10 | IDENTIFYING THE GAPS—WHAT WE NEED TO KNOW

Geoffrey A. Targett,[a] Shunmay Yeung,[a] and Marcel Tanner[b]

10.1 | Introduction

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

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

[a]London School of Hygiene & Tropical Medicine, London, UK; [b]Swiss Tropical Institute, Basel, Switzerland

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

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

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

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

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

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

10.2 Case Studies

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

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

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

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

BOX 10.1 | Elimination Case Study: Mauritius

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

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

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

10.3 | Checklist for Health Systems

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

ACCESS TO DIAGNOSIS AND TREATMENT

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

BOX 10.2 | Elimination Case Study: Morocco[5]

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

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

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

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

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

Key linked questions include the following:

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

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

ORGANIZING THE MAJOR NONCLINICAL FUNCTIONS IN MALARIA ELIMINATION

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

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

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

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

10.4 | Checklist for Finance and Economics

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

COST COMPARISONS

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

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

COST BENEFITS

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

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

COST-EFFECTIVENESS

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

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

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

10.5 Checklist for Surveillance

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

FOCI OF INFECTION

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

The key questions are these:

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

FINDING ALL PARASITES

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

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

Key questions include the following:

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

COMMUNITY INVOLVEMENT

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

10.6 | Monitoring and Evaluation

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

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

GETTING TO ZERO

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

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

HOLDING THE LINE

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

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

MEASURES OF EXPOSURE

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

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

The key question is this:

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

POPULATION MOVEMENTS/MIGRATION

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

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

INDICATORS

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

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

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

10.7 Checklist for Diagnosis

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

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

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

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

The key questions are the following:

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

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

10.8 | Checklist for Drugs

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

DRUGS FOR TREATMENT

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

GAMETOCYTICIDAL DRUGS

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

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

MASS DRUG ADMINISTRATION OR MASS SCREENING AND TREATMENT

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

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

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

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

Key questions include the following:

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

P. VIVAX AND *P. OVALE* HYPNOZOITES

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

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

MONITORING FOR RESISTANCE

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

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

10.9 | Checklist for Vector Control

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

FOCI OF INFECTION

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

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

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

Key questions include the following:

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

INSECTICIDE RESISTANCE

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

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

Key questions include the following:

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

REPELLENTS

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

The key question is this:

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

BREEDING SITES

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

Key questions include the following:

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

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

COMBINING VECTOR CONTROL INTERVENTIONS

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

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

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

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

Key questions include the following:

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

10.10 Conclusion

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

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

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

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

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