zoogeographical region you know best.

**Exercise 2.4**

Open the file “Exercise 2\_4.xls”, which is an MS Excel spread sheet with all the instructions included. Essentially, it represents the formula of vectorial capacity shown above that will allow the computations, depending on the numerical values of the parameters you choose. Play with the figures. Identify the parameters that influence the vectorial capacity best. Use ranges of values that would apply in the area in which you work, then reduce these values through various vector control interventions. Discuss your findings in plenary.



# LEARNING UNIT 3

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## Road map to elimination: from advanced control to the prevention of reintroduction

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### Learning objectives

By the end of this Unit, the participants should be able to:

- Describe the continuum of malaria control to elimination
- Explain the objectives of each programme phase
- Describe the major programme reorientations and approaches, from malaria control to elimination to prevention of reintroduction
- Identify major programme transition milestones, interpret them, and discuss their limitations

## Reading material

Before starting this learning unit, you should read Chapter 2 of *Principles and practice of malaria elimination* and annexes 2 and 3 of *Malaria elimination. A field manual for low and moderate endemic countries*.

This learning unit deals with programme reorientation from control to elimination and from elimination to the situation in which a country or area is recognized as malaria-free and reintroduction must be prevented.

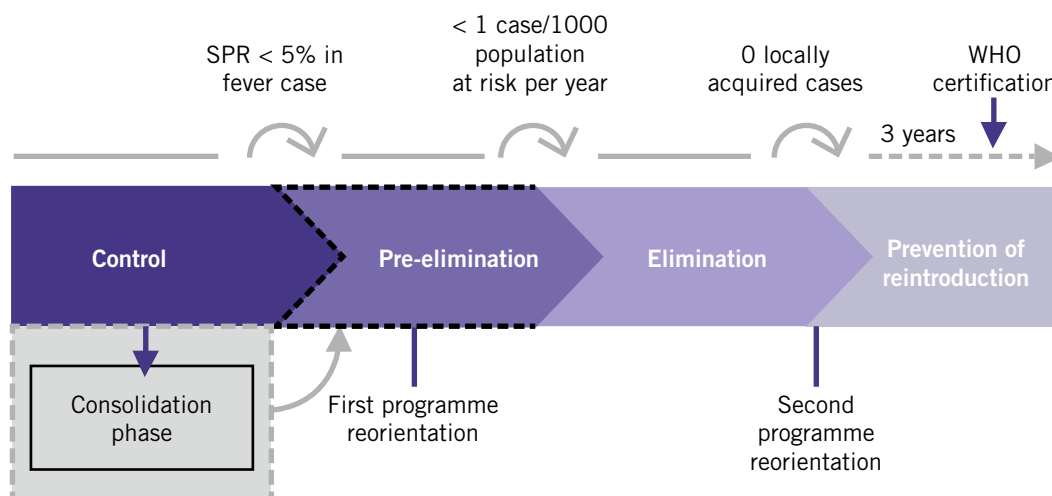
### 3.1 Continuum of malaria control to elimination

Depending on local conditions and available resources, a malaria programme may take many different forms (phases); malaria elimination can be considered one of them. In some cases, the local parasitic system of malaria is so strong (see learning unit 2) that interruption of malaria transmission is impossible with existing tools. This does not mean that nothing should be done. The potential impact of antimalarial action in these settings, in terms of decreases in mortality and incidence, may be much larger than the impact on mortality and morbidity of elimination activities in populations of a similar size with a low malaria burden.

Elimination of malaria is an option, not an obligation. It can be envisaged when a malaria control programme is succeeding in reducing the burden of mortality and morbidity to marginal levels. Fig. 3.1 provides an overview of the continuum from control to elimination.

When countries in areas of previously high transmission have achieved a marked reduction in malaria transmission, the first objectives are to sustain the control achievements and progressively to augment coverage of interventions in target populations, ensuring that health services are equipped to deal with the changing clinical and epidemiological situation. In some cases, it may be found after some years of control, including strong surveillance, that the epidemiological and contextual situation has changed to an extent that it is possible to consider elimination.

Elimination can be undertaken at subnational level. This is particularly relevant for large countries and for countries in which some areas are isolated, such as island countries. Elimination can be an attractive option in a local perspective, as it may help attract investments and tourists. National programmes should not, however, prioritize elimination in low-burden areas to the detriment of control in high-burden areas.

**Figure 3.1. Malaria programme phases and milestones on the path to malaria elimination**

SPR, slide or rapid diagnostic test positivity rate

These milestones are indicative; in practice, the transitions will depend on the malaria case load that a programme can realistically handle and on a feasibility assessment

Country elimination success is driven by ministries of health and reflects sustained national commitment to public health, often over several decades. The decision to embark on elimination should not be taken lightly. There may be pressure from some quarters to proceed to elimination without a feasibility analysis; however, such a decision can lead to waste of resources and compromise the idea of eliminating malaria (and other diseases, which might actually be eliminated locally) and even malaria control.

### 3.1.1 Advanced control phase

Elimination is not yet considered feasible, but it is considered possible that it will be in the future, i.e. no biological determinants contradict the possibility of elimination with existing tools. (See learning units 2 and 8.)

Antimalarial activities should be continued, adapted to changing epidemiological realities (in many cases, a change in vulnerable groups and age profile) and intensified, with particular reference to the following.

*Strengthen malaria control*, for example by:

- ▶ ensuring appropriate infrastructure, such as health facilities, offices and stores;
- ▶ improving the malaria surveillance system;
- ▶ attaining universal health coverage of target populations;
- ▶ ensuring uninterrupted supplies and equipment;
- ▶ training health providers and promoting the health education of the population;
- ▶ intensifying collaboration with the private sector; and
- ▶ introducing new, cost-effective tools.

Strengthening malaria control requires a local situation analysis. It may be rational, for example, to improve the quality of outpatient services, ensuring that every febrile patient who does not have other obvious causes of fever is tested with laboratory tests for malaria, and to prevent stock-outs and enhance collaboration with the private sector. It will not be possible to introduce key elimination approaches like case investigation with house visits if health workers are already overloaded. Similarly, close follow-up for outpatient malaria cases will have no impact on transmission if most patients obtain their treatment from unregulated street pharmacies.

*Collect evidence for planning possible future elimination:*

- ▶ collection of basic information on vulnerable population groups, parasites and vectors;
- ▶ mapping information on climate, landscapes, hydrology, breeding places, transmission foci, coverage of health services;
- ▶ monitoring coverage and documenting the success and failure of operations;
- ▶ stratification to identify areas suitable for elimination;
- ▶ using results of applied field research and other research; and
- ▶ identifying potential health system weaknesses and how these can be addressed (e.g. health service coverage).

### 3.1.2 Pre-elimination phase

Pre-elimination is a stage of *transition* or reorientation of a malaria programme. The programme should be reoriented towards elimination approaches, indicators, operational and surveillance systems and progressively move from total coverage to selective use of vector control interventions. Pre-elimination denotes a dynamically changing programme and not a static situation. Malaria programmes do not “achieve” pre-elimination status, they go through it.

#### *Criteria for entering the pre-elimination phase*

As a broad indication, programme reorientation may become possible in areas where not more than 10 malaria cases occur per week per district (or up to 500 cases per 100 000 persons per year), and competent staff are available to deal with the additional workload. Roughly, this corresponds to a situation in which high-quality health facility data indicate that the monthly positivity rate from slides or rapid diagnostic tests (RDTs) among patients with suspected malaria is consistently < 5% throughout the year. Before embarking on programme reorientation in such areas, it is advisable to *confirm in a population-based survey during the peak transmission season* that the malaria parasite rate is indeed low, for instance < 5% among people of all ages with current fever or a history of fever in the past 2–3 days. The purpose of the survey is to confirm a low prevalence in the population and to confirm that malaria infection is rare and localized. Some countries have had very little malaria for decades, and surveillance data are good enough to indicate that the positivity rate among febrile patients is well below 5%. In such situations, a population survey is not necessary.

At this point, a *feasibility assessment must have been conducted with a positive result* (see learning unit 8), building on good data from malaria surveillance.



### Stratification

Most advanced malaria control programmes apply some kind of stratification scheme in planning activities. For elimination, it is useful to define at least three strata for all areas in which elimination is contemplated:

1. areas in which there is no malaria risk: where malaria has never occurred and/or the transmission of malaria is considered impossible for climatic or ecological reasons;
2. areas in which there is a risk for malaria, but there is no current transmission; and
3. areas in which transmission is currently occurring.

Surveillance activities should be differentiated according to these strata. In some countries, the second stratum may be subdivided into high and low risk according to criteria defined by the programme from its experience.

Once the pre-elimination reorientation phase is completed and the programme enters the elimination phase, the third stratum should be completely described as active foci, and the second stratum is likely to include some *residual non-active* and *new potential foci* (see definitions of these terms in the box below). Within the second stratum, once transmission has been interrupted for several years, areas will be classified as *cleared-up* foci (see Box 3.1). If elimination efforts are successful, these types of foci may be added to the second stratum. Gradually, as foci are cleared up, the third stratum will become smaller and the second stratum larger. In contrast, the first stratum will remain constant. The important operational implication of this stratification is that no foci can emerge in the first stratum, except possibly *pseudofoci* (see Box 3.1), which, as the name indicates, are not foci.

#### Box 3.1. Operational classification of foci

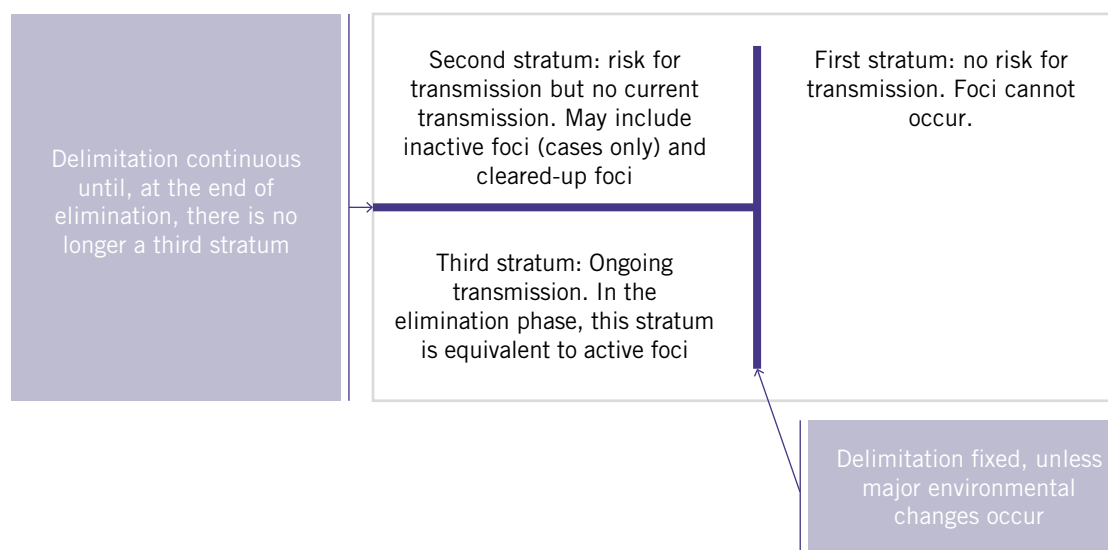
- ▶ *Residual non-active*: transmission interrupted, no indigenous cases, but possible occurrence of relapsing ones
- ▶ *Residual active*: transmission not interrupted
- ▶ *New potential*: presence of imported cases, no evidence of transmission, but its renewal is possible
- ▶ *New active*: renewed transmission: first degree, only introduced cases present; second degree, malaria established and indigenous cases are present
- ▶ *Cleared-up*: no history of recent transmission and no malaria cases
- ▶ *Pseudofocus*: conditions for transmission of malaria are not present throughout the year

Some reviews of programmes in countries that are progressing towards elimination indicate that malarious areas are stratified according to certain epidemiological criteria (e.g. annual slide positivity rate among febrile patients of < 5% and annual malaria incidence of < 1 case per 1000 people at risk) into control, pre-elimination and elimination phases. This is a mistake. Progress towards elimination depends on completion of a feasibility assessment for a specific target date and not on the use of epidemiological parameters as “thresholds” for pre-elimination or elimination. Some districts and subdistricts may have fewer than 1 per 1000 cases per year;

yet, if the operational requirements of the pre-elimination phase have not been met, they are still in the control phase. If the operational and epidemiological requirements for entering the elimination phase have been met in a district where the incidence is  $< 1$  per 1000 per year, some villages in the district may have  $> 10$  cases per 1000 per year. These villages are of course not in the control phase; they should be identified and managed as specific types of foci. Fig. 3.2 shows the stratification to be used in the pre-elimination phase; it should be compared with Fig. 4 in the malaria elimination field manual.

In many cases, adoption of an elimination objective makes it possible to simplify any stratification schemes. Applying more than one stratification scheme at the same time places an unnecessary burden on staff. Efforts should concentrate on the correct classification and management of foci.

**Figure 3.2. Basic stratification to be applied in the pre-elimination phase**



### *Benchmarks and criteria for completion of programme reorientation to elimination*

See the malaria elimination field manual.

### 3.1.3 Elimination phase

#### *Criteria for entering the elimination phase*

Elimination programmes may start once pre-elimination reorientation has been completed, systems are ready, and the malaria incidence in the targeted areas is very low.

There has been much debate about the milestone of incidence or prevalence below which countries could be considered to “be in the elimination phase”. In 2007, WHO published the indicative milestone of  $< 1$  infection per 1000 people at risk per year (assumed to be equal to  $< 100$  new cases per year in a district with a population of 100 000 people), noting that “in practice, the transitions will depend on the caseloads that a programme can realistically handle (including case notification, case investigation, etc.)”. In other words, the milestone depends on the availability of human resources in the areas in which elimination is contemplated. Recent successful elimination efforts were initiated by countries in which the total nationwide malaria case-load was  $\leq 1000$  per year.

Confirmation of such low levels is assessed as described in the malaria elimination field manual. Note that genotyping has not yet been introduced routinely in elimination programmes.

#### *Programme needs for malaria elimination*

As a programme moves from control to elimination, increasingly high quality and precise targeting of operations are required in increasingly narrowly defined areas of intervention, from the wider population to transmission foci. Note the requirements for malaria elimination in the field manual (pp. 11–12).

#### *Programme activities in the elimination phase*

All the essential activities are described in the malaria elimination field manual. Note that, in the elimination phase, the great majority of activities are centred on correct classification of foci and cases and corresponding action. At this stage, study figures 3 and 4 in the malaria elimination field manual carefully, with annexes 2 and 3.

### 3.1.4 Prevention of reintroduction phase

For brevity, this may also be called the maintenance phase. In this phase, surveillance is termed vigilance.

#### *Criteria for entering the phase of preventing re-establishment of transmission*

A malaria elimination monitoring committee should make an independent assessment to determine whether the following objectives have been achieved.

- ▶ Adequate surveillance shows complete interruption of local transmission.
- ▶ There have been no or only extremely few sporadic cases due to local transmission in recent years.
- ▶ All other malaria cases can be positively identified as having been imported.
- ▶ Routine vector control operations, apart from environmental hygiene, have ceased except in restricted areas of high receptivity and vulnerability (see Box 3.2).

#### **Box 3.2. Definitions of receptivity and vulnerability**

- ▶ *Receptivity*: the abundant presence of anopheline vectors and the existence of other ecological and climatic factors that favour malaria transmission. It is a reflection of the vectorial capacity of local anophelines during the season most favourable for malaria transmission.
- ▶ *Vulnerability*: either proximity to malarious areas or resulting from the frequent influx of infected individuals or groups and/or infective anophelines.

Prevention of the re-establishment of malaria is mainly the responsibility of *the general health services*, as part of their normal function in communicable disease control. Learning unit 6 describes this programme in more detail.

Continued importation of cases indicates that the quality of case detection is high. The patterns of vigilance that must be applied to ensure successful maintenance of malaria-free status depend on vulnerability and receptivity in an area. If the threat of re-establishment of malaria is considerable,

the malaria component of the communicable diseases section of the general health services should be strong enough to deal with it.

When there is clear, convincing evidence of the absence of locally acquired cases for at least 3 consecutive years *in a Member State*, application can be made for *WHO certification* of malaria elimination (learning unit 9).

## Unit 3 exercises

### Exercise 3.1

Working in groups, compare different programme phases by filling in the tables below.

#### Comparison of programme phases

Item	Advanced control	Pre-elimination	Elimination	Prevention of reintroduction
Main programme goal				
Epidemiological objective				
Transmission objective				
Unit of intervention				
Milestone for transition to next programme type				
Data source for measuring progress towards reaching milestones				

#### Comparison of critical health systems and programme issues in different programme phases

Issue	Control	Pre-elimination	Elimination	Prevention of reintroduction
Health system issues				
Programme issues				

### Exercise 3.2

Each group should select a country that is in the pre-elimination phase or which is applying some pre-elimination approaches. Describe what is happening, in particular, how the human resource base is being developed to meet the requirements. If no country of the participants in the group is at that stage, select one that is fairly advanced, and discuss the initial measures for completing the requirements of pre-elimination.

# LEARNING UNIT 4

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## Approaches and interventions in pre-elimination, elimination and prevention of reintroduction

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### Learning objectives

At the end of this unit, the participants should be able to:

- List the objectives of malaria treatment in elimination programmes
- Describe antimalarial treatment strategies for *P. falciparum* and *P. vivax* malaria in elimination programmes
- Describe the indications and objectives of mass drug administration
- List the different vector control methods and their roles in malaria elimination
- Describe the technical and operational issues related to vector control measures
- Review the interventions that can be applied, from the pre-elimination to the prevention of reintroduction stage
- Describe the four approaches (strategic elements) that define a malaria elimination programme

## Reading material

*Chapter 4: Tools and approaches. Malaria elimination. A field manual for low and moderate endemic countries.*

## Introduction

This learning unit describes the different tools and approaches that should be applied in the three phases: pre-elimination, elimination and prevention of reintroduction. First, the armamentarium of current antimalaria interventions is reviewed; this is followed by examination of how they should be selected, phased, combined and deployed in each of the three phases.

## 4.1 Interventions based on antimalarial medicines

### 4.1.1 Malaria case management

In elimination programmes, the objective of case management is to reduce the parasite reservoir, prevent transmission, cure disease and avert complications and death. This implies that all malaria-infected individuals, whether symptomatic or asymptomatic, should be identified and treated radically, so that all malaria parasites in the body are killed.

#### *Diagnosis of malaria*

In elimination programmes, the diagnosis of malaria must be sensitive (cases are not missed), species-specific, rapid and universally available. It must therefore be laboratory-based; the methods of choice for case management and routine surveillance are examination of thick films by high-quality malaria microscopy and effective RDTs. Quality assurance is essential. For details, see learning unit 5 (Surveillance).

#### *Treatment of malaria cases*

The aim of treatment of malaria in the context of elimination is complete parasitological cure, including killing of the parasites in their sexual stages. The treatment should be fully effective and instituted so early that, not only is severe disease prevented, but also the emergence of gametocytes in *P. falciparum* is prevented, so that the risk for transmission from the treated case is minimized.

#### *Treatment of uncomplicated falciparum malaria*

To improve treatment outcomes and to counter the development of resistance to monotherapy, WHO recommends ACTs as the treatment of choice for all cases of uncomplicated falciparum malaria.<sup>19</sup> The first-line treatment is selected on the basis of the results of therapeutic efficacy studies in the country, while treatment of imported malaria cases should be based on information on the situation at the origin of infection. ACTs are available as fixed-dose formulations or co-administered therapy (for artesunate plus sulfadoxine–pyrimethamine only). The currently recommended ACTs are listed below; detailed descriptions of each are provided in the WHO malaria treatment guidelines.

<sup>19</sup> Guidelines for the treatment of malaria, 3rd ed. Geneva: World Health Organization; 2015 (<http://www.who.int/malaria/publications/atoz/9789241549127/en/>, accessed 11 September 2015).

- ▶ artemether plus lumefantrine
- ▶ artesunate plus amodiaquine
- ▶ artesunate plus mefloquine
- ▶ artesunate plus sulfadoxine-pyrimethamine
- ▶ dihydroartemisinin plus piperaquine

Artemisinin (and therefore ACTs) reduce gametocyte carriage by destroying a substantial proportion of immature, developing gametocytes when they are sequestered in the microvasculature, resulting in a significant reduction in the release of mature gametocytes into peripheral blood. But they are not effective against mature gametocytes.

Primaquine selectively kills gametocytes. A single oral dose of 0.25 mg base/kg body weight (bw) primaquine is recommended in programmes for reducing falciparum transmission, particularly in low-transmission areas. The drug should be given on the first day of ACT treatment. The single low dose of 0.25 mg base/kg bw can also be given to patients with G6PD deficiency; therefore, G6PD testing is not required before low-dose primaquine is given as a gametocytocide for falciparum malaria. Primaquine should not be given to pregnant women or children < 1 year.

#### *Treatment of uncomplicated non-falciparum malaria*

The goal for treatment of *P. vivax* infection is to cure the infection and to prevent relapses by clearing hypnozoites from the liver. *P. vivax* remains sensitive to chloroquine in most parts of the world. The recommended medicines and guidelines are described below.

For chloroquine-sensitive vivax malaria (as in most places where *P. vivax* is prevalent), oral chloroquine at a dose of 25 mg/kg bw is well tolerated and effective. It is given at an initial dose of 10 mg/kg bw, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day. This should be combined with primaquine, an anti-relapse medicine, at a dose of 0.25 mg base/kg bw, taken with food once daily for 14 days by patients without G6PD deficiency. In the Southwest Pacific and South-East Asia, however, the dose of primaquine should be increased to 0.5 mg/kg bw once daily for 14 days. For practical reasons, primaquine treatment should be started at the same time as chloroquine. New point-of-care tests are available to detect G6PD deficiency, and WHO recommends their use before giving primaquine for radical cure of vivax malaria. Some programmes need experience with G6PD testing and in giving primaquine to G6PD-deficient individuals under medical supervision, at a dose of 0.75 mg base/kg bw once a week for 8 weeks (see malaria treatment guidelines).

- ▶ There is evidence that amodiaquine, mefloquine, piperaquine and quinine are effective in the treatment of chloroquine-resistant vivax malaria. An ACT based on amodiaquine, mefloquine or piperaquine, rather than monotherapy, is the recommended treatment. Such ACTs should be administered with primaquine as for chloroquine-sensitive vivax malaria.
- ▶ Where ACTs have been adopted as first-line treatment for falciparum malaria, they may also be used for vivax malaria in combination with primaquine for radical cure. Artesunate plus sulfadoxine-pyrimethamine should not be used, because it is not effective against *P. vivax*.

- ▶ *P. ovale* and *P. malariae* infections are sensitive to chloroquine. Treatment for *P. ovale*, a relapsing malaria, is the same as for chloroquine-sensitive *P. vivax*, i.e. with chloroquine and primaquine. *P. malariae* forms no hypnozoites; therefore, treatment with only chloroquine is sufficient.
- ▶ In *P. vivax*, *P. malariae* and *P. ovale*, gametocytes appear in the bloodstream at the same time as the non-sexual stages; therefore, effective treatment with schizontocidal drugs is sufficient to abolish the infectivity of the circulating parasites.
- ▶ *Mixed infections*: ACTs are recommended for mixed infections of *P. falciparum* and other species. A 14-day course of primaquine should be included for mixed infections including *P. vivax* and/or *P. ovale*.

#### *Treatment of severe malaria*

See the malaria treatment guidelines. In principle, severe malaria is treated in the same way in elimination as in control programmes, except that the single dose of primaquine should be added once the patient can take oral treatment. It should be postponed in cases of severe anaemia, given the (low) risk of haemolysis. Until primaquine can be given, patients should sleep under a mosquito net to ensure that they cannot infect mosquitoes.

#### *Quality assurance and logistics of antimalarial medicines for case management*

The quality of antimalarial medicines is as important in elimination as in control. The specific problem that emerges when malaria is disappearing is the maintenance of small stocks of effective medicines within the expiry date for prompt treatment. Often, stocks have to be recalled, destroyed and replaced as they approach the expiry date. It may be necessary to identify strategic locations for these stocks. In densely populated areas with good communications, it may not be necessary for all hospitals to stock antimalarial medicines; however, on isolated islands and in remote locations, it may be necessary to maintain stocks, even if the probability of malaria is low. The challenge of stocking of medicines for the treatment of severe malaria is particularly great, as they are needed rarely but with great urgency. It is important not only to maintain those stocks but also to ensure that clinicians, whether in the private or the public sector, are aware of them.

#### *Role of the private health care sector in case management*

The aim of elimination programmes is to reach 100% detection *and notification* of malaria cases. This will require:

- ▶ full cooperation of the private health sector;
- ▶ services to diagnose and treat malaria that are free of charge to patients, whether nationals, temporary or permanent immigrants, people in transit or residents of neighbouring countries who live in border areas; “free of charge” must include consultation fees;
- ▶ monitoring of the national supply of antimalarial medicines;
- ▶ a ban on over-the-counter sale of antimalarial medicines; and
- ▶ maintenance and updating of the skills of health personnel as the disease becomes less frequent.

During the pre-elimination phase, the coverage of good-quality curative and preventive health services in all transmission areas should be effective. The private sector must be increasingly



engaged in the malaria programme, and a *census of private health providers* in malaria risk areas should be drawn up during this period.

By the time the elimination programme starts (except in the rare situation in which there are no private health care providers or it is rational to demand from them that they refer all patients suspected of having malaria), private health facilities should have been completely integrated into the malaria surveillance system. It should no longer be possible for febrile patients to obtain antimalarial treatment through private clinics, pharmacies or otherwise, without a quality assured confirmatory diagnosis and without the central malaria elimination programme being promptly informed and a case investigation being carried out.

#### 4.1.2 Use of antimalarial drugs to reduce the parasite reservoir

In an elimination programme, treatment of all infected people in a community, whether they are symptomatic or asymptomatic, is the primary objective for interrupting transmission. Usually, this is achieved over some years through surveillance and radical treatment of identified cases. There are rapid approaches which aim to treat all human parasite carriers in a given area radically and thereby reduce the parasite reservoir to such an extent that transmission is interrupted. An obvious weakness of these methods is that infected mosquitoes may still be present.

##### *Mass drug administration*

During mass drug administration campaigns, every individual in a defined population or geographical area is required to take antimalarial treatment simultaneously. Depending on the contraindications of the medicines used, pregnant women, young infants and other population groups may be excluded. The concept of mass drug administration is that, if all people living in a given area could be effectively treated and rid of malaria parasites in 1 day and the procedure is repeated at intervals thereafter, the parasite reservoir of malaria in the area could eventually be eliminated. Well-conducted mass drug administration will result in a major reduction in the parasite mass, but the area will eventually return to its original prevalence level unless the vectorial capacity is reduced in parallel and maintained at a very low level. The time it takes to return to the original level of transmission will depend on the prevailing vectorial capacity. There is some concern that mass drug administration could select for drug-resistant parasites, and, the larger the population of parasites that is targeted, the greater the risk. As an intervention to interrupt transmission of falciparum malaria, mass drug administration can be considered in endemic island communities and in low-endemic non-island settings approaching elimination, where there is minimal risk of re-introduction of infection, good access to treatment, and implementation of vector control and surveillance. Use of mass drug administration to rapidly reduce malaria morbidity and mortality can be considered for epidemic control as part of the immediate response, while other interventions are put in place.

In view of the growing threat of multidrug resistance and the need to use extreme measures, mass drug administration can be considered as a component of malaria elimination efforts in the Greater Mekong subregion, in areas with good access to treatment, vector control and good surveillance.

The treatment to be used in such schemes is usually the same as in case management for the species targeted but is preferably with an ACT different from the first-line treatment to reduce the risk for resistance. Primaquine should always be included. At present, mass treatment is under

consideration for the elimination of foci of multi-drug resistant falciparum malaria in South-East Asia; however, this poses considerable difficulties, which are outside the scope of this text.

For the success of mass drug administration, the *full cooperation of the community* is essential, because the impact relies on coverage, which must be very high. In some settings, groups of adult men are mainly at risk but may not be accessible because of an occupation that exposes them to malaria.

#### *Mass screening and treatment*

Using current recommended diagnostic tests (microscopy and RDTs), MSAT and FSAT are not suitable as interventions to reduce malaria parasite reservoir.

#### *Seasonal mass treatment to reduce *P. vivax* hypnozoite carriers*

In temperate and some sub-tropical areas, the transmission of *P. vivax* is distinctly seasonal, lasting usually only 3–5 months. During most of the year, when there is no transmission, the parasites occur almost exclusively in the human liver stage. If the foci are small and high coverage can be achieved, it is possible—in principle—to reduce the parasite reservoir by treating all members of the target population with primaquine for 14 days outside the transmission season (except of course pregnant women and infants < 1 year). Such exercises are usually conducted in spring, about 2 months before the usual onset of transmission.<sup>20</sup> In the past, this approach was used in several Asian countries as part of vivax elimination, without G6PD testing. In order to avoid the risk for primaquine-induced acute haemolytic anaemia in G6PD-deficient patients, this intervention requires G6PD testing. It is thus very difficult to implement.

To treat any asymptomatic low-density blood-stage carriers, a standard 3-day course of chloroquine is given with the primaquine.

### 4.1.3 Chemoprophylaxis for travellers

In an elimination setting, nationals and residents who travel abroad and their travel health advisers should note the ABCD of malaria protection:

- ▶ Be **A**ware of the risk, the incubation period, the possibility of delayed onset and the main symptoms.
- ▶ Avoid being **B**itten by mosquitoes, especially between dusk and dawn.
- ▶ Take antimalarial drugs (**C**hemoprophylaxis) when appropriate, to prevent infection from developing into clinical disease.
- ▶ Immediately seek **D**iagnosis and treatment if a fever develops 1 week or more after entering an area where there is a malaria risk and up to 3 months (or, rarely, later) after departure from a risk area.

Depending on the malaria risk in the area visited (see [www.who.int/ith](http://www.who.int/ith)), the recommended prevention method may be only prevention of mosquito bites (very limited risk for malaria transmission), mosquito bite prevention in combination with chloroquine (area with chloroquine-

<sup>20</sup> Kondrashin A, Baranova AM, Ashley EA, Recht J, White NJ, Sergiev VP. Mass primaquine treatment to eliminate vivax malaria: lessons from the past. *Malar J* 2014;13:51.

sensitive vivax malaria) or, in certain areas, in combination with atovaquone–proguanil, doxycycline or mefloquine (selected according to the reported resistance pattern).

In some countries, soldiers who are at high risk for vivax malaria receive chloroquine while exposed and a “terminal prophylaxis” course of primaquine for 14 days at the end of exposure.

## 4.2 Vector control measures

Vector control is the main intervention for reducing malaria transmission and can also play an important role in knocking out the last foci of transmission in the later stages of elimination. Interventions with vector control methods comprise the following:

- ▶ Core interventions: insecticide treated nets and indoor residual spraying
- ▶ Supplementary interventions: larval source management and improved housing, including screens.

Insecticide treated nets and indoor residual spraying are the two most powerful, most broadly applied vector control interventions. They work mainly by reducing the longevity of mosquitoes and by reducing human–vector contact; thus, the effect of both is maximized when the coverage level is high in each targeted community.

Criteria and guidelines for the use of these methods are available in many texts published by GMP/WHO and the WHO Pesticide Evaluation Scheme (WHOPES) and are available on WHO websites: <http://www.who.int/malaria/areas/en/> and <http://www.who.int/whopes/en/>. Participants in training courses on malaria elimination are expected to be acquainted with these texts and to have practical experience in vector control. Consequently, only a few issues of special relevance to elimination are highlighted here.

### 4.2.1 Core interventions

Selected references:

WHO guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets, March 2014 ([www.who.int/malaria/publications/atoz/who-guidance-combining-irs-llins/en/](http://www.who.int/malaria/publications/atoz/who-guidance-combining-irs-llins/en/), accessed 12 September 2015).

WHO recommendations for achieving universal coverage with long-lasting insecticidal nets in malaria control, September 2013 (revised March 2014) ([www.who.int/malaria/publications/atoz/who\\_recommendation\\_coverage\\_llin/en/](http://www.who.int/malaria/publications/atoz/who_recommendation_coverage_llin/en/), accessed 12 September 2015).

Global plan for insecticide resistance management in malaria vectors (GPIRM), May 2012 ([www.who.int/malaria/publications/atoz/gpirm/en/](http://www.who.int/malaria/publications/atoz/gpirm/en/), accessed 12 September 2015).

#### *Insecticide-treated nets*

ITNs, which include both LLINs and conventional nets treated with an insecticide, work both at the individual level (by protecting a person sleeping under the net) and the community level (by extending the effect to an entire area). WHO recommends universal coverage of at-risk populations with ITNs and urges a switch to LLINs. Given that the vast majority of nets procured and distributed today are LLINs, the remainder of this section focuses on LLINs.

To meet the target of universal access, WHO recommends that one LLIN be distributed for at least every two people at risk for malaria. As many households have an odd number of members, the calculation must be adjusted for quantification at population level. For procurement purposes, an overall ratio of one LLIN for every 1.8 persons in the target population is recommended.

LLINs procured with public health funds should be provided free of charge to all populations at risk. Universal access to LLINs is best achieved by free mass distribution campaigns every 3 years or less. However, to ensure that coverage is maintained, it is essential to complement these campaigns with continuous distribution programmes (e.g. at antenatal and routine immunization services) before, during and after a mass campaign. Given that most countries are far from achieving universal LLIN coverage, improving access to LLINs should be the most important priority of distribution programmes. Evidence suggests that about 90% of the population with access to mosquito nets actually use them. In areas where LLIN use is lower, behaviour change communication programmes should be implemented.

National malaria control programmes and global malaria partners should procure only LLINs that have been recommended by WHOPEs. At present, 15 LLIN products are recommended by WHOPEs (as per September 2015). Independent quality control should be undertaken before shipment, and the cost of the analysis should be borne by the suppliers, including the cost of sending samples to an accredited or recognized laboratory for analysis on behalf of countries that do not have adequately equipped or staffed national quality-control laboratories. Detailed guidance on good practices in the handling and use of products containing insecticides and on quality control in procurement can be found on the WHOPEs website.

The lifespan of LLINs depends on the product type and the setting in which the products are used. Therefore, all large-scale LLIN programmes should monitor LLIN durability locally (see *WHO guidance note for estimating the longevity of long-lasting insecticidal nets in malaria control*, issued in 2013). The collection of local data on the comparative durability of LLIN products, derived by rigorous, auditable methods, would allow procurement decisions to be made on the basis of *price per year of protection* rather than *unit price per net*. This, in turn, would lead to substantial cost savings.

### *Indoor residual spraying*

IRS involves application of insecticides to the inner surfaces of dwellings, targeting anopheles mosquitoes that rest on walls after having taken a blood-meal. IRS programmes can rapidly reduce local malaria incidence and mortality, provided that most of the houses and animal shelters in targeted communities are sprayed. WHO recommends spraying of at least 80% (and ideally 100%) of houses, structures and units in the targeted area in any round of spraying.

IRS is applicable in many epidemiological settings, provided that its operational and resource feasibility is considered in policy and programming decisions. IRS requires specialized spray equipment and techniques, and, given the difficulty of carrying out spray operations, it also requires scrupulous maintenance of the equipment, timing and quality of application, and monitoring and disposal capabilities.

Currently, WHOPEs recommends 15 insecticide compounds and formulations (as per March 2015) belonging to four chemical classes for use in indoor spraying programmes.

### Combination of IRS and LLINs

It is often observed that antimalaria programmes decide to “aim for elimination” and therefore decide to add IRS to LLINs. This is usually done without a feasibility analysis, modelling or examination of operational and entomological factors. The feasibility analysis should determine whether elimination is possible, which mix of interventions will be required and for how long. It is a mistake to assume that IRS is the key to elimination.

Current evidence and recommendations from WHO stipulate that, in settings where there is high coverage with LLINs and they remain effective, IRS may have limited effect in reducing malaria morbidity and mortality. IRS may be used in areas where there are LLINs as part of an insecticide resistance management strategy. If LLINs and IRS are to be deployed together in the same geographical location, IRS should be done with non-pyrethroid insecticides. Malaria control and elimination programmes should therefore prioritize delivery of either LLINs or IRS at high coverage and to a high standard, rather than introducing the second intervention as a means of compensating for deficiencies in implementation of the first.

Moreover, evidence is required on the effectiveness of combining IRS and LLIN in foci of malaria transmission, including low-transmission settings. Evidence is also needed from different eco-epidemiological settings outside Africa. WHO further recommends that all programmes in any transmission setting that invest in combined use of LLINs and IRS include a rigorous programme of monitoring and evaluation (e.g. a stepped wedged introduction of the combination) to confirm whether the additional input has the desired impact. Countries that are already using both interventions should similarly evaluate the effectiveness of combining as opposed to either LLINs or IRS alone.

#### 4.2.2 Supplementary interventions

In a few settings and circumstances, the core interventions (LLINs and IRS) may be supplemented by larval source management, which includes four subcategories: vector habitat modification, habitat manipulation, larviciding and biological control. Currently (October 2013), WHOPEP recommends 12 compounds and formulations for mosquito larva control. Detailed guidance on larval source management is available in *Larval source management. A supplementary measure for malaria vector control. An operational manual*, released in 2013 (<http://www.who.int/malaria/publications/atoz/9789241505604/en/>, accessed 12 September 2015).

#### Larviciding

Larviciding, the most widely used approach to larval source management, involves regular application of a biological or chemical insecticide to water bodies, breeding larvivorous fish or other predators to reduce the number of mosquito larvae and pupae. WHO recommends larviciding only where mosquito breeding sites are *few, fixed and findable*, i.e. are easy to identify, map and treat. Larviciding can be an attractive complement to malaria control. The cost compares favourably with those for IRS and LLINs, especially where larval habitats are easily accessible and discrete. Nevertheless, an intensive monitoring and treatment system is required, with weekly application to maintain coverage of all potential larval habitats. Furthermore, not all larvicides are appropriate for treating drinking-water. The recommended classes of formulations of larvicides

and insect growth regulators and measures for quality control are listed on the WHOPES website (<http://www.who.int/whopes>).

#### *Modification and manipulation of larval habitats (environmental management)*

*Habitat modification* is permanent alteration of the environment, including landscaping, surface water drainage, filling and land reclamation, coverage of water storage containers with mosquito-proof lids or permanent slabs and coverage of water surfaces with a material impenetrable to mosquitoes (e.g. expanded polystyrene beads). It also includes precautionary measures, such as ensuring that culverts are built in road construction.

*Habitat manipulation* is a recurrent activity, including water-level manipulation (e.g. stream flushing, keeping drains clear of vegetation so that water can flow too fast to support mosquitoes) and filling or draining borrow pits and rock quarries.

Environmental management consists of more than habitat modification and manipulation; it also includes mobilization and education of health workers and the community for implementing and maintaining larval source management.

#### *Improved housing and location of settlements in relation to breeding sites*

Poor housing is linked to higher risks for human–vector contact. For example, incomplete houses with open walls and wide or unscreened eaves and houses with open windows and doors or without ceilings favour mosquito entry. Better housing (design, construction and alteration, including screening or mosquito-proofing) can deter mosquito entry and indoor resting and, consequently, could have longer-lasting effects than insecticide-based methods. Screening of windows, eaves and doors can be an effective means of reducing human–vector contact. It is considered to have played an important role in the elimination of malaria from parts of the USA; however, some air-conditioners have water containers, which may serve as breeding sites for *Ae. aegypti* and, on the Indian subcontinent, for *An. stephensi*.

#### *Repellents, mosquito coils and protective clothing*

The use of repellents and protective clothing are useful for people who are outdoors during peak vector biting periods. There is no proof that most of these methods are effective in public health, but this should not lead to the conclusion that they are ineffective, as there have been very few trials. Rigorous trials are starting now in South-East Asia, which should clarify the role of these methods in control and elimination. Until then, major investment by programmes is not justified.

### **4.2.3 International airports, sea and land transport and desinsection**

Desinsection (or disinsection) comprises a set of measures intended to free certain objects from certain kinds of insects. The current standard measures are a combination of residual spraying and space spraying. These measures are probably not fully effective because mosquitoes can hide in many crevices in cargo, but they represent the best that can be done with existing techniques.

Desinsection is relevant in malaria control and elimination:

- ▶ to prevent “airport malaria”, which is malaria resulting from the bite of an infected anopheline that has arrived in a malaria-free area by aircraft; and

- ▶ to prevent the introduction of exotic disease vectors in an area where they might multiply.

For technical details, refer to the WHO report of the informal consultation on aircraft disinsection.<sup>21</sup>

It is thought that the importation of *An. gambiae* to Brazil from Africa in the late 1920s was by sea. This is also the only good explanation for the presence of anophelines on many islands located hundreds of kilometres from continents. Theoretically, anophelines could also be moved by land transport, but, so far, there are no documented examples of this.

### 4.3 Interventions in the pre-elimination phase

Pre-elimination programmes are initiated when an analysis has indicated that elimination is feasible in a given area. These programmes involve mainly capacity-building to ensure that the health system is fully prepared at any time to embark on the elimination phase. In most cases, the interventions of the control phase are continued; however, at the outset of pre-elimination programmes, when the malaria prevalence is typically about 5%, control might have to be intensified in smaller and larger areas to reduce transmission to a low level with focal distribution. Characteristically, there is a major reduction in vector control coverage in this phase, as the area of transmission contracts.

#### 4.3.1 Case management and surveillance

During the pre-elimination phase, case management and surveillance must be strengthened to include, for example, anti-gametocyte treatment for *P. falciparum*. Diagnostic practices should be fully adapted to the requirements for malaria surveillance in the elimination phase. There are few policy choices, apart from selection of the most suitable ACT for local conditions. The norms are clear (see 4.1); the challenge to the programme is to plan implementation so that standards for case management and surveillance are fully met when the elimination phase starts.

#### 4.3.2 Mass screening and treatment and mass drug administration

These interventions have no role in the pre-elimination phase.

#### 4.3.3 Chemoprophylaxis for travellers

This measure is not essential but is useful and potentially life-saving for travellers visiting highly endemic areas in the pre-elimination phase. In countries where it has not been widely practised before, full implementation may take time, so it is strategic to take the first steps in pre-elimination. If a country plans to eliminate only at subnational level, chemoprophylaxis may be needed for travellers from that area who visit domestic or foreign endemic areas.

#### 4.3.4 Vector control

Vector control usually plays a central role in this phase and often must be strengthened in some areas to increase the population coverage and the quality. As explained in learning unit 8, this entails maximizing the fraction of the at-risk population that is fully protected. Doing so requires:

<sup>21</sup> Report of the informal consultation on aircraft disinsection, 6–10 November 1995. Geneva: International Programme on Chemical Safety, World Health Organization; 1995 ([http://whqlibdoc.who.int/HQ/1995/WHO\\_PCS\\_95.51\\_Rev.pdf](http://whqlibdoc.who.int/HQ/1995/WHO_PCS_95.51_Rev.pdf), accessed 12 September 2015).

- ▶ assessing the fraction that is fully protected at the outset,
- ▶ identifying the reasons for incomplete measures,
- ▶ identifying cost-effective remedial measures and
- ▶ considering alternative or supplementary interventions.

During the pre-elimination phase—if not before—the focality should gradually emerge, whereby surveillance data show that some areas no longer have any malaria transmission; preventive interventions should be withdrawn from such areas. This may be difficult, because:

- ▶ the population has become used to preventive tools, especially LLINs, and may appreciate them, especially if they reduce nuisance due to non-malaria mosquitoes;
- ▶ the health staff would like to continue doing what they have become accustomed to do; casual labourers who have carried out vector control activities may lose their income; and
- ▶ the health staff and sometimes the population do not trust surveillance data.

The last concern can be managed only if the surveillance system is strong. *Certain characteristics of the surveillance system* are important in this respect.

- ▶ The incidence of malaria is analysed at village level.
- ▶ Surveillance is complete: nearly all cases of fever suspected as malaria are observed by the health services (whether public or private) in accordance with the “3T” principle (tested, treated and tracked), and all results of malaria testing are reported. Whether this is the case can be assessed in population surveys of treatment-seeking behaviour and in health facility surveys for completeness of reporting.
- ▶ Surveillance is case-based, so that each case can easily be classified by its probable geographical origin.

Usually, a country entering the pre-elimination phase already has *malaria stratification*, with rules determining which areas should receive which vector control measures, depending on surveillance data. Such rules could include: “If a previously endemic village has not had any locally transmitted malaria cases for 3 (or 2) years, if the surveillance system is good and it does not usually receive migrants from endemic areas, then vector control (LLINs or IRS as the case may be) ceases.”

Of course, it is then essential that strong surveillance be maintained. The health services and the population should be informed that testing local cases of fever with no other obvious cause and all cases of fever from endemic areas will prevent the re-establishment of malaria.

The indicators of continued effective surveillance are:

- ▶ continuing detection of imported malaria cases and
- ▶ the absence of gametocyte-positive falciparum cases, which indicates that cases are detected and treated promptly.



## 4.4 Interventions in the elimination phase

### 4.4.1 Defining the approaches of malaria elimination programmes

It is important to understand the radical difference between a control strategy, in which a menu of interventions is used to gradually reduce the burden of the disease in a population, and an elimination strategy, in which highly targeted, locally adapted measures are used to track down the last foci and cases of malaria, making sure that all parasites are killed. The standard strategy can be conceptualized as comprising four approaches (Box 4.1). In these approaches, malaria surveillance is the common denominator and backbone of elimination.

#### Box 4.1. The four approaches to malaria elimination

1. Early detection of all cases
2. Prevention of onward transmission from cases
3. Management of malaria foci
4. Management of importation of malaria parasites

The first two approaches are closely linked; they include case management, in which a “case” includes not only symptomatic but also asymptomatic infection with plasmodia in humans.

#### 1. Early detection of cases

Elimination programmes involve tracking down individual human parasite infections (“cases”) and the localities in which they are acquired: “foci” in the case of local transmission and “importation” when they are acquired outside the programme area.

The tools are listed in the malaria field manual, Section 4.1, p 28. In relation to the text, the following should be noted.

- ▶ *Active case detection* is not limited to routine house-to-house visits; it may also be undertaken reactively in a given area, for example where an unexpected case has been detected. Active case detection is not compulsory in elimination programmes, but it is often necessary because not enough people with suspected malaria present themselves to health services and because asymptomatic infections may occur, despite low transmission and low immunity. More guidance will be provided under Surveillance in this course.
- ▶ While microscopy is the standard method of diagnosis in elimination programmes, the use of RDTs is not proscribed; the levels of sensitivity of good RDTs are similar to those of quality-assured microscopy. Further details of laboratory methods are discussed in learning unit 5.

#### 2. Prevention of onward transmission from cases

When cases are found, transmission from the patients to mosquitoes is addressed by immediate radical treatment. If there is reason to believe that the patient could have infected local mosquitoes before being treated, additional measures are needed (see foci, below).

### 3. *Management of malaria foci*

In this situation, transmission is assumed to occur or there is a risk for transmission, which must be dealt with on a long-term basis. The following should be noted:

- ▶ Community involvement has high priority, as communities (as well as local health services and authorities) often have essential knowledge about the potential determinants of malaria, and their collaboration in all interventions is important. Other sectors, such as plantations, mines and the military, may also play important roles.
- ▶ If local authorities are to take over responsibility for vector control, the required capacity must have been built. Premature decentralization is associated with several risks.

As general suppression of transmission proceeds, a few foci in which the situation is particularly difficult remain to be dealt with. When the target locations have been identified, vector control must be directed with great intensity. Remnant foci of transmission could result from conditions that require an alternative or supplementary method of vector control, such as:

- ▶ operational problems resulting in less effective coverage;
- ▶ lack of public acceptance of the vector control method, resulting in less effective coverage;
- ▶ vector variations, e.g. different vector species, sub-species or sub-populations with different behaviour or insecticide resistance;
- ▶ differences in human behaviour (e.g. population movement); and
- ▶ illegal or clandestine activities, such as drug trafficking and smuggling of people and goods.

Generally, the management of foci is based on optimized implementation of a locally appropriate menu of vector control interventions, case management and active case detection. The aim is to interrupt transmission as rapidly as possible and to document this by intense surveillance. When the data indicate that transmission has been interrupted, vector control should be interrupted (typically at the transmission season after the last local case), but intense surveillance should be maintained until the risk for importation is shown to be very low (often until national elimination has been achieved and sometimes after that). Interventions such as mass drug administration may be considered a supplement to those mentioned, especially if transmission cannot be completely interrupted by other methods.

### 4. *Management of importation of malaria parasites*

This approach includes measures to prevent importation and measures to deal with cases that were imported despite these measures. The second set of measures is closely related to early detection (see above). The tools, including chemoprophylaxis, are listed in the malaria elimination field manual, section 4.4.

#### 4.4.2 **Role of Mass drug administration**

Mass drug administration can be used as a tool to interrupt transmission of malaria in low endemic island communities and non-island settings approaching elimination, where there is minimal risk of re-introduction of infection, good access to treatment and vector control and surveillance are also implemented.

## 4.5 Interventions for prevention of reintroduction

The strategy includes proactive and reactive approaches.

### 4.5.1 Case management and surveillance (called “vigilance” in this phase)

The strategy is technically the same as that in the elimination phase; operationally, there should be full integration with general health services. Active case detection may be continued in some high-risk areas but should be phased out over a few years. If the health services are well prepared and treatment-seeking is adequate, active case detection should no longer be needed. The greatest challenges are in communication and sustainability. The main population groups that could include imported cases should be identified, and ways should be found to inform them about where to seek treatment in case of malaria-like symptoms. Pamphlets could be distributed to people arriving from certain countries. Collaboration could be established with their employers.

Use of mass drug administration to rapidly reduce malaria morbidity and mortality can be considered for epidemic control as part of the immediate response, while other interventions are put in place.

#### *Operational challenges*

Over the years, clinicians in the general health services will tend to forget malaria. Maintaining the diagnostic skills of clinicians and the competence of microscopists is difficult. Stocks of diagnostics and antimalarial medicines may become obsolete or outdated. Stocks of drugs (one to two full doses) should be placed at strategic points, usually in administrative centres. The programme (which by then may no longer be a malaria programme but a communicable or vector-borne disease control programme) must find innovative ways to communicate, for example through articles, professional meetings and web-based training (which can be made compulsory). Prevention of malaria mortality is an objective that is more understandable to some clinicians than prevention of reintroduction.

### 4.5.2 Chemoprophylaxis

For travellers, chemoprophylaxis is highly relevant in this phase; again, innovation may be necessary in communication to both travellers and prescribers. It may be useful, for example, to collaborate with travel agencies.

### 4.5.3 Vector control

#### *Proactive*

Long-term measures to reduce the risk for an outbreak are rational in areas with high receptivity and vulnerability. Vector control interventions that are too weak to be useful in the initial phases, such as larviciding and environmental management, may be relevant more because they are acceptable in the long term than because they are cost-effective. An important technical advantage of anti-larval measures is that the problem of insecticide resistance is less acute than in measures against adults. LLINs and IRS should be reserved for special situations, such as the arrival of workers or students from a highly endemic country. Exceptionally, one of these interventions might be maintained in the medium term in an area that is both highly receptive and vulnerable.

### Reactive

The programme must anticipate the possibility of reinvasion and possible epidemics. A robust surveillance system is needed, covering the entire population, including remote areas where outbreaks are possible. 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 similar to those used to control unstable and epidemic malaria. For this purpose, IRS is commonly assumed to have particular advantages; recent experience in Indonesia suggests that ITNs can be deployed rapidly on a large scale. The choice between these methods is less important than *preparedness*. It is necessary to have stocks of supplies and trained staff who can rapidly assess the situation and deploy the selected intervention.

## Unit 4 exercises

### Exercise 4.1

Discuss the technical and operational conditions for optimal implementation of IRS and LLINs interventions, respectively.

### Exercise 4.2

What factors determine whether and how quickly malaria will return if vector control is stopped?

### Exercise 4.3

In what ways can operational research guide and promote case management in malaria elimination, including diagnosis and the use of antimalarial drugs?

### Exercise 4.4

After 2 years with 0 reported locally transmitted falciparum malaria cases in a country in the Arabian peninsula, three cases are detected in an oasis with 3000 inhabitants. The oasis frequently hosts overland travellers, some of whom might come from areas in which malaria is endemic. The spray team has started a total coverage operation. The Minister of Health wants you to conduct mass drug administration, unless you have convincing arguments for a better strategy. The Minister has also told you that any severe side-effects of mass drug administration must be avoided.

What are your options? Discuss the pros and cons of each.

### Exercise 4.5

Prepare a matrix with the rows representing all the interventions discussed here and four columns representing the four phases, from control to prevention of reintroduction. Fill in the cells for a selected country or area in which elimination is contemplated to identify the role of each intervention in each phase.

# LEARNING UNIT 5

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## Surveillance, including laboratory methods

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### Learning objectives

By the end of this unit, participants should be able to:

- Describe the role of surveillance in different phases of malaria elimination
- Describe the role of microscopic diagnosis in malaria elimination
- Interpret laboratory reports
- Describe key issues in the establishment and maintenance of quality assurance for microscopy
- Describe the role of geographical information in malaria elimination
- Use meteorological data in relation to malaria transmission (using Moshkovsky's method in temperate and subtropical areas)
- Organize case detection activities
- Conduct an investigation of a malaria case
- Classify cases of malaria
- Classify foci of malaria
- Explain epidemiological indicators used in surveillance
- Establish a surveillance system for malaria elimination

## Reading material

*Disease surveillance for malaria elimination. An operational manual.* Geneva: World Health Organization; 2012 ([http://whqlibdoc.who.int/publications/2012/9789241503334\\_eng.pdf](http://whqlibdoc.who.int/publications/2012/9789241503334_eng.pdf), accessed 12 September 2015).

*Malaria microscopy quality assurance manual.* Version 1. Geneva: World Health Organization; 2009:7–40 ([http://www.who.int/malaria/publications/atoz/mmicroscopy\\_qam/en/index.html](http://www.who.int/malaria/publications/atoz/mmicroscopy_qam/en/index.html), accessed 12 September 2015).

## Introduction

This unit will guide you through the above-mentioned manual on disease surveillance, which will be referred to as “surveillance manual for malaria elimination”. It also provides some additional information on laboratory diagnosis and use of geographical information and meteorological data. While the text of this learning unit is relatively short, participants are expected to read the *surveillance manual for malaria elimination* thoroughly.

### 5.1 Surveillance in different phases of malaria elimination

Read pages 1–5 of the surveillance manual for malaria elimination. Note the differences between surveillance for malaria control and elimination (Table 1.1).

► **Now, do exercise 5.1.**

### 5.2 Malaria laboratory diagnosis and its quality assurance for elimination programmes

The central concept of surveillance during malaria elimination is that identification and investigation of a malaria case and a malaria focus define the presence of malaria transmission. The absence of new cases due to local transmission is an indication of interruption of transmission and cessation of activity of a focus. For reasons that will be explained below, cases are, *as a rule*, recognized in elimination settings only if they have been confirmed by parasitological diagnosis. In blood-induced malaria, a rare case in a donor may be recognized retrospectively, even if parasites are no longer detectable in the blood, on the basis of the fact that malaria developed in a recipient. Therefore, reliable microscopic diagnosis is a cornerstone of elimination.

#### 5.2.1 Microscopy

Since the discovery of malaria parasites by Laveran in 1880, microscopy has been a mainstay of diagnosis; however, it is by no way ideal, hence a continuous search for newer methods. Microscopy is a sensitive method for malaria diagnosis. Expert microscopists can detect about 10 parasites per microliter blood by routine examination, which satisfies clinical needs, as malaria is usually asymptomatic at densities below this threshold.

While the epidemiological importance of cases of very low parasite density is limited according to experience from past elimination programmes, recent studies suggest that human infections

with sub-microscopic gametocyte densities may be infective for anophelines.<sup>22</sup> Cases of very low asexual parasitaemia may be important sources of malaria transmitted by blood, especially when a large amount of blood is injected, as in blood transfusion.

The other principal advantages of microscopy over other methods are that it allows identification of the malaria parasite species and stages and provides quantitative information. In addition, a properly stained smear is a piece of evidence that can be conserved for many years and used for retrospective quality control, consultation and training. The technique may be shared with other disease control programmes (e.g. for tuberculosis), because the equipment and basic skills of the personnel are essentially the same.

The disadvantages of microscopy are that it is labour-intensive and time-consuming: it takes at least 30 min to obtain results after blood collection. It is exacting and depends on the competence of the microscopist, good laboratory standards and close supervision. Microscopy performed in general health services is often much less sensitive and precise than in experts' hands due to a multitude of problems that will be discussed further.

Newer methods have been proposed, and some have been commercialized. They include modifications of staining, for example by using fluorescent dyes and advanced concentration methods such as quantitative buffy coat. These methods do not offer significant advantages over traditional microscopy to justify the increased cost.

## 5.2.2 Non-microscopic methods

Non-microscopic methods for diagnosis of malaria include:

- ▶ antigen-detecting tests (RDTs),
- ▶ nucleic acid-based amplification techniques, such as PCR and
- ▶ serological methods to detect antibodies.

### *Antigen-detecting tests (RDTs)*

RDTs based on immunochromatography involve detection of malaria parasite antigens in lysed blood with monoclonal antibodies. RDTs are produced as kits containing diagnostic strips or cassettes and auxiliary equipment and reagents (such as lancets, pipettes and buffer solution).

Several types of antigen may be detected by commercialized RDTs. HRP2 is produced only by *P. falciparum*, while aldolase is produced by all four species and can therefore be used to identify all human malaria parasites. Parasite lactate dehydrogenase (pLDH) is also common to all four species and can be detected by antibody-binding antigen epitopes that are common to all species (pLDH-pan) or specific to the pLDH of a particular species (i.e. pLDH-Pf, specific for *P. falciparum*; pLDH-Pv specific for *P. vivax*; and pLDH-Pvom, specific for the three non-falciparum malaria species). While pLDH with sequences specific to *P. malariae* and *P. ovale* exist, commercial products that target these antigens are not yet available. RDTs specific for pLDH-Pvom have begun to appear commercially.<sup>23</sup>

<sup>22</sup> Ouedraogo AL, Bousema T, Schneider P, de Vlas SJ, Ilboudo-Sanogo E, Cuzin-Quattara N, et al. Substantial contribution of submicroscopical *Plasmodium falciparum* gametocyte carriage to the infectious reservoir in an area of seasonal transmission. *PlosOne* 2009;4:e8410.

<sup>23</sup> Good practices for selecting and procuring rapid diagnostic tests for malaria. Geneva: World Health Organization; 2011.

Their sensitivity relative to microscopy is reasonable (> 90%) if parasite densities are > 100 per microlitre, and their specificity is > 90%. Parasitaemias < 100 per microlitre that are poorly detected by RDTs, especially non-falciparum, may produce symptoms in non-immune people.

The advantages of RDTs over microscopy are:

- ▶ simpler to perform,
- ▶ faster (15–20 min),
- ▶ robust (little variation between users and little subjectivity),
- ▶ do not require equipment (microscope) or electricity,
- ▶ relatively low cost (in the order of US\$ 0.50 per test) and independent of the number of test performed per day,
- ▶ may be learnt in a few hours with good retention even by people with elementary school education,
- ▶ the result can be shown to the patient or guardian,
- ▶ the shelf life is 2–3 years, and many products are thermostable at high temperatures.

Their disadvantages in comparison with microscopy are:

- ▶ gametocytes of *P. falciparum* are not detected and are not distinguished from asexual cells in the other tests;
- ▶ interpretation is not always straightforward, as positive results may persist for up to 4 weeks after treatment in the case of HRP2-detecting RDTs; therefore, RDTs cannot be used to investigate treatment failures; and
- ▶ quantification is not possible with commercially available products (although possible in principle).

In elimination programmes, lack of stage specificity is a relative shortcoming in comparison to microscopy. Recent studies have shown, however, that microscopy results in significant underestimation of the frequency *P. falciparum* gametocytes as compared with nucleic acid-based amplification techniques.

RDTs can be used in certain situations in elimination programmes.

- ▶ In areas of no transmission, RDTs may be useful for screening travellers returning from malarious areas as a rapid, preliminary test.
- ▶ Where there is an acute malaria problem but no skilled personnel at hand, such as in complex emergencies, organized groups in remote areas (military, geologists, ship crews) could use RDTs.
- ▶ In health care facilities in which the patient load is low and cases of suspected malaria are rarely seen, RDTs may be a useful for screening, especially if it would take more than 1 day to obtain the result of a slide sent to a reference laboratory.

In all such situations, confirmatory microscopy is also required, irrespective of the RDT result.



### *Molecular-based diagnostic tests of malaria*

A number of different PCR diagnostic techniques exist: single-step, nested, multiplex and quantitative. Alternative nucleic acid amplification techniques have been developed that do not require thermocyclers; the commonest are loop-mediated isothermal amplification and nucleic acid sequence-based amplification. PCR is highly sensitive for detecting a variety of infections, including malaria. It readily distinguishes between the four species of human malaria as well as several animal malaria species. It can also be applied for genetic characterization of strains and of the diversity of infections.

PCR is currently used routinely in malaria for:

- ▶ distinguishing reinfection from recrudescence in clinical trials of antimalarial drug efficacy;<sup>24</sup>
- ▶ blood bank screening; and
- ▶ distinguishing *P. malariae* from *P. knowlesi* in areas of Malaysia where humans are frequently infected by the latter.

In a number of studies, PCR has proven considerably more sensitive, especially when used to examine samples from asymptomatic individuals. Generally, the use of more sensitive diagnostic tools should be considered only in low-transmission settings where there is already widespread use of malaria diagnostic testing and treatment and low parasite prevalence rates (e.g. < 10%). If a programme wishes to adopt PCR for surveillance, the most rational approach would be to discuss the situation with a national research institution that already has experience with PCR, not necessarily for malaria. Submicroscopic *P. falciparum* and *P. vivax* infections are common in low- as well as high-transmission settings. A number of nucleic acid amplification techniques are available and are more sensitive for detecting malaria than RDTs and microscopy. Use of such methods in malaria programmes should be considered for surveys to map the prevalence of malaria, including submicroscopic infections, and to increase the power of surveys at low transmission intensity.

### *Serological methods*

These methods are used to detect current or past infection. They cannot be used reliably to diagnose individual cases because of many uncertainties, including low sensitivity for fresh infections. Serology is widely used in epidemiological studies, especially for obtaining information on the occurrence of malaria in the past; however, it is often difficult to interpret sero-epidemiological results. It is important to note that:

- ▶ the results become positive only several days after the onset of disease: a patient may die before the test becomes positive; and
- ▶ the titres depend on the duration and severity of parasitemia and the duration of the infection(s): if a patient has had malaria several times and did not receive adequate treatment, the concentration of antibodies is high and the patient may remain seropositive for decades after the cure; in contrast, a promptly treated attack produces only a transient, low concentration of antibodies.

<sup>24</sup> Medicines for Malaria Venture. Methods and techniques for clinical trials on antimalarial drug efficacy. Geneva: World Health Organization; 2008.

Generally speaking, high titres indicate actual or recent blood infection of a certain duration; therefore, serology may be useful for screening blood donors, in particular to detect asymptomatic carriers of *P. malariae*. Low titres may indicate an infection that started recently, an infection that was promptly cured after a short attack or a series of past infections that lasted for years before being cured, which might be decades previously.

▶ **Now, do exercise 5.2.**

### 5.2.3 Role of laboratory diagnosis in malaria elimination programmes

In an elimination programme, every single case of malaria must be detected and a *reliable parasitological diagnosis* must be made, including species. Species-specific diagnosis is essential for:

- ▶ clinical management, including choice of treatment;
- ▶ epidemiological prognosis (whether secondary cases are likely and their potential importance);
- ▶ selection of appropriate measures to prevent further transmission; and
- ▶ documentation of the disappearance of particular species.

The diagnosis should be *prompt* so that species-specific treatment can be started the same day and onward transmission is prevented during the following night.

In areas previously infested with *P. malariae*, asymptomatic carriers may persist for many years after the interruption of transmission. For example, in the southern part of the former Soviet Union, transmission of *P. malariae* was relatively high during the Second World War, which left a trail of induced cases in subsequent years. The problem had gradually dissipated by the end of the 1970s, as potential carriers ceased to donate blood because of their advanced age. These carriers could usually not be detected by blood microscopy because of low parasitaemia; however, serology proved useful. This problem has not been encountered often since, possibly because widespread use of chloroquine has reduced the reservoir of *P. malariae* in many countries.

### 5.2.4 Reporting and inference

#### *Reporting of microscope examinations*

Standard reporting includes identification of the species of parasite and the stage (only for *P. falciparum* and only distinguishes asexual and gametocytes). Parasites and stages to be reported are:

- ▶ asexual forms of *P. falciparum*,
- ▶ gametocytes of *P. falciparum* and;
- ▶ all forms of *P. malariae*, *P. ovale* and *P. vivax*.

In all positive slides, parasite density should be determined by counting parasites in thick blood films against white blood cells.<sup>25</sup> In elimination programmes, it is essential that 100 fields of thick film are examined to determine whether *P. falciparum* gametocytes are present or whether an infection is mixed.

<sup>25</sup> Basic malaria microscopy. Part I. Learner's guide, Part II. Tutor's guide. 2nd edition. Geneva: World Health Organization; 2010.

An unequivocal coding system must be used for reporting results by species, including density. A slide can be declared negative only after examination of 100 thick field films. A negative result should be denoted by, for example, “Negative” or “Neg”, but not by “–”. Any abbreviations should be understandable even to people who are not acquainted with the programme; this will facilitate external assessment, including for WHO certification and later research on the history of malaria in the country.

Correct reporting of *P. falciparum* gametocytes is essential. The interpretation is based on the following considerations.

- ▶ Gametocytes of *P. falciparum* develop for 12 days in a hidden state and appear in peripheral blood only after their maturation is complete.
- ▶ Immature gametocytes may appear in peripheral blood before the 12th day, especially when asexual parasitaemia is high; such gametocytes are spindle-shaped and are readily distinguishable from banana-shaped mature gametocytes.
- ▶ The lifespan of individual gametocytes is several weeks (up to 4–8).
- ▶ Immature gametocytes < 6 days of age, i.e. before they appear in the peripheral blood, are eliminated by the artemisinins.
- ▶ Mature *P. falciparum* gametocytes are eliminated only by primaquine (and related medicines, which are not currently marketed).
- ▶ In any *P. falciparum* infection that is not known to have been contracted < 12 days earlier, mature gametocytes and infectiousness should be assumed to be present, even if none are detectable by microscopy.
- ▶ In most infections with asexual parasites, gametocytes are detectable by molecular amplification methods. All malaria infections (microscopic and submicroscopic) should be considered potentially infectious and capable of contributing to ongoing transmission. For research applications, nucleic acid sequence-based amplification (i.e. QT-nucleic acid sequence-based amplification or real-time qPCR) are the recommended detection tools.

Therefore:

- ▶ The concurrent presence of trophozoites and gametocytes of *P. falciparum* seen by microscopy is an indication that the disease started more than 10–12 days previously.
- ▶ The presence of gametocytes in the absence of trophozoites is usually the result of treatment with a blood schizonticide after the sixth day of the disease; if the patient received early, complete treatment with ACT, gametocytes could not appear in the peripheral blood.
- ▶ In elimination programmes, all *P. falciparum* infections should be treated with a single low dose of primaquine, given on the first day of ACT.

In other species, *P. vivax*, *P. ovale* and *P. malariae*, the presence of gametocytes has no special meaning, as they appear from the beginning of parasitaemia and disappear at the same time as the asexual forms (e.g. during treatment with blood schizonticides). Therefore, there is no need for separate recording of sexual forms of those species.

- ▶ **Now, do Exercise 5.3.**

### 5.2.5 Quality assurance

#### Reading material

*Malaria microscopy quality assurance manual*. Version 1. Geneva: World Health Organization; 2009:7–40 ([http://www.who.int/malaria/publications/atoz/mmicroscopy\\_qam/en/](http://www.who.int/malaria/publications/atoz/mmicroscopy_qam/en/), accessed 12 September 2015).

The main points of the quality assurance manual are summarized in Annex 1 of the surveillance manual for malaria elimination. Annex 1 of this module highlights some points of quality assurance that are particularly important for elimination programmes. These supplement the quality assurance manual.

## 5.3 Geographical information

Analysis of geographical information is always important for malaria, but its role varies. Generally, geographical information and mapping can be used in malaria programmes for:

- ▶ **Stratification**, which can be carried out at macro level when a country is divided into regions that are relatively homogeneous for malaria and its known or presumed determinants, and at micro level, in which each district, sub-district or (optimally) village is classified according to an algorithm. The criteria for stratification are usually epidemiological, supplemented by ecological (e.g. altitude, forest cover) and in some cases entomological criteria. See section 3.1.2 for the minimal requirements for macro-stratification in the elimination phase.
- ▶ **Micro-planning of control operations**, especially IRS and larviciding. In the days of the Global Malaria Eradication Programme, this use of geographical information was called “geographical reconnaissance”, defined as “the operation which provides the basis for the choice of field centres and depots, for detailed schedules and itineraries of spraying and surveillance personnel, for the final deployment of transport, and for numerical control of the completeness of work accomplished. It includes collection of information on the number, type, location and means of access of all houses and field shelters, as well as on communications, health units, vehicle-repair facilities, population movements and other relevant factors.”<sup>26</sup> In those days, sketch maps were often prepared for this purpose. Nowadays, *detailed printed or electronic maps* and *village databases* are often available, making this task much easier. The ideal tool, which serves as a platform for operational planning and monitoring, is a web-based public information system combining maps with village databases.
- ▶ **Presentation**, in which the distribution of malaria, identified by surveillance, including surveys, is shown in tables and graphs. Planners and decision-makers, however, need a picture that can be rapidly appraised and may even stimulate thinking about important determinants, risks related to geographical proximity or deficiencies in the surveillance system. *Choropleth maps* (thematic maps in which areas are shaded, coloured or patterned according to, for example, malaria incidence rate) have been used for this purpose since the inception of organized malaria programmes. Nowadays, such maps are easily produced by geographical information system (GIS) software, which also facilitates visual correlation with other thematic layers, such as road networks, human habitations, rivers, forests, health service coverage and poverty levels.

<sup>26</sup> Terminology of malaria and of malaria eradication: report of a drafting committee. Geneva: World Health Organization; 1963.

- ▶ **Analysis.** GIS is a tool for observation and presentation but not analysis; however, it may be the first step in identifying new correlations between variables. To prove such correlations and measure their strength, statistical data analysis is needed. *Spatial statistics* allows refined analysis of many factors with varying geographical distributions over given areas. These techniques also make it possible to estimate, for example, malaria incidence and prevalence in areas where they have not been measured, through a kind of interpolation that takes into account environmental and other covariates, e.g. *kriging*.<sup>27</sup> Spatial statistics require a high density of data points and specialized training and are now widely applied in malaria research but not yet in control programmes.

The above functions are more or less well developed in control programmes and should be continued and modified in the elimination phase to the extent that they can be useful. In the elimination phase, however, the number of malaria cases is so low that statistical analysis plays a limited role. The mindset of the statistician is needed but even more that of the detective: why does transmission continue here, why was this person infected, who is at risk?

In the elimination phase, the priority is to prepare and maintain:

*Large-scale maps of malaria foci*, which show:

- ▶ residence, where cases have been detected;
- ▶ the minimum features of cases, i.e. contracted at residence or elsewhere;
- ▶ breeding sites or potential breeding sites; and
- ▶ boundaries or location of the focus (boundaries may be fuzzy).

These maps must be updated whenever new cases are detected or at frequent intervals. They are helpful to indicate:

- ▶ how control operations can be conducted,
- ▶ neighbouring areas of high risk and
- ▶ landscape features that may be related to the malaria risk (e.g. proximity to a forest, a construction site, a mine, an irrigation project or an airport).

*Small-scale maps of malaria foci*, which show the dynamics of malaria foci in a whole country or the area targeted for elimination year by year. In large countries, these maps may be prepared by province, state or region. They should show all the foci (active, non-active, potential and cleared-up) and also pseudofoci. They should show hydrological networks, landscape divisions, altitude, roads and health facilities. In mountainous areas, malaria transmission *cut-off altitudes* should be shown, i.e. the highest altitude at which malaria transmission has been shown to occur. If both *P. falciparum* and *P. vivax* are endemic, there will be two cut-off altitudes. In countries with large distances from north to south, the cut-off altitudes will vary by geographical region.

### Mapping platforms

Currently, the most widely available electronic mapping platform, which covers most needs, is probably Google Earth™. This application does not, however, cover all parts of the world in equal detail. The related Wikimapia™ might be tried, although questions have been raised

<sup>27</sup> <http://en.wikipedia.org/wiki/Kriging>

about its verification system. A good alternative is *large-scale topographical paper maps*. They can be enlarged on a photocopier, which will give sufficient space to insert sketches of each house, breeding place and other relevant details, with landmarks that are usually marked on such maps. Numbers, which are also used in the database, should be attributed to each household with case(s) and breeding places. *GPS* can be used to determine the coordinates of any point and to link it to a point on the map grid.

▶ **Now, do exercise 5.4.**

## 5.4 Meteorology

Generally, malaria programmes could better exploit the wealth of meteorological information in any country. Often, indications of the high temperature and floods that trigger epidemics may be found in reports of ministries of health, although these reports are seldom substantiated by data.

The meteorological data used in malaria programmes is, in most cases, limited to:

- ▶ the average daily temperatures on each day for the period with temperatures  $> 16^{\circ}\text{C}$ ;
- ▶ daily rainfall; and
- ▶ in some cases, the water level in rivers, sometimes far upstream, as in the Horn of Africa.

### *Temperature*

Monitoring of temperature is indicated only in situations in which the average daily temperature drops below  $20^{\circ}\text{C}$  for extended periods. In these cases, daily or weekly average temperatures can be used to estimate the duration of development of sporozoites and, through this, to identify periods important for forecasting epidemics, such as:

- ▶ the beginning and end of the period of effective infection of mosquitoes (i.e. infection that results in complete development of infective sporozoites);
- ▶ the beginning and end of the period of transmission from mosquito to humans; and
- ▶ the date of possible onset of the first case of fresh human infection during the given season.

For further details, see Annex 2 (Moshkovsky's method).

### *Rainfall*

No general rule can be used to predict whether a particular deviation from the normal rainfall pattern will increase the risk for malaria transmission. All depends on the bionomics of the local vectors and the local environment. Both insufficient and very heavy rainfall can inhibit transmission, and the impact also depends on the temperature. In some cases, even drought may provoke epidemics if the local vector favours small, shallow water bodies, like *An. culicifacies* in Sri Lanka and parts of India. Long-term accumulation of data and comparisons of meteorological and epidemiological information are necessary to develop methods of prediction.

Meteorological data are usually gathered by a network of meteorological stations, and information on specific foci is, as a rule, unavailable and must be interpolated from data at the nearest stations. Interpolation may be dependable in plains but not in mountainous areas, where the altitude and orientation of slopes greatly modify the climate. If the difference in altitude between a place and

the meteorological station is known, a correction can be made on the basis of the assumption that the temperature drops by about 6 °C with every 1000 m of altitude.

These indicators are needed in real time and should be obtained from a meteorological station daily or at least weekly. When malaria transmission depends strongly on temperature or rainfall and it must be known whether recent changes in the situation are related to meteorology (for example in rigorous evaluations of malaria control), indicators are also required for the past, in the form of daily averages over, for example, 10–20 years. These averages are considered to be the normal values of the indicators, and current observations are compared with these averages to give an idea of whether the current conditions are above or below the usual level for the given area and in what direction receptivity is evolving.

Unfortunately, there has been a tendency in recent years for meteorological institutions to charge for their data, because they are underfunded. Vector-borne disease control programmes may therefore require budgetary allocations for this purpose. Some sites on the Internet show free meteorological information, but they do not cover all countries. One website, dedicated to climate and malaria in Africa (<http://iridl.ldeo.columbia.edu/maproom/Health/Regional/Africa/Malaria/>, accessed 14 September 2015), is reasonably user-friendly. Many other websites with meteorological data are interesting but difficult to use for people who have not been trained in geography or meteorology.

## 5.5 Malaria case detection and epidemiological investigation

Read pages 6–21 of the surveillance manual for malaria elimination. Discuss the salient points with the tutor, with special reference to the definitions of a “case” and a “focus”. Use examples from your own practice. Investigation and classification of malaria cases and foci are hallmarks of surveillance during malaria elimination programme activities. It is essential that malaria programme staff understand case and focus investigation, as these form the basis for nearly all subsequent programme activities.

Note that, while the WHO definition of an *imported case* is one in which the infection was contracted in another country, it may be rational during pre-elimination and elimination phases to also distinguish cases that were contracted in the country in which they were detected but not in the same locality. Such cases could be called “domestically imported” cases. Depending on the size of the country and the structure of the programme, these may be further differentiated, as for example imported from within same district or province or the same state. Rapid information for the health authority in the area in which the infection was contracted is of course an essential function of surveillance.

► Now, do exercises 5.5 and 5.6.

## 5.6 Malariometric indicators

The following malariometric *indicators*, which are generated by malaria surveillance systems in which microscopy is used for diagnosis, are most useful *in advanced control programmes and in the pre-elimination phase*. In the elimination phase, the indicators listed in Box 3.1 in the surveillance manual for malaria elimination are of higher priority.

### 5.6.1 Indicators based on microscopy

#### *Prevalence of plasmodial infection among people examined*

*Slide positivity rate* (see definition in the surveillance manual for malaria elimination, p. xi). In areas where there is more than one species of malaria, species-specific indicators should be used for the two main species, *P. falciparum* and *P. vivax*, the slide falciparum rate (SfR) and the slide vivax rate (SvR), respectively.

#### *Incidence*

Parasite incidence is the number of positive cases detected in an area over a defined time divided by the population of the area, usually expressed per 1000 people. Parasite incidence is often measured annually, in which case it is referred to as the annual parasite incidence. Other intervals may be used, e.g. 1 month, in which case the indicator would be the monthly parasite incidence, which may be convenient for describing malaria epidemics. In areas where there is more than one species of malaria, species-specific indicators should be used for the two main species.

#### *Coverage of case detection*

Coverage of the population by blood examination is measured as the blood examination rate, the number of people whose blood was examined microscopically divided by the population surveyed. The rate is usually expressed as a percentage and measured annually, in which case it is referred to as the annual blood examination rate.

None of the three indicators (slide positivity rate, parasite incidence and blood examination rate) provides complete information on the malaria situation. For example, the annual parasite incidence may be low because malaria became rare, but it would also be low if the health services stopped collecting blood for examination. The information would be complete if at least two of the three indicators were used. In other words, if two indicators are known, the third may be derived from the following equations:

$$PI = SPR \times BER$$

$$SPR = PI / BER$$

$$BER = PI / SPR$$

where PI is the parasite incidence, SPR is the slide positivity rate, and BER is the blood examination rate. Note that the dimensions of the terms should be the same, e.g. all must be presented as proportions or percentages.

#### *Percentage of *P. falciparum**

This is a proportion in which the numerator is the number of *P. falciparum* cases, and the denominator is the total number of confirmed cases. An increase may be due to an increase in the prevalence of *P. falciparum* and/or a decrease in the prevalence of *P. vivax*.



Discuss the following example:

100 cases of malaria were detected in an area: 50 *P. falciparum* and 50 *P. vivax*. After an intervention, the numbers decreased to 12 and 8 cases, respectively. The percentage of *P. falciparum* before the intervention was 50%, and that after the intervention was 60%. Does this increase in the indicator mean that the situation of *P. falciparum* has deteriorated?

## 5.6.2 Disease surveillance indicators based on other criteria

### *Malaria detected by RDT*

In malaria elimination programmes, if RDTs are used only as preliminary tests and their results confirmed by blood microscopy, the results should not be included in the computation of the malarionetric rates, to avoid double counting. Malaria diagnosed by RDT without slide examination should be included in a full case investigation and in calculation of malaria epidemiological rates.

### *Fever rate and incidence of suspected malaria*

As clinical suspicion of malaria is an indication for examination of blood for malaria, it is essential to know how often people attend health facilities and are considered to have suspected malaria. In the elimination phase, malaria is a rare disease, and not all people with fever are expected to have their blood examined for malaria. Each programme should establish criteria for “suspected malaria”. Such cases should be tested. They usually include people with no other obvious explanation of the fever and those with an epidemiological risk factor, such as having sojourned in an endemic area within the past 6 months. In active foci, to increase the probability of detecting most infections, all fever cases should be considered as suspected malaria; current fever or a history of fever within the past 2–3 days is usually an adequate criterion. In active foci, information could be collected on the time of fever, such as:

- ▶ fever now
- ▶ fever 1–3 days previously but not now
- ▶ fever > 3 days previously.

## 5.7 Data recording and reporting

Read pages 22–27 of *surveillance manual for malaria elimination*. Discuss the salient points with the tutor. Use examples from your own practice

## 5.8 Establishing a surveillance system in the elimination phase

Read pages 28–31 of *surveillance manual for malaria elimination*. Discuss the salient points with the tutor. Use case studies from your own practice.

This section describes the transformation of surveillance conducted for malaria control to surveillance conducted for malaria elimination. For more details on establishing malaria

surveillance in areas with limited or inadequately developed malaria surveillance, see *Disease surveillance for malaria control*.

► **Now, do exercise 5.7.**

## Unit 5 exercises

### Exercise 5.1

In small groups, on the basis of the boxes 1.1–1.3 in *surveillance manual for malaria elimination*, prepare a table illustrating features of the malaria surveillance system in three types of setting (the first line of the table is partially filled in):

Feature	Control phase (high and moderate)	Control phase (low)	Elimination phase
Registers of individual cases	Cases, sometimes without parasitological confirmation, at health facility level only (e.g. in log book form)	Cases, all confirmed parasitologically at health facility level, with aggregate data at district level	...
...			

### Exercise 5.2

In small groups, discuss the methods for diagnosing malaria and the advantages and disadvantages of each method. Prepare a table illustrating your points. Discuss your findings in plenary.

Method	Advantages	Disadvantages

### Exercise 5.3

In small groups, discuss the kind of information that should be given in laboratory reports, and express your views in a table, as follows (the first line is filled in as an example):

Feature	Purpose	Examples
Species	For a clinician, - to guide treatment - to make a clinical prognosis	In a case of falciparum malaria, the treatment must be ACT  The prognosis may be bad, depending on the other features listed
Species	For an epidemiologist, ...	...

### Exercise 5.4

Visit the website <http://www.jsk.gov.in/distpop.asp>, which was prepared by the Jansankhya Sthirata Kosh (National Population Stabilization Fund) to support health care planning in India. Select a rural district, and look at the information found under “Map” and “Distance”. In relation to malaria, what can this website be used for, and what can it not be used for?

Identify a village on the “Distance” Excel sheet. Note its name, population, the sub-district (*taluka*) and the district in which it is located. Now, try to find this village in Google Earth™ or Google Map™. Imagine that three malaria cases have been found in the village; from the sketch maps, you know the houses in which they were found. Likewise, you can identify breeding sites near the village.

How will you prepare a map of the focus? How will you update it? How will you make a map of the state showing all the foci? Which features of the maps on the website and of Google Earth™ and Google Map™ are useful for this exercise and in which way?

Use the guidance below to delimit a focus in your own country. If you know the location of one or more malaria cases, locate them on Google Earth™. If you do not know the exact geo-coordinates, put “placemarks” (see below) where you think they occurred. You may also choose a particularly receptive area and placemarks for imaginary cases. Note that the markers should be placed at the patient’s residence at the time of detection, which is not necessarily where the patient was infected. Then, use the guidance below to draw a polygon delimiting the focus. Create a jpeg file, and insert it in a work document. Supplement the image with explanatory notes. Discuss the results within the group and with a facilitator.

**Practical delimitation of a focus** (excerpt from draft guidelines on malaria elimination surveillance for Namibia)

A focus is identified and delimited as follows:

1. One or more cases are detected and classified in a particular area, which may be a part of a city, a village or several villages or homesteads that are relatively close together.
2. The most likely exact place of infection of each case is identified from the case investigation form and, if possible, a visit to the patient’s home. This place is identified on a map, which is large enough to show houses in a village. For each case, longitude and latitude are determined. This can be done with a modern cell phone. If it is done on Google Earth™, mapping can start at the same time. If you are not familiar with Google Earth™, download it (free) from the Internet, and spend some hours taking an online tutorial and playing with it (for example, to find your house and those of your relatives). Then, open Google Earth™ on the Internet, find the location of the case(s), and put a placemark there. (Placemarks are electronic yellow thumbnails in the software; the tool is on the bar above the map.) If the information is not sufficient to identify the location right away, print the area from Google Earth™ (Command File>Print>. Screenshot), take the printed map to the field, identify the place where the patient was probably infected and mark it with a pen, return to your computer and place the placemark. Alternatively, take a tablet to the field and place the placemark directly. At this point, active case detection can be begun in nearby houses, which may lead to the detection of more cases.
3. Identify potential breeding places by asking local people about where to find water collections that might be potential breeding sites within a maximum distance of 2 km. Inspect those sites to determine whether they qualify as potential breeding sites according to the above descriptions. If you know how, look for anopheline larvae, and, if you think you have found most breeding sites and you have larvicide, apply it right way. Using local information or Google Earth™, identify other potential breeding sites. Mark actual and potential breeding

sites on the map printout or on the tablet, using the polygon drawing tool, which is opened from the bar above the map.

4. Delimit the focus. Now, on the basis of the location of:

- ▶ the identified malaria cases (the index case and others that may have been found in the area since),
- ▶ potential and actual breeding sites,
- ▶ the distribution of the population and
- ▶ local population movement,

draw a line around the area that you consider to be the focus in Google Earth™ with the polygon drawing tool.

Then, click File>Save>Image to obtain a jpeg file, which can be stored and copied into a Word document (Fig. 5.1).

**Figure 5.1.** Attempted delimitation of a focus around an index case in Khorixa, Namibia



As this exercise was done only on a computer, important elements may have been overlooked. The picture indicates dried-out streams, around which breeding sites could have formed. They are so widespread that they have not been delineated. The white line shows the delineation of the focus made with the polygon tool. As the cursor was placed at the house of the index case, the geographical coordinates of the case appear in the lower right corner with the altitude above sea level, in feet. Near the lower left corner is a horizontal red line made with the ruler tool to mark a distance of 1 km.

In this example, delimitation of the focus was easy. There was a concentrated human habitation in a small area, and the terrain, with numerous temporary streams, suggests the presence of breeding sites in the rainy season. There was no nearby human habitation outside the village (see screenshot, Fig. 5.2).

Figure 5.2. Khorixa, Namibia, and surrounding area in Google Earth™



By zooming out in Google Earth™, it can be seen that there is no human habitation within a radius of 5–8 km from the assumed focus, so it is unlikely to be larger.

### Exercise 5.5

Study an example of reintroduction of malaria in a village in the Russian Federation (file Exer5\_5.pptx), and discuss it with the tutor. Also use examples from your own practice.

### Exercise 5.6

In small groups, do the following exercises on cases and foci classification. Use the keys on pp. 14 and 21 in *Disease surveillance for malaria elimination*. Discuss the results in plenary.

All the events described in the situations below are real and taken from published or unpublished sources.

#### *Situation 5.6.1*

This situation took place in Moscow, Russian Federation, where local transmission of malaria had been interrupted about 15 years earlier. Climatic conditions usually make transmission of malaria possible during about 2 months, between June and August.

Description of cases:

Miss M., a biologist living in Moscow, visited tropical islands in the Pacific Ocean, including New Guinea, aboard an oceanographic ship in June, July and August 1971. She became acutely ill soon after returning home. She was hospitalized and treated with chloroquine (3 days) and primaquine (14 days). On 3 January 1972, she became ill again; *P. vivax* was demonstrated in a thick smear.

Dr B., also from Moscow, was planning to start research on malaria serological diagnosis and required malaria antigen. At that time, slides of heavily infected blood were used for this purpose. He decided to produce the antigen from his own blood and injected a portion of blood from Miss M. into himself. He became ill with vivax malaria on 10 January.

Questions:

1. To which category does case M. belong?
2. To which category does case B. belong?

### Situation 5.6.2

Situations 2 and 3 occurred in Azerbaijan. Malaria was controlled and transmission interrupted in most districts by the end of the 1950s. *P. falciparum* had been eliminated, and no renewed transmission was detected in the country subsequently; however, sporadic cases of *P. vivax* malaria continued to occur in a few districts in the Kura-Aras lowlands. They were the source of a major outbreak starting in 1969, which spread over several districts by 1971.

Transmission of malaria in Azerbaijan usually takes place between mid-May and the beginning of September. As temperatures are high during this period, development of *P. vivax* in mosquitoes takes about 12 days. Vectors (mostly *An. sacharovi*) were abundant in villages, as, in the absence of tap water, people in almost every household stored water in small basins.

In spring 1971, before the beginning of the transmission season, drastic measures were undertaken: every person who had been at risk in 1970 was given mass prophylactic treatment with chloroquine (3 days) and primaquine (14 days). There was a considerable incidence of malaria due to late manifestation of infections from 1970, but malaria became sporadic immediately after the mass drug administration, although cases continued to emerge.

The health services were fully accessible and functional, and intensive surveillance was conducted during the described period.

During summer 1972, four cases of malaria were detected in a district (population about 50 000): three in Minbashly village (one detected on 11 June and two on 13 July) and one in Molday village (detected on 19 July). In Minbashly, some cases of malaria had been found in 1971, but Molday had been free from malaria since 1970.

Description of cases:

Two brothers living in Minbashly, A.A. and A.V., aged 4 and 7 years, became acutely ill on 12 July and were admitted to the district hospital. Vivax malaria was diagnosed in both on 13 July. Epidemiological investigation did not show any other case in Minbashly. The children had not left Minbashly during the summer of 1972. Their mother told interviewers that her sister, M., aged 13 years and living in Molday, was also ill. A team went to Molday and found *P. vivax* in the thick film taken from M. on 19 July 1972. M. had often visited her sister's family. Epidemiological investigation did not reveal any other case of malaria in Molday.

Questions:

1. To which category do the cases A.A. and A.V. belong?
2. To which category does the focus in Minbashly at the end of July 1972 belong?

3. To which category does the case M. belong?
4. To which category does the focus in Molday at the end of July 1972 belong?

### Situation 5.6.3

For a description of malaria prevalence in Azerbaijan in the 1970s, refer to situation 5.6.2.

In a district with about 50 000 population, four cases of malaria were detected during the summer of 1972, three in Meghrably and one in Shaumian.

In Shaumian, a female patient, A., 15 years old, became acutely ill on 30 September 1972. On 2 October, she was examined by a medical officer, who took a thick blood film, in which *P. vivax* was found on 3 October. The patient lived in the centre of the village near the Shaumian rural hospital. She had not left home during the summer of 1972. This was the only case of malaria in this village in 1972.

It was found that, 1 month before the case of A., another case of malaria had been treated in Shaumian. The patient, H., a 67-year-old man living in Meghrably, became ill on 27 August 1972 and was admitted to the Shaumian rural hospital on 3 September 1972. The condition was first diagnosed as acute cholecystitis, but the correct diagnosis of vivax malaria was established on 6 September.

Questions:

1. To which category does case A. belong?
2. To which category did case H. belong, when in Shaumian?
3. To which category does the focus in Shaumian belong by the end of October?

### Situation 5.6.4<sup>28</sup>

In Kern county, California, USA, malaria had been absent since the Second World War. In February 1971, three cases of vivax malaria were detected in patients who had never left the USA. All were drug addicts who used heroin intravenously by sharing syringes. Epidemiological investigation revealed 47 cases of vivax malaria, which were confirmed by positive films, and eight parasite-free but serologically positive cases. All the cases were in heroin addicts in several towns in the county.

Only one (a sero-positive case, C.L.) had has malaria before this outbreak. He had become ill in July 1970, in Viet Nam, and had received chloroquine. After returning home, in August 1970, he experienced some attacks of febrile illness, but was not examined by a physician. The first secondary case began in November 1970 and the last in April 1971.

Questions:

1. To which category does case C.L. belong?
2. To which category does the other cases belong?
3. To which category does the foci belong?

<sup>28</sup> From Friedmann CT, Dover AS, Roberto RR, Kearns OA. A malaria epidemic among heroin users. *Am J Trop Med Hyg* 1973;22(3):302–7.

### Situation 5.6.5<sup>29</sup>

In Shirpur *taluk* (sub-district), Dhulia district, Maharashtra State, India, with a population of 160 000, transmission of malaria had been virtually stopped by 1962. In that year, seven cases of malaria (all due to *P. vivax*) were detected; five were classified as imported from Madhya Pradesh State and two as relapsed cases. Surveillance operations were well established.

In January 1963, 27 cases of vivax malaria were detected in three villages of Boradi section in the *taluk* (see table). During 1962, there had been no cases in that section.

Village	Population	No. of cases, 1–15 January	No. of cases, 16–31 January
Malkatar	120	8	7
Lakkadpur	110	0	7
Kolsapani	40	0	5
All	270	8	19

The following features were found in all cases:

- ▶ All had an attack of fever 2–3 days before blood was taken.
- ▶ None had experienced the same type of fever in the past 2 years.
- ▶ Only adult males were affected.
- ▶ All had visited a particular area of the forest shortly before falling ill.

About 70 men had gone in groups with bullock carts in January 1963 to cut bamboo, with the permission of the Forest Department. They camped in the jungle on a cleared spot near a temple known as Lakdya Hanuman (dedicated to the monkey god Hanuman), by a stream called Kalapani. The water of the stream was considered to be bad, and it was known as “black water”. The journey to and from the spot took about 2 days, and they had spent about five nights at Lakdya Hanuman. They fell ill 8–10 days after returning from the forest.

Two mass blood examinations in February and March 1963 gave negative results, and no other cases were detected in the area in 1963.

Questions:

1. To which category do the cases belong?
2. To which category of foci do the three villages belong?
3. Is the area around Lakdya Hanuman a focus of malaria?
4. What was the source of infection in this case?

### Situation 5.6.6<sup>30</sup>

The cases described occurred in the region of Lviv, Ukraine, in 1985.

A patient A., a 55-year-old man, had undergone surgery for cholelithiasis in December 1984. Complications developed, and he was operated on twice again, on 2 and 13 April 1985. Between 3 and 20 April, he received 15 blood transfusions for several episodes of intense bleeding. After that, his condition stabilized, but his relatives considered that another transfusion might speed

<sup>29</sup> Personal communication from Mr Kulkarni, District Malaria Officer, Maharashtra State, India, 1982.

<sup>30</sup> Personal communication from L.I. Dan'shina, parasitologist, Lviv, Ukraine, 1986



his recovery. They somehow convinced the doctors and found two young men who volunteered to donate blood. A direct blood transfusion was given on 30 April.

One of the donors, B., had served in Afghanistan and had been demobilized in December 1984. He later recollected that he had had malaria in October 1984 for a rather long time but had not received a full treatment course. He fell ill 2 weeks after having donated blood, on 15 May. He sought medical care on 17 May and told the staff that his condition might be malaria; *P. vivax* was found in his blood the same day. He also told the doctor that he had donated blood.

The recipient, A., was therefore contacted the same day. His status corresponded to his surgical condition, and he had no fever; however, on 21 May, his temperature rose to 39 °C with slight chills and rigor, and *P. vivax* was found. Chloroquine was started, but the fever attacks continued in the evening of 22 May and the morning of 23 May, with his temperature reaching 38.4 °C. After that, his condition rapidly improved, and he was discharged on 6 June 1985.

Questions:

1. Classify cases A and B.
2. Do you think B had parasites in his blood during the last days of April and at what density?
3. Why was A asymptomatic during most of May?
4. What is unusual about this case?
5. Is there any indication that the parasites in B. were resistant to chloroquine?

#### Situation 5.6.<sup>31</sup>

Oman started a campaign to eliminate malaria in 1991. As a result, the annual number of cases after 2000 dropped from about 300 000 to isolated cases. Certification of malaria elimination was contemplated. Unfortunately, an outbreak of local transmission occurred in 2007 in Izz, Manah, Dakhliya region.

Izz is a rural community in the desert, with good roads, electricity and some air-conditioned modern houses, where relatively poor immigrant labourers live in compounds; they tend to sleep outside at night. Mosquito breeding places are created by small-scale irrigation systems on local farms, where water is directed through open channels (*falaj*) to date palm plantations and open storage tanks.

*Patient 1:* On 9 July 2007, a 22-year old Pakistani national who had returned to Oman from home leave 15 days earlier (on 22 June), fell ill with fever. Vivax malaria was diagnosed on 16 July, 7 days after the onset of symptoms. The case was investigated by the local authorities.

During July–September 2007, nine other cases of vivax malaria occurred in the same locality, all among immigrant labourers. Therefore, a full investigation was launched by the central team on 11 September.

Patients 2, 3 and 5 (diagnosed on 4, 4 and 20 August, respectively) were not in Izz when they contracted malaria (taking the incubation period into account), and were therefore not part of this outbreak.

<sup>31</sup> Personal communication from Dr Said al-Mukhaini, Malaria Elimination Programme, Oman, participant in a WHO course in Moscow, 2010

*Patient 4:* On 8 August 2007, a 29-year-old Bangladeshi national who lived in the same locality as patient 1 but who had lived continuously in Oman for the past 4 years, fell ill with fever. Vivax malaria was diagnosed on 14 August, 6 days after the onset of symptoms. The case was investigated and classified as “imported”; however, the notification form and the investigation form for this patient lacked the date of arrival in Oman, which would have alerted the authorities to the likelihood of a locally acquired infection.

*Patient 6,* in whom vivax malaria was diagnosed on 22 August, lived in the same compound as patient 1. He had arrived from India 10 months earlier.

*Patients 7* (diagnosed on 27 August) and *10* had arrived relatively recently in Oman before falling ill, after 26 days and 2 months, respectively.

*Patients 8 and 9:* On 1 September 2007, a 36-year old Bangladeshi who shared the compound with patient 4 and their 23-year-old Pakistani neighbour (living about 200 m away) fell ill with fever. Vivax malaria was diagnosed on 6 and 7 September, respectively. Both men had lived continuously in Oman for the preceding 2 years, making it very likely that their infections were acquired locally.

Several breeding sites positive for *Anopheles* larvae were identified in the locality, and adult mosquitoes were detected in the house of patients 4 and 8. Intervention measures were started on 12 September, including case detection, fogging and larviciding. No further cases occurred.

Questions:

1. Classify the cases.
2. Classify the focus (a) on 12 July, (b) on 12 August and (c) on 12 September.
3. What important information was missing? Is this information critical for decision-making?
4. Were the interventions pertinent? Was anything missing?
5. Do these events jeopardize the certification of malaria elimination in Oman?

### Exercise 5.7

Prepare a plan for establishing a surveillance system for the country of one or several members of the group. Discuss it in plenary.

Note that this may be the main course exercise and will be continued in following learning units. The tutor will provide guidance.

# LEARNING UNIT 6

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## Prevention of reintroduction

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### Learning objectives

By the end of this unit, participants should be able to:

- Explain the relations between receptivity, vulnerability and malariogenic potential and the likelihood that malaria will be re-established
- Define vigilance, and describe the patterns of vigilance required to prevent re-establishment of transmission in different settings
- Describe the required capabilities and organization of the health services in countries that have recently been freed from malaria transmission
- Determine the training required for adequate malaria vigilance in different settings

## Reading material

Malaria elimination field manual, Chapter 6 (p. 40–44)

## Introduction

This learning unit deals with requirements after malaria-free status has been attained. As will be discussed later, especially in learning unit 8, an assessment of the possibility of preventing reintroduction is essential for the assessment of feasibility of malaria elimination. In national elimination endeavours, the challenges of maintenance often become apparent long before national-level malaria-free status is near, when some areas have been rid of malaria while others are still endemic. This unit introduces the important concepts of receptivity and vulnerability, which are in fact useful in all phases of elimination.

### 6.1 Prevention of reintroduction

Importation of malaria has two types of consequence:

- ▶ clinical consequences: disease or even death of the person who imported malaria, and
- ▶ epidemiological consequences: reintroduction of malaria, with resumption of malaria transmission from imported cases.

During the advanced stages of the programme, when complete interruption of malaria transmission has been achieved, activities will be focused on preventing re-establishment of malaria transmission in the area covered by the programme. The tasks of the programme at this stage will be:

- ▶ In relation to the risk for importation of parasites and vectors (*vulnerability*, as explained below):
  - ▶ to reduce the risk for importation of parasite carriers;
  - ▶ to minimize the time during which an imported case can act as a source of infection,
  - ▶ to reduce the risk for importation of infected vectors; and
  - ▶ to reduce the risk for importation of new vectors.
- ▶ In relation to the risk for local transmission (mainly *receptivity*):
  - ▶ to maintain the vectorial capacity at its lowest possible level, with priority to vulnerable areas.
- ▶ In relation to the ability of the health systems to react (*vigilance*):
  - ▶ to detect possible sources of infection promptly;
  - ▶ to ensure that they do not infect local mosquitoes or become sources of induced malaria;
  - ▶ to maintain good practice in public and private health services in relation to malaria cases, by training, dissemination of information, awareness-raising and logistics;
  - ▶ to maintain the capability of local health services to react promptly to any outbreak, by adequate training, financing and logistics; and
  - ▶ to influence the practices of relevant populations, including those at high risk, in relation to malaria, by health education and collaboration.

## 6.2 Vulnerability and receptivity

The concepts of vulnerability and receptivity are explained in learning unit 3 (section 3.1.4). They were introduced at a WHO conference in 1978.<sup>32</sup> Unit 8 provides more quantitative treatment of these concepts.

### 6.2.1 Vulnerability

Malaria is usually imported by infected humans. Less frequently, the disease may be imported by infected vectors.

The degree of vulnerability can be indicated by the traditional patterns of travel into the area and any recent changes found during epidemiological investigation of recent cases or of data on migration (see unit 8). The number of people arriving, their origin, the categories of people involved, their local destination and their length of stay are relevant to assessing changes in vulnerability. The probability of importation of vectors should also be considered.

#### *Vulnerability related to importation by humans*

Vulnerability is conditioned by patterns of human migration from areas where malaria transmission is likely. The roles of the two main groups—local people going abroad and incoming immigrants—are different.

#### *Travel by local people*

Local people travelling abroad are not usually immune to malaria. If they return infected, they usually have acute, overt disease, which incites them to seek medical treatment. Delays in detection usually occur because of errors by medical staff who fail to take a travel history and do not request blood examination. Detection may also be delayed because of the behaviour of travellers, who may not wish to disclose their travel for one reason or another or may fail to appreciate the seriousness of the disease.

The probability of contracting malaria is directly related to the duration of the stay and the local risk for malaria; however, even a one-night halt may be sufficient to incur a fatal infection (e.g. cases of malaria imported by aircraft crews). People who stay longer may have several episodes of malaria when abroad and may develop some immunity.

The nature of activities when abroad is a strong determinant of contracting malaria. Tourists who stay in large cities or resorts are less exposed than people who engage in eco-tourism; volunteers working and living among villagers are particularly susceptible. Military personnel are often prone because of their operations under arduous conditions and because the risk for malaria increases during military conflicts. This was seen during the large-scale operations by the USA in Viet Nam and, later, by the former USSR in Afghanistan.

Sailors belong to a category that is often overlooked. They may contract malaria in ports without going ashore and develop malaria on board or after reaching home.

<sup>32</sup> Receptivity to malaria and other parasitic diseases: report on a WHO working group. Izmir, 11–15 September 1978. Copenhagen: WHO Regional Office for Europe; 1979 (EURO Reports and Studies No. 15; [http://whqlibdoc.who.int/euro/r&s/EURO\\_r&s\\_15.pdf](http://whqlibdoc.who.int/euro/r&s/EURO_r&s_15.pdf), accessed 14 September 2015). It is not clear how these terms were selected. In mnemotechnics, **r**eceptivity represents mainly the **e**ntomological factor and vulnerability mainly the **h**uman factor.

In general, the probability that returning local people are a source of reintroduction is lower than that of immigrants.

### *Immigration*

Immigrants can be subdivided into several categories. Those who may play a major role in the importation of malaria are migrant labourers and refugees; exchange students, diplomats, business people and other short-term travellers play a minor role.

The role of immigrants as sources of resurgence of transmission depends on several interrelated factors. A major factor is the level of endemicity in the place of origin. High endemicity not only increases the probability that the person is infected but also increases the level of immunity, making cases less easy to detect. Adults from endemic areas often do not take malaria seriously: they know the symptoms of malaria, know how to treat it and sometimes have antimalarial drugs with them.

Sometimes, new immigrants spend a few days in a transit place, which might be a small, temporary settlement, before finding a job and moving elsewhere. This scenario is important because, if they infect local mosquitoes during this initial stay, secondary cases will be detected several weeks later, when it is impossible to identify the primary case. The locations of such transit camps (which are often unofficial) are vulnerable.

Immigrants seeking economic opportunities and refugees often live in rural areas under precarious conditions, e.g. in unfinished buildings. This may also be the case for long-distance lorry drivers, who were implicated in disseminating malaria from Azerbaijan to the Islamic Republic of Iran during the conflict over Karabagh between Azerbaijan and Armenia in the 1990s.

In areas of seasonal transmission, special attention should be paid to transmission periods; however, importation may be important during any season if imported cases are not detected promptly and radically treated.

### *Vulnerability related to importation by vectors*

The two types of vector importation are of infected vectors and of alien vectors previously not present in the area.

#### *Importation of infected vectors*

Most importation is by aircraft. The term “airport malaria” (an incorrect translation of the French “paludisme aéroporté” which means “airborne malaria”) is applied to cases in local people (often airport workers) due to exotic infected mosquitoes that arrive by plane. These vectors can tolerate the low pressure and low temperature in the cargo bay. They resume their activity on arrival, infecting a few people, but cannot survive for long or procreate; however, they can make short journeys by land transport in the vicinity of airports.

International sanitary rules mandate desinsection of aircrafts arriving from endemic countries. Not only malaria vectors are targeted, but many other vectors and pests. Concern about possible importation of malaria vectors to North Africa along the trans-Saharan highway during its construction in the 1970s proved to be misplaced, as anophelines probably cannot withstand long journeys by land because of their behaviour: they cannot breed in the small containers that

may be on board a lorry and seek breeding places every 1 or 2 days. It was suggested that malaria vectors could be imported by land in baggage, but this has not been documented.

Importation across land borders is important when the malaria situation is different on the two sides of the border. This was the case on the Tajik–Afghan border in the 1970s. Malaria had been almost eliminated in Tajikistan, while in Afghanistan the national malaria eradication programme faltered. Release of labelled mosquitoes on the Afghan side of the border showed that they easily crossed the Panj River to the Tajik side. This mechanism was given as the cause for lingering transmission in the border villages of Tajikistan at the time.

#### *Introduction of more potent vectors*

This topic does not fall exactly under vulnerability; however, it is highly relevant to malaria elimination and should be understood. With increasing south–south air travel, such risks must be kept in mind. In Brazil in the 1930s and in Egypt in 1942, the recipient areas were endemic, with *P. falciparum* present; however, local vectors were unable to maintain a high level of transmission. This changed when a new vector appeared in these regions, which belonged to the *An. gambiae* complex (probably *An. arabiensis*). Because of the increase in vectorial capacity, massive epidemics followed, with high mortality. It took years of intensive larviciding to get rid of the newly introduced vector. How the new vector arrived in Brazil is not clear, but it was probably by boat. In Egypt, it arrived through the Nile valley.

### 6.2.2 Receptivity

Receptivity is the ability of an ecosystem to support malaria transmission; it is closely related to vectorial capacity. Receptivity is conditioned by ecology in a broad sense, i.e. a combination of abiotic, biotic and human factors.

#### *Physical environment*

A limiting factor is temperature, which may support the development of sporozoites in local mosquitoes or allow at least limited survival of an imported infected mosquito. Otherwise, the environmental characteristics that favour receptivity are those that favour high density and longevity of locally important vector species.

#### *Biotic elements*

Local populations of vectors are usually present at the time of transition to maintenance. Once depleted, they tend to be restored and may return to the pre-elimination state. Often, however, vector populations are not restored because of environmental changes such as land reclamation, a shift from subsistence agriculture to export crops and better sanitation. Pollution from increasing industrial development may also be detrimental to mosquito populations.

Species of larvivorous fish that might have been used during elimination may find suitable habitats and become part of the local fauna.

All anopheline species are not susceptible to various species and strains of malaria parasites. Palearctic mosquitoes do not support the development of Afrotropical *P. falciparum*; although *P. falciparum* from sub-Saharan Africa is the type most often imported into Europe, not a single case of re-establishment of *P. falciparum* transmission has been documented in Europe, North

Africa or Palearctic areas of the Middle East. The compatibility of parasites and vectors is crucial for the success of importation.

### *Human factors*

Except on the Indian subcontinent, urban conditions are less favourable for mosquito breeding, and their receptivity is low. Large cities are not, however, totally exempt from malaria transmission. In some countries in which malaria transmission was interrupted, reintroduction occurred more than once in locally receptive areas in large cities, such as in Moscow, Nizhni-Novgorod and Perm in the Russian Federation and Houston and New York in the USA. This should be understood in the context of the vulnerability of many large cities, which offer a variety of job opportunities.

Small rural settlements are often more prone to lingering transmission after reintroduction because they are neglected or are not considered to be separate foci for administrative convenience.

Convenience may act in either direction. For example, electricity allows the use of air conditioners, which decreases mosquito–human contact. At the same time, people are more likely to spend time in the open air when there is electric light, which may increase transmission if the vector is exophagic.

The availability of piped water decreases the proliferation of mosquitoes, because people do not need to store water. At the same time, broken pipes may create additional breeding places.

### **6.2.3 Malariogenic potential**

Vulnerability results in importation of malaria, whereas receptivity reflects its ability to take root after importation. Some highly vulnerable areas have limited receptivity to malaria and vice versa. Thus, vulnerability and receptivity together define the malariogenic potential of a territory. If either of these factors is 0, the probability that malaria will become re-established is 0, even if the other factor has a high value. Both factors can change over time. For example, vulnerability may increase with the arrival of a group of refugees, migrant workers, international civil servants or exchange students from a malarious country. Receptivity may be increased by a development project that creates breeding sites and increases human–vector contact. Large development projects may also attract external workers, thus possibly increasing vulnerability; irrigation projects, mining and clearing of forests for agriculture are typical examples. Malariogenic potential may vary seasonally and cyclically.

Formerly malarious areas remain, as a rule, more receptive, but not always. Sometimes, elimination of malaria is associated with a profound change in the environment, including land reclamation and better housing, sanitation, health infrastructure and educational level. These make the spread of malaria more difficult.

Malariogenic potential should be stratified on the basis of the maps used during elimination. Such maps should be constantly updated.

## **6.3 Vigilance**

After the first successes of the Global Malaria Eradication campaign, maintenance of the no-transmission status of the countries that achieved it after the launch of the campaign in 1955 became urgent. The first recommendations on this subject were made by the WHO Expert



Committee on Malaria at its 12th and 13th meetings<sup>33,34</sup>. It stated that a system of vigilance had to be established to counteract the risk for re-establishment of malaria, with an epidemiological service and an organization for initiating prompt remedial measures. Vigilance was defined as a function of the public health service during the maintenance (prevention of reintroduction) period, consisting of “alert watchfulness for any occurrence of malaria in an area in which it had not existed or from which it had been eradicated, and the application of the necessary measures against it.”

The Committee stressed that vigilance must totally cover the territory in space and in time and be adequate to find any case of malaria occurring at any time anywhere in areas free of malaria transmission. Vigilance activities should be taken over by the general health services, although a specialized antimalarial service should remain part of the country’s epidemiological service and should share the responsibility for case detection, epidemiological investigation and remedial measures with the general health services.

The transition from activities to interrupt transmission to maintenance can be precarious, with a high risk that malaria transmission will resume. The absence of cases can result in loss of interest in malaria by health professionals, politicians and the general public, who will be increasingly reluctant to commit personnel, time and expenditure to a disease that no longer occurs. Loss of skills in clinical and microscopy diagnosis of malaria and epidemiological investigation of cases may be expected, and there will be little opportunity for training with actual cases.

Vigilance activities should be adapted to the malariogenic potential and the level of development and effectiveness of the general health services in the area.

- ▶ In areas with low receptivity and vulnerability, early case detection by a vigilant general health service, complemented by epidemiological investigation of every case and focus and appropriate remedial measures, may be sufficient to prevent re-establishment of transmission.
- ▶ With increasing malariogenic potential, these activities might have to be supplemented by active case detection, which might be combined with other regular health activities, including house visits.
- ▶ In highly vulnerable and receptive localities, receptivity might have to be reduced by appropriate vector control measures.
- ▶ The essential activities include continuous reduction of vulnerability by universal access of the entire population, including visitors, to diagnosis and treatment.
- ▶ Under exceptional circumstances, especially when the risk for imported malaria is high, the activities may include screening of immigrants for malaria and use of prophylactic radical treatment. This measure has been used for military personnel and similar groups on their return from highly malarious areas. Screening cannot, however, identify hypnozoites of relapsing malaria, and there is some evidence that microscopy or RDTs may not be sufficiently sensitive to detect asymptomatic carriers.

<sup>33</sup> WHO Expert Committee on Malaria. *Twelfth report*. World Health Organization, Geneva, 1966 ([http://apps.who.int/iris/bitstream/10665/39822/1/WHO\\_TRS\\_324.pdf](http://apps.who.int/iris/bitstream/10665/39822/1/WHO_TRS_324.pdf) accessed 14 September 2015).

<sup>34</sup> WHO Expert Committee on Malaria. *Thirteenth report*. World Health Organization, Geneva, 1967. ([http://apps.who.int/iris/bitstream/10665/40651/1/WHO\\_TRS\\_357.pdf](http://apps.who.int/iris/bitstream/10665/40651/1/WHO_TRS_357.pdf) accessed 14 September 2015).

Other important vigilance activities are:

- ▶ dissemination of information on the current malaria situation to the medical profession and, in cases of special risk, the general public; it is important to include private medical services, which are often the front-line service providers; and
- ▶ counselling of prospective travellers to malarious countries and ensuring their access to effective chemoprophylaxis and other measures (see unit 3).

## 6.4 Mechanisms and organization to prevent reintroduction

### 6.4.1 Tasks and responsibilities of the malaria nucleus

See the malaria elimination field manual, section 6.3.

### 6.4.2 Evaluation of success

The absence of secondary transmission is, of course, an indicator of success, but only if there is evidence that case detection is going on, with full coverage in space and in time and with a distinction between autochthonous and imported malaria and between species of malaria.

Some administrators consider that the absence of any recorded malaria case is their country's goal. As one minister of health put it, "I do not want to have any case of malaria in my country". His services promptly complied, although heavy importation was obvious. In fact, *the absence of imported cases is an indication that detection of malaria cases is inadequate and that remedial action is badly needed.*

## Unit 6 exercise

### Exercise 6.1

- ▶ Each participant is asked to prepare a short (one-page) summary of a specific country experience on the prevention of malaria reintroduction or a history of a post-elimination outbreak.
- ▶ Participants from countries that have no malaria-free areas should present a situation analysis of an area that is approaching elimination and outline a plan to ensure vigilance. This can be done as a continuation of exercise 5.7 on planning a surveillance system for malaria elimination.

# LEARNING UNIT 7

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## Health systems and inter-sectoral and cross-border collaboration

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### Learning objectives

By the end of this unit, the participants should be able to:

- Explain how the various components of the health systems are related to effective malaria control and elimination
- Give examples of common weaknesses in health systems, which constrain malaria elimination, and identify ways to overcome those weaknesses
- Describe measures for reorienting the health system towards malaria elimination
- Determine the roles of the private sector, the community, other sectors and inter-country collaboration
- Identify suitable topics for operational research on elimination

## Introduction

The Global Malaria Eradication Programme depended on vertical operations: centrally organized activities run by staff hired by the programme. These operations—consisting largely of IRS—often by-passed health systems, as it was assumed that they could be run most efficiently with minimal collaboration, as stated by the WHO Malaria Expert Committee in 1957: “the administration of malaria eradication should be distinct and separate so as to secure the efficient management of the programme. In countries where the public service is not well developed, the development of an eradication service will serve as a nucleus around which the public service will be built.”<sup>35</sup> In the later phases of the first eradication era, it became clear that some form of chemotherapy was also needed to reduce transmission and that good surveillance was essential. Greater attention was then paid to integrating malaria eradication activities into health services.

Malaria elimination now usually evolves from successful malaria control. Reorientation to elimination is often associated with greater central control or “verticalization”, which is usually necessary for quality assurance and for meeting standards of operations, surveillance and documentation. When the objective of elimination is almost reached, the focus shifts back to the general health services, which assume responsibility for vigilance.

### 7.1 What is a health system?

In 2000, WHO formulated a comprehensive definition of a health system as

“the people, institutions and resources, arranged together in accordance with established policies, to improve the health of the population they serve, while responding to people’s legitimate expectations and protecting them against the cost of ill-health through a variety of activities whose primary intent is to improve health.”<sup>36</sup>

In 2007, WHO devised a conceptual framework for health systems, which, like the definition, has been widely adopted.<sup>37</sup> It contains six “health system building blocks” (Fig. 7.1):

1. **Governance:** ensuring strategic policy frameworks, with effective oversight, coalition-building, accountability, regulations, incentives and attention to system design;
2. **Human resources:** responsive, fair and efficient, given the available resources and circumstances, and available in sufficient numbers;
3. **Financing:** raising adequate funds for health in ways that ensure that people can use the services they need and are protected from financial catastrophe or impoverishment because they have to pay for them;
4. **Medicines and technologies:** including medical products, vaccines and other technologies of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use;

<sup>35</sup> Expert Committee on Malaria. Sixth report. Geneva: World Health Organization; 1956 (WHO/MAL/180) ([http://whqlibdoc.who.int/malaria/WHO\\_Mal\\_180.pdf](http://whqlibdoc.who.int/malaria/WHO_Mal_180.pdf), accessed 14 September 2015).

<sup>36</sup> The world health report 2000: health systems: improving performance. Geneva: World Health Organization; 2000 ([http://www.who.int/whr/2000/en/whr00\\_en.pdf](http://www.who.int/whr/2000/en/whr00_en.pdf), accessed 14 September 2015).

<sup>37</sup> Everybody’s business—strengthening health systems to improve health outcomes: WHO’s framework for action. Geneva: World Health Organization; 2007 (<http://www.who.int/healthsystems/strategy/en/>, accessed 14 September 2015).

5. **Information:** ensuring the production, analysis, dissemination and use of reliable, timely information on health determinants, health systems performance and health status; and
6. **Service delivery:** including effective, safe, high-quality personal and non-personal health interventions provided to those in need, when and where they are needed (including infrastructure), with a minimal waste of resources.

Figure 7.1. Health system building blocks



This framework was extended in 2008–2009 to include the role of *people*, not just at the centre of the system as mediators and beneficiaries but as key actors in driving the system itself.

In the international discussions on health systems in recent years, two concepts have been highly influential. The first is a political choice; the second is an approach to analysis and management:

- ▶ **Universal coverage and access** to essential health interventions and to protection against financial disaster as a result of health-related events. In line with the WHO definition—“Universal coverage ensures that all people can use health services without financial hardship.”—universal care and universal access can be seen as redefinitions of primary health care and health for all. Thus, in the early twenty-first century, financial access is the main problem of health care access in many countries. Technically adequate services exist, but the poor may not be able to avail themselves of them, and they therefore do not receive the care they need or are driven to economic ruin by health expenditure.
- ▶ **Systems thinking** Systems are more than the sum of the parts, and “systems thinking”, as developed and used for other complex systems, should be applied in health. Applied to problem-solving, systems thinking addresses the dynamic, mainly non-linear linkages, interactions and behaviour of the elements of the entire system.

“Systems thinking” works to reveal the underlying characteristics and relationships of systems. Work in fields as diverse as engineering, economics and ecology shows systems to be constantly changing, with components that are tightly connected and highly sensitive to change elsewhere in the system. They are non-linear, unpredictable and resistant to change, with seemingly obvious solutions sometimes worsening a problem.

“All health interventions have system-level effects to a greater or lesser degree on one or more of the system’s building blocks. Many may be relatively simple interventions or incremental changes to existing interventions—e.g. adding vitamin A supplementation to routine vaccination—and not all interventions will benefit from or need a systems thinking approach. However, more complex interventions—e.g. the scaling-up of antiretroviral therapy—can be expected to have profound effects across the system, especially in weaker health systems. They thus require a systems thinking approach to illuminate the full range of effects and potential synergies.”<sup>38</sup>

In malaria programmes, it is well known that important policy changes, especially about antimalarial treatment, take a very long time, typically about 2 years, to implement. Experience indicates that programme managers might find it useful to review the critical processes and the interrelationships between the agents involved. Such an analysis might shorten delays by addressing certain issues and agents early on. Systems thinking is related to the planning technique known as “critical path analysis”.<sup>39</sup>

## 7.2 Health system requirements for malaria elimination

For elimination to be successful, a health system should have certain characteristics. These may be more or less strongly developed, and they should apply to the local context.

### 1. Governance

- ▶ Does an effective *central and peripheral government administration* cover the entire national territory? In particular, is it clear for each element where it belongs administratively? If health administration has boundaries that are different from general administrative boundaries, are all areas and populations clear about their relation to the health administration?
- ▶ Is there *national political commitment* to elimination? Is it based on an analysis of options? Is it expressed in a binding way?
- ▶ Are the necessary *legislation and regulations* in place for malaria elimination? Are they adopted and enforced? If not, is there a road map for adoption and enforcement?

### 2. Human resources

- ▶ Are human resource policies and administrative practices sufficiently flexible to allow the recruitment of the additional staff that may be needed for elimination? These could range from a database manager and GIS expert to casual or permanent personnel for vector control and active case detection.
- ▶ Are policies for recruitment, contracting, remuneration and supervision adequate to ensure that staff are highly qualified and motivated to perform with professionalism and integrity?

### 3. Financing (and governance)

- ▶ Is there is national political commitment to elimination, and is it supported by reasonable fund allocation from the national revenue? The annual per capita expenditure on health is another important indicator. If it is low, any commitment to heavy expenditure per capita for malaria elimination should be questioned. Is it rational to prioritize malaria elimination?

<sup>38</sup> Alliance for Health Policy and Health System Research and WHO. Systems thinking for health systems strengthening. Geneva: World Health Organization; 2009.

<sup>39</sup> [http://en.wikipedia.org/wiki/Critical\\_path\\_method](http://en.wikipedia.org/wiki/Critical_path_method), accessed 14 November 2015.

Could another use of the money yield greater health benefits? Is the commitment to malaria elimination politically sustainable, or could priorities change after the next election? At the microlevel, one issue that often comes up in relation to malaria control (and perhaps even more for elimination) is the remuneration or incentivization of malaria control activities for health volunteers or community health workers. A malaria programme might find it expedient to reward workers per test conducted, per positive case found or per patient fully treated; each of these options has its pros and cons. In a general health system, the situation is more complicated, because use of incentives in one programme might be disruptive for other programmes. There is no right answer, except that these issues should be thoroughly discussed by everyone involved and that the outcomes must be monitored.

#### 4. **Medicine and technology**

- ▶ Do national policies and regulations ensure the availability of appropriate quality-assured medicines and diagnostics at relevant service points?

Note that this may be considered the responsibility of the malaria programme during the elimination phase. The question is whether general health services will be able to assume this role once the disease has been eliminated.

#### 5. **Information**

- ▶ Is public health work supported by a solid *demographic database*? Are censuses carried out regularly? Are populations at the lowest level administrative division known? Is there a reliable, regularly updated village database? Is there a civil registration system that is effective in areas of risk for malaria? (Demographics and civil registration are not usually the responsibility of the health sector, but they are mentioned here because they are so important for the health system).
- ▶ Is there understanding throughout the health system of the need for epidemiological and operational information that is precise, accurate, timely and honest, with a culture of quality and integrity? (This is also an issue of human resources and governance.)
- ▶ Is there a good surveillance system for communicable diseases?

#### 6. **Service delivery**

- ▶ Are there adequate national services for achieving universal coverage in areas at risk for malaria? For details, see 7.4.

Note that malaria elimination requires attention not only to health system blocks but also to people. Attention to training, commodities, logistics, health education and community mobilization is relatively easy in a malaria programme that has adequate human and financial resources, including leadership capacity. In contrast, the characteristics listed above are more difficult to change by short-term interventions. It may be necessary to find explanations for any weaknesses and the broader implications of intervention, by system thinking.

### 7.3 **Addressing service delivery**

Service delivery is the most important aspect of health systems for elimination. Without solid health service coverage in areas at risk for malaria, transmission cannot be interrupted, surveillance cannot document malaria-free status and that status cannot be maintained.

Malaria services can be divided into vector control and curative services; sometimes, preventive use of antimalarials is included.

**Vector control services** are usually the domain of specialists; when local health services are involved, these usually receive specialized guidance from higher levels. The capability required for vector control in the elimination phase is usually the same as in the control phase; the concern is maintaining the capacity for vector control and entomology after elimination. In most countries, other vector-borne diseases persist after malaria elimination, and the capability for entomology and vector control is probably best maintained in integrated vector management or general vector control units.

The main issue in **curative services** is whether all people at risk for malaria have access to high-quality health services for rapid diagnosis and treatment and the reporting of cases, so that the necessary public health measures are taken. Thus, health services must be:

- ▶ affordable
- ▶ geographically accessible: usually, a maximum of 1 h of walking time to a health facility or service provider; and
- ▶ socially accessible: no population groups are excluded, such as illegal immigrants and small nomadic tribes in remote areas.

Usually, residual problems are found in certain underprivileged, remote or thinly populated areas. The tools for assessing the health services in such locations include:

- ▶ use of statistics, maps and data;
- ▶ site visits, including interviews with service providers, members of the population and representatives of other sectors; and
- ▶ special-purpose surveys.

The following indicators may be available:<sup>40,41</sup>

#### *Availability of health personnel*

The density of the health service network is usually given as the number of doctors or nurses per 10 000 inhabitants. If such figures are available only at national level, they are usually not very useful for elimination; if they are available at district or subdistrict level, they may be meaningful. According to WHO, a minimum of *23 doctors, nurses and midwives per 10 000 population* is necessary to deliver essential maternal and child health services. This is also probably a reasonable benchmark for malaria services, although, in many settings, malaria services may be delivered by personnel with less training.

<sup>40</sup> Analysing disrupted health sector. A modular manual. Geneva: World Health Organization; 2009 ([http://www.who.int/hac/techguidance/tools/disrupted\\_sectors/en/](http://www.who.int/hac/techguidance/tools/disrupted_sectors/en/), accessed 14 November 2015).

<sup>41</sup> Monitoring the building blocks of health systems. A handbook of indicators and their measurement strategies. Geneva, World Health Organization; 2010 (<http://www.who.int/healthinfo/systems/monitoring/en/index.html>, accessed 14 November 2015).



### General health service delivery

- ▶ Annual number of outpatient visits to health facilities relative to the population of a geographical area:

$$\frac{\text{Annual number of outpatient visits to health facilities, not including for vaccination}}{\text{De facto (mid-year or mean) population of the same geographical area}}$$

Method for data collection: routine health facility reporting system or population-based surveys. The main problem is usually obtaining data from private providers.

Examples: 0.2 in the Democratic Republic of the Congo; 0.8 in Sudan

- ▶ Coverage with a third round of diphtheria, tetanus and pertussis vaccination
- ▶ As the coverage with antenatal care is measured annually, it provides timely evidence of the current state, access and use of services:

$$\frac{\text{Number of women who used antenatal care services at least once during pregnancy}}{\text{Number of live births}} \times 100$$

- ▶ Proportion of expected new cases of tuberculosis found

The data for the last three may be more accurate and precise, but the data for the first may be more relevant for malaria control.

### Indicators of malaria services

A good indicator of health system performance in relation to malaria may be the annual blood examination rate, which is discussed under “Surveillance”.

In principle, the proportion of fever cases suspected to be malaria that have been tested for malaria is even more relevant. These data may be available from demographic health surveys, multiple indicator cluster surveys or malaria indicator surveys. The problem is having good data from a sufficient sample of all age groups in malaria foci.

Few texts suggest norms for health service delivery. A book that was highly influential in the 1970s<sup>42</sup> suggests that there should be 700 outpatients per day for a population of 100 000; for a 5-day working week, that would correspond to 175 000 outpatient visits per year or 1.75 per person per year, which seems rather high. About one visit per person per year would perhaps be more realistic. Planning departments in national ministries of health may have norms based on local studies or consultations that could guide their decision on this subject.

### Example of planning norms in 1969

“In most developing countries, health care is planned on a regional basis often using districts as the basic geopolitical units. The health needs and resources discussed earlier can be translated into the setting of a hypothetical rural district of 100,000 people. Without describing the disease pattern, we can say that the needs or demands in this district would include roughly: 700 outpatients per day; 3000 hospital admissions per year, a continuous requirement for 115 beds; 3500 births per year or about 70 per week; and other elements of a comprehensive health programme that would reach 100–200 separate communities distributed over more than 500 square miles [1300 km<sup>2</sup>].

<sup>42</sup> Bryant J. Health and the developing world. New York: Cornell University Press and Rockefeller Foundation; 1969.

“The resources might include: one or two doctors; one or two nurses, one with midwifery experience; one or two health inspectors (senior sanitarians)...”

### *Assessment and decision-making*

An overall assessment of whether the health system delivers adequate service in a given malaria risk area should be based on a review of data relevant to all the above indicators. Inadequate services are often due to problems in a few village clusters in some districts. Such situations can be addressed, for example, by:

- ▶ active case detection by mobile teams on regular visits during the transmission season;
- ▶ community health workers, community volunteers or community pharmacists;
- ▶ dispensaries with regular, formally trained health staff;
- ▶ giving incentives to attract private medical practitioners or nurses to work in remote areas; or
- ▶ medical outreach services, which in some areas may be outsourced to nongovernmental organizations or private practitioners.

These services may be specialized for malaria, broader (e.g. community integrated management of childhood illness, malaria services for adults, febrile disease) or provide comprehensive primary health care. Usually, it is easier and less costly to establish a highly specialized service, but a broader service will better address the population’s needs and demands in the long term. As malaria becomes a rare disease, it becomes difficult to attract people to a completely specialized service.

Thus, system thinking is warranted. In a poor, underserved area, a major investment in malaria services could create serious imbalances; however, attempts to establish integrated services rapidly may also lead to problems. In some countries, drug sellers are commonly found in villages or on a market serving several villages. If one of them or a newly recruited volunteer is trained as a general health worker, other drug sellers might sabotage efforts to strengthen the local health system so that they do not lose income.

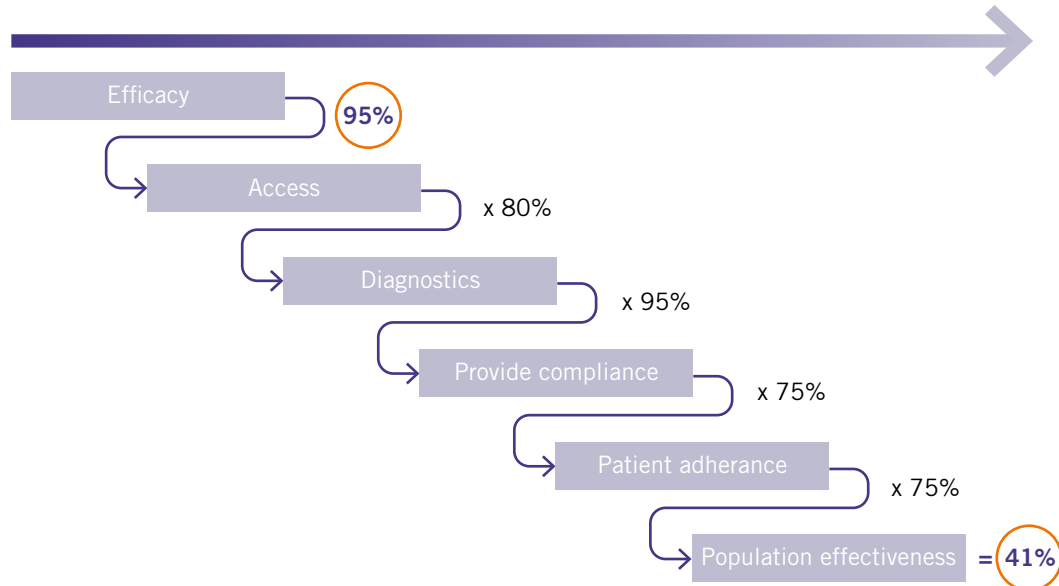
Decisions are required to address not only immediate needs but also needs after attainment of malaria-free status. A reduction in service provision for malaria after interruption of transmission may be acceptable if the malaria risk in the area is low. If the area has high receptivity and vulnerability, high coverage must be maintained. After elimination, this should be the responsibility of the general health services. Thus, in the pre-elimination and elimination stages, the malaria programme should analyse the situation jointly with the authorities responsible for health service delivery in critical areas. These authorities may be central or devolved, depending on national health policy.

## **7.4 Analysing and improving the quality of service delivery**

The “systems effectiveness framework” is a useful means for understanding the dynamics of health systems and the barriers to access. Figure 7.2 shows how the effectiveness of interventions diminishes in a cascade of interacting system barriers, such as poor access or provider adherence (including inappropriate diagnosis and prescribing by health workers), in both the public and the private sectors. The recommendations for monitoring surveillance in elimination programmes address some of the factors identified in this framework. Learning unit 8 returns to this framework,

with the term “fraction fully protected”, which is close to “population effectiveness” but also incorporates biological constraints on effectiveness.

Figure 7.2. From efficacy to effectiveness: a systems effectiveness framework



## 7.5 The private health care sector

During a pre-elimination programme, coverage with effective, good-quality curative and preventive health services in all transmission areas. In most countries, private health care providers account for a substantial proportion of primary contacts for febrile disease and must therefore be engaged in the malaria programme. A census of private health providers should be drawn up during this period.

By the time the elimination phase starts, private health facilities should be completely integrated into the national malaria surveillance system, with full cooperation on case detection, treatment, continuing education and quality assurance. Febrile patients should no longer be able to obtain antimalarial treatment in private clinics, pharmacies or anywhere else in the programme zone if they do not have a quality-assured diagnosis; if they attempt to obtain treatment, the central malaria elimination programme must be informed and a case investigation initiated.

After elimination has been achieved, private medical practitioners are the main source of curative care in many countries. They must therefore be updated regularly on risk groups and risk areas, new methods of diagnosis and treatment, referral facilities and the protection of travellers.

Use of private providers is easy in well-regulated health systems, where services are delivered by qualified medical practitioners and pharmacists. Where most private providers are informal drug-sellers and quacks, the challenge is more complicated. Engaging private providers is often a problem in the malaria control phase, and programmes have been more or less successful in harnessing them. Countries in which malaria has been eliminated had reached a level of development at which informal health services had largely disappeared before they entered the elimination phase.

## 7.6 Intersectoral collaboration

The most important sectors in relation to malaria elimination are:

- ▶ **Business and corporate sector:** for-profit entities that produce goods and services. These are usually private but may be state-owned. In many cases, importation of malaria or intranational movement of people with malaria is related to economic activities; collaboration with employers is therefore essential, in particular for early detection of cases. In many countries, tourism agencies and transport companies should be engaged in detecting malaria in travellers.
- ▶ **The military:** Soldiers and sometimes police forces are often highly exposed to malaria. The full cooperation of military health services in elimination activities is crucial.
- ▶ **Civil society:** Nongovernmental, faith-based and civil service organizations are non-profit entities that express community beliefs and values by service provision and advocacy and contribute to collective goods and services. In some places, this description is a charade, as these organizations may in fact be small businesses trying to profit as much as possible from public funds allocated to a major health problem. Others act as mediators between communities and government programmes or provide services, for example by outsourcing. Their role is perhaps more important in the control phase, as many elimination programmes have been successful with strong government services and minimal involvement of civil society. An important task of national malaria programmes is to distinguish between genuinely committed, competent organizations and those that are merely out to make money.
- ▶ **Government:** general and specialized governance institutions at local and national levels. Collaboration with local government is sometimes useful for enforcement, regulation and intersectoral collaboration.

## 7.7 Cross-border collaboration

Countries pursuing elimination may have to deal with continued malaria transmission in neighbouring countries. A number of approaches have been used, depending on the political, economic geographical and demographic situation. In many cases, well-intentioned declarations have been made, but these have not always been effective at ground level.

The most problematic cross-border migrations are usually those in which there are large differences in income, resulting in a considerable influx of people seeking economic opportunities. Less commonly, migration is motivated by insecurity or persecution. The problem is most difficult to deal with when migration is clandestine; a malaria programme must then design approaches to attract migrants, for example to screen them and tell them where to seek care if they fall ill. Inter-country collaboration may or may not be of help under such circumstances. What malaria programmes can always do is to share epidemiological information regularly across borders, including information on special problems, such as about a group that is moving in a certain direction, a malaria outbreak or the emergence of drug resistance.

Many migrants who carry malaria parasites do not come from neighbouring countries but from far away. Thus, some countries in the Middle East attract labourers from the Indian subcontinent and the Far East. As they usually arrive by air, it may be easy to set up screening on arrival, but intercountry collaboration is not always evident.

### *Regional initiatives for malaria elimination*

Collaboration can have many benefits, including joint political support, advocacy and global awareness, alignment of strategies, collaboration on control and prevention activities and sharing successes and challenges. Collaboration between malaria-endemic countries is particularly important for those that share borders but also applies to island countries, as many coastlines are functional borders. The main regional initiatives for malaria elimination include:

▶ **Asia Pacific Malaria Elimination Network**

Bhutan, China, Indonesia, Malaysia, Democratic People's Republic of Korea, Philippines, Solomon Islands, Republic of Korea, Sri Lanka, Vanuatu

▶ **Elimination Eight Regional Initiative**

Angola, Botswana, Mozambique, Namibia, South Africa, Swaziland, Zambia, Zimbabwe

▶ **The Tashkent Declaration**

Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkey, Turkmenistan, Uzbekistan

▶ **Saudi–Yemeni Partnership in Combating Malaria**

Saudi Arabia, Yemen.

## Unit 7 exercises

### Exercise 7.1

In country X, one of the last foci is a village tract in district Y. The district, with a population of 150 000, is thinly populated, with small, poor villages in some hilly areas, where the population speaks a dialect that is not understood by the majority of the population. The district has 10 doctors and 15 nurses, all of whom work at the hospital in the district capital and in one rural health centre. There are two private medical practitioners in the district capital. The focus village tract, a, has a long border with a similar hilly area in the neighbouring country. a has a population of 10 000 people living in 25 scattered villages and hamlets. The largest seven villages have a volunteer who has been trained in health education, first aid, referral and collaboration in the Expanded Programme on Immunization but is not allowed to provide curative services (diagnosis or treatment). The distance between the remotest hamlet and the centre of the village tract is 50 km. There is frequent local population movement across the border. The district health director and his supervisor at provincial level have been reluctant to strengthen health services in a, because they are convinced that any clinic there would soon be overwhelmed by patients from nearby villages on the other side of the border. During the past 5 years, LLINs have been supplied regularly, and active case detection has been carried out monthly in some of the most severely affected villages by two sanitary inspectors from the district capital. The number of malaria cases has decreased gradually; it is believed to be going down on the other side of the border as well, but, unfortunately, cross-border collaboration and information exchange have not been possible because of political problems. As the health programme in country X is devolved, the provinces have administrative control and the power to decide on the structure of the health services and to deploy personnel.

Working in small groups, answer the following questions.

- ▶ How could health care delivery be strengthened?
- ▶ How should the malaria control programme manager (who hopes soon to be the malaria elimination programme manager) do this?

### Exercise 7.2

Browse the case study on Turkmenistan (*Elimination malaria: case study 1. Achieving elimination in Turkmenistan*. [http://apps.who.int/iris/bitstream/10665/75848/1/9789241504300\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/75848/1/9789241504300_eng.pdf?ua=1)). Read in detail about the outbreak in 2002-3 (p.12, 18,19).

Identify actions to strengthen the health system and intersectoral collaboration for elimination.

### Exercise 7.3

Read the case study on Cape Verde.<sup>43</sup>

- ▶ Draw out relevant data on the health system.
- ▶ Explain what these data indicate about the chances for achieving and maintaining malaria-free status.
- ▶ Do you require additional data?
- ▶ What studies of the health system would you propose?
- ▶ What activities of the health system would you recommend in the context of elimination?

### Exercise 7.4

Identify priorities for operational research on malaria elimination, and outline how the questions could be addressed.

### Exercise 7.5

Review the surveillance planning initiated in unit 5.

- ▶ What are the implications for health systems?
- ▶ What human resources will be required for surveillance of elimination at various levels of the health system?
- ▶ Will it be possible to meet these requirements?

<sup>43</sup> Eliminating malaria- Case-study 2: Moving towards sustainable elimination in Cape Verde. Geneva: World Health Organization; 2012.

# LEARNING UNIT 8

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## Assessment of the feasibility of malaria elimination

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### Learning objectives

By the end of this unit, the participants should be able to:

- Describe the purpose of a feasibility assessment
- Describe the technical, operational and financial factors that should be considered in assessing the feasibility of malaria elimination
- Clearly define the problem for a feasibility assessment in your own country
- Carry out a feasibility analysis based on technical and operational data from your own country
- For African countries, apply the simplified elimination scenario planning method to assess feasibility, including a timetable for reducing the *P. falciparum* burden to a very low level
- Formulate interim targets for malaria elimination on the basis of the analysis
- Analyse the financial feasibility of elimination in a given area, and explain how the cost–effectiveness of elimination and control could be compared

## Introduction

This learning unit takes a step back, to reflect, but it also builds on all the preceding ones. The material in this unit should help participants to make a correct decision about elimination. Attempting malaria elimination where it is not feasible can be a grave mistake, but the opposite may be dangerous as well.

We start with an overview of the fundamental determinants of the pre-elimination, elimination and maintenance (prevention of reintroduction) phases. This is followed by a review of the possible scope and outcomes of a feasibility study, who is responsible for doing it and how to proceed. A distinction is made between technical, operational and financial or economic feasibility, although it is recognized that the analytical work in the three areas may overlap. Using a simple model based on transmission dynamics, fitted to African data, we introduce two new concepts, “malaria baseline” (malaria prevalence in the absence of control) and “fraction of at-risk population fully protected”, reflecting the proportion of a population that is protected, given both operational and biological constraints. It is then shown how survey data and basic knowledge of local health systems and local vectors can be used to forecast possible reductions in *P. falciparum* prevalence and over what time in given areas. Finally, we discuss planning, costing, budgeting and financial and economic analysis.

This learning unit is accompanied by extensive exercises. The additional file, ESP Worksheets.xls, can be used to organize the data to be used in the group work. After reading this text, you should familiarize yourself with these worksheets.

## 8.1 Purpose of feasibility studies

A study of the feasibility of malaria elimination must apply to a given area; it must answer two fundamental questions:

- ▶ Is it practically possible to interrupt malaria transmission in the area?
- ▶ If yes, is it practically possible to maintain malaria-free status, so that locally transmitted cases will not occur again in that area?

In the following, we use the term “maintenance phase” for the period after transmission has been interrupted, when reintroduction must be prevented, and we examine the feasibility of the pre-elimination and elimination phases and then of the maintenance phase.

### 8.1.1 Feasibility in the pre-elimination and elimination phases

Feasibility depends mainly on whether the reproduction rate can be reduced to  $< 1$  but also on the risk for introduction of malaria infections.

#### *Reproduction rate under control*

In learning unit 1, the basic reproduction rate,  $R_0$ , was defined as the number of secondary cases resulting from one primary case in a human population with no immunity in the absence of control measures. We can define the *reproduction rate under control*,  $R_C$ , similarly, the only difference being that it represents a steady state established under control.



- ▶  $R_c$  is the product of the vectorial capacity under control ( $C_c$ ) and the mean duration of infectivity under control ( $D_c$ ):  $R_c = C_c \times D_c$ .
- ▶ When control has had some effect,  $R_c < R_0$ .
- ▶ If control has been so effective that transmission is interrupted,  $R_c < 1$ .

Learning unit 1 explored how  $C_c$  is affected by vector control interventions. In real life, their effect depends on many factors, the most important being:

- ▶ the *effective coverage*, e.g. the proportion of the population sleeping under effective ITNs or living in villages where over 80% of households have been correctly sprayed and the insecticide is still effective;
- ▶ *entomological factors* like resistance and exophily; and
- ▶ the *heterogeneity* of vector-biting and of effective coverage: Even in a small unit, like a village, the prevalence of malaria may be higher than average in some households, for example near a river; furthermore, if IRS and use of LLINs are implemented, both with coverage rates of 80%, certain subpopulations of the vector may systematically not be covered by the intervention and could therefore contribute to maintaining the transmission. Some population groups may be systematically disadvantaged, with poor access to case management.

Under control,  $D_c$  is reduced, as early detection and effective treatment are more widespread. However, estimation of the duration of infectivity becomes problematic, as the situation is different in sub-populations with different access to treatment.

### Imported cases

As the incidence of indigenous cases falls, imported cases become more important. If  $R_c$  is far below 1, importation is not an important challenge. There may be thousands of imported cases, but it is very unlikely that their presence will lead to local transmission. As long as  $R_c < 1$ , such transmission will, however, tend to die out. In contrast, if  $R_c$  is only slightly  $< 1$ , even a few imported cases can result in local transmission.

### 8.1.2 Feasibility in the maintenance phase

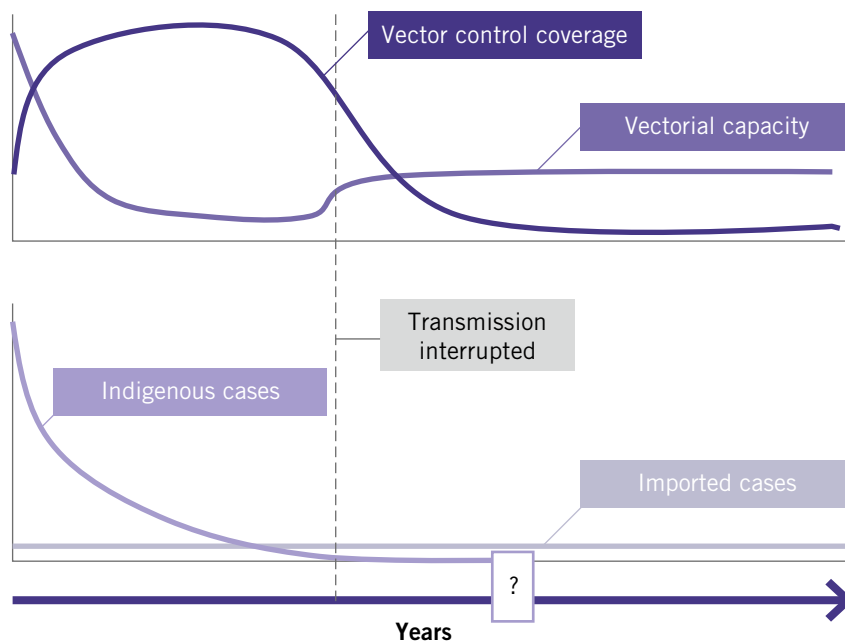
In countries where malaria has been eliminated, costly vector control operations are usually stopped or at least greatly reduced once transmission is interrupted. As noted in learning unit 3, activities are usually withdrawn gradually during progressive interruption of transmission in a given area. As a result, vectorial capacity will increase, and, if no other changes have occurred, it may reach the original level; yet in many cases, it will be mitigated by environmental changes, improved housing and maintenance of operations in the most critical areas. If diagnosis, treatment and surveillance are good,  $D_c$  should remain at a low level, but  $R_c$  may be  $> 1$ , at least in some areas. If there is no importation, that is not a problem, but in the presence of significant importation, the risk that some cases will infect vectors is high. The importance of imported cases depends on how good the surveillance system is. If all imported cases can be detected and treated early, so that the duration of infectivity is approximately 0, they will not infect local vectors; however, if some of the imported cases are asymptomatic, early detection may be difficult. If they are due to *P. vivax*, some will even be undetectable hypnozoite carriers. When they relapse, they can become infective before they become symptomatic. Thus, in this phase, feasibility depends on

three factors: the risk for importation, the strength of surveillance and the vectorial capacity “after control”.

### 8.1.3 Feasibility in both phases

Thus, feasibility in both phases depends on the dynamics of vectorial capacity as it is affected by vector control and other determinants, on duration of infection, which is affected by changing epidemiology and surveillance, and on the risk for importation. This is illustrated in Fig. 8.1, which highlights the gradually growing importance of importation, even when the rate is constant.

**Figure 8.1.** Typical variation in vectorial capacity and indigenous and imported cases in elimination and maintenance phases



#### *Receptivity and vulnerability*

In feasibility assessment and planning, especially for the advanced elimination and maintenance phases, the concepts of receptivity and vulnerability have proven useful. In this text, definitions are proposed, which are consistent with earlier ones as found in for example WHO’s malaria elimination field manual but are more rigorous. See Box 8.1.

### Box 8.1. Definitions of receptivity and vulnerability

#### *Receptivity*

The vectorial capacity in a given area at a given time in the absence of deliberate control measures is determined mainly by the interaction between local vectors and ecology, including outside nocturnal human activities, type of housing and use of mosquito nets.

#### *Vulnerability*

Vulnerability is the risk that imported human or mosquito malaria parasite carriers are present in a given area at a given time. Human carriers who stay a long time in the area and those who are asymptomatic are the most important. Infected vectors can enter by flying across land borders or by air transport (“airport malaria”).

On the basis of these definitions and the above analysis, the risk for reintroduction in a given malaria-free area is proportional to the product of receptivity and vulnerability. The stronger the surveillance (vigilance) system, the lower the risk. A fourth factor plays an important role in some areas, namely zoogeographical barriers. As mentioned in learning unit 1, Palaearctic vectors do not transmit Afrotropical *P. falciparum*. This was probably crucial for the ability of European and North African countries to remain malaria-free despite extensive importation of *P. falciparum* infections.

In the elimination phase, as the programme increases vector control coverage, vectorial capacity is reduced. With good access to diagnostic and treatment services and efficient surveillance, the mean duration of infection is also reduced (not shown). Together, these changes are sufficient to interrupt transmission (reduce  $R_c$  to  $< 1$ ), so that the number of indigenous cases reaches 0. However, some imported cases continue to occur every year, and, in the maintenance phase, with reduced vector control coverage, vectorial capacity increases. It is now uncertain whether malaria-free status can be maintained, as it depends on the risk of imported cases (vulnerability), the vectorial capacity (receptivity) and the strength of surveillance.

## 8.2 Scope, timing and possible outcomes of a feasibility study

Deciding whether to embark on an elimination programme requires a thorough analysis. Proposing a plan for elimination is different from declaring that elimination is the ultimate goal of a malaria programme. Such a declaration has no operational consequences, and nobody would disagree with it. An elimination (or related) programme must be planned to reach its objective *within a specified time*.

### 8.2.1 Scope

Learning unit 3 indicated that, although elimination certified by WHO must be national and encompass all species of human malaria parasite, national authorities may aim for subnational and/or species-specific elimination or for achieving a state of “controlled non-endemic malaria”. These aims may be seen as temporary or intermediate. This training material addresses elimination, which may be *P. falciparum*-specific or complete, subnational or national. For subnational

elimination, it is important to select entities that have natural boundaries or are of a reasonably large size, so that there is not a high risk for importation relative to the population of the area for which elimination is contemplated. Islands and island groups are often good candidates for elimination. Otherwise, it is inadvisable to try to eliminate malaria in small entities, as the burden of proof may be costly and the risk of losing the achievement through importation may be high. States and provinces in larger countries may be good candidates under some circumstances. Elimination is a deliberate effort. It is not meaningful to put much effort into proving that a particular city that has no suitable breeding sites for anophelines and has not had evidence of malaria transmission for many decades is malaria-free.

### 8.2.2 Timing and time-frame

Good *timing* is essential. If a feasibility assessment is undertaken too early but there is political pressure in favour of elimination, the evidence may not be sufficient, ultimately leading to failure. In areas with a significant malaria burden, solid data on the impact of well-conducted control operations are the most useful evidence for the analysis. If the analysis is delayed for too long, opportunities may be lost, and there may be long-term wastage of resources and attrition of political capital, as malaria lingers on as a neglected disease, possibly concentrated in neglected population groups. In some cases, malaria programmes have even been accused of avoiding elimination because they were more concerned about keeping their annual budget than about the population's health!

Generally, a feasibility assessment is a good investment when the parasite rate reaches 5% in an area that could be a candidate for elimination. Malaria that has become focal is a related factor that favours a feasibility study. (See learning unit 5.) An earlier study might be justified when control efforts have resulted in a relatively rapid reduction in the malaria burden; the study would indicate whether an aggressive strategy to interrupt transmission is justified or whether it would be more sensible to pursue time-unlimited malaria control and perhaps return to the question later.

How long can the time-frame be? The longer the time between the decision to undertake elimination and expected interruption of transmission, the greater the uncertainties. It would be unwise to plan for elimination more than 15 years after the starting point, because much could change in the interval. In most cases, a time-frame of 5–15 years until transmission is interrupted would allow realistic planning. Models (to be examined below) provide some indication of the timeframe.

### 8.2.3 Outcomes of a feasibility study

A feasibility study for a defined area may have the following *outcomes*, of which “elimination” is one of the phases described above.

“Elimination” cannot be considered feasible in the area, at least not at this time.

- ▶ The conclusion should be justified and accompanied by an overview of the malaria control strategy that is considered the most rational at present.

“Elimination” is likely to be feasible, but the available knowledge is insufficient to determine a target date or timeline.

- ▶ In this case, it is often rational to undertake pre-elimination activities; however, it should be clear that elimination is not guaranteed. A date should be set for a new feasibility study, with investigations to support it.

“Elimination” is feasible, and the target date for interruption of transmission (the first year with 0 locally transmitted cases) is [range of years].

- ▶ This outcome must be accompanied by an outline of a plan, with a timetable, a budget and economic justification for choosing elimination rather than control. Unless all the elements of pre-elimination are present, this will include pre-elimination and elimination activities.

In some cases, elimination is an obvious choice, such as on islands with strong health systems and low vectorial capacity and vulnerability. In such situations, a feasibility study is easy and should immediately be combined with a plan of operations. In other cases, the decision requires longer deliberation and examination of the pros and cons.

## 8.3 Responsibilities and resources for a feasibility assessment

### 8.3.1 Who should undertake a feasibility study?

A feasibility assessment is the responsibility of a national malaria control programme, perhaps supported by WHO, other consultants and scientists. A distinction should be made between the study (analysis), which is done by specialized staff, and decision-making, which is usually done at ministerial level. The analytical work is best conducted by people with knowledge of malaria, disease surveillance and health planning. It should result in a report, with clear conclusions, which may recommend either one course of action or several options. Ministers will usually request general health planners to review the analysis before they take a decision. In large countries, feasibility studies may be undertaken by state, regional or provincial malaria control programmes, but they should be submitted for endorsement to the national malaria or vector-borne disease programme, which has stronger expertise and a better overview, before presentation to the local government.

### 8.3.2 What resources are required for a feasibility study?

A feasibility study requires data and information that are usually available to the national malaria programme and the ministry of health. The information is much the same as that required for planning. For certain elements, such as human migration, data should be sought from internal and external sources that may not be immediately obvious to malaria control programmes; they are described below.

## 8.4 Structure of a feasibility study

### 8.4.1 Three-way analysis

The information required for a feasibility assessment can be classified as technical, operational and financial. The *technical* information should indicate whether elimination is possible *with existing tools* (not necessarily those currently used in the country), assuming there are no operational or financial constraints.

If elimination is technically possible, *operational* information should indicate whether there are significant obstacles in the health system, including the malaria programme, or in broader contextual elements. If there are, it should be determined whether they can be overcome.

If elimination appears to be feasible from the technical and operational perspectives, a *financial and economic* analysis should be conducted to determine whether the cost would be reasonable and justified and how it could be covered. Various options should be presented.

The feasibility assessment should be as factual as possible; however, it cannot be purely scientific. Technical problems that would be obstacles in one country might be overcome in another in which the malaria programme and the health system are strong. Although solid indicator data should be used as much as possible, some assessments are necessarily judgemental. The results of modelling can inform the outcome but not decide it; interpretation of model outputs and the conclusion of a feasibility study must take into account many elements that cannot be captured in a mathematical framework.

#### 8.4.2 Subregions

Most areas in which elimination is contemplated are so varied that they must be divided, to examine combinations of factors in each area. Ideally, areas should be as homogeneous as possible with regard to epidemiological and operational determinants of malaria (as in epidemiological stratification); however, the way in which information is organized and the kinds of units that are acceptable candidates for elimination might have to be taken into consideration. The units would usually be delimited by administrative or political boundaries. Such division is acceptable as long as areas of very different malaria risk are analysed, e.g. a rural lowland province that includes a mountainous part, a city, a forest or an agricultural development project. The units that are defined for the purposes of feasibility will be referred to as “subregions” below.

▶ **Now, do exercise 8.1.**

### 8.5 Technical feasibility

According to the above, assessment of technical feasibility requires an analysis of factors relating to:

- ▶ vectorial capacity and receptivity;
- ▶ the duration of infectivity, which depends on the availability of diagnostic and treatment services and the efficiency of the surveillance system; and
- ▶ the risk for importation, or vulnerability.

For each of those elements, the requirements can be formulated qualitatively and then be examined to determine whether entomological, environmental, human ecological and socioeconomic factors favour elimination. Measured or estimated quantitative data should be sought for the more important factors. It is not always possible to differentiate the technical and operational elements clearly, as they often overlap in intervention effectiveness.

Main determinant	Area	Favourable factors and indicators
Vectorial capacity and receptivity		
Is vectorial capacity low at the outset?		<ul style="list-style-type: none"> <li>• Low vectorial capacity: vectors short-lived, not very anthropophilic, low density</li> <li>• Low prevalence rates and entomological inoculation rates</li> </ul>
Can it be reduced to a level compatible with elimination?	Entomology	<ul style="list-style-type: none"> <li>• Highly endophilic and endophagic vectors, mainly night-biting</li> <li>• Focal distribution</li> <li>• Man-made and/or easily identifiable, well delimited breeding sites</li> <li>• Not insecticide-resistant (although alternative insecticides are available)</li> <li>• Short transmission season</li> <li>• Evidence of a rapid, major impact of vector control</li> <li>• Certain vectors cannot transmit <i>P. falciparum</i> from certain heterologous zoogeographical regions</li> </ul>
	Physical environment	<ul style="list-style-type: none"> <li>• High altitude with temperature-dependent transmission, often small houses with sprayable walls (highland fringe)</li> <li>• Arid, with precipitation-dependent transmission (desert fringe)</li> <li>• Terrain does not pose problems of permanent or seasonal access</li> </ul>
	Human ecology	<ul style="list-style-type: none"> <li>• Houses with sprayable walls, not multi-storey</li> <li>• Spontaneous use of personal protection measures</li> <li>• High-quality housing, air-conditioning</li> <li>• No activities outside in late evening, night or early morning</li> <li>• No nomadic habits, no forest plot agriculture</li> <li>• Piped water available</li> <li>• Moderate population density</li> </ul>
	Control effectiveness	<ul style="list-style-type: none"> <li>• Possible to achieve and maintain highly <i>effective</i> coverage with selected intervention(s)</li> <li>• Collaboration of all affected communities and potential partners (inter-sectoral)</li> </ul>
Can it be maintained below a threshold thereafter?	Environment, development	<ul style="list-style-type: none"> <li>• Current or expected changes in natural or human ecology favour lower vectorial capacity, depending on zoogeographical region and local vector bionomics (e.g. deforestation, desertification, pollution, urbanization)</li> <li>• Absence of natural or man-made disasters</li> </ul>
Duration of infectivity		
Can the duration of infectivity be reduced to and maintained at a very low level?	Parasitological	<ul style="list-style-type: none"> <li>• No <i>P. vivax</i>, especially in tropical areas</li> <li>• No resistance to antimalarial agents (although resistance is a reason for attempting elimination!)</li> </ul>
	Human ecology	<ul style="list-style-type: none"> <li>• Possible to ensure adequate treatment-seeking behaviour and treatment adherence</li> <li>• No cultural, political or legal barriers</li> <li>• No subgroups of patients (among indigenous or imported cases) who are less likely to obtain timely, high-quality case management</li> </ul>
	Control effectiveness	<ul style="list-style-type: none"> <li>• Possible to achieve highly <i>effective</i> coverage of case management and surveillance</li> <li>• Possible to adapt treatment to any resistance, inclusion of anti-gametocyte and -hypnozoite medicines</li> </ul>

Main determinant	Area	Favourable factors and indicators
Vulnerability		
Can importation of infections be reduced or maintained at a low level?	Social and economic	<ul style="list-style-type: none"> <li>• No, or little and controllable, population movement leading to importation of malaria</li> <li>• Low malaria risk in neighbouring or strongly connected countries, especially in border and contact areas</li> <li>• No expectation of major increase in the rate of immigration of potential parasite carriers, resulting for example from political instability in neighbouring country or increasing domestic demand for foreign labour</li> <li>• Adequate services for all migrants (with respect for human rights)</li> </ul>

### Assessments for technical feasibility

Generally, national malaria control programmes would be expected to have all the relevant information available; however, there may be exceptions, and it may be useful to check local information against the published literature and other sources. Much can be found by literature searches, but a few key references could be useful in many countries, as indicated below.

### Vectorial capacity, entomology and receptivity

For each subregion, characterize the entomological situation on the basis of information on the bionomics of the *main vectors*, of which there are often two or three in a given area; long lists are often found in the literature, but closer scrutiny reveals that most of the listed species are only secondary and play no role of there is effective control. If ample data are available on the situation before systematic vector control operations, it may be possible to calculate the vectorial capacity. This is rarely the case. In this learning unit, a simple model (elimination scenario planning, ESP) will be used. It is based on the concept of a baseline for falciparum malaria under African conditions. In this scenario, the estimated parasite prevalence in the absence of control is used as an indicator of the basic reproduction rate at the time the assessment is made, in the absence of vector control.

### Key references

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- ▶ Kiszewski A, Mellinger A, Spielman A, Malaney P, Sachs SE, Sachs J. A global index representing the stability of malaria transmission. *Am J Trop Med Hyg* 2004;70(5):486–98 (Tables of data on longevity and anthropophily of all major malaria vectors).

### *Duration of infectivity*

Infectivity is the component that is most susceptible to control measures, once the stage of low endemicity has been reached (when the prevalence is < 5%). It is important to design the programme in such a way that all infections are detected early and radically treated. For vector control, the challenge is to identify the effective coverage rates and mix of interventions that are adequate to interrupt transmission in each stratum or subregion. For case management and surveillance, only 100% is enough, because each patient must be protected from risks for complications and death and because every patient who is treated too late is an epidemiological risk in the elimination and maintenance phases.

### *Importation or vulnerability*

*Infected vectors:* Importation by infected mosquitoes is usually sporadic and accidental and therefore almost impossible to quantify. In some cases, mosquito importation has been shown to be important (see unit 6). The only way to control the importation of infected mosquitoes across land borders is vector control near the border as part of malaria control or elimination in the neighbouring country. Importation by aircraft is controlled by desinsection (See learning units 3 and 6) and is not usually an impediment to elimination.

*Infected humans:* In most situations, human importation is far more prevalent than vector importation. It is therefore a priority to identify the ground, sea or air routes by which humans enter the area of interest and the numbers who travel via those routes. An attempt should be made to estimate the annual rate of incoming infections per 1000 people living in receptive areas. Receptivity varies widely; however, most carriers of imported parasites are in cities, which are not receptive at all in most countries. Thus, a large proportion of imported carriers can be excluded from the analysis.

Assessment of vulnerability can proceed as follows:

1. Examine subregions (see above) with different levels of receptivity.
2. Multiply estimates of the number of migrants moving into each receptive subregion per year by the estimated parasite prevalence in the region of origin in order to obtain an annual estimate of the number of infected migrants into that subregion.
3. Relate this figure to the resident population of the subregion.

Example: If the data sources indicate that 1000 migrant workers enter a given subregion annually from a neighbouring country with a malaria prevalence of about 20%, and 10 000 workers enter from a different region with a prevalence of about 5%, the estimated number of infected migrants per year would be  $(1000 \cdot 20\%) + (10\,000 \cdot 5\%) = 700$ .

*What is importation?* Importation is usually considered as transport of something into one country from another; however, when elimination is considered for a subregion in a country, all infections contracted outside that subregion must be considered as imported. This gives rise to a serious dilemma in stratification for elimination: stratification into small units increases the chance of

identifying some with the epidemiological and operational conditions that make interruption of transmission feasible. Continued transmission in neighbouring subunits may be the origin of so much importation, however, that the establishment and maintenance of malaria-free status are impossible at reasonable cost.

The importation rate into a particular subregion may be classified as follows:

Class	Annual estimated number of imported infections per 100 000 inhabitants
Very low	< 10
Low	10–< 100
Moderate	100–< 1000
High	≥ 1000

Assessments should be further revised with information on the duration of stay of potential parasite carriers.

#### Data sources:

- ▶ household surveys such as the World Bank Living Standard Measurement surveys, which are available for several endemic countries, include data on e.g. time spent in other locations, length of stay in the current location and location of previous residence. Some countries include information on travel in malaria indicator surveys or demographic health surveys.
- ▶ transport data, such as road networks, with estimated traffic;
- ▶ labour force surveys, which may provide information on employment-related travel, places of residence and places of work;
- ▶ records of arrivals and departures at international airports;
- ▶ company records of workforce movements and other information;
- ▶ reports on migration by ministries of customs or immigration;
- ▶ anonymized mobile telephone records, from which internal movement may be estimated;<sup>44</sup> and
- ▶ international data, such as World Bank estimates of international migration.<sup>45</sup>

Besides the rate of imported infections, it might also be important to consider the absolute number, in order to understand the total workload of the health services. Future levels of importation are hard to predict. Economic growth may lead to importation of foreign labour forces; increased overseas travel and tourism may also contribute.

Quantifying importation may yield clues to means of reducing it; for example, if certain risk groups appear to contribute particularly to imported infections, surveillance or prevention could be focused on these groups. The activities may include giving travellers prophylaxis,

<sup>44</sup> Tatem AJ, Qiu Y, Smith DL, Sabot O, Ali AS, Moonen B. The use of mobile phone data for the estimation of the travel patterns and imported *Plasmodium falciparum* rates among Zanzibar residents. *Malar J* 2009; 8:287

<sup>45</sup> Parsons CR, Skeldon R, Walmsley TL, Winters LA. Quantifying international migration: a database of bilateral migrant stocks (World Bank Policy Research Working Paper 2007; 4165. Washington DC: World Bank; 2007 ([http://www-wds.worldbank.org/external/default/WDSContentServer/WDSP/IB/2007/03/06/000016406\\_20070306151900/Rendered/PDF/wps4165.pdf](http://www-wds.worldbank.org/external/default/WDSContentServer/WDSP/IB/2007/03/06/000016406_20070306151900/Rendered/PDF/wps4165.pdf), accessed 14 September 2015).

cross-border collaboration or reinforcement of preventive or curative services for certain labour or military forces.

## 8.6 Operational feasibility

Most operational determinants influence several of the major technical areas. The factors and indicators are therefore best presented in a simple framework: context, health systems, malaria programme and research institutions. For more detail, refer to learning unit 7, Health systems.

### *Context*

- ▶ political and social stability, especially in malaria-risk areas;
- ▶ effective government, with clear geographical demarcations and division of responsibilities;
- ▶ good collaborative relations with the countries from which carriers could be imported;
- ▶ a collaborative private sector (health and non-health) in malaria risk areas; and
- ▶ good demographic data and databases, with mapping of villages.

### *General health system*

- ▶ Governance
  - ▶ politically and technically strong leadership and political stability,
  - ▶ culture of reliance on evidence and reliable data from a health information system and
  - ▶ regulation of the private health care sector, including pharmacies.
- ▶ Health services
  - ▶ geographically, economically and culturally accessible in risk areas (distance to provider, outpatient consultations per year)
- ▶ Human resources for health
  - ▶ sufficient educated, trainable, motivated, properly remunerated and stable

### *Malaria control programme*

- ▶ technical and administrative capacity and leadership;
- ▶ ability to mobilize financial resources;
- ▶ enough fiscal space (can be authorized to expand the budget as required);
- ▶ enough “human resource space” (can be authorized to recruit enough people with the requisite skills);
- ▶ excellent malaria microscopy services or a strategy for achieving that goal;
- ▶ excellent surveillance or a strategy for achieving that goal;
- ▶ good entomological and epidemiological support;
- ▶ good management of preventive and curative services, including supply chain and human resources;

- ▶ good capacity for communication and advocacy; and
- ▶ good information technology support, including mapping, and capacity to obtain and use meteorological information and to stratify the national malaria problem.

#### *Research institutions*

- ▶ good research capacity for public health problems in the country and
- ▶ capacity to genotype plasmodia.

#### *Sources of information on public institutions and services*

The World Bank Government Effectiveness Index is a measure of “the quality of public service provision, the quality of the bureaucracy, the competence of public servants, and the independence of the civil service from political pressures”. Information about various countries is maintained by the World Bank.<sup>46</sup>

## 8.7 Assessing feasibility on the basis of epidemiological and operational data

Before embarking on the third major assessment—economic feasibility, we present a pragmatic, user-friendly framework and mathematical model for joint assessment of technical and operational feasibility, known as “elimination scenario planning” (ESP). It is based on data from sub-Saharan Africa and should therefore not be used with data from other parts of the world. Nevertheless, it helps to sharpen thinking about the overlap between technical and operational aspects; therefore, it is also recommended for study by people working on malaria in other parts of the world. The framework includes various approaches, including web-based models, which are presented in the manual published by WHO.<sup>47</sup> In the following, we propose a method for assessing feasibility, which is based on one of the tools of this framework (“ESP tool”).

### 8.7.1 Fraction of population fully protected by interventions

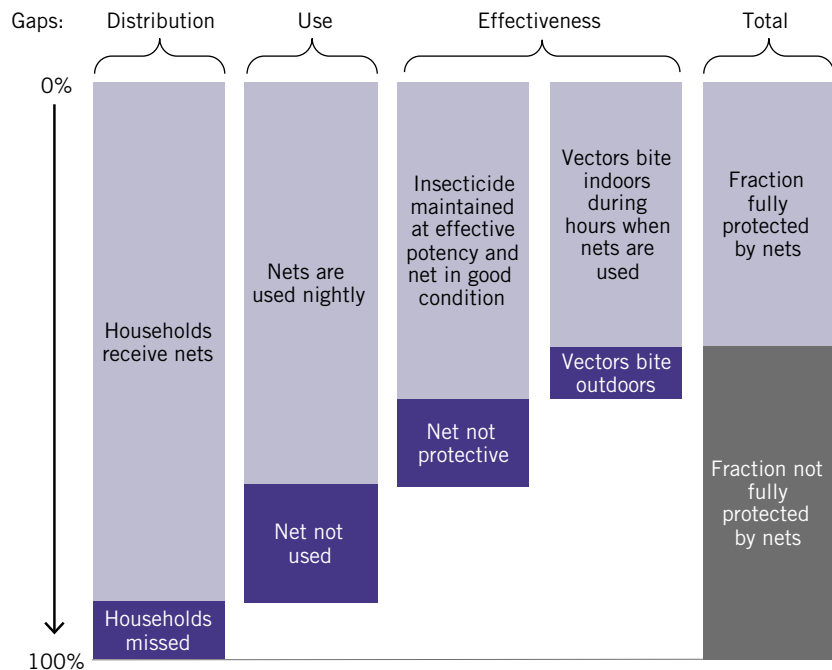
In the following modelling exercises, the concept of the fraction of the population that is fully protected is important. This is the proportion of the at-risk population in a given subregion that is not only fully covered but also fully protected by a given intervention. Operational records and surveys provide various coverage indicators; *indicators of effective coverage* are the most rigorous (e.g. the proportion of the eligible population that reports having slept under an effective ITN or LLIN the night before the survey). The *fraction fully protected* is even narrower, as it *incorporates all operational and biological limitations to effectiveness* such as holes in the nets, early biting, rapid decay of an insecticide (limiting the effectiveness of IRS) and delay in treatment-seeking or diagnosis, which limits the effectiveness of case management. Such factors as exophagy and exophily, which cannot be changed by vector control, are factored in. If in a theoretical example, 100% of the population of a village lives in households that were correctly sprayed with an effective insecticide throughout the transmission season; then, if 50% of the infectious vector bites are by mosquitoes that always rest outside, the fraction that is fully protected is only about 50%.

<sup>46</sup> World Bank. Worldwide governance indicators. Washington DC; 2013 (<http://data.worldbank.org/data-catalog/worldwide-governance-indicators>, accessed 14 September 2015).

<sup>47</sup> From malaria control to malaria elimination: a manual for elimination scenario planning. Geneva: World Health Organization; 2014 (<http://www.who.int/malaria/publications/atoz/9789241507028/en/>).

Figure 8.2 shows how a combination of operational and biological factors can greatly limit the effectiveness of ITNs.

**Figure 8.2. Hypothetical example of potential coverage gaps that determine the fraction of the population fully protected by ITNs or LLINs**

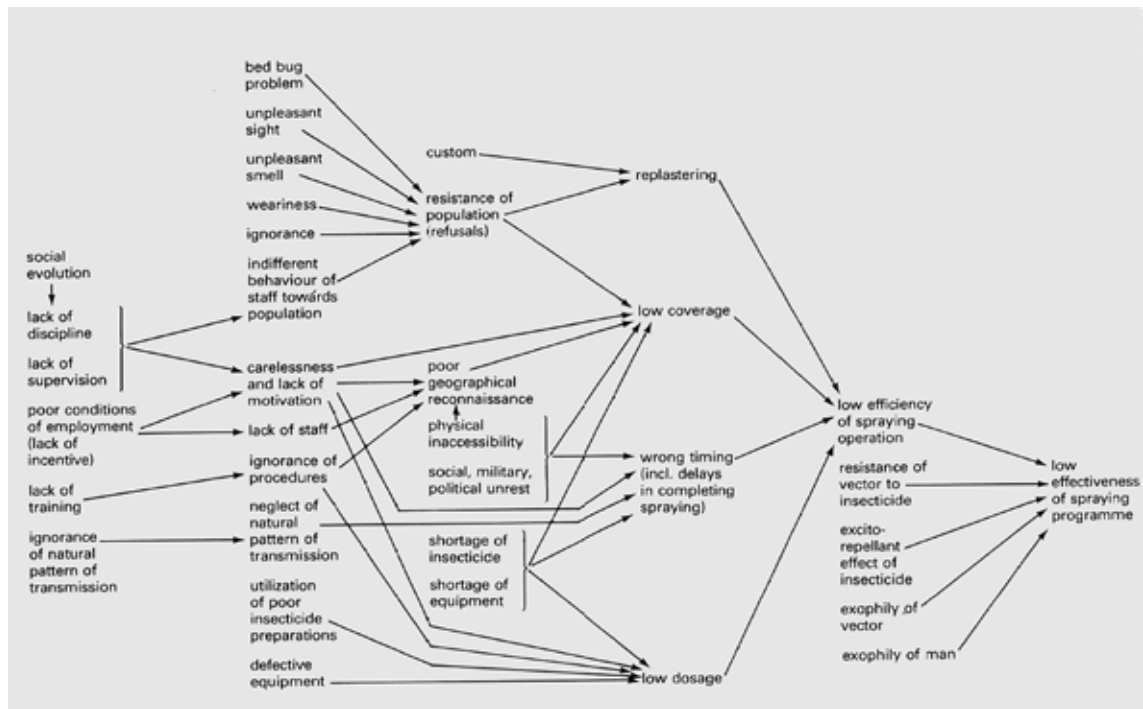


Likewise, for IRS, factors such as the following should be considered:

- ▶ Some wall surfaces or eaves are incompletely sprayed.
- ▶ Resting surfaces are unsuitable for IRS.
- ▶ Houses have many openings.
- ▶ Some people replaster their houses before the end of the transmission season.
- ▶ There is an epidemiologically significant degree of resistance to the insecticide used in the programme.

A broader array of potential causal chains is proposed in Fig. 8.3. It includes the “bedbug problem”, which has been observed mainly with use of DDT, as bedbugs (*Cimex lectularius*) easily become resistant to this insecticide; they then become excited and aggressive after DDT spraying.

Figure 8.3. Problem-tree analysis of potential causes of ineffectiveness of IRS



Some information is usually available for most of the operational factors, but it is rarely quantitative. For example, even if survey data show that 48% of nets have holes, the reduction in effectiveness must be estimated. Thus, the important operational factors must be estimated on the basis of information from the field, not on mere guesses. In contrast, there are often quantitative data on the prevalent vector species in the country, although not necessarily the situation in the subregion; entomological expertise is required to translate these data into estimates of the reduction in the fraction of the population that is fully protected.

LLINs and especially IRS have community-wide protective effects when sufficient coverage is achieved; consequently, more people may be protected than those who are effectively covered. The ESP tool is based on the relation between the observed reduction in prevalence and the effective coverage rate, the observed proportion of individuals in the population who are more or less protected.

### 8.7.2 Overview of the ESP tool

What proportion of the population should be covered with particular interventions to achieve malaria elimination? What would be required technically to maintain the gains achieved in reducing malaria, despite continued importation of infections? And, if elimination is not feasible, what reduction in malaria is technically possible?

The function of the ESP tool is to assess the technical, operational and financial resources required to reduce and eventually eliminate malaria, the timelines and how malaria-free status could be sustained. The results obtained with this tool should be interpreted with caution in view of the important factors that are not captured.

The ESP tool provides expected reductions in *P. falciparum* malaria resulting from various levels of implementation of interventions. It is based on Macdonald's model of the basic reproduction rate, with a number of assumptions that allow a better fit to observed relations: that people develop immunity to malaria; that some people are bitten by mosquitoes more than others because of their proximity to a larval habitat, their attractiveness to mosquitoes or another reason; and that people can be "superinfected" or harbour multiple infections at the same time.<sup>48,49,50</sup> Use of this model to extrapolate from empirical observations provides estimates of malaria rates in a particular place in different intervention scenarios. So far, the model is available only for *P. falciparum* in areas where the predominant vectors are Afrotropical; it is based exclusively on African data. Until more general models are available, it is worth applying this model to data to *falciparum* malaria in other regions.

The following steps should to be followed *for each subregion*:

1. Estimate the baseline prevalence of malaria in each subregion in the absence of intervention.
2. Assess the technical requirements for reducing malaria to a very low level in each subregion.
3. Evaluate whether current operational capacity is sufficient to meet the technical requirements in each subregion or whether operational strengthening is necessary.
4. Evaluate the technical and operational feasibility of maintaining elimination in each subregion despite importation of infections from neighbouring subregions and abroad.
5. Evaluate the financial feasibility of achieving and maintaining elimination.
6. Establish the long-term goals of the malaria control programme.

### 8.7.3 Malaria baseline

The baseline can be conceived as the basic reproduction rate ( $R_0$ ) in the absence of intervention *at the time the feasibility study is undertaken*, not before control started. Characteristics of the malaria system at that time cannot usually be measured directly because control is being implemented.

The main indicator of the malaria baseline in this model is the prevalence of *P. falciparum*, despite its limitations (see learning unit 1). It was selected because it is relatively easy to measure in a representative way for a particular area; prevalence is more readily available than other measures of malaria transmission. Sources include malaria indicator surveys, demographic and health surveys and others.

Even on a short timescale, the malaria baseline will not be constant, as there will be regular seasonal variation as well as more unpredictable fluctuations related to migration patterns or climatic variation. In Figure 8.4, the grey lines represent the oscillations that are commonly observed, which are due to many factors. They can be smoothed into a general seasonal pattern, depicted in blue. Pragmatically, this "noisy" picture of malaria prevalence is generalized as an average in a specific place at a particular time in the absence of control measures. In this hypothetical case,

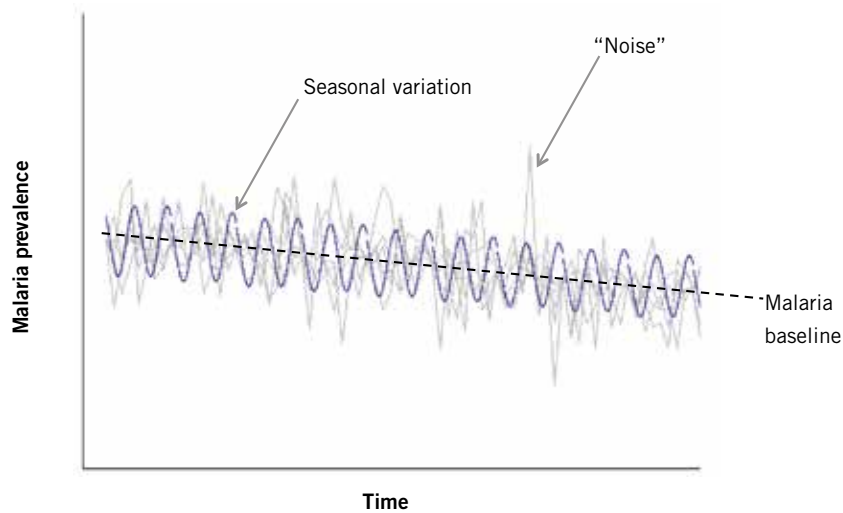
<sup>48</sup> Smith DL, Hay SI, Noor AM, Snow RW. Predicting changing malaria risk after expanded insecticide-treated net coverage in Africa. *Trends Parasitol* 2009;25:511–6.

<sup>49</sup> Smith DL, Hay SI. Endemicity response timelines for *Plasmodium falciparum* elimination. *Malaria J* 2009;8:87.

<sup>50</sup> Cohen JM, Moonen B, Snow RW, Smith DL. How absolute is zero? An evaluation of historical and current definitions of malaria elimination. *Malar J* 2010;9:213.

the baseline slowly falls over time due to factors extrinsic to the malaria control programme, such as changing land use or housing.

**Figure 8.4.** Regular and noisy variation are simplified by describing average malaria metrics rather than at a precise time.

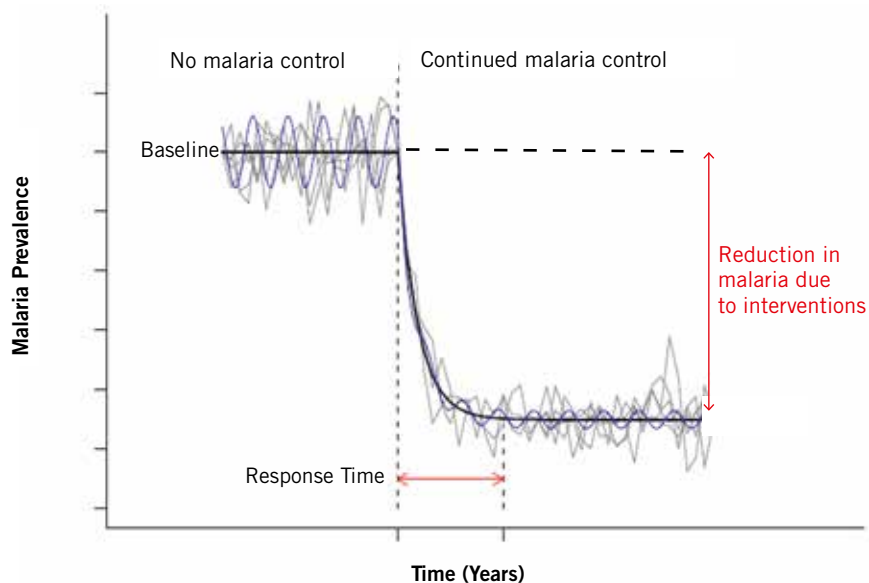


#### *Reductions from the baseline*

Malaria programmes can reduce the prevalence from its baseline by interventions. Protecting a certain proportion of an at-risk population with effective measures will reduce the prevalence by a specific amount from the baseline level over a certain response time.

Figure 8.5 shows a reduction in malaria prevalence relative to the baseline by the introduction of malaria control measures during the response time; the new, lower prevalence of malaria is sustained by continued malaria control. As with characterization of the malaria baseline, the fine fluctuations in prevalence over time are of less interest than smoothed rates.

**Figure 8.5.** Protecting a certain fraction of the population with effective control measures will reduce the prevalence of malaria by some amount from its baseline over a certain response time.





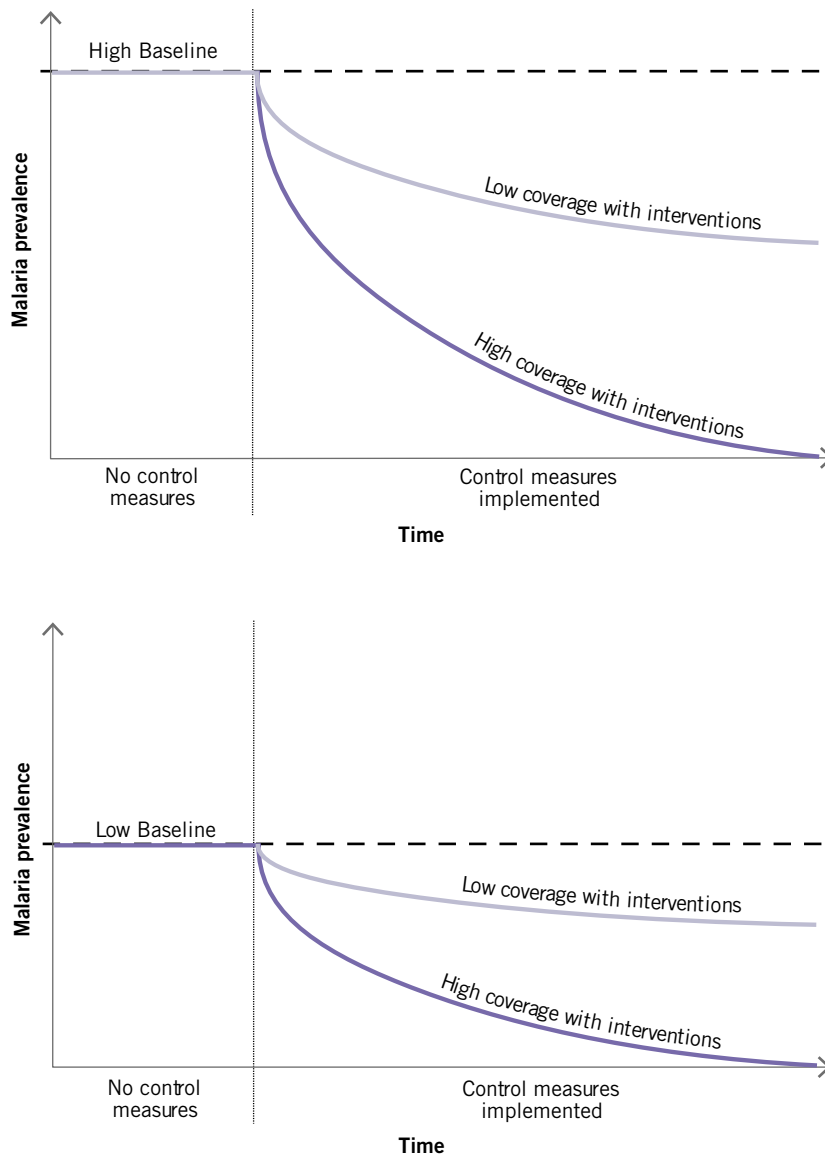
### Extent of reduction relative to the baseline

The degree to which the prevalence of malaria will be reduced in a given subregion is determined primarily by two factors:

- ▶ *the baseline*: In general, the higher the baseline, the larger the proportion of the at-risk population that must be protected by control interventions in order to achieve a reduction in transmission to a given threshold.
- ▶ *The proportion of the at-risk population that can be fully protected by effective control measures*: The larger that proportion, the larger the reduction to be expected.

Figure 8.6 illustrates these two determinants for two hypothetical subregions, one with a higher baseline (left) and one with a lower baseline (right).

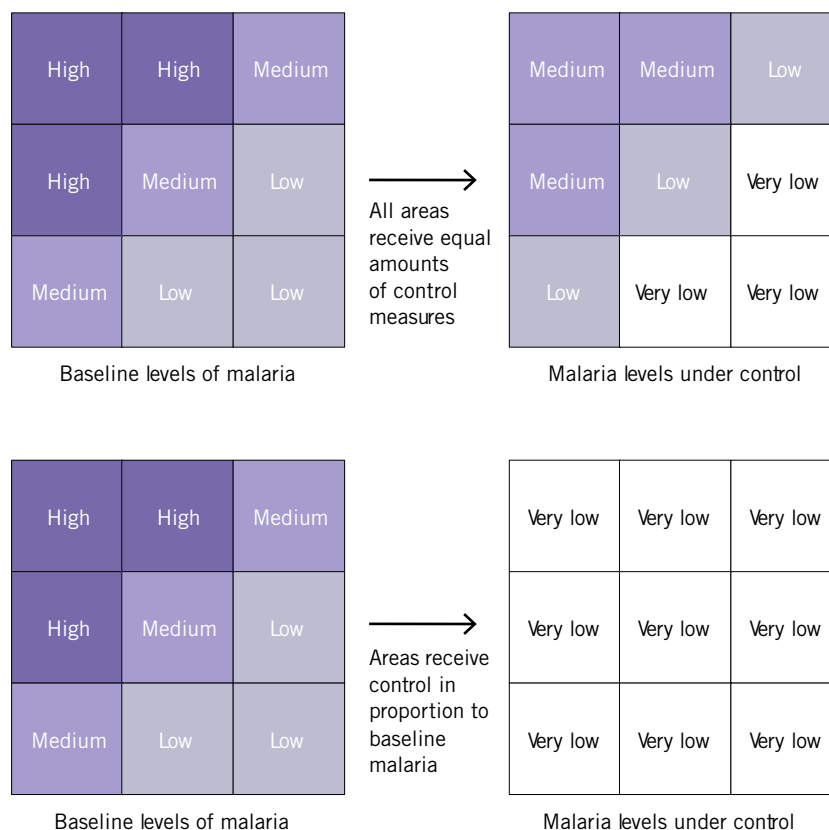
**Figure 8.6.** In this hypothetical illustration, the malaria burden after interventions is determined by both the fraction of the population covered by the control measures and the baseline prevalence (a and b).



For populations starting with a higher baseline prevalence (left), some proportion would have to be fully covered with an intervention in order to reach an end-point that resembles the lower baseline at which other populations start (right). The two factors listed above—the baseline prevalence and the fraction of the population protected by interventions—determine the level to which the prevalence can be reduced. Thus, subregions with a higher malaria baseline will have to cover a higher proportion of the population effectively to reach the same low level of transmission as subregions with a lower baseline prevalence; the greater the effective coverage rate, the greater the reduction (Fig. 8.7). Areas with a higher baseline may also be more resilient to control efforts, resulting in a quick rebound if control is not maintained.

This description is a simplification. The relation between intervention coverage and impact is not linear, and the model parameters vary with the baseline. With intense transmission, the percentage reduction in the malaria burden tends to be lower, although the number of cases prevented or lives saved may be greater because the baseline burden is greater.

**Figure 8.7.** Protecting the same fraction of the population in subregions with different baseline prevalence of malaria will result in different outcomes; to achieve reductions to the same level in all subregions, a larger fraction of the at-risk population must be protected in subregions with a higher baseline prevalence.



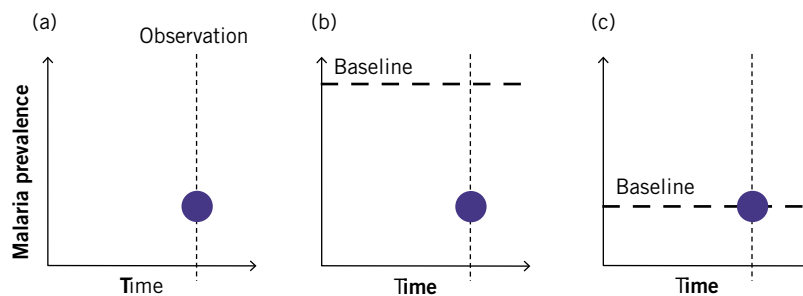
*Without control, the prevalence of malaria will return to the baseline level.*

The reductions achieved with malaria control do not represent permanent changes. As long as transmission is not interrupted, removal of control measures will be followed by an increase in prevalence to the baseline level.<sup>51</sup>

### *Estimating the baseline*

The prevalence of malaria observed in a survey is a “snapshot” at a given time. Interpretation requires information on the control interventions. A single prevalence survey is illustrated in Figure 8.8 a. The interpretation will be quite different when there has been a substantial reduction from a high baseline prevalence, as in 8.8b, from when there has been no or only a small reduction from baseline, as in 8c. In the first case, considerable reductions have been achieved, while, in the second, there has not yet been an impact on malaria in the region.

**Figure 8.8.** Interpreting a prevalence survey requires understanding how it relates to control interventions and the known or unknown malaria baseline.



If little control was applied before the observation, it is reasonable to expect that more intense control will have a greater impact. If, however, the prevalence was measured after universal coverage with vector control, it might be difficult to achieve additional reductions.

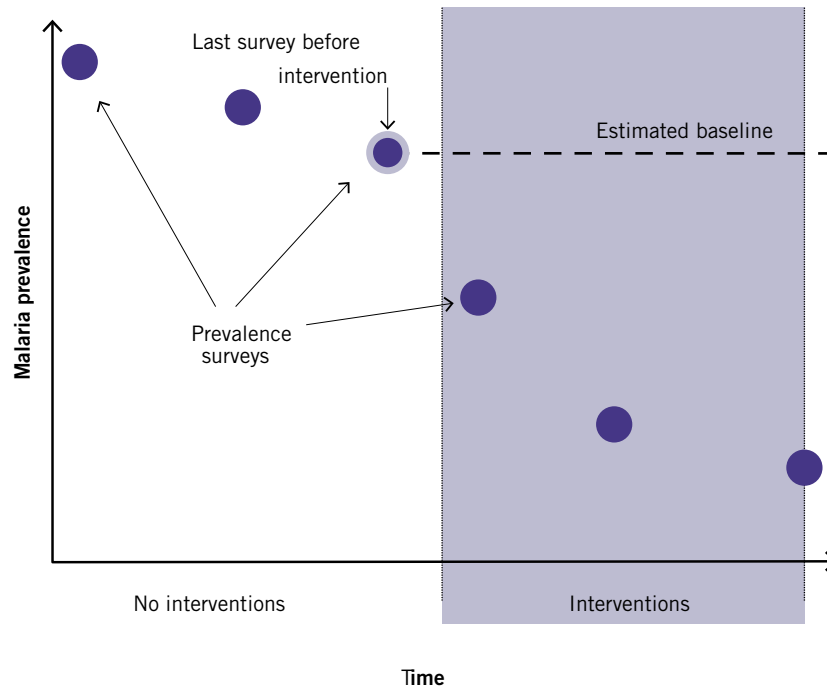
Three approaches can be used to estimate the baseline prevalence of malaria.

#### *1. Estimating baseline prevalence from one recent pre-intervention survey*

If the prevalence of malaria is constant over time, that observed in any survey conducted before control measures were implemented should represent the prevalence to which it would return if the measures were removed. In reality, the baseline is rarely constant and changes, usually downwards, over time. A survey conducted before control could provide an acceptable estimate of the baseline prevalence of malaria if it was done recently, for example < 5 years previously (Fig. 8.9).

<sup>51</sup> Smith DL, Cohen JM, Moonem B, Tatem AJ, Sabot OJ, Ali A, et al. Solving the Sisyphean problem of malaria in Zanzibar. *Science* 2011;332(6036):1384–5.

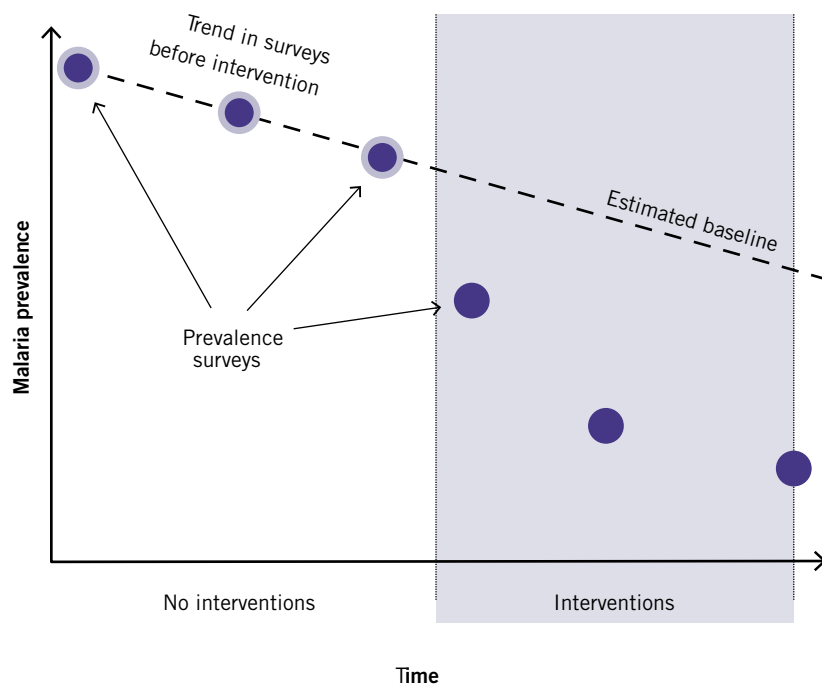
Figure 8.9. Baseline prevalence can be estimated from the last survey conducted before interventions were introduced.



## 2. Estimating baseline prevalence from serial pre-intervention surveys

If several surveys were conducted before control measures were introduced, any obvious trend in prevalence can be used to extrapolate to the baseline in the absence of control measures. For example, in Fig. 8.10, the downwards trend in baseline prevalence is assumed to be the same during the period in which interventions were made. Such extrapolation will probably result in a lower estimate of the baseline prevalence than that measured in a recent survey before interventions.

Figure 8.10. Extrapolating a trend in malaria baseline prevalence from before control interventions

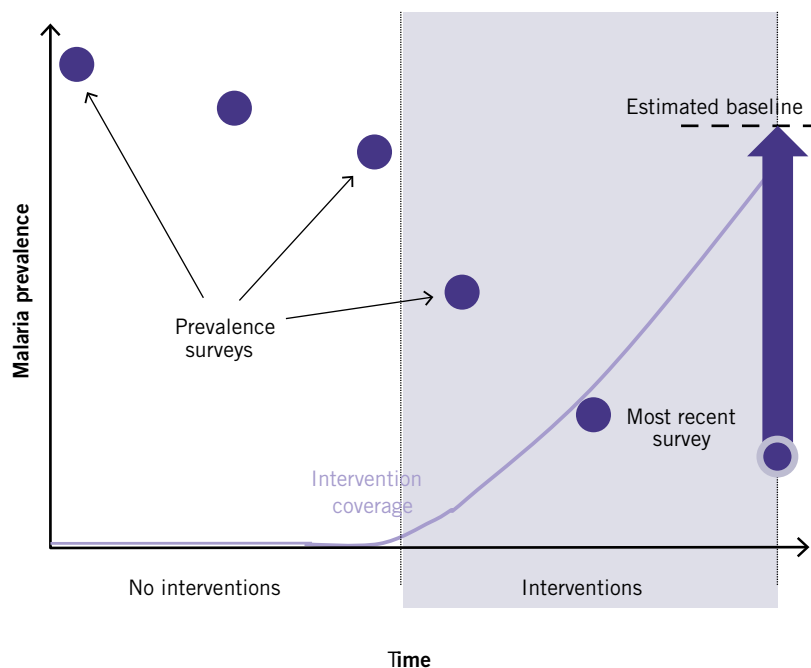


In reality, data on malaria prevalence are often scattered and available for only some times and places. If no survey data are available for certain subregions, the prevalence may be estimated by inter- or extrapolating from data for nearby, ecologically and socially similar subregions.

### 3. Estimating baseline prevalence from current prevalence and interventions

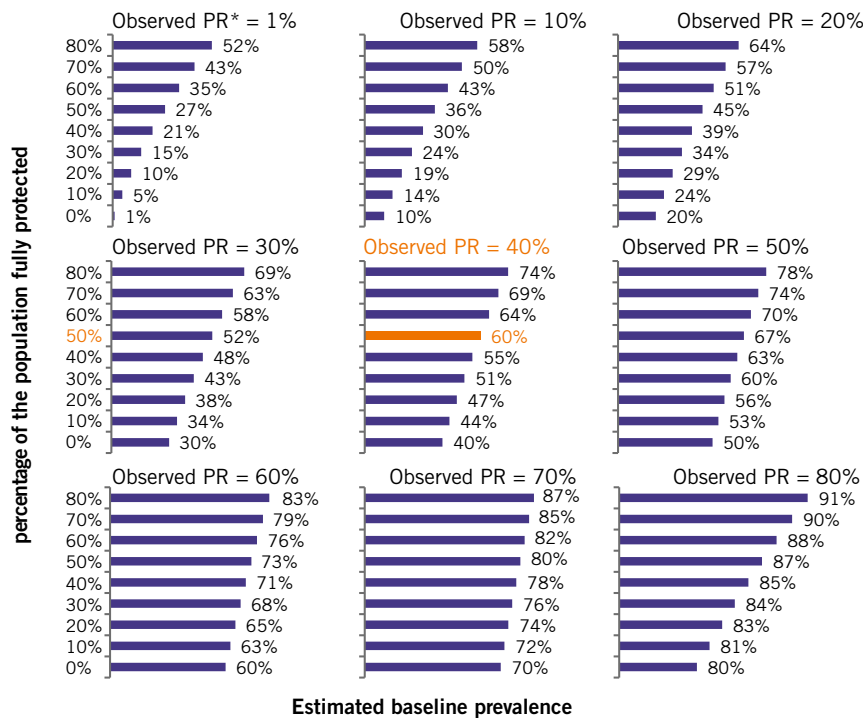
The baseline prevalence in a subregion can also be estimated by combining the prevalence observed at present with information on the fraction of people fully protected by malaria control measures before and at the time of the survey. By applying mathematical models to estimate the reduction that a given level of malaria control is expected to achieve, it is possible to back-calculate (extrapolate) the prevalence that would be found in the absence of the interventions (Fig. 8.11). The figure suggests that extrapolation from past, pre-intervention surveys would give a lower baseline prevalence than modelling from present prevalence and intervention coverage; the opposite would also be possible.

**Figure 8.11.** Estimating the baseline prevalence of malaria from a survey conducted during control interventions, from the output of mathematical models



This method requires the measured prevalence at a specific time and the proportion of the population fully protected by interventions until then. The panels in Fig. 8.12 show how the baseline prevalence can be estimated from the two data elements: the observed prevalence in a given subregion in the most recent malaria survey and the estimated fraction of the population of that subregion that is fully protected. Each panel in the figure corresponds to a different measured prevalence, and each bar in the panel indicates the estimated baseline prevalence depending on the fraction of the population fully protected from transmission. Values that fall between the figures given here can be estimated by interpolation. For example, if the measured prevalence is 5% when an estimated 50% of the population is protected, the baseline malaria prevalence can be estimated as between 27% (from the first panel, corresponding to a prevalence of 1%) and 36% (from the second panel, corresponding to a prevalence of 10%).

**Figure 8.12.** Estimation of the baseline prevalence from the observed prevalence and the percentage of the population fully protected against transmission. As shown in orange: if a prevalence of 40% is observed while 50% of the population is protected, the middle panel indicates that a baseline malaria prevalence of 60% is expected.



PR\*, prevalence rate

An example is highlighted in orange: if a prevalence of 40% is observed, while 50% of the population is protected, the middle panel indicates that the baseline malaria prevalence would be expected to be 60%.

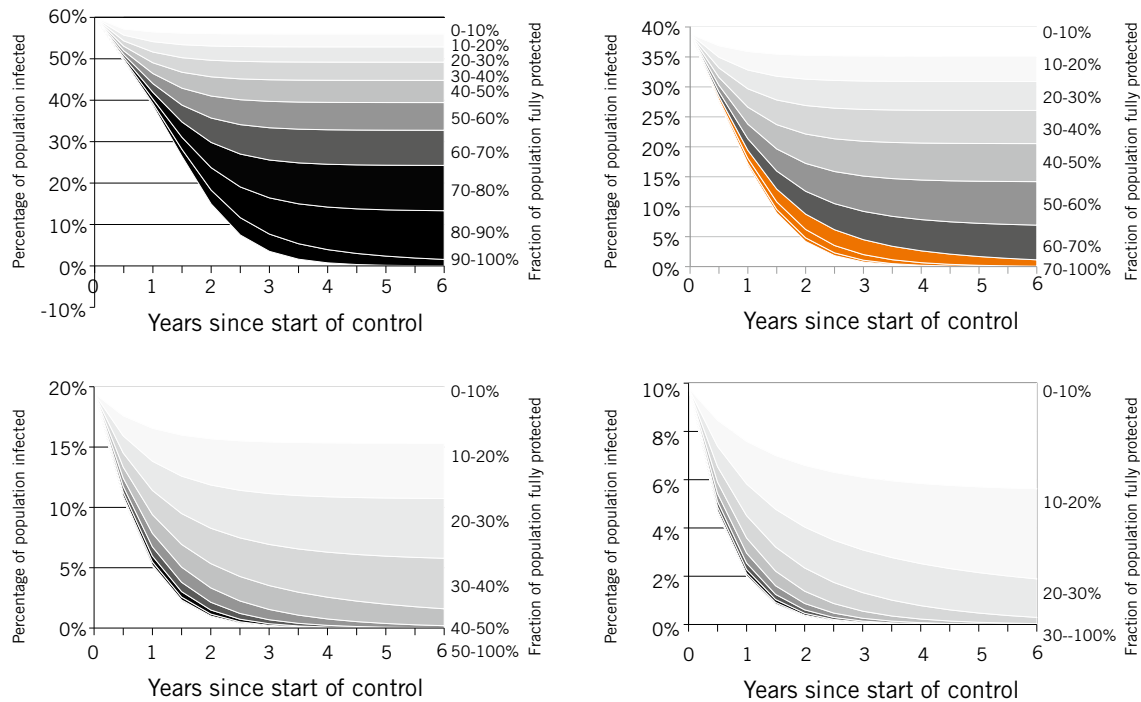
When possible, two or three of these methods should be used to estimate the baseline malaria prevalence in each subregion. When the methods give similar answers, greater confidence can be placed in the estimate; when they give different answers, they may suggest a range in the baseline prevalence, and the extremes of the range can be used to estimate what will be required to reduce the prevalence to a very low level.

### ► Now, do exercise 8.2

#### 8.7.4 Estimation of reductions from baseline achieved by different coverage with vector control with ITNs or IRS

On the basis of the estimated baseline prevalence, we can now estimate reductions in *P. falciparum* malaria over time. For each baseline value, the size of the expected reduction depends on the percentage of the population fully protected by effective interventions. This section shows timelines for reductions in malaria prevalence in a given subregion to 1%, at which reorientation of the malaria programme to elimination could be considered (Fig. 8.13).

**Figure 8.13.** Expected reductions in baseline parasite prevalence over time by 60%, 40%, 20% and 10% for different fractions of the population that are fully protected



An example is highlighted in orange: for a subregion with a baseline prevalence of 40%, > 70% of the population at risk would have to be fully protected to achieve a prevalence < 1% within 5 or 6 years.

The baseline prevalence of malaria in subregions is unlikely to be exactly 60%, 40%, 20% or 10%. Approximate reductions can be estimated for intermediate values by using these figures as ranges; for example, the response to control measures in a region with 15% baseline prevalence should fall between the 10% and 20% curves.

The reductions depicted here are simplifications. First, the curves in Fig. 8.13 are smooth. In reality, as depicted earlier, the prevalence of malaria tends to vary in a “noisy” way. Secondly, these curves depict expected reductions after interventions have been scaled up all at once, whereas scaling up is often gradual in reality. Slower scaling up will result in slower reductions over a longer time than that depicted here. The reduction may also be slowed by breaks in programme implementation due to interruption of funding, extreme weather events, war and other factors.

### ► Now, do exercise 8.3

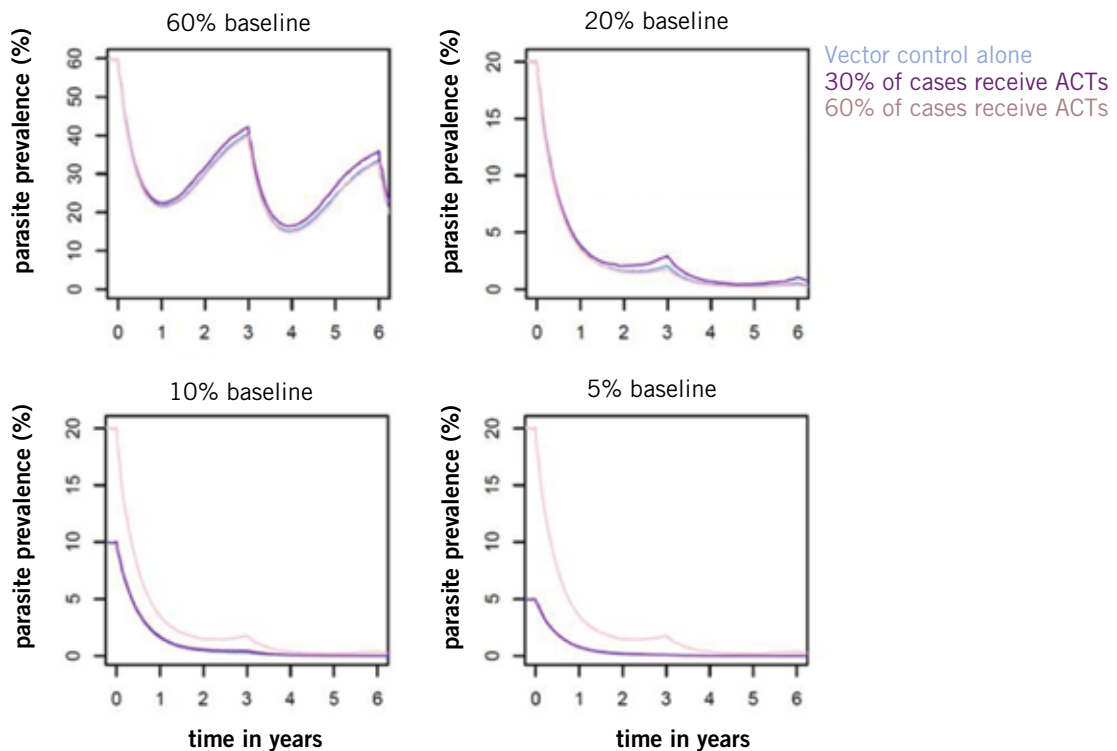
## 8.7.5 Combining vector control with ACT treatment

In most situations, the largest proportion of the at-risk population that can be fully protected will rarely be > 50%. For example, even with major programme efforts, there are few places where > 75% of the population reports having slept under an ITN or LLIN the night before. Lack of use of nets is often compounded by other operational problems, such as degradation of the active ingredient on nets, reducing their effectiveness. As IRS is now often conducted with relatively short-lasting insecticides, the full transmission seasons in a year are rarely covered. Furthermore, there are few places in which all the important vectors have favourable bionomics, so the effect is often reduced by 30–50% or more by factors such as exophily, exophagy and early biting.

When the baseline prevalence is moderate to high, there is usually a limit to what can be achieved with vector control. In these situations, it can be combined with various coverage levels with ACT.

Fig. 8.14 shows a realistic level of coverage with ITNs or LLINs with fluctuation of impact according to various levels of coverage with ACT. At a high baseline prevalence of 60%, ACT has practically no effect on transmission, as reflected by the prevalence. This is probably because most infections are asymptomatic. At lower prevalence rates, moderately good coverage with ACT can reduce the prevalence to close to 1%.

**Figure 8.14.** Estimated reductions in malaria prevalence from various baseline rates due to high coverage with nets and different coverage of clinical cases with ACT



### 8.7.6 Identifying gaps and reviewing interventions

The simple analyses presented here suggest that the chances of achieving elimination with a baseline prevalence of  $\geq 60\%$  are extremely slim. Evidence on Afrotropical vectors would certainly support this conclusion, as a prevalence of 60% represents very high vectorial capacity and some degree of exophily. In other parts of the world, such high prevalence rates were not uncommon in the 1950s, and, in areas with mainly endophilic vectors, as in the coastal plains of northeastern South America and rural areas of western India and northern Viet Nam, malaria was easily “sprayed away” within a few years. Malaria has returned to some of these areas but at a much lower level.

To assess the operational feasibility of achieving the technical requirements for elimination, compare the maximum fraction of the population that can realistically be fully protected in a subregion with the minimum levels required to reach 1% or 0 prevalence, using the technical



feasibility analysis. In most cases, it will be seen that present intervention coverage levels are not sufficient to reduce the prevalence to 1%. Before determining whether the gaps can be closed and how, it is worth considering whether the intervention mix is optimal for the situation.

### *Which interventions?*

Generally, *good case management* and surveillance should provide the highest coverage possible, whether or not elimination is pursued. Vector control may well reduce the number of cases that require treatment, but it will not reduce the testing required or curative services in the short or medium term. Even if case management is considered to contribute little to reducing transmission, the coverage should be optimized to save lives and possibly to prepare for the high demands of the surveillance phase.

Adulticidal *vector control* nearly always reduced the incidence of the disease to some extent. In areas with a low baseline prevalence, good use of ITNs or IRS and good case management can reduce the prevalence to around 1%. In areas with a somewhat higher baseline prevalence, this may not be enough. Exophily and exophagy usually occur together; therefore, if these factors limit the fraction of the population that is fully protected, it is doubtful that combining good use of ITNs or IRS and good case management will add much. If, in contrast, the biting and resting habits are favourable, the combination may be worth trying, preferably in a pilot project before major scaling up. In arid areas, where the main vector is a highly exophilic species like *An. arabiensis*, larval control might be used as an adjunct. This is rarely realistic in Southeast Asian and South American forest malaria, for which methods for reducing outdoor biting should be considered as an adjunct to LLINs or treated hammock nets.

### *Closing the gaps*

The analysis is likely to show that, whatever the mix of interventions, there are gaps in effective coverage that must be closed in order to interrupt transmission. An assessment of **operational feasibility** addresses whether—given the realities of infrastructure, communication and geographical, social, political and economic conditions—it will be possible to protect or treat a sufficient fraction of the population to achieve and maintain the epidemiological objectives.

If there is a significant gap between the current and the estimated effective coverage rate required for interrupting transmission, it might be useful to estimate the maximal achievable effective coverage rate of an intervention. This is best done in a pilot project or a research project, in which all the important operational constraints are reduced as much as possible and the resulting effective coverage is monitored over for example 1 year. The work involved should be sustainable on a larger scale over several years at a reasonable expenditure.

### *LLINs*

For each of the following steps, estimate the current coverage gap and the degree to which that gap can be closed. For all coverage gaps, what is the total fraction of the population that can be protected with this intervention?

- ▶ **Distribution** can be estimated from household surveys that include net ownership. For full protection, enough nets must be available for all members of the household.

- ▶ **Use** can be estimated from household surveys that include a question on whether individuals sleep under nets.
- ▶ **Net effectiveness** is not easily measured from surveys, although methods for rapid evaluation are being devised. The average length of time nets have been used can serve as a reasonable proxy for net effectiveness; currently available nets have an estimated effective life of 3 years. It might sometimes be rational to reduce the interval between distributions or to conduct annual top-up campaigns; elsewhere, it might be more rational to concentrate on educating people on maintaining the nets in good condition.
- ▶ **Vector behaviour** can be assessed in entomological evaluations, although translating the results into the fraction of the population that is protected by nets requires entomological expertise. In Southeast Asia, it has been observed in research projects that LLINs provide a level of protection of about 30% in areas with highly exophilic forest vectors and 50% in areas with more common degrees of exophily and exophagy.

### IRS

- ▶ **Community coverage** can be estimated by assessing the percentage of households *by village* reported in a survey to have been sprayed. If there is wide heterogeneity, with the IRS coverage of some villages far below the standard, the priority is to correct that problem. For example, if only 30% of houses in a village have been sprayed, the operation has probably been a complete waste of time in that locality.
- ▶ **Insecticide effectiveness** is not easily measured from surveys, although methods for rapid evaluation are being devised. The average time since a house was sprayed may serve as a reasonable proxy for effectiveness; if a house was just sprayed, the effectiveness can be expected to be high, while, after a year, the effectiveness will have decreased as the insecticide wears off. This must be seen in relation to the duration of the season. The maximum duration of effectiveness of any insecticide is known.
- ▶ **Vector behaviour** can be assessed in an entomological evaluation, although it is difficult to translate the results of entomological studies into the fraction of the population that is protected by IRS. The estimate of this fraction must be based on entomological data

### Case management and surveillance

The coverage of adequate case management is usually assessed in population surveys and health facility surveys. These methods have important limitations. Although this is not the place for a detailed discussion, the following factors should be considered:

- ▶ **The symptomatic fraction** is not a typical measure collected in malaria programmes, but it can be assessed in prevalence surveys. It changes over time with changes in endemicity: more infections will be symptomatic as the endemicity decreases because of decreasing immunity. As long as the measured prevalence rate is  $\geq 5\%$ , detection and treatment of asymptomatic cases is not justified. This strategy becomes important in the elimination phase, i.e. as the prevalence approaches 1%.
- ▶ **Treatment-seeking** can be assessed from household surveys like demographic health surveys and malaria incidence surveys.

- ▶ **Diagnosis** in the public sector may not always be done according to guidelines; the fraction of malaria cases that will be properly diagnosed can be estimated from the known strengths and weaknesses of the health system. In the informal sector, diagnosis is not always performed, as most individuals self-diagnose malaria.
- ▶ **The availability of treatment** can be assessed from supply chain data on stock-outs at health facilities and other outlets at which individuals seek treatment for malaria.
- ▶ **Adherence** depends on many factors; however, the assumption that all individuals receive an effective dose of antimalarial drugs may result in an overestimate of the fraction of infections that are rapidly cured.

### 8.7.7 Operational requirements for interruption of transmission

If it is technically feasible to reduce the malaria prevalence in a subregion from its baseline to a very low level, it is useful to *evaluate the additional time required to achieve elimination in that subregion*.

Transmission dynamics models can be used (see learning unit 2), but their relevance is questionable, because, when the prevalence of *falciparum* malaria is < 1% in for example a population of 100 000 living in 100 villages, it is unlikely that the infections are homogeneously distributed in those villages. It may be possible to identify at most 10–20 villages in which all cases are found at one time. While other villages are probably at risk and their coverage with basic curative and preventive services must be preserved, it is possible to identify *active foci*, investigate the epidemiological situation of each and use a package of additional tailored interventions.

### 8.7.8 Dealing with vulnerability

The classification of imported cases and the strategies that can be used were addressed in learning unit 6. Earlier in this learning unit, we examined how vulnerability can be quantified. It is likely that a moderate-to-high importation rate combined with a reproduction rate > 1 is incompatible with malaria-free status. If, for example, transmission is interrupted in an area with a population of 100 000 where the vectorial capacity is just over 1 (corresponding to a baseline prevalence well below 5%), the importation of 100 cases in 1 year will almost inevitably lead to a few secondary cases. Even with the best efforts to educate the population about malaria and to ensure early radical treatment, some infected humans will infect some vectors. This situation may well be compatible with non-endemic controlled malaria, however, if surveillance and the response system are strong.

### 8.7.9 The specific challenges of *P. vivax* malaria

It usually takes several years longer to eliminate *P. vivax* than *P. falciparum*. Not only is the duration of untreated infection longer, the infection is present but undetectable for long periods. If, however, there is no or very little importation, persistent application of elimination tools will eventually kill the residual *vivax* infections.

- ▶ **Now, do exercise 8.4.**

### 8.7.10 Assessing the duration of the final stage

If the analysis indicates that elimination is feasible, the time it takes to eliminate foci depends less on the longevity of untreated infections or even the local residual vectorial capacity as on *the programme's capacity to rapidly deal with cases and foci* and follow up with intensified surveillance. The epidemiology of residual focal malaria is governed by stochastic processes that are not reflected well in mechanistic models. The duration of this phase is longer in a large population for the simple reason that the risk of one outbreak in a population of 10 million is much higher than that in a population of 10 000 if the two have the same receptivity and vulnerability. It can be said that programme capacity in this phase is more “brain” than “brawn”; however, if malaria is to be eliminated in a country with 10 million inhabitants, the necessary intelligence must be present in many provinces or districts. It is physically impossible for a central unit to serve a whole country.

From the time the incidence has been reduced to about 1 per 1000 per year in malaria-risk areas, the time to interruption of transmission in an at-risk population of several million is often 5–10 years, and closer to 15 years when *P. vivax* is involved. It is therefore advisable to undertake feasibility studies by subregion, so that elimination (or, initially, only interruption of transmission) can be proposed for areas with a low malaria burden, where elimination can already be envisioned. A gradual approach also provides a strong learning process as a collateral benefit. As a national programme accumulates lessons, feasibility assessments and planning can be done with greater confidence.

#### *Assessment by log–linear least squares regression and extrapolation*

When transmission has been of low intensity for some years and is declining due to regular application of a standardized package of interventions, the remaining duration can sometimes be estimated by linear extrapolation of log-transformed data. The assumption is that malaria incidence is reduced exponentially over time, i.e. that the rate of decrease at any time is proportional to the case load at that time. The extrapolation can be done in several ways. The method described below is easy to use on an Excel sheet.

For a given area with good annual surveillance data for a number of consecutive years, tabulate the logarithm of the incidence rate (y values) against the years (x values). Set the first year to 0 (i.e. if 2012 is the first year, calculate year as (calendar year–2012)). The incidence rate should be for only one parasite species and preferably only local cases. Decide on an incidence rate that is so close to elimination that it will take < 1 year to reach the goal, usually when only about 10 local cases are detected in 1 year. If the denominator population is for example 100 000, the threshold incidence rate will be 0.00001. (The incidence rate cannot be set at 0, as 0 has no logarithm.)

Draw a graph showing year on the x axis and the log incidence rate on the y axis. Check visually that the relation is approximately linear. If it is not, do not proceed unless you have special skills in correlation techniques (and then on your own responsibility!). If the relation looks linear, click Layout>Trendline>Linear trendline, which shows a linear least-squares regression of y against x. Find the year (value of x) at which the trendline meets  $y = 0.00001$ . That is the year in which the incidence rate is expected to reach the chosen threshold value.

The calculation can also be done by simple arithmetics by using Excel commands with the same names to find the values of intercept and slope. The slope will be negative if the incidence rate is decreasing. Intercept is the least-squares regression value of  $y$  for  $x = 0$  (the selected year 0); if the year values had not been transformed by subtracting the value of the first year, the intercept would give the extrapolated incidence rate about 2000 years ago! According to least-squares regression,

$$y = \text{intercept} + \text{slope} \times x$$

We are interested in the value of  $x$  for  $y = 0.00001$ . This is easily calculated as:

$$x = (y - \text{intercept})/\text{slope} = (0.00001 - \text{intercept})/\text{slope}$$

(remember that the slope remains negative). This  $x$  value will be identical to that found by graphical extrapolation. If it is well below 10 years, some credence may be given to it. The higher the  $x$  value, the greater the uncertainty; if it is  $> 15$ – $20$  years, it is questionable whether elimination is feasible with the package of interventions being applied.

## 8.8 Financial and economic feasibility

Two principal financial questions are of interest when considering elimination:

- ▶ How much would the programme cost over time?
- ▶ Can sufficient funds be made available from domestic and external resources?

And one economic question:

- ▶ Is elimination cost-effective in comparison with alternative malaria strategies or other use of public money?

### 8.8.1 Estimation of costs

#### *Costs required for capacity development in the pre-elimination phase*

These costs obviously depend on the existing capacity. The requirements should be easily identifiable from learning units 4 and 5. It is a frequent mistake to assume that capacity-building is the same as training. In many cases, a number of staff positions and work spaces must be established, and the considerable costs of on-site supervision must be taken into account.

#### *Costs required to achieve a very low prevalence of malaria above the baseline level, including closing coverage gaps*

A comparison of five regions—two provinces of China, Mauritius, Swaziland and the islands of Zanzibar—found that per capita costs had or would increase between control and elimination by anywhere from 30% in Zanzibar to 182% in Swaziland; most of the difference appeared to be related to the baseline costs of the control programme. The reasons for the increases varied from region to region, depending on the strengths and weaknesses of the control programme. In the Chinese provinces and Swaziland, the greatest increase in costs was due to improved surveillance, including the introduction of active case detection and screening in identified risk areas. Other cost categories that were increased included prevention, diagnosis and case management.<sup>52</sup>

<sup>52</sup> Sabot O, Cohen JM, Hsiang MS, Kahn JG, Basu S, Tang L, et al. Costs and financial feasibility of malaria elimination. *Lancet* 2010;376(9752):1604–15.

Closing coverage gaps is not only a question of “adding more of the same” but also of improving the quality of operations. Identifying the best ways to do that and monitoring the operational changes *under local conditions* are the hallmarks of expertise in a programme. Some examples are given for LLINs, IRS and case management. This is not a check-list; it is important to consider which approaches and activities will be most efficient to increase the fraction of individuals who are fully protected.

### LLINs

- ▶ Improving *distribution* requires increasing the magnitude or frequency of campaigns; each will involve commodity costs, personnel costs and logistics costs.
- ▶ *Use* can be improved by education campaigns or such strategies as directly hanging nets in houses; each will involve personnel, travel, training and equipment costs.
- ▶ *Net effectiveness* should be considered when planning which nets to purchase and the frequency of replacement; the types of net that correspond to users’ preferences and needs should also be considered.

### IRS

- ▶ Improvements in *community coverage* require increasing the magnitude, frequency, monitoring or quality of campaigns; each will involve costs for additional or alternative insecticide, costs for additional workers and transport costs.
- ▶ *Household coverage* can be improved by education or training; each will require a situation analysis, development and testing of materials, personnel, training and commodity costs. It may be necessary to invest in better spray equipment, maintenance and monitoring *during and after* operations.

### Case management and surveillance

- ▶ *Access to adequate services*. In the pre-elimination phase, the priority may be to establish more service points for case management and passive case detection; this may be linked with strategies for engaging the private sector. Some of the many publications on models for such strategies also address the costs. All countries have some experience with community health workers, which should be used.
- ▶ *Treatment-seeking* could be improved by education campaigns, which require personnel and costs.
- ▶ *Diagnosis* requires that reliable diagnostics be available, that health care workers know how to use them and adhere to the results, and that febrile individuals are aware of the importance of being tested; improving each of these areas may involve costs for commodities and education and training campaigns.
- ▶ *Availability of treatment* can be improved by strengthening supply chain management.
- ▶ *Surveillance* capacity can be strengthened in various ways, as described in learning units 4 and 5.

### Costs in the maintenance phase

The requirements can be identified from learning unit 6. They usually include:

- ▶ strong surveillance systems, with both passive and active measures and continued education of private and public general health services;
- ▶ vector control in areas where receptivity and vulnerability are high; and,
- ▶ in some cases, control of importation, either by screening migrant populations or working with neighbouring regions to reduce importation at its source.

While it is likely that some malaria activities can be scaled back once elimination is achieved, many interventions (especially those related to surveillance) must continue for decades to ensure that imported malaria does not lead to a resurgence of transmission.

In five regions for which the costs of maintaining elimination were calculated,<sup>51</sup> annual expenditure after elimination of malaria was generally expected to be lower than that for achieving elimination; however, regions with high rates of importation required considerable recurrent expenditure for surveillance and prevention through vector control.

### 8.8.2 Financing

If the malaria control programme depends on international donors, continued funding is likely to become increasingly difficult to obtain as malaria recedes. Donor aid can be volatile; therefore, increased domestic spending must be encouraged. While some donors have been active in supporting elimination and eradication, it is uncertain that they will continue to make major allocations to maintaining malaria-free status if this will be to the detriment of countries that still have very high rates of malaria mortality in young children.

The long-term feasibility of elimination may therefore depend on a number of factors.

- ▶ Increased domestic funding is essential. No donor should be expected to fund elimination if it is not backed by a demonstration of national commitment. Also, national governments should be motivated to provide continued financing in the maintenance phase in order to avoid the potential embarrassment of a resurgence of malaria after certification of malaria-free status.
- ▶ Innovative solutions are required, bearing in mind that the tourism sector, national airlines and some enterprises may be among the chief beneficiaries of elimination.
- ▶ Modest financial input for training or research, for example from WHO, could catalyse domestic funding, as was observed in the WHO Eastern Mediterranean Region.
- ▶ Analysis or operational research is necessary to optimize allocative and technical efficiency. Some countries spend funds on entomological monitoring in areas that have been malaria-free for decades, without taking a decision on the basis of the results. Furthermore, updating general practitioners on malaria prophylaxis and malaria risk in different parts of the world is often neglected.

### 8.8.3 Does elimination make economic sense?

If elimination is found to be technically, operationally and financially feasible, a final consideration is whether spending funds on malaria elimination is justified, given competing health priorities. In most settings, malaria elimination should not be attempted to save costs. Although it is generally perceived that elimination will be cheaper than continuous, long-term malaria control, the cost of maintaining adequate surveillance and response capacity will mean that there is no

great difference in programme costs. In Zanzibar, it was estimated that maintenance of absolute malaria-free status would be much more costly than maintenance of a state of controlled non-endemic malaria. In this training module, analyses are restricted to possible malaria scenarios. Ideally, such analyses should take into consideration other, competing health investments. A practical tool is now available.<sup>53</sup>

Preferably, financial information should be presented for at least two scenarios: one for elimination within a given time and another for malaria control during the same time-frame. The two options can then be compared on the basis of:

- ▶ the total cost each year and
- ▶ the cost each year per person of the population in the areas being considered for elimination. This will allow a crude comparison with the costs of other public health programmes, including an alternative malaria control programme.

If two options, e.g. elimination and control, are compared, the annual costs can be summed over the selected time-frame, but they should be discounted by a certain percentage each year. This is either selected by the ministry of health planning department or can be set at 5% per year.<sup>54</sup>

Table 8.1 shows the result of discounting cost with an annual rate of 5%. The value of US\$ 100 in year 0 becomes US\$ 105 in year-1 dollars. The value in year-0 dollars of the US\$ 100 cost in year 1 is  $100/1.05$ , the value in year-0 dollars of the US\$ 100 cost in year 2 is  $100/(1.05)^2$ , etc.

**Table 8.1. Discounting costs with an annual discount rate of 5%**

	Year 0	Year 1	Year 2	Year 3	Year 4	Total in year-0 (US\$)
Cost each year	100	100	100	100	100	500.00
Discount factor	1	1.05	1.1025	1.1576	1.2155	
Discounted cost	100	95.24	90.70	86.38	82.27	454.60

### *Comparative cost–effectiveness analysis*

The indicator of interest is *the cost per case averted*. For an elimination programme, the time-frame should theoretically be extended to infinity. The estimated number of cases averted per year should then be adjusted for demographic changes *and discounted in the same way as financial costs because of the accumulating uncertainties of estimates for the distant future*. Such calculations are best left to health economists trained in dynamic modelling.

A simple, informative cost–effectiveness analysis could be set up as follows.

1. Limit the exercise to subregions for which the analyses indicate that elimination *may* be the better option. Decide on a time-frame of, for example, 20 or 30 years. The following steps may be taken for the whole area, if it is homogeneous, or for each of the subregions of interest with summation for the whole area.
2. Estimate the total population for each year from data on actual and projected population growth.
3. Tabulate the annual costs of the elimination programme and the preferred alternative control programme.

<sup>53</sup> OneHealth tool (<http://www.who.int/choice/onehealthtool/en/>, accessed 11 November 2015).

<sup>54</sup> Witter S, Ensor T, Jowett M, Thompson R. Health economics for developing countries. London: Macmillan; 2000.



4. Discount the costs by 5% (or the alternative) per year, and sum them to estimate the total programme cost in “year-0 US\$” (or another currency) over the period. Then, calculate the difference between the two options. If the elimination programme is less costly, there is no need for further analysis: as it will surely avert more cases, it is the dominant option, and it would be wrong not to choose it. If the elimination programme is more costly, continue.
5. Estimate the annual number of malaria cases (*P. falciparum* and *P. vivax*, if both are considered) in the absence of a control programme from past records, taking into consideration that a gradual reduction year by year is plausible, in line with any reduction in baseline prevalence found in the feasibility analysis. In some countries, urbanization may lead to a significant reduction; however, the demographic and social development of certain remote areas may be different from national trends. The annual number of cases should be the estimated real number, not the number recorded in the health management information or surveillance system. The WHO method from the World malaria reports may be used. It is important to factor in population growth.
6. Estimate the annual number of malaria cases under the control programme and under the elimination programme. The modelling described in this learning unit does not provide these estimates directly; incidence is not proportional to prevalence when there are major changes in epidemiology. The estimates should also be based on the impact of interventions and the estimated times to about 1% prevalence and interruption of transmission.
7. Subtract the annual number of cases in the two programme options from the number in the absence of control. The result is the number of cases averted each year with each strategy. Discount this number with the factor as applied for costs. Then, sum the numbers of averted cases in all years.
8. Presumably, more cases will be averted by the elimination programme. Calculate the incremental cost per case averted by choosing elimination over control as: *Difference in total discounted cost divided by difference in total discounted number of cases averted*. Is it lower than the cost per case averted under control? If so, the elimination programme should probably be considered the better option, unless the available money would be better spent on a public health purpose that clearly gives a better return. Is the incremental cost per case averted higher than the cost per case averted under control? If it is much higher, the options should be carefully discussed. If it is only a little higher, then it *may* be reasonable to prefer elimination, because the analysis, which is limited to 20 or 30 years, is slightly biased: it is expected that in subsequent years elimination will continue to avert more cases than control.
9. Discuss the findings with health economists, public health experts and health system specialists, who may be more objective about the issues and challenges than malaria specialists. The potential collateral benefits of elimination should also be recalled at this stage.

## Unit 8 exercises

### Exercise 8.1

- ▶ Consider how the region of interest should be stratified on the basis of operational and epidemiological considerations, such as burden and vectorial capacity before intervention, remoteness or environment.
- ▶ Divide the area of interest into operationally meaningful subregions that are reasonably homogeneous in terms of their suitability for malaria transmission.

### Exercise 8.2

- ▶ Assemble data on prevalence and coverage with malaria interventions within each subregion over time from household surveys.
- ▶ Estimate values for missing subregions from data for surrounding regions or other periods.
- ▶ Estimate the baseline prevalence from the most recent survey in each subregion before scaling up antimalaria interventions.
- ▶ If multiple surveys were conducted before scaling up, evaluate whether any trends in the data could be extrapolated.
- ▶ Estimate the baseline prevalence from the most recent survey in each subregion and the fraction of the population protected at that time.
  - ▶ Estimate the proportion of the population effectively covered with interventions like ITNs and IRS.
  - ▶ Find the baseline prevalence in Fig. 8.12 from the observed prevalence and the fraction of the population effectively covered by interventions.
- ▶ Compare the results of two or three methods and choose the most likely value for the baseline prevalence in each subregion or a range of values.

### Exercise 8.3

- ▶ For each subregion, choose the curve from Fig. 8.13 that most closely matches the estimated baseline prevalence. If the baseline prevalence for a subregion falls between two figures, use the figure on either side to approximate it.
- ▶ On the figure, identify the minimum fraction of the at-risk population that must be fully protected from transmission in order to reduce the malaria prevalence from baseline to a very low level ( $< 1\%$ ), and record that value for each subregion.
- ▶ Identify the time required to reduce the malaria prevalence from baseline to a very low level in each subregion. Add 1–2 years to the value derived directly from Fig. 8.13 to account for added time due to gradual scaling up of interventions.
- ▶ Does a reduction in the prevalence of malaria from its baseline to a very low level appear to be technically feasible in all subregions?

### Exercise 8.4

- ▶ For each subregion, use available knowledge and readily accessible data sources to assess the kinds of population movement that may lead to importation.
- ▶ Quantify the importation rates, and classify them on a scale from very low to high. Remember that “imported” means any case originating from outside the subregion being considered.
- ▶ For each subregion and each type of population movement, assess by how much surveillance, chemoprophylaxis and other measures might reduce the importation rate.
- ▶ Assess whether it will be possible to maintain malaria-free status in view of the number of imported infections that will be taken up by vectors despite the measures that can be implemented and the number of secondary cases arising from each imported infection.
- ▶ If much of the importation appears to be from neighbouring subregions, decide whether they should be clustered into a larger unit.

### Exercise 8.5

- ▶ For each subregion, estimate the annual cost of filling the operational gaps in order to achieve elimination, including capacity development for the elimination phase.
- ▶ For each subregion, estimate the cost of measures required in the maintenance phase.
- ▶ Calculate the annual cost per inhabitant of the subregion, and compare it with the cost of a good control programme.
- ▶ Evaluate whether the budget could realistically be obtained mainly from domestic sources
- ▶ If you have prepared a realistic long-term annual cost assessment of two options, evaluate the cost–effectiveness of elimination in comparison with control.

### Exercise 8.6

If you have good surveillance data from your country or a subregion, carry out an extrapolation exercise with the method presented under 8.7.10, with the facilitator’s guidance. Examine the results in the light of knowledge about local malaria epidemiology, the interventions used and the role of vulnerability. Formulate your interpretation.



# LEARNING UNIT 9

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## WHO certification of malaria elimination

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### Learning objectives

By the end of this unit, participants should be able to:

- Explain the concept of burden of proof in the context of malaria elimination
- Describe the steps in the process of certification of malaria elimination and
- Explain the reporting requirements for countries that have been certified malaria-free

## Reading material

*Malaria elimination. A field manual for low and moderate endemic countries*, Chapter 7 and annexes 11–13.

## Introduction

The general principles of certification are fixed.

- ▶ Certification is given to a country as a whole and for all four human malaria species.
- ▶ The process is managed by WHO (Global Malaria Programme in collaboration with the regional office concerned).
- ▶ Inspection and evaluation are carried out by an independent team, which recommends certification if appropriate.
- ▶ The final decision rests with the WHO Director-General.

### 9.1 Requirements and burden of proof

When a previously endemic country has recorded 0 locally acquired malaria cases for at least 3 consecutive years, it can request WHO to certify that it is malaria-free.

Certification of malaria elimination requires proof beyond reasonable doubt<sup>55</sup> that the chain of local human malaria transmission by *Anopheles* mosquitoes has been fully interrupted in the entire country. The burden of proof of elimination falls on the country requesting certification. The bolder a claim of malaria elimination appears to be, the higher the standard of proof that will be required, and the less it will be taken for granted or assumed to be true without additional investigation.

Absolute mathematical certainty of elimination can never be obtained. Thus, a defensible, plausible argument must be made that, beyond reasonable doubt, malaria transmission has ended in a given place and at a given time. This implies that all the available evidence has been evaluated and has been found to be consistent with the assertion that malaria elimination has been achieved and that good-quality surveillance systems (see Box 9.1) are in place that would be capable of detecting local transmission if it were occurring.

#### Box 9.1. Assessing the quality of a surveillance system

The annual blood examination rate is an indicator of the performance of a surveillance system; it can be used despite its limitations (see unit 5). More detailed investigations should be conducted when both quantitative coverage and the quality of surveillance operations are to be assessed in each focus (active or not) and during each month of the transmission season for several years. For further details, see the malaria elimination field manual, Box 3, p. 47.

<sup>55</sup> Reasonable doubt is defined as actual and substantial doubt reasonably arising from evidence, from the facts or circumstances shown by the evidence or from the lack of evidence.

## 9.2 Procedure for certification

Eight steps are required to reach the final stage of recognition and certification of malaria elimination by WHO.

- ▶ **Request sent to WHO:** The national government sends a request for certification to the WHO regional director. WHO responds by communicating the elimination criteria, certification process and the documents necessary to provide clear, convincing evidence that malaria transmission has been interrupted throughout the country (see malaria elimination field manual, Annex 11).
- ▶ **Formulation of a plan of action:** WHO and the national government jointly prepare a plan of action for certification.
- ▶ **Implementation of the plan and submission of supporting documentation:** The national government prepares the necessary documentation.
- ▶ **Evaluation visit(s) and preparation of the report:** A WHO-led evaluation team, preferably consisting of experts from WHO headquarters and regional offices and from outside WHO, visits the country, verifies the documents, makes site visits and examines anything else of relevance. The team prepares a report with a recommendation to WHO on granting certification (see malaria elimination field manual, Annex 12).
- ▶ **Report review by a wider group of experts:** The WHO Secretariat shares the report with WHO and non-WHO experts on malaria elimination for critical review.
- ▶ **Review by the WHO Expert Committee on Malaria:** The outcome of the wider review is compiled by the WHO Secretariat and sent with a recommendation for certification, with the accompanying documents, to the Chairperson of the WHO Expert Committee on Malaria. The Chairperson communicates directly with the national government for any further clarification of the dossier and makes a recommendation to the Director-General of WHO for a final decision.
- ▶ **Final decision:** The Director-General of WHO takes the final decision on granting malaria-free status and communicates it in an official letter to the national government.
- ▶ **Publication of certification in the WHO Weekly epidemiological record:** The WHO Secretariat publishes positive decisions in the *Weekly epidemiological record*.

In summary, the activities to be carried out by a country requesting certification are:

- ▶ submission of a request to WHO;
- ▶ formulation of a plan of action for certification, with WHO (first assessment mission);
- ▶ preparation of supporting documentation; and
- ▶ reception of assessment missions.

The activities to be organized by WHO are:

- ▶ receipt of country request for certification;
- ▶ confirmation of agreement to launch certification procedure;
- ▶ assessment of malaria elimination:

- ▶ by WHO staff (first assessment mission) and
- ▶ by independent consultants (second assessment mission);
- ▶ review of the assessment report by a group of malaria experts;
- ▶ review of the report by the WHO Malaria Expert Committee;
- ▶ final decision on granting certification by the WHO Director-General; and
- ▶ publication of certification in the WHO *Weekly epidemiological record*.

### 9.3 What the assessment teams consider

The objectives of the independent assessment are to:

- ▶ verify the certification documentation and the national report on the basis of local realities;
- ▶ evaluate whether the documents provide an evidence-based, coherent, complete history of the disappearance of malaria transmission in the country and whether the country will be able to prevent re-establishment of malaria transmission; and
- ▶ make a recommendation to WHO on granting certification.

In order to be confident that durable interruption of transmission has been achieved, a number of preconditions must be met, as listed in Box 9.2. They address two broad areas: confirming the absence of transmission and assessing the ability to maintain malaria-free status. Some preconditions are essential, others desirable. The parameters that will be verified by the assessment teams will also be of interest to national staff in the later stages of the elimination programme.



### Box 9.2

To confirm the absence of transmission and the ability of maintaining a malaria-free status, the following prerequisites must be met:

#### *Essential:*

- ▶ good surveillance mechanism with full coverage of all geographical areas;
- ▶ central case register, notification and full immediate reporting by public and private health services;
- ▶ adequate health services for early detection and effective treatment and follow-up of imported cases;
- ▶ high-quality laboratory services for diagnosis of malaria by microscopy;
- ▶ epidemiological investigation of every malaria case;
- ▶ capacity for early detection of and rapid response to epidemics, gradually becoming part of the system to control outbreaks of vector-borne diseases in general;
- ▶ entomological surveillance and monitoring of insecticide resistance in areas with high receptivity, gradually becoming part of integrated control of vectors and nuisances; and
- ▶ a comprehensive national plan of action and continued political and financial support for the activities required to prevent re-establishment of transmission.

#### *Desirable:*

- ▶ central computerized geo-referenced database of cases and the latest foci (complementary to the central case register);
- ▶ system to prevent importation of malaria by travellers, with awareness-raising, prevention of mosquito bites and chemoprophylaxis; and
- ▶ a functional inter-country coordination system, depending on migration patterns or the presence of adjacent malarious areas.

Operational research can maintain staff interest and knowledge when there are only a few cases. Regular publication of research results and surveillance data can help maintain the interest of the wider medical community at country level.

The assessment team should therefore also evaluate the capacity of the national programme to conduct good-quality operational research projects, as evidenced by ongoing and published research projects on malaria elimination and prevention of its reintroduction.

## 9.4 Follow-up of certification and maintenance

Certification of malaria elimination is based on an assessment of the current situation and the likelihood that elimination can be maintained. Countries are requested to report to WHO annually on the maintenance of their malaria-free status. The information to be included in the annual report to WHO is outlined in the malaria elimination field manual, Annex 13.

Outbreaks of *falciparum* malaria in a usually or recently malaria-free country should be reported to WHO immediately, so that WHO can provide assistance where needed and can alert international travellers to take suitable preventive measures when visiting the affected area. In certain circumstances, malaria may be notifiable under the International Health Regulations (2005) (see malaria elimination field manual, Box 4, p. 51).

As certification represents recognition of a considerable operational achievement, countries will remain listed as having achieved malaria elimination even if they subsequently have a temporary reoccurrence of local transmission.

An indication of the re-establishment of transmission would be the occurrence of three or more introduced and/or indigenous malaria infections linked in space and time to local mosquito-borne transmission in the same geographical focus, for 2 consecutive years for *P. falciparum* and for 3 consecutive years for *P. vivax*.

Re-establishment of transmission will be reported in the annual updates of the WHO publication *International travel and health*.<sup>56</sup> To protect international travellers, reports of falciparum malaria outbreaks in “malaria-free” countries will be posted on an ad hoc basis in the *Weekly Epidemiological Record*.

## Unit 9 exercise

### Exercise 9.1

Select a country that has recently been certified as malaria-free (from the latest WHO *World malaria report*), and write an account giving the historical background and progress to certification in that country. Try to retrieve information about successful elimination programmes. Examples are:

Eliminating malaria: case-study 1: achieving elimination in Turkmenistan. Geneva: World Health Organization; 2012 ([http://www.who.int/iris/bitstream/10665/75848/1/9789241504300\\_eng.pdf](http://www.who.int/iris/bitstream/10665/75848/1/9789241504300_eng.pdf), accessed 14 November 2015).

Malaria in Morocco: relentless efforts towards the goal of elimination. Cairo: World Health Organization Regional Office for the Eastern Mediterranean. <http://www.emro.who.int/dsaf/dsa777.pdf>, accessed 14 September 2015).

Selected summaries will be presented orally and discussed in plenary.

<sup>56</sup> International travel and health. Geneva: World Health Organization; 2015:Chapter 7 ([www.who.int/ith/2015-ith-chapter7/pdf](http://www.who.int/ith/2015-ith-chapter7/pdf), accessed 12 September 2015).

## ANNEX 1. KEY ISSUES IN QUALITY ASSURANCE FOR MALARIA MICROSCOPY IN THE ELIMINATION PHASE

This annex describes some aspects of quality assurance that are particularly important for elimination programmes. These supplement the quality assurance manual<sup>57</sup> and Annex 1 of the surveillance manual<sup>58</sup>.

Some practices for quality assurance of malaria diagnosis were established during the malaria eradication programmes in 1950s and 1960s. The main one was re-examination of all positive and a random sample of 10% of negative slides. Most discrepancies that were considered important were between positive results later found to be negative and vice versa.

Contemporary malaria elimination programmes require, first of all, precise species identification. Quantification is necessary for clinical assessment and also for analysing laboratory errors. Early detection of cases is a major concern: hence the need to record the presence or absence of *P. falciparum* gametocytes. Parasite density may give an idea of how recent a case is.

The success of diagnostic work depends on motivation and self-discipline, especially as the number of positive slides decreases. Laboratory staff must remember that behind every slide there is a patient whose life may depend on the quality of the laboratory work. In the final stages of elimination, all efforts must be made to ensure that there are no more cases. This will obviously require the examination of many slides; detection of a single infection may have momentous implications. Technicians must understand their findings and recognize signs of urgency, e.g. very high parasitaemia or finding *P. falciparum* in an area where it has not been found recently.

Details of supervisory visits, cross-checking and training are described below.

### Supervisory visits

This activity is neglected in many programmes. Although on-site assessments are time-consuming and costly, they are essential, because they enable the supervisor to:

- ▶ observe working habits,
- ▶ correct incorrect procedures,
- ▶ relate the conditions of work to the results of external cross-checking,
- ▶ assess the internal quality-control procedures and the procedures for maintaining equipment and supplies,
- ▶ discuss with the technicians and the laboratory management any problems encountered and resolve them on the spot,
- ▶ make decisions about training and retraining and
- ▶ build communication with the staff.

The deficiencies best dealt with at the source are:

- ▶ poor motivation,

<sup>57</sup> Malaria microscopy quality assurance manual. Version 1. Geneva: World Health Organization; 2009:7–40.

<sup>58</sup> Disease surveillance for malaria elimination—an operational manual. Geneva: World Health Organization; 2012 (<http://www.who.int/malaria/publications/atoz/9789241503334/en/>, accessed 11 September 2015).

- ▶ poorly maintained microscopes,
- ▶ badly prepared, stored or transported blood slides,
- ▶ badly stained blood slides,
- ▶ poorly labelled blood slides and
- ▶ excessive, monotonous workload.

Supervisory visits are a good opportunity to talk with the people who are meant to use laboratory results. The following questions may have to be asked:

- ▶ Do they trust the results?
- ▶ Do they consider that the information provided is useful?
- ▶ Do they understand what the results mean?
- ▶ Do they use the results in making decisions?

### *Cross-checking*

In many programmes cross-checking of laboratory results became a mere formality, i.e. when the discrepancy rates are lower than the results of on-site spot checks.

Often, cross-checking should be reorganized to:

- ▶ ensure that the technician does not know the patient's symptoms;
- ▶ check species, forms of *P. falciparum* and parasite densities;
- ▶ ensure the quality of collection and staining, including problems of fixation;
- ▶ analyse the sources of errors; and
- ▶ analyse time elements to identify bottlenecks.

Slides should be dispatched for cross-checking promptly, as poorly stained slides tend to fade rapidly.

With improved cross-checking, continuous monitoring and evaluation of *individual laboratories and technicians* should be organized so that the progress or deterioration of each be clearly documented and comparable. The central laboratory should not only indicate discrepancies but also identify possible sources of error. In some cases, it is easy, e.g. when slides are of the wrong colour, thick films are fixed, or films are destroyed.

Systematic quantification provides additional opportunities for understanding the origin of errors, as shown in Table A.1.1.

**Table A.1.1. Common errors in malaria microscopy and their causes**

Sign (results of technician and of cross-checking)	Causes of errors
Too many cases of low density. On re-examination, parasites are not found in the majority of such cases.	The microscopist confounds parasites with particles of dust, etc. The problem is often aggravated by substandard staining, use of uncleaned slides or poor maintenance of the microscope.
The reported densities are systematically lower than those at cross-checking.	The microscopist recognizes parasites only when they are numerous.
Many slides with gametocytes of <i>P. falciparum</i> are present and trophozoites are absent. This often occurs in combination with the previous sign.	The microscopist recognizes only gametocytes, which are more conspicuous than trophozoites. or The microscopist stops examination as soon as a gametocyte is seen, while examination of 100 fields would record trophozoites as well, or Staining is defective, so trophozoites are not seen but gametocytes, which are slightly stained, are detected because of their natural pigmentation.
High densities reported correctly but many low-density parasitaemias are missed.	The microscopist does not examine the required number of fields.

### *Training and slide banks*

For institutions interested in setting up a slide bank, a didactic video, *Malaria slide banking*, prepared by the Research Institute for Tropical Medicine, Alabang, Metro Manila, Philippines, is available on a CD from the WHO Regional Office for the Western Pacific (MVP-unit@wpro.who.int, accessed 14 September 2015).

## ANNEX 2. MOSHKOVSKY'S METHOD FOR DETERMINING TRANSMISSIBILITY OF MALARIA AS A FUNCTION OF TEMPERATURE IN TEMPERATE AND SUBTROPICAL AREAS

In elimination programmes, meteorological information is required mainly to identify the period during which malaria transmission is possible. It can be used to answer questions such as:

- ▶ On what date did malaria transmission become possible during the current year?
- ▶ Was a given vivax case contracted recently or during the previous year?
- ▶ When, if at all, can introduced cases be expected after a given imported case?
- ▶ If there are two autochthonous cases, is it possible that the first was the source of the second?

### *The malaria season*

The malaria season is the part of the year during which malaria transmission takes place and most malaria cases are detected.

- ▶ **The season of manifestations** is the period of the year during which most malaria manifestations start. In areas with widespread vivax malaria, this includes the period in which recently contracted malaria cases emerge and the time when true (exo-erythrocytic) relapses and primary cases with long incubation period are seen. Therefore, the season of manifestations consists of: the **season of past manifestations**, during the spring and the beginning of summer, followed by the **season of fresh manifestations**. The two overlap at the beginning of the summer, and it is generally impossible to determine whether an emerging case was due to transmission in the current or the previous year.
- ▶ **The season of effective temperatures** is the period in which the average daily temperatures are consistently  $> 16^{\circ}\text{C}$  for *P. vivax* and  $18^{\circ}\text{C}$  for *P. falciparum*.
- ▶ **The season of effective infectiveness** is the period in which mosquitoes can contract the parasite from infected humans (infectiveness), provided that the mosquitoes have enough time at a favourable temperature to have fully developed parasites (effective infectiveness). The starting point of this element is either the start of the season of effective temperatures or the moment of emergence of the first generation of mosquitoes from breeding places. Infections at the end of the season of effective temperatures are ineffective: although the temperatures allow parasites to develop in mosquitoes, there is insufficient time to complete development.
- ▶ **The season of transmission of malaria** starts at the end of the first maturation of parasites in mosquitoes and comes to an end when mosquitoes go into hibernation and stop feeding.

The interrelation of these elements is shown in Fig. A.1.1.

Fig. A.1.1. Interrelation of the elements of the malaria season (e.g. in southern Russian Federation)

Season of manifestations											
Season of effective temperatures						Season of effective infectivity					
Season of transmission											
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII

### Moshkovsky's method

In temperate and some subtropical areas, where seasonal temperatures determine the malaria transmission season, the method proposed by Moshkovsky in 1946 is useful for assessing the following elements of the malaria season:

- ▶ the date of the beginning of the period of effective infectivity, i.e. the period during which parasite can mature completely in mosquitoes;
- ▶ the date of the first possible mosquito–human transmission in the current season; and
- ▶ the date of the last possible effective infection of a mosquito.

The method is based on the concept from agricultural science that the growth of a plant depends on the total amount of heat to which it is subjected during its lifetime, accumulated as degree–days. By analysing the speed of development of *Plasmodia* in controlled experiments, Moshkovsky found that the same concept is applicable to the development of parasites in mosquitoes and calculated the parameters for *P. falciparum*, *P. vivax* and *P. malariae*. For each parasite species, the fundamental parameters are threshold temperature (below which the parasite does not develop), base temperature and the sum of (daily) temperatures in excess of the base temperature required for completion of sporogony. All parameters are expressed in degrees centigrade:

Species	Lower threshold of development (A)	Base temperature (B)	Required sum of temperatures above the base temperature, degree–days (C)
<i>P. vivax</i>	16	14.5	105
<i>P. falciparum</i>	19	16	111
<i>P. malariae</i>	18	16	144

At the threshold temperatures, development of the parasites takes an infinitely long time. At temperatures > 30 °C, the conditions for the development of parasites worsen, and at 37 °C they die out rapidly.

### Calculations

The formula *at constant temperature* is:

$$\text{Duration (in days)} = C / (\text{average daily temperature} - B)$$

For example, at 19 °C, the development of *P. falciparum* takes:

$$C / (19 - B) = 111 / (19 - 16) = 37 \text{ days.}$$

Here,  $19 - 16 = 3$  °C is the effective temperature accumulated by the parasite during a day.

*At variable temperatures*, the effective temperatures are calculated for each day and added. Only days with temperatures above the threshold (A) are counted, i.e. above 16 °C for *P. vivax* and > 18 °C for *P. falciparum*. *When the sum of effective temperatures reaches the required sum, C, the maturation of sporozoites is completed.*

The calculations are performed in the following way (with *P. vivax* as an example):

- ▶ Identify the date on which the average daily temperatures pass the threshold of 16 °C in a stable way.
- ▶ If the first generation of vectors is already present, this is the date of the beginning of the season of effective infectivity. If not, the date of mass emergence of the first generation is taken as the starting point. For example, in the Russian Federation, vector mosquitoes of the first generation are already present when the temperatures are not yet favourable for sporogony. In this case, an average daily temperature of 16 °C would be the starting point for computations with Moshkovsky's formula. In Central Asia, the opposite is true: in early spring, the temperature is high enough, but adult mosquitoes are still not there. In this case, the start is the time of mass emergence of adult mosquitoes.
- ▶ Starting from this date, calculate the excesses of average daily temperature > 14.5 °C for each day.
- ▶ Sum the daily excesses to obtain the cumulative sum of average daily temperatures.
- ▶ If the average daily temperature is > 16 °C, add nothing to the cumulative sum.
- ▶ If the average daily temperatures are < 16 °C for > 7 days, the sporozoites in the middle of their development are presumed dead, and the calculations are started anew from the next date with an average daily temperature > 16 °C.
- ▶ Continue the calculations until the average daily temperature drops and remains < 16 °C.

The algorithm is simple, but the calculations are tedious when performed manually. An electronic spreadsheet makes the task much easier. Average daily temperatures are the only input needed.

#### *Questions that can be answered with Moshkovsky's method*

The method answers questions that are pertinent to the epidemiological analysis of cases in territories with no or limited malaria transmission:

- ▶ *If a case of vivax malaria was imported on date X, when, if at all, can the first introduced case be expected?* To answer this question, find the first day after importation of the case on which the average daily temperature was stably > 16 °C, and adult vectors had already emerged. If the case was still infective then, start calculating the cumulative sum of average daily temperatures from that date. On the date at which the cumulative sum reaches 105, a vector that bit the imported case might have become infective. If this date is before the end of the season of effective temperatures, i.e. the average daily temperature is still > 16 °C, a minimum incubation period of 10 days (for *P. vivax* in humans) is added in order to obtain the earliest possible date of onset of a secondary case. Because of variation in the incubation interval, the case might have started a little later, as the usual duration of short incubation is 14–16 days. As the case



is *P. vivax* malaria, it might have started after an incubation period of several months and will occur the following year.

- ▶ *When there are two P. vivax cases—an imported case that started on date X and a second that started on date Y—can the latter originate from the former?* Yes, if it occurs after the earliest day on which an introduced case could be expected, as calculated above, provided the average daily temperatures were still > 16 °C 10 days (minimum incubation period) before it manifested. If not, the second case is not linked to the first one; they have independent origins.
- ▶ *Is it possible that a given case of P. vivax malaria was contracted during the current transmission season, or it is a result of the last year's transmission (a late manifestation)?* Check whether the cumulative sum of average daily temperatures on the date of onset of the case minus 10 days is > 105. If it is, the case might have been contracted during the current season.

### Exercise

Trainees should work individually or in groups of two using an MS Excel package. Open the spreadsheet (file *Meteo\_Annex 2.xls*), and follow the instructions. Discuss the results in plenary.

Long experience in the former USSR and in the Russian Federation shows that the method may be useful for epidemiological analysis, although there are several uncertainties:

- ▶ The initial basic measurements were made for a limited number of strains. There is no certainty that tropical strains would behave in the same way as temperate ones. Hence, it is not clear whether this method could also be used in mountainous areas of the tropics.
- ▶ The method is reasonably accurate in the areas in which mosquitoes belonging to the *An. maculipennis* group are the vectors. They hibernate at the stage of the imago and do not feed during the winter. The method should be validated for areas outside the Palaearctic and Nearctic regions.
- ▶ The temperatures used are from the nearest meteorological station, not from mosquito resting places. Therefore, the average daily inside and outside temperatures may differ by several degrees.
- ▶ The impact of temporary reduction of the temperature below development thresholds has not been quantified. It is known only that, after a short drop in temperature, sporozoites recover and continue their development; sporozoites of *P. vivax* are more tolerant to falls in temperature than those of *P. falciparum*; more mature sporozoites are more tolerant; and steeper decreases kill more sporozoites.







**FOR MORE INFORMATION, PLEASE CONTACT:**

Global Malaria Programme  
World Health Organization  
20 avenue Appia  
1211 Geneva 27  
Switzerland

E-mail : [infogmp@who.int](mailto:infogmp@who.int)  
<http://www.who.int/malaria>

ISBN 978 92 4 154942 4

