GLOBAL MALARIA CONTROL AND ELIMINATION:

report of a technical review

17–18 January, 2008
Geneva, Switzerland

World Health Organization

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EXECUTIVE SUMMARY

Malaria is endemic in 109 countries and territories in tropical and sub-tropical zones, spanning all continents of the world except Antarctica and Australia, with intensities of transmission that vary from very low to extremely high. Since the launch of the Roll Back Malaria Initiative by WHO in 1998, and particularly in the past few years, malaria control has intensified in endemic countries, supported by a greatly increased investment of financial resources and technical assistance from the international community. As a consequence of the resulting high coverage with malaria interventions, especially in sub-Saharan Africa where the burden of malaria is greatest, the malaria burden is being reduced, albeit variably, in all regions of the world. In some countries in Africa with high malaria burdens, there is evidence of significantly decreasing malaria incidence and deaths among children and adults. In countries with lower transmission intensities, such as southern Africa and Asia, the malaria burden has been reduced to such an extent that it has ceased to be a major public health problem. In 16 endemic countries, the risk is limited to *Plasmodium vivax* malaria, some of those countries having eliminated *P. falciparum* over the years. A few countries in which the malaria burden was relatively low but persistent have completely eliminated malaria: in 2007, the United Arab Emirates was certified by WHO as being malaria-free, and another five formerly endemic countries have reported no locally acquired malaria cases in recent years. In 11 countries, programmes are under way to eliminate the disease.

Given the moral imperative of eliminating malaria, control and elimination of the disease have been contemplated since the beginning of the twentieth century. It was soon realized, however, that the achievements of aggressive, time-limited campaigns were unsustainable and that progress required continuous effort. Before the Second World War, most of western Europe had virtually eliminated the disease by focal vector control and by making diagnosis and treatment widely available. In the decade that followed, the availability of DDT and chloroquine, both with impressive efficacy, led to a resurgence of campaign spirit and, in 1955, the launching of the Global Programme for Malaria Eradication, a campaign that targeted all endemic countries except mainland sub-Saharan Africa and Madagascar. The campaign demanded perfect execution of prescribed activities by a highly disciplined workforce, which was to spare no effort in reaching the remotest houses. Nevertheless, mosquito vectors and parasites did not respond everywhere as expected, and progressive attrition began in both the operational *esprit de corps* and discipline as well as in the collaboration of the population. The progress of the campaign slowed, and malaria outbreaks occurred

during the consolidation phase of the programme in some areas that had initially responded well. Analysing the failures during the consolidation phase, WHO recognized that the basic requirements for achieving and sustaining malaria control are (1) integration of malaria control into a reasonably well-established health system, (2) an uninterrupted, continued effort and (3) research into new and improved tools. In 1978, WHO reoriented its policy from eradication and elimination to control. During and following the Global Malaria Eradication Programme, up to 1982, 24 endemic countries were certified by WHO as malaria-free.

The objectives of malaria control programmes range from reducing the disease burden and maintaining it at a reasonably low level, to eliminating the disease from a defined geographical area, and ultimately to eradicating the disease globally. These levels of control are defined as follows (WHO, 2007):

- *Malaria control*: reducing the disease burden to a level at which it is no longer a public health problem
- *Malaria elimination*: interrupting local mosquito-borne malaria transmission in a defined geographical area, i.e. zero incidence of locally contracted cases, although imported cases will continue to occur. Continued intervention measures are required.
- *Malaria eradication*: permanent reduction to zero of the worldwide incidence of malaria infection.

Since the last attempts at malaria elimination or eradication more than half a century ago, the landscape in which antimalarial activities are being conducted has changed considerably. New, more effective tools are available, communication technology has improved, as has the wealth of nations and the social and economic standards of people living in endemic areas. These changes, combined with the malaria control achievements of the past few years, have inspired the governments of malaria-endemic countries and major international donors to aspire to a more ambitious, accelerated effort. History shows that new goals and targets for global malaria control, elimination and possible eradication must be realistic in order to avoid disappointment and disillusionment and the devastating implications of disease resurgence, experienced in the past. The lessons of the past and the efficacy and effectiveness of the current tools will serve as guides to setting realistic targets. Potential threats to malaria control—the prevailing state of health systems and the epidemiology of malaria in endemic countries—must also be taken into account in setting realistic targets.

Effective mosquito control tools (including long-lasting insecticidal nets and indoor residual spraying) and medicines for early, effective termination of human infections (including artemisinin-based combination therapy) are available today, with which substantial reductions in the malaria burden have and can be achieved. With these tools, elimination of local transmission has been possible in areas where transmission is marginal; however, these preventive and curative tools rely heavily on chemical entities—insecticides (pyrethroids) and therapeutic agents (artemisinins)—that are vulnerable to resistance by the mosquito vector and parasite, respectively. The development pipeline for alternatives to pyrethroids and artemisinins is weak at present, placing malaria control at considerable risk.

The unit of measurement of the spread of malaria (transmission) is the basic reproduction rate, which is the number of new malaria cases generated by a single case. This is an expression of the efficiency of the mosquito vector (vectorial capacity) and the magnitude of the infective parasite pool in humans. Vectorial capacity is determined by the density of mosquitoes, their feeding frequency on humans, their daily survival rate and the duration of the parasite's development cycle in the mosquito. It is extremely sensitive to changes in the daily survival of the mosquito and, to a lesser extent, to their density and human biting frequency. For malaria to be eliminated, the basic reproduction rate (the number of new malaria cases generated by a single case over the duration of infection) has to be less than 1. With the existing arsenal of tools, only the density of mosquitoes, the daily survival rate of the mosquito, their human biting rate and the duration of infection in humans can be manipulated by intervention. Current antimalarial interventions lead to a reduction in the basic rate of reproduction of malaria by reducing human infectivity with early and effective treatment and reducing vectorial capacity with mosquito control measures. Indoor residual spraying reduces the daily survival rate of the mosquito; insecticide-treated mosquito nets reduce the human biting rate of the mosquito and, to a lesser extent, its daily survival rate.

On the basis of the best current knowledge on the efficacy of current tools and taking into account experiences of the past, the meeting made the following assessment of the feasibility of global malaria control, elimination and eradication:

1. With rapid scaling up of the available tools and sustained efforts, a major impact can be made on morbidity and mortality due to malaria in all epidemiological situations within a relatively short time.
2. In areas or countries with low-intensity malaria transmission, optimal deployment of the available tools will have a strong impact and might

reduce parasite incidence to an extent that would interrupt local transmission. Thus, countries in areas of low, unstable transmission should be encouraged to proceed to malaria elimination. Before taking that decision, however, the overall feasibility, including the malaria situation in neighbouring countries, should be taken into account. Malaria elimination might require regional initiatives and support and will require strong political commitment. Complete interruption of local transmission would require the continuing availability of effective malaria control tools for a variety of epidemiological settings and a stringent approach to malaria elimination, including greatly strengthened monitoring, surveillance and, eventually, vigilance. It is extremely important that temporary lapses in control, elimination and prevention of reintroduction be avoided for as long as areas remain receptive to resumption of transmission and are exposed to importation of parasites.

3. The most recent experience in some African countries confirms that substantial reductions in transmission intensity (measured as reported disease incidence and parasite prevalence rates) can be achieved in areas of stable high transmission by full-scale deployment of the available tools, given a minimum of political stability and the right socioeconomic conditions. Pursuing full-scale deployment rapidly by 'front-loading' i.e. concentrating financial investment at the beginning will have the advantage of speedily reducing malaria morbidity and saving more lives. This will require sustained funding and substantially more support for ongoing control and surveillance.

4. There is no evidence to indicate that, given current resources and healthcare systems and the existing tools, local malaria transmission can be interrupted, nor that 'malaria-free' status can be sustained in high-transmission areas that have unrelentingly high vectorial capacities. Complete interruption of malaria transmission in high-transmission situations will require additional, novel control tools.

5. In areas of high stable transmission that have achieved a marked reduction in malaria transmission, a 'consolidation period' should be introduced, in which (i) the achievements are sustained even in the face of limited

disease, (ii) health services adapt to the new clinical and epidemiological situation, and (iii) surveillance systems are strengthened to respond rapidly to new cases. This transformation phase must precede a decision to proceed with programme reorientation towards elimination. As countries achieve marked reductions in levels of transmission, they should review their malaria control strategies. Failure to sustain malaria control and the resulting resurgence of malaria, as has occurred in the past, must be avoided at all costs. Therefore, public and government interest in intensified malaria control and elimination must be sustained, even when the malaria burden has been greatly reduced.

6. Malaria control relies heavily on a limited number of tools, in particular artemisinin derivatives and pyrethroids, which could be lost to resistance at any time. The future of global malaria control and elimination depends, therefore, on the ability of research and development to deliver a steady output of replacements for tools that are being lost to resistance and to supply new tools to make elimination of malaria possible in high-transmission situations.

7. Malaria eradication requires that malaria elimination in countries and regions is achieved and sustained on a cumulative basis, over decades rather than years. Although at present local malaria transmission can be interrupted in many low-transmission settings and strongly reduced in many areas of high transmission, global eradication cannot be expected with the existing tools.

In summary, the current resurgence of global interest in malaria control and the renewed goal of elimination or eradication should be seen as a tremendous new opportunity to reduce the devastating impact of malaria on human health and development. In order to do this, health administrations and external supporting agencies must commit themselves to strengthening local competence and infrastructure, both for supporting the development of local health services and for the control programme. Sustained investment in human development, health services, malaria control and research and development is essential to achieve and sustain the goals of malaria control and to attain malaria elimination in more countries. Such commitment may make malaria eradication a possibility in the long-term.

1. INTRODUCTION

Since the launch of the Roll Back Malaria Initiative by WHO in 1998, malaria control has featured high on the world's health and development agenda. The inspiration behind the Initiative was as much a desire to alleviate poverty and strengthen health systems in malaria-endemic countries as the necessity of addressing the enormous global public health problem represented by malaria. The past few years have seen increasing national political commitment to controlling malaria and intensified efforts in endemic countries. These have been supported by greatly increased investments of global financial resources and technical assistance from United Nations organizations (WHO, UNICEF) and other partners. As a result, efforts to achieve high coverage with malaria interventions are now under way in most malaria-endemic countries of the world, especially in sub-Saharan Africa, where the burden of malaria is greatest.

The global financial input to malaria control in the past five years averaged US$ 250 million per year, the main sources being the Global Fund to fight AIDS, Tuberculosis and Malaria and, to a lesser extent, the United States President's Malaria Initiative and the World Bank's Booster Programme. These funds still fall short of the estimated requirements for malaria control globally and of those required to achieve the revised targets set by African Heads of State in Abuja, Nigeria, in 2000, of 80% population coverage with the key malaria interventions by 2010 (Kiszewski et al., 2007). Even at this current, relatively slow pace of achieving coverage, however, an impact on the malaria burden is being seen in countries with high malaria burdens, such as Burundi, Kenya, Rwanda, The Gambia, the United Republic of Tanzania Zanzibar and Zambia. In countries with lower transmission intensities, such as China, Malaysia, the Philippines, South Africa, Sri Lanka and Viet Nam, the malaria burden has been reduced to such an extent that it has ceased to be a major public health problem. In 16 endemic countries, the risk is limited to *Plasmodium vivax* malaria, some of those countries having eliminated *P. falciparum* over the years. In a few countries in which the malaria burden was low but persistent, the momentum of the antimalarial drive has enabled a move towards elimination of malaria. In 2007, the United Arab Emirates was certified by WHO as being malaria-free, and another seven formerly endemic countries have reported no locally acquired malaria cases in recent years. In 11 countries (Algeria, Argentina, Armenia, Democratic People's Republic of Korea, Egypt, El Salvador, Iraq, Paraguay, Republic of Korea, Saudi Arabia and Turkmenistan), programmes are under way to eliminate the disease.

These achievements and experiences of the past few years inspired the governments of malaria-endemic countries and major international donors to undertake a more ambitious and accelerated effort, by providing the necessary financial investments for achieving the 80% coverage target over the next three years, as opposed to a gradual scaling-up at the current pace which would take over a decade to accomplish. The Director-General of WHO has committed the Organization to this approach for a global accelerated malaria control and elimination programme.

The Global Malaria Programme of WHO convened a meeting of experts on 17–18 January 2008, bringing together specialists in malaria prevention, treatment, entomology, disease control and public health, epidemiology, transmission and mathematical simulation, to review:

- the definitions and terminology of malaria control, elimination and eradication; and
- the feasibility of malaria elimination, in relation to the intensity of transmission and vectorial capacity.

They were also to make recommendations on:

- the directions and approaches that countries should take in each epidemiological situation and transmission intensity, when the disease burden has been decreased at the end of an intensified phase of malaria control over the next few years;
- the feasibility of malaria eradication, given the tools available today and the epidemiology of malaria in various regions of the world; and
- the gaps in knowledge and priorities for research and development in the next phase of malaria control.

This report presents a summary of the presentations, group work, plenary discussions and outcome of this meeting.

2. DEFINING THE PHASES OF ANTIMALARIAL ACTIVITY, FROM MALARIA CONTROL TO ELIMINATION AND ERADICATION

Malaria is currently endemic in 109 countries and territories in tropical and subtropical zones, spanning all continents of the world except Antarctica and Australia, with intensities of transmission that vary from very low (populations receiving less than one infective bite per year per 100 persons living in areas at risk of malaria, which is marginally above the threshold needed to sustain malaria) to extremely high (more than one infective malaria bite per person per night). This has resulted in a correspondingly wide range of disease burdens in endemic countries across the world, varying from malaria as an infrequent febrile illness to which persons in all age groups are susceptible, to a primarily childhood illness with an extremely high mortality rate among children under the age of 5 years, while adults are partially immune.

The objectives of malaria control programmes range from reducing the disease burden and maintaining it at a reasonably low level, to eliminating the disease from a defined geographical area and, ultimately to eradicating the disease globally. Current WHO recommendations define the progressive steps for eliminating malaria from a country or area with low-to-moderate endemicity as shown in Figure 1. When the malaria incidence rate is decreased to five new cases or fewer per 1000 population at risk per year[1], the case load is considered 'manageable' enough to allow the intensive follow-up of cases that is required in an elimination programme. At that point, the country can start reorienting its malaria control programme towards elimination. This transition is called the 'pre-elimination phase'.

Thereafter, when malaria distribution becomes increasingly patchy, the incidence rate declines progressively to below 1 per 1000 population at risk and necessary programme adaptations have been made, the country can move to the elimination phase. Moving from the control to the elimination phase demands changes in strategies. While the focus of the malaria control phase is achieving population coverage with preventive methods and access to treatment, the defining aspects of malaria elimination programmes are:

[1] No single month with a slide positivity rate above 5% among febrile patients who attend health-care services could be used as a proxy measure, provided it is confirmed by subsequent population surveys.

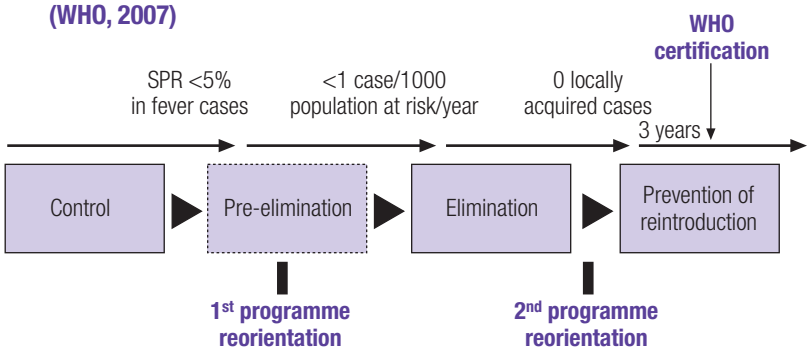
- detection of all malaria cases
- prevention of onward transmission
- management of malaria foci and
- management of importation of malaria parasites.

Elimination programmes require more technical malaria expertise than general control programmes, and are driven by national expertise in malaria epidemiology and entomology. Experience shows that most countries adopt the elimination strategy in a phased approach, either by parasite species (e.g. *P. falciparum* first) or by geographical area.

When the number of locally acquired cases becomes very low (perhaps below 100, 10 or even fewer nationwide), continuing importation of malaria parasites from abroad becomes a greater threat than the last, dwindling local parasites, and prevention of reintroduction of malaria into the country from outside becomes increasingly important (WHO, 2007). Finally, after a three-year period in which no local transmission has been reported despite good surveillance mechanisms, WHO certification for elimination can be requested. This transition from the phase of malaria control to that of elimination and onwards is more gradual than that of the historical Global Malaria Eradication Programme, which relied heavily on an intensive 'attack phase' to reduce the malaria burden from its original high levels.

Almost all countries that have thus far proceeded to elimination or have achieved it are located in areas of low and unstable transmission. Previously highly endemic areas with stable malaria transmission do not yet have any elimination experience to build on. In such areas, innovative intervention packages (control tools and strategies) for the elimination of malaria and prevention of its re-introduction are needed, to cope with their continuing potential for high transmission.

Fig. 1 **Malaria programme phases and milestones on the path to malaria elimination[a] from a country or area with low-to-moderate endemicity (WHO, 2007)**



SPR – slide or rapid diagnostic test positivity rate.

[a] These milestones are only indicative: in practice, the transitions will depend on the malaria burden that the programme can realistically handle (including case notification, case investigation, etc).

3. CURRENT POSITION OF MALARIA-ENDEMIC COUNTRIES IN THE SPECTRUM OF CONTROL TO ELIMINATION

As a result of malaria control efforts across the world, 80 countries are now in the phase of malaria control; 12 countries are making the programme transition to elimination; 11 countries are operating malaria elimination programmes; and 6 countries are actively engaged in preventing re-introduction of malaria. The latter countries are all located along the margins of the global malaria distribution map. The only exception is El Salvador, which is surrounded by endemic countries.

Of the 109 countries and territories that were considered malaria-endemic in 2007, 7 have reported no local cases in recent years: Algeria, Armenia, Egypt, Morocco, Oman, Syrian Arab Republic and Turkmenistan (Algeria reported 1 locally acquired case in 2006, and Oman reported 4 introduced cases in 2007). They may become eligible for certification of their malaria-free status by WHO in the near future.

Six countries are seriously involved in preventing reintroduction, including Morocco, Oman, Mauricius and the Syrian Arab Republic, which have recently been free from transmission, and Jamaica and the Russian Federation, which have experienced programme setbacks due to heavy importation of parasites. Globally, over 90 countries have only imported malaria and are considered non-endemic for malaria.

During and after the Global Programme for Malaria Eradication, 24 countries were certified by WHO as malaria-free in the period up to 1982. Since then, 3 additional countries have achieved malaria-free status: Tunisia (1979), the Maldives (1984) and the United Arab Emirates (2007).

4. EPIDEMIOLOGY OF MALARIA FROM THE PERSPECTIVE OF CONTROL AND ELIMINATION

Malaria parasites of the genus *Plasmodium* are transmitted to and from humans by a female anopheline mosquito. The goal of malaria control is to reduce the morbidity (incidence) of and mortality from malaria. The goal of elimination is to interrupt the chain of local malaria transmission. These goals require a reduction and complete interruption of transmission, respectively, for which an understanding of the dynamics of malaria transmission is fundamental. The unit of measurement of the spread of malaria (transmission) is the basic reproduction rate [Z_0] which is the number of new malaria cases generated by a single case. This is an expression of the efficiency of the mosquito vector (vectorial capacity) [C] and the magnitude of the infective parasite pool in humans (denoted by the daily rate of loss of human infectivity) [r] as follows:

$$Zo = b.C/r$$

where *b* is the proportion of mosquito bites which are actually infective. For malaria to be eliminated, the basic reproduction rate must be less than 1.

The parameters that determine vectorial capacity [C] are the density of mosquitoes [m], their feeding frequency on humans [a], their daily survival rate [p] and the duration of the parasite's development cycle in the mosquito (sporogonic cycle) [n] and is expressed as,

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

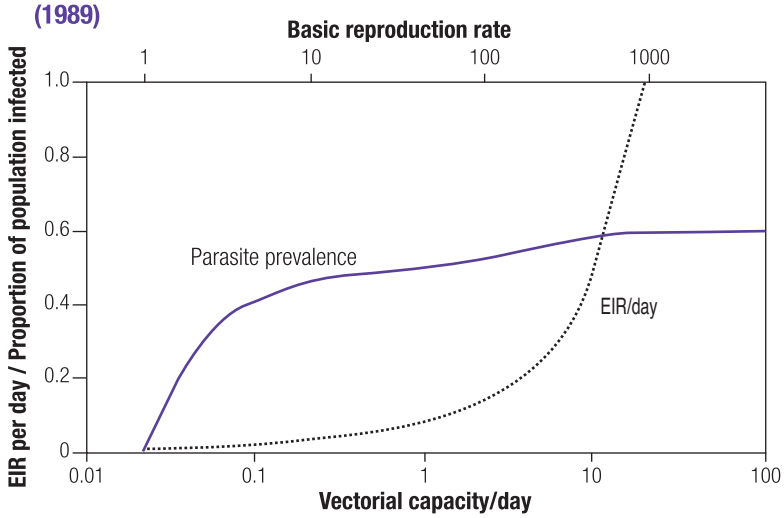
Vectorial capacity is extremely sensitive to changes in the daily survival of the mosquito, e.g., a 20% reduction in the mosquito's daily survival rate could result in a 98% reduction in vectorial capacity, whereas, under the same circumstances, a similar reduction in the human biting rate and the frequency of bites on humans will result in no more than a 20% and 36% reduction in vectorial capacity, respectively. The nature and intensity of malaria transmission (and the susceptibility of malaria to interventions) depend largely, therefore, on the bionomics of the mosquito vector prevalent in the area (Zahar, 1984–1994).

The relation between the prevalence of malaria and vectorial capacity or basic reproductive rate is represented in Figure 2. The force of malaria infection in an area is measured by the entomological inoculation rate, which is the number of infectious mosquito bites received per person per unit time. In situations with annual entomological inoculation rates below about 10, the malaria prevalence rate is almost directly proportional to the rate, and, conversely, malaria control measures lead to an almost proportionate reduction in both the prevalence of malaria and the incidence of disease. In situations in which this range of inoculation prevails, malaria transmission tends to be unstable and is considered to be of low-to-moderate intensity.

At annual entomological inoculation rates of above 10 or so, people receive multiple infectious bites, which leads to overlapping infections, a state referred to as 'superinfection'. In this case, a reduction in inoculation rates by malaria control methods will reduce the incidence of disease but not the malaria prevalence, until entomological inoculation rates are lowered to below 10 or so. In situations where rates of > 10 prevail, malaria transmission intensity is considered high and tends to be stable, although entomological inoculation rates below 10 are found in some areas of stable transmission.

Malaria transmission is not homogeneous. As there is heterogeneity in both the distribution of malaria inoculations in a population and the susceptibility of humans to infection, a small proportion of people tend to receive a large proportion of inoculations and become infected. This heterogeneity in human–mosquito contact and human susceptibility to malaria increases the tenacity of transmission.

Fig. 2 **The relationship between vectorial capacity, basic reproduction rate, entomological inoculation rate, and prevalence of patent parasitaemia based on Dietz et al (1974) and adapted from Wernsdorfer & McGregor (1989)**



Epidemiological analysis of the malaria situation in target countries plays a key role in making a realistic projection of the expected results of interventions. The basic parameters that should be considered are the stability of malaria, seasonal patterns of transmission and the age-specific prevalence and incidence rates of malaria. For projections of the expected impact of interventions, the area-specific basic reproduction rates will provide useful indications, even though the only elements that can be manipulated by intervention are the density of mosquitoes, their human biting rate, the daily survival rate of the mosquito and the duration of infection in humans.

Current antimalarial interventions lead to a reduction in the basic reproduction rate of malaria by reducing human infectivity due to early, effective treatment of patients and reducing vectorial capacity by mosquito control measures. Indoor residual spraying reduces the daily survival rate of the mosquito; insecticide-treated mosquito nets reduce the human biting rate of the mosquito and, to a lesser extent, its daily survival rate.

5. REVIEW OF THE GLOBAL MALARIA ERADICATION PROGRAMME: CONCEPT, ACHIEVEMENTS AND SHORTCOMINGS

Evolution of global malaria distribution and malaria control efforts

Up to the mid-nineteenth century, malaria was endemic in most countries and territories of the world, with the exception of the Pacific islands east of the longitude of Vanuatu (the Buxton line), which are free from anopheline mosquitoes. At that time, before the discovery of malaria parasites by Alphonse Laveran in 1880, the distribution of malaria in the northern hemisphere reached the Arctic Circle. An estimated 90% of the world's population lived in malarious areas (Figure 3A).

In the second half of the nineteenth century, well before the discovery of the mode of transmission of malaria by Ronald Ross in 1897, Sweden became malaria-free following changes in its agricultural land use. The same was seen in parts of North America. Towards the end of the nineteenth century, the discovery of the causative parasites and elucidation of the mode of malaria transmission laid the foundations for rational control of malaria transmission.

Between the First and Second World Wars (1918–1939), vector control by source reduction, water management, environmental sanitation, larviciding and use of individual protective measures succeeded in eliminating malaria from the extreme margins of its distribution (Najera, 2001).

Intensive research in the 1930s–1950s resulted in novel, highly effective tools for malaria control, namely residual insecticides and generally well-tolerated medicines that permitted radical cure of infection with any of the human pathogenic *Plasmodium* species. Soon after the Second World War, when most of the world's population still lived in malarious areas (Figure 3B), several countries undertook intensive malaria control.

From its establishment in 1948, WHO has been involved in international coordination of antimalarial operations. The operations were initially oriented towards control of the disease, but in the early 1950s malaria eradication became the avowed goal in numerous countries. In 1955, the Eighth World Health Assembly decided on a policy of malaria eradication for all endemic countries except mainland sub-Saharan Africa and Madagascar, where malaria control was to remain the objective until suitable, economically

feasible methods became available for complete elimination of the disease. The Global Malaria Eradication Programme was thus never as global as the name would suggest as, from the start, it did not include all malaria-endemic countries. Furthermore, the Programme cannot be classified as an 'eradication programme' by current terminology but rather as a series of (often successful) national elimination programmes.

Malaria eradication was defined in 1955 as "ending the transmission of malaria and the elimination of the reservoir of infective cases in a campaign limited in time and carried to such a degree of perfection that, when it comes to an end, there is no resumption of transmission". Owing to the narrow host specificity and limited natural life span of *P. falciparum*, *P. vivax* and *P. ovale*, elimination of these species could theoretically be achieved if transmission could be interrupted during the period required for the natural disappearance of the parasites. (By contrast, the fourth human malaria species, *P. malariae*, can also infect non-human primates; its natural life span in humans is up to 40 years or even more, during which time it maintains a sub-patent level of blood infection.) This hypothesis had proven to be correct in areas at the margins of the global distribution when effective anti-malarial measures were applied with the required precision and intensity, following the four programme phases of preparation, attack, consolidation and maintenance (WHO, 1969, 2006a).

The minimum requirements for embarking on a malaria eradication programme were initially defined fairly broadly but were subsequently refined by the WHO Malaria Expert Committee as experience accumulated:

- In 1956 (WHO, 1956), it promoted global eradication even in the absence of health services.
- In 1960 (WHO, 1960), it recognized the need for the support of general health services and promoted pre-eradication programmes.
- In 1962 (WHO, 1962), it recognized that the feasibility of eradication depended on the degree of development of health services.
- In 1967 (WHO, 1967), it defined the conditions to be met before initiating a malaria eradication programme.

Fig. 3A **Malaria distribution in the world in the mid-nineteenth century** (Wernsdorfer 1980)

Fig. 3B **Malaria distribution in the world in 1945** (coutesy W.H. Wernsdorfer)

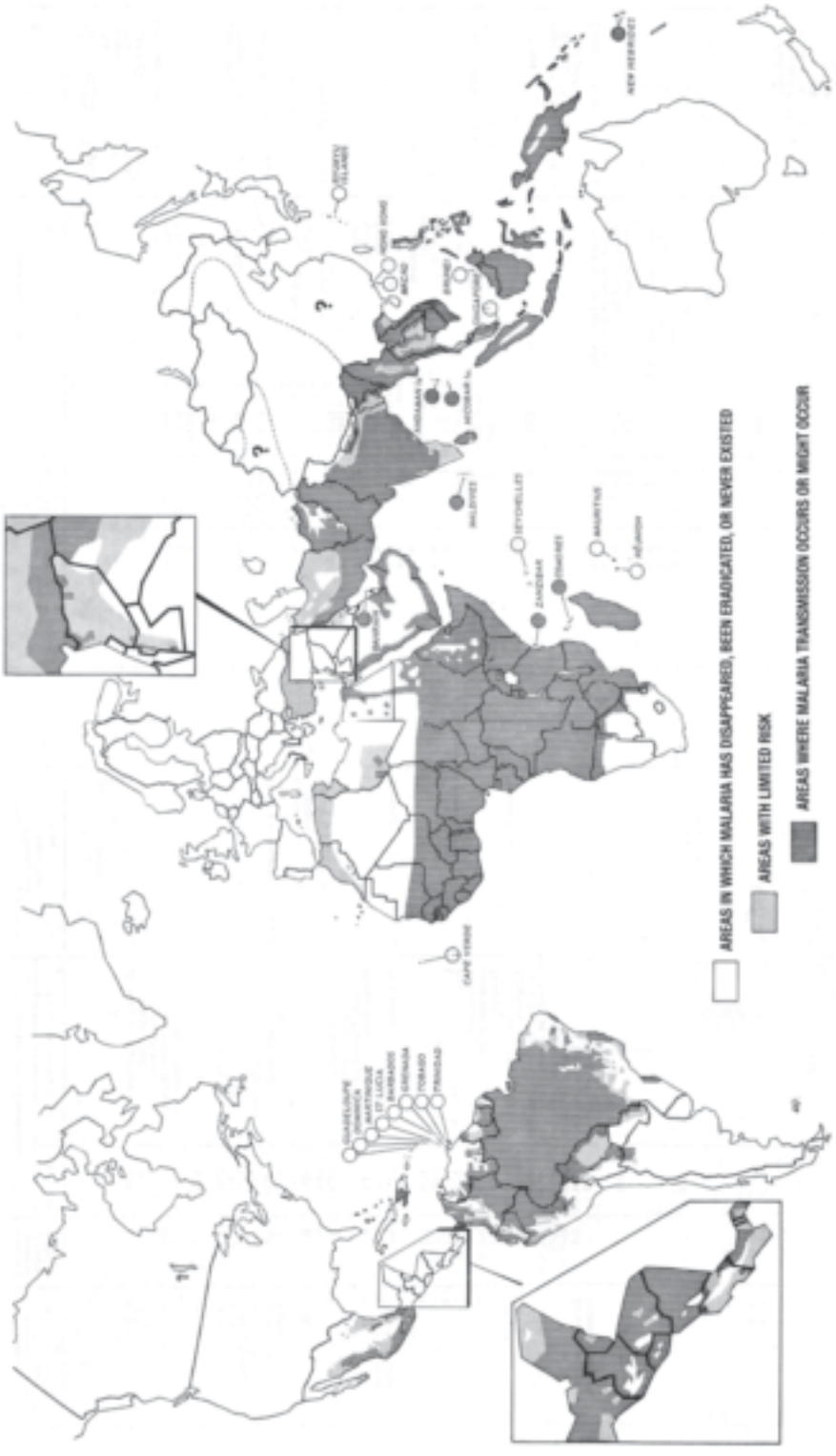
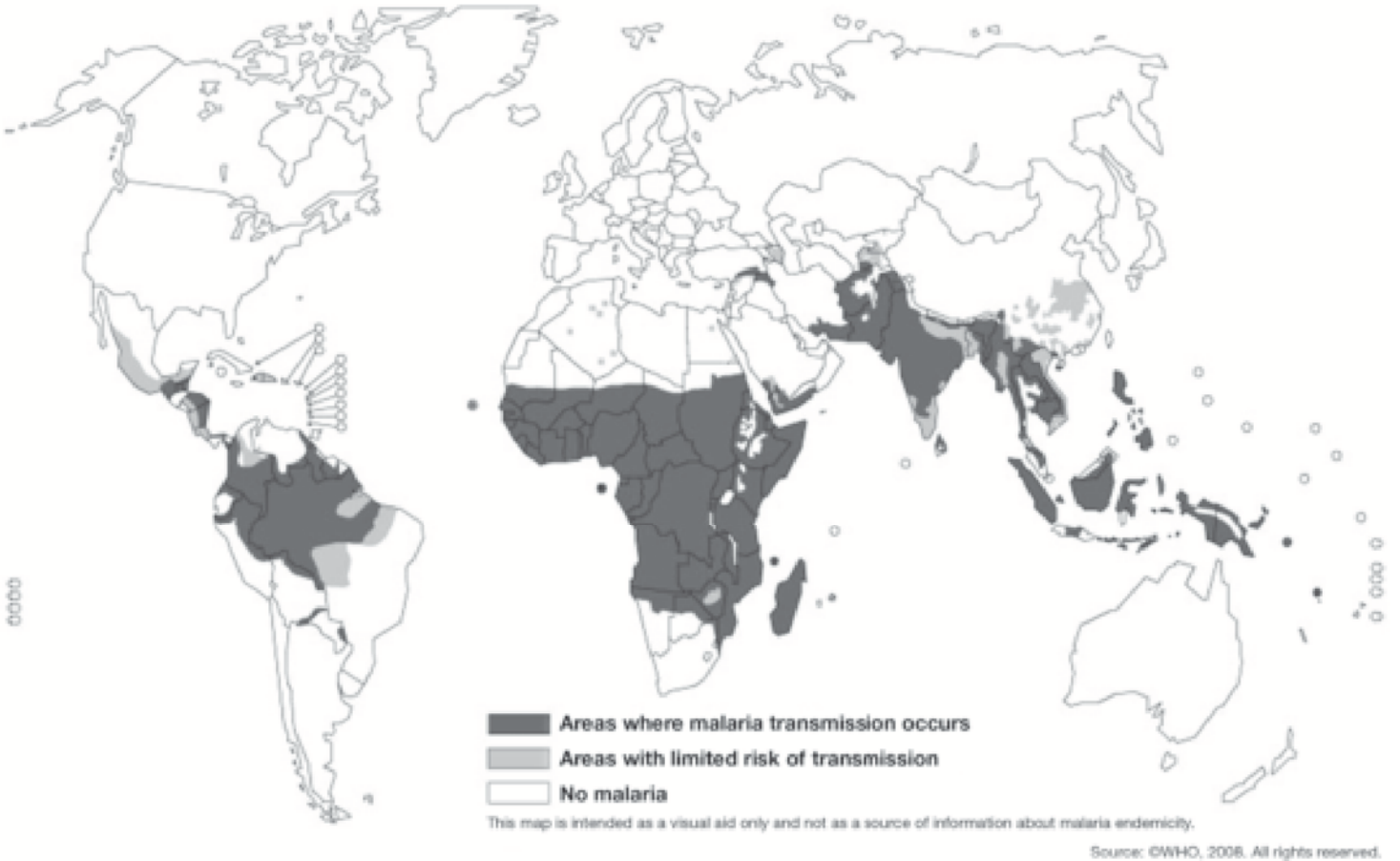


Fig. 3C **Malaria distribution in the world in 1977** (WER 1979)

Fig. 3D **Malaria distribution in the world in 2007** (*International Travel and Health*, WHO, 2008)



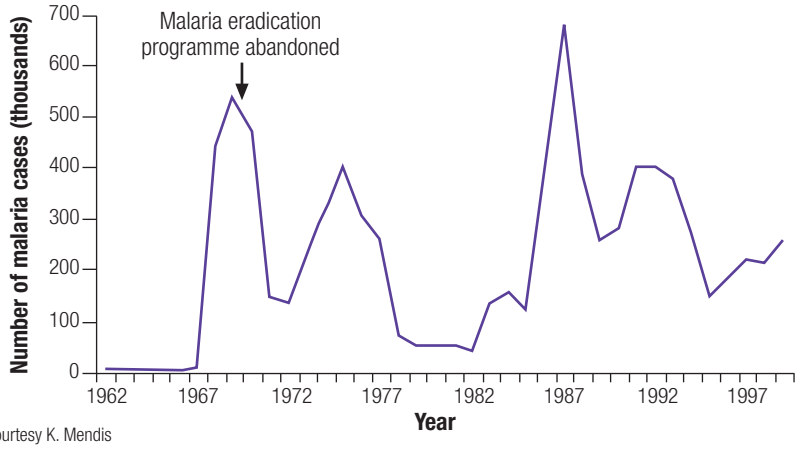
The activities of the Global Malaria Eradication Programme led to elimination of the disease from countries at the edges of global malaria distribution, where the intensity of transmission was quite low to start with. In all, 37 of the 143 countries that were endemic in 1950 were freed from malaria by 1978, with 27 of these in Europe and the Americas. In many other countries, major gains were made in decreasing the burdens of disease and death. In India, for example, the number of malaria cases was reduced from an estimated 110 million in 1955 to less than 1 million in 1968, and mortality due to malaria was virtually eliminated. In Sri Lanka, the incidence of malaria was reduced to a mere 18 cases in 1966 from an estimated 2.8 million cases in 1946.

Many countries discovered that it was not as easy to achieve malaria eradication as anticipated. In some, the situation in neighbouring endemic countries made elimination in border areas impossible (e.g. Thailand); in others, civil strife or illegal economic activities made parts of the country inaccessible for the eradication programme (e.g. Colombia); in some, the programme never quite got off the ground (e.g. Myanmar), or being poorly prepared for the consolidation phase of the programme, had disastrous results (e.g. Sri Lanka) (Figure 4).

The countries that were successful in eliminating malaria from their territory shared some important commonalities:

- political stability,
- firm political and financial commitment to malaria eradication,
- good organizational and technical infrastructure,
- high quality of training and personnel,
- fully developed, functional general health services,

Fig. 4 **Malaria cases in Sri Lanka between 1962 and 1997**



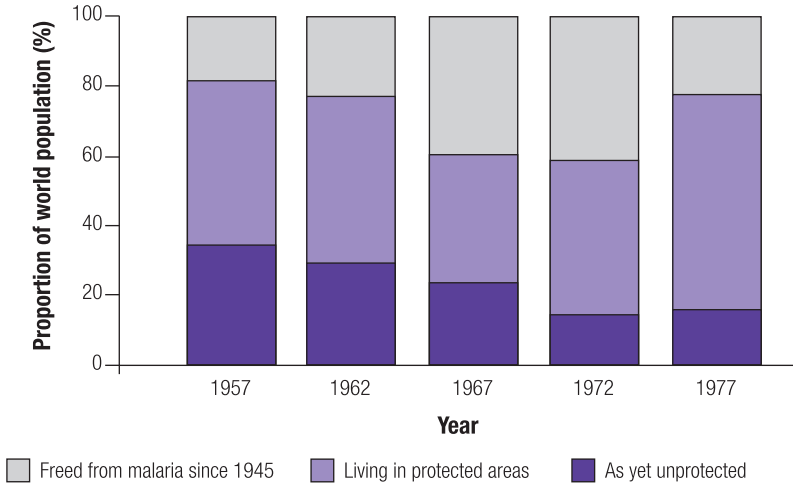
Courtesy K. Mendis

- absence of internal and external conflicts,
- absence of major population movements from neighbouring malarious countries and
- malaria originally unstable or of low-grade intermediate stability.

Examples of the financial costs of durably maintaining malaria eradication (i.e. prevention of the reintroduction of transmission) are available for two islands. La Réunion maintained an average annual budget of US$ 3.35 million for malaria after eradication. Of this, 77% was devoted exclusively to vector control for a population of 570 000, i.e. US$ 5.9 per person per year (Denys, Isautier, 1991). Mayotte continued an active control programme after eradication, at an annual expenditure of about US$ 6 per person per year (Julvez, 1990).

In the course of the Global Eradication Programme, the population at risk for malaria in the world decreased steadily until the 1970s (Figure 3C, 5), after which malaria control began to suffer seriously from the decreasing efficacy of medicines and insecticides, combined with the phasing-out of bilateral and international assistance. In 1978, WHO reoriented its policy from eradication and elimination to malaria control. During the 1980s, several countries persevered in the original objective of eradication ('elimination' by current terminology) and pursued it vigorously. Thus, China has eliminated malaria from most of the country, the Maldives and Tunisia have become free of malaria, and several countries in North Africa have come close to achieving the objective. Malarious areas of the world had shrunk further by 2007 (Figure 3D).

Fig. 5 **Malaria status of world population, 1957–1977**



The Garki experience, 1972–1973

Malaria elimination has so far not been achieved in areas with stable high intensity malaria transmission. A study conducted in Garki, Nigeria, in 1972–1973 provides useful insights into the feasibility of intervening against malaria in an area of high, stable transmission (Molineaux, Gramiccia, 1980).

In Garki, two interventions were used in a cluster of villages where the main vectors were *Anopheles gambiae ss, An. arabiensis* and *An. funestus* and where the entomological inoculation rate ranged from 20 to 120 during the wet season. The interventions were indoor residual spraying with propoxur, achieving nearly complete coverage (97–99%) per round to a population of approximately 50 000; and mass administration of sulfalene and pyrimethamine to a population of 16 000 persons, achieving 73–92% population coverage.

During the two-year project, the interventions had major impacts. The entomological inoculation rate fell from 130 to 10 and from 18 to 2 in the villages with the highest and lowest baseline entomological inoculation rates, respectively. Infant and child mortality rates decreased by 30–50% in the intervention as compared with the control villages. The incidence of fevers in children under 9 years were 3.8% and 12.8% in two intervention village clusters and 11.1% and 17.1% in control villages, respectively. Parasite prevalence rates fell markedly, from 70% to around 1%.

Thus, it is possible to bring about a marked reduction in parasite prevalence and almost certainly have some effect on mortality and clinical malaria (although the latter were not studied at the time). Despite the high intervention coverage achieved, however, transmission was not interrupted in Garki in the relatively short period under consideration.

Caution is needed in drawing parallels between what happened at Garki and today's situation because the tools used in Garki were not optimal by today's standards: Propoxur was not very effective for indoor residual spraying, insectide-treated mosquito nets were not used, access to early diagnosis and treatment of malaria was not readily available, and gametocytocidal drugs were not used in mass treatment. Besides, the social and economic conditions and the resulting general well-being and health of populations have since improved. The Garki experience nevertheless highlights the challenge of achieving elimination of malaria in high-transmission situations, which will by all estimates require more innovative control tools and strategies than those available today.

6. POTENTIAL IMPACT OF THE GLOBAL SCALING-UP OF ANTIMALARIAL INTERVENTIONS: A SIMULATION

The impact on the current global malaria situation of global scaling-up of antimalarial interventions was simulated on the basis of the estimated incidence (cases of malaria) and its current distribution in the world and the effectiveness of the key antimalarial interventions: prompt and effective treatment and prevention with long-lasting insecticidal nets or indoor residual spraying. The number of cases of malaria that a person is likely to incur each year at each endemicity level was summarized in an extensive review by Korenromp et al. (2004). This information was combined with the estimated population at risk at each level of endemicity to arrive at a crude estimate of the number of cases occurring in a country or region. With this approach, the number of malaria cases globally was estimated to be in the range of 300–350 million in 2005. For the purpose of this exercise, malaria endemicity levels in the world were classified as holo-, hyper-, meso- and hypo-endemic, as defined in Table 1.

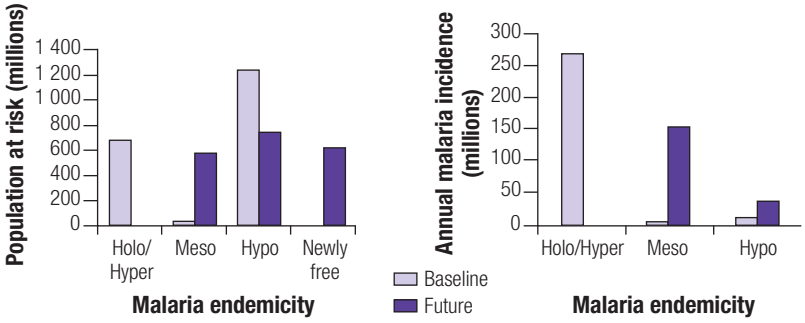
Randomized controlled trials suggest that the number of malaria cases can be reduced by as much as 50% through coverage of insecticide-treated nets. Indoor residual spraying is known to be similarly effective in preventing cases. Provision of effective treatment, particularly artemisinin-based

Table 1. **Classification of malaria endemicity levels**

Criterion	Hypoendemic	Mesoendemic	Hyperendemic	Holoendemic	
Spleen rate: 2–9 years	0–10%	11–50%	50%+	75%+	*WHO 1951*
Parasite prevalence: 2–9 years	0–10%	11–50%	50%+	75%+	*WHO 1951*
Stability	Unstable		Stable		*WHO 2005*
Types of epidemic	True	Exaggerated Seasonal			*WHO 2002*
MARA transmission suitability		0.25	0.75		*Craig et al 1999*
Entomological Inoculation Rate	<0.25	0.25–10	11–140	>140	*Beier et al 1999*

Source: *Systems for the Early Detection of Malaria Epidemics in Africa*, WHO, 2006

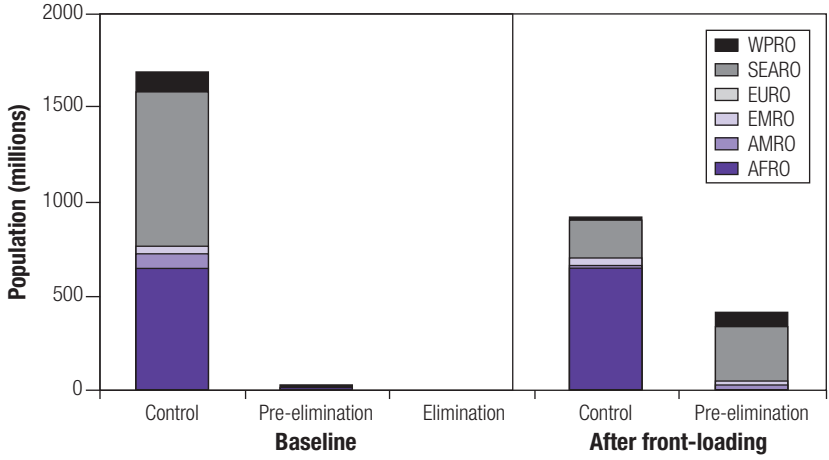
Fig. 6 **Estimated populations at risk, and malaria case incidence at the various levels of malaria risk at present, and following a global scale-up of antimalarial interventions**



combination therapies, is known to reduce the parasite reservoir and subsequent transmission when coverage is high but the impact in reducing case incidence, particularly in combination with other interventions and in different environments is not known with precision. Nevertheless, a few well-documented country experiences suggest that reductions in case incidence of 75% can be achieved within five years if preventive measures (indoor residual spraying or insecticide-treated mosquito nets) are used on a wide scale in combination with widely available, efficacious treatment (Vietnam, South Africa, Zanzibar, Eritrea).

The inference was that, if widespread coverage with antimalarial interventions were to be achieved globally, a 75% reduction in case incidence could be expected, with the following consequences (personal communication, R. Cibulski, Global Malaria Programme, WHO). In much of the African continent, the levels of malaria risk (endemicity) would be reduced from current holo- and hyperendemic levels to mesodemic levels, resulting in a lower incidence of disease (Figure 6) but there would still be more than 100 million cases per year. There would also be a dramatic shift in the age distribution of cases in Africa, with almost half occurring in persons aged 15 years and over, from just 15% now. The size of the population at risk for malaria in Africa would not be affected significantly, except in a few countries (Botswana, Eritrea, Namibia, Somalia, South Africa). Hence, continued investment in preventive measures across Africa would be necessary to preclude a reversal to holoendemicity.

Fig. 7 **Estimated world population in the different phases of malaria control and elimination, at present, and following a global scale-up of antimalar interventions, by WHO Regions**



Outside Africa, a large increase in interventions can be expected to result in a substantial reduction in the number of populations at risk, presenting many countries with the possibility of proceeding to elimination (Figure 7).

In conclusion, near complete coverage with current interventions, assuming that they retain their current efficacy, would lead, at the end of the intervention period, to a major reduction in the level of risk for malaria and therefore the case incidence worldwide, including Africa. In many parts of the endemic world outside Africa, it would also significantly reduce the population at risk for malaria; in Africa, however, the populations living at risk for malaria would not change substantially, although the level of risk would be much lower.

7. RECENT COUNTRY AND REGIONAL EXPERIENCES OF MALARIA CONTROL AND ELIMINATION

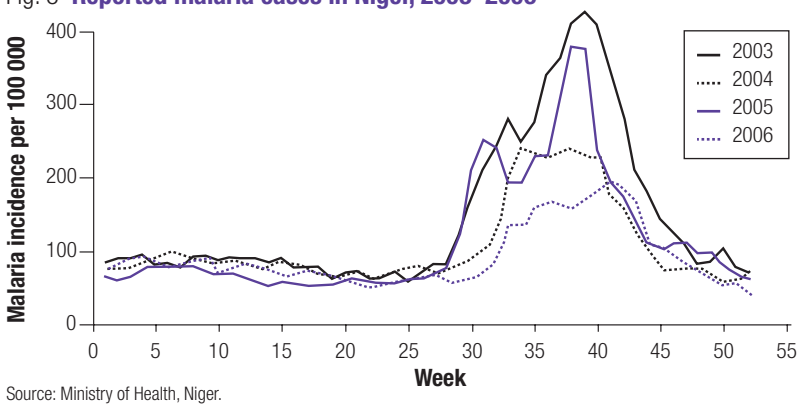
Countries with high, stable transmission: Niger, Rwanda and United Republic of Tanzania Zanzibar

The past 5 years of experience with malaria control in some countries with high, stable transmission in Africa show that the incidence and mortality can be reduced substantially by rapidly scaling up current antimalaria interventions, as in Niger, Rwanda and Zanzibar.

Niger achieved rapid scaling up of all interventions between 2005 and 2007, increasing coverage with artemisinin-based combination therapy (artemether and lumefantrine) to 100% of health facilities, achieving up to 86% coverage of households with long-lasting insecticidal nets and a coverage with intermittent preventive treatment in pregnancy of 65%. Data for 2006 showed a decrease in malaria incidence to 48 per 1000 population from 75 per 1000 in 2003 (Figure 8). Similarly, the incidence of malaria-related deaths dropped from 0.19 per 1000 (total, 2248 deaths) in 2003 to 0.09 per 1000 (total, 1150 deaths) in 2006.

In Rwanda, prompt access to effective treatment was provided at health facilities and through an effective programme of home-based community management, which now covers 16 districts and is being scaled up. Rwanda used a non-artemisinin-based therapy combination consisting of amodiaquine and sulfadoxine-pyrimethamine as first-line treatment until 2006, when, because of increasing failure rates, an artemisinin-based combination

Fig. 8 **Reported malaria cases in Niger, 2003–2006**



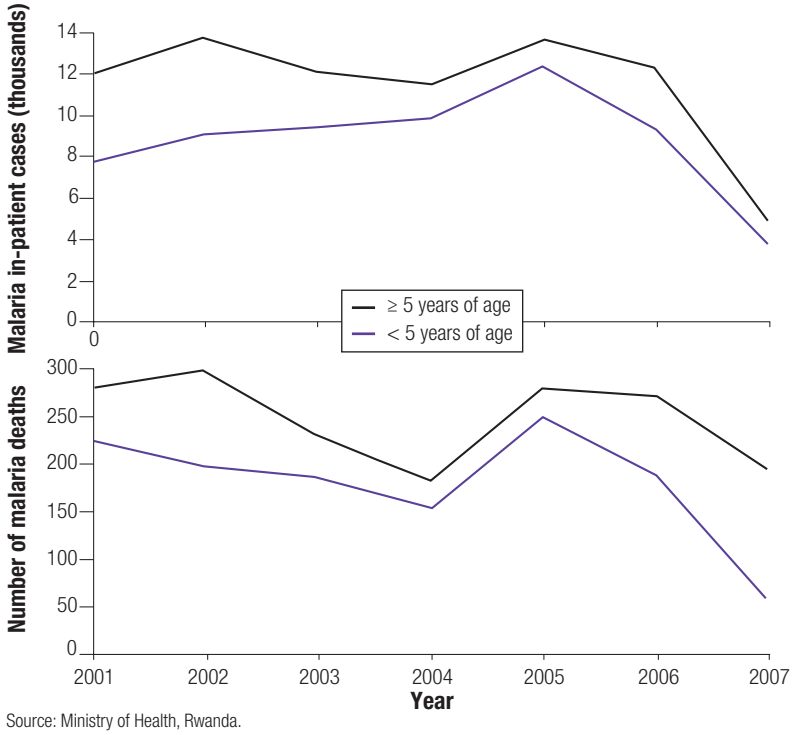
Source: Ministry of Health, Niger.

(artemether and lumefantrine) was introduced. Long-lasting insecticidal nets were distributed country-wide, targeting vulnerable groups (children under 5 years and pregnant women); from 2005, highly subsidized or free nets were introduced through various channels. Intermittent preventive treatment for pregnant women was also increased.

With a marked increase in coverage with insecticide-treated mosquito nets and improved access to effective antimalarial treatment, a significant reduction in both morbidity and mortality due to malaria was achieved (Figure 9). The incidence of severe anaemia decreased from 5.7 per 1000 children in 2005 to 0.14 per 1000 in 2007, and surveys of malaria indicators conducted in 2007 revealed a parasite prevalence rate of 2.4% in 2842 children under 5 years of age.

Zanzibar introduced malaria interventions in a stepwise manner, starting with the introduction of artemisinin-based combination therapy (artesunate plus amodiaquine) at all public health facilities in 2003, wide distribution of insecticide-treated mosquito nets to vulnerable groups (children below 5 years and pregnant women) and intermittent preventive treatment in pregnancy in 2005 and indoor residual spraying in 2006. With access to free artemisinin-based combination therapy and insecticide-treated mosquito nets achieving 74% coverage of vulnerable groups and with indoor residual spraying in 97% of households, a significant reduction in malaria morbidity

Fig. 9 **Reported malaria admissions and malaria deaths in Rwanda, 2001–2007, by age group**



Source: Ministry of Health, Rwanda.

was achieved by 2007 (Figure 10). Deaths due to malaria also decreased with data from three sentinel district hospitals showing reductions from 67 and 68 in 2002 and 2005, respectively, to 24 in 2007. Community-based survey data from two districts indicated parasite prevalence rates of 0.8% (68/8650) overall and 0.4% (9/2123) in children under 5 years of age.

Thus, in 2007, countries with high transmission that had greatly reduced their malaria burden faced the challenge of maintaining high levels of coverage in the face of changes in the clinical and epidemiological profile of malaria. Some, such as the islands of Zanzibar, also face the challenge of malaria introduced from the African mainland, which is continuous and becoming a relatively greater problem than locally transmitted malaria.

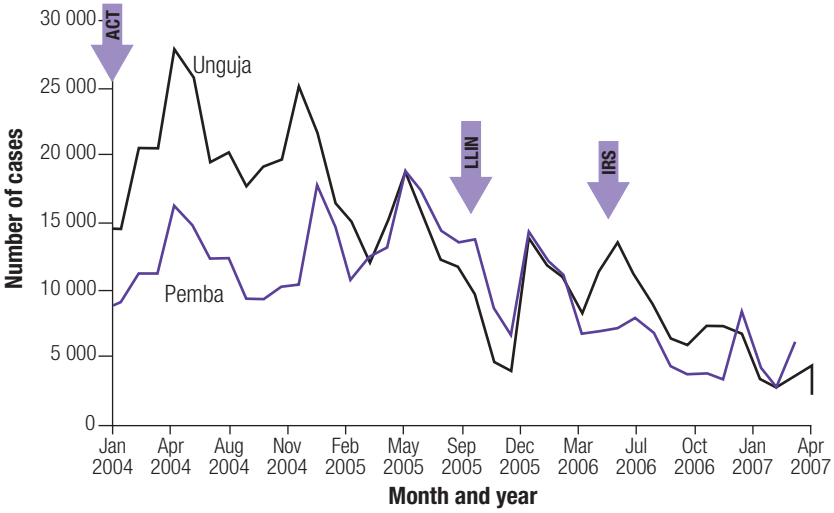
Regions and countries with unstable, low-to-moderate transmission

Western Pacific and South-East Asian regions

The total number of malaria cases and reported mortality associated with malaria in the Western Pacific region have been decreasing steadily during the past decade, even though some countries (the Solomon Islands and Papua New Guinea) have made limited progress or even experienced an increased malaria burden.

The Philippines in particular has seen a substantial decline in its malaria burden, 22 of 79 provinces now being considered 'malaria-free'. The current national objective is to declare another 10 provinces malaria-free by 2014

Fig. 10 **Clinical cases of malaria in all outpatient departments in the islands of Pemba and Unguja of Zanzibar, United Republic of Tanzania, 2004–2007. ACT, artemisin-based combination therapies; LLIN, long-lasting insectide-treated nets; IRS, indoor residual spraying**



Source: Zanzibar, Ministry of Health, United Republic of Tanzania.

and to reduce the overall burden of malaria in the country by 50% in comparison with 2006. Essential components of the approach are to:

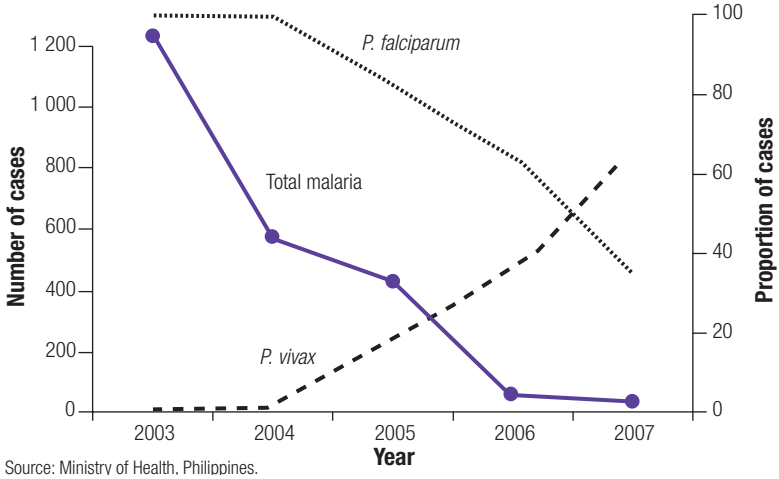
- achieve universal access to high-quality diagnostic and treatment services;
- scale up vector control to protect at least 80% of the population in malaria-endemic areas;
- strengthen sustainable community-based malaria control; and
- strengthen the malaria surveillance and information system.

Quality assurance of microscopy has been a focus of attention. Other projects are a package approach for malaria in pregnancy, health education for schoolchildren, strengthening the surveillance, health monitoring and information systems, promoting 'health in the workplace' and corporate social responsibility programmes.

The technical issues encountered include an unexpected rise in vivax malaria as falciparum cases decline (Figure 11); heavy reliance on village health workers and the need to provide them with good training for case follow-up as a micro-epidemiological basis for malaria control; the need for adequate training of indoor residual spraymen, combined with supervision and follow-up; and harmonization with ongoing health sector reform.

The Pacific islands west of the Buxton line have had mixed success in controlling and eliminating malaria. Initial success in the Solomon Islands suffered a serious setback with cyclone Namu in 1986 and the civil conflict in 1999–2003. This country, with Papua New Guinea, currently has one of the highest rates of malaria outside tropical Africa. A real success story from a Pacific island, based on a tailormade strategy (see Box 1) illustrates how

Fig. 11 **Total malaria cases and the proportion of *P. falciparum* and *P. vivax* malaria in Quirino Province, Philippines, 2003–2007**



Source: Ministry of Health, Philippines.

malaria was eliminated in the early 1990s from a small, remote, sparsely populated island that is wholly dependent on tourism for its livelihood (Kaneko et al., 2000).

A new initiative has recently been launched in collaboration with WHO and donor support from Australia to attempt to eliminate malaria from a larger part of the Pacific area comprising Vanuatu, the Solomon Islands and Papua New Guinea. There is concern, however, about whether the required financial and human resources will be available and if the current tools and the prevailing health systems will support elimination, owing to population

Box 1. Elimination of malaria from a Pacific island

Aneityum is a very small volcanic island at the southernmost tip of the Vanuatu archipelago. It is located just below the Buxton line, which defines the southeastern ward limit of anopheline breeding; *An. farauti* is the main malaria vector. In early 1991, the island was inhabited by only 718 people living in three villages. Access to the outside world was at the time limited to a monthly supply boat and twice-weekly flights from Port Vila of a 10-passenger aircraft. A monthly stop by a cruise ship was the source of nearly all the income for the island. Malaria was seasonal, the parasite prevalence in the population varying from 21% (60% falciparum, 40% vivax) in the wet season to 11% (15% falciparum, 85% vivax) in the dry season.

In the early 1990s, subsequent to the occurrence of malaria infections among cruise-ship passengers, thought to be linked to their visit to Aneityum, the island received an ultimatum from the cruise-ship company to eliminate malaria or be by-passed by the ships in future. Vanuatu approached WHO for assistance.

An intensive malaria elimination campaign was launched, covering the whole population. The campaign included 9 weeks of mass drug administration, sustained vector control with high coverage with insecticide-treated mosquito nets, community-based surveillance to prevent reintroduction, and strong community participation.

At the outset, the entire population received antimalarial treatment with a combination of chloroquine (full dose), sulfadoxine–pyrimethamine (full dose) and primaquine (45 mg). This was followed by weekly chloroquine (300 mg) plus primaquine (45 mg). In weeks 5 and 9, weekly chloroquine was replaced by sulfadoxine–pyrimethamine (full dose). Ninety percent of the population complied with this regimen.

Insecticide-treated mosquito nets were distributed at a rate of one net per person – 680 nets of various sizes in total, and the nets were re-treated annually with permethrin. All people received health education on use of the nets. Community microscopists checked all cases of fever and took blood films from all arrivals on the two flights per week.

P. falciparum disappeared from the island 5 weeks into the programme, and P. vivax had disappeared by 1993. Only two imported cases of *P. vivax* have been reported since. The active community participation and the resulting success of the campaign have been attributed to the major economic incentive for the islanders. At present, two ships make monthly visits, and there are daily trips from Port Vila to Mystery Island – a major tourist destination.

movements between islands and the subsequent risk of re-introduction. India's experience in malaria control is described in Box 2.

Countries in the Eastern Mediterranean and European regions

Countries in the WHO Eastern Mediterranean and European regions were the first to approach malaria elimination (Table 2), starting with individual countries and progressing to blocks of neighbouring countries. WHO has been the driving force behind intercountry initiatives on malaria elimination in both regions.

Box 2. Malaria control: the Indian experience

India launched its national malaria eradication programme in 1958, with 276 million people to be covered in the 'attack phase' of indoor residual spraying with DDT, the number being expanded to 424 million people in 1961–1962. In the first few years, the impact of DDT was spectacular, as the number of cases was reduced dramatically, from 110 million in 1955 to less than 1 million in 1968, and deaths due to malaria were almost completely eliminated.

Resistance of *An. culicifacies* to insecticides began to compromise indoor residual spraying, although operations against the other malaria vectors remained unaffected. In the late 1960s, social, financial, administrative and operational problems began, including communities refusing DDT spraying, shortage of supplies, financial constraints, hilly terrain and inaccessible areas, administrative problems, inadequate surveillance, shortage of experienced, trained personnel and understaffing at all levels. As a result, the initial gains could not be maintained. In 1968–1969, the approach reverted from consolidation and maintenance to a renewed attack phase for a population of 91 million, leading to an unexpected 50% increase in the demand for DDT spraying that year. In some areas in the east of the country, the eradication programme did not achieve real success in the first place, and these areas were covered by a persistent attack phase that lasted 13–17 years. By the early 1970s, the malaria incidence (measured as the annual parasite incidence) was seen to be multiplying exponentially nationwide.

Other approaches were tried. The 'urban malaria scheme' was launched in 1971–1972 to cope with an increasing problem in urban areas. The programme, consisting of anti-larval measures against the vector, *An. stephensi*, was introduced in phases; it took nearly three decades to cover the 132 towns that had originally been identified as having populations of > 40 000 and an annual parasite incidence > 2 per 1000. The urban situation continued to deteriorate and at present contributes 8–10% of the national malaria burden. Other initiatives were a 'modified plan of operation', launched in 1977 in an effort to maintain the gains of the eradication days and eliminate mortality due to malaria, and the *P. falciparum* containment programme, which was stopped in 1988.

In India, indoor residual spraying programmes have so far not been accompanied by systematic efforts to reduce the receptivity of the environment. Hence, new mosquitoes continue to emerge, filling year after year the niches vacated by adulticiding, compromising vector control operations. At the same time, residual parasite populations after relapses and recrudescences multiply in the presence of vectors (susceptible and resistant) and are disseminated in receptive and vulnerable environments. The result is persistent perennial malaria transmission.

In the Eastern Mediterranean region, the critical ingredients of the elimination approach have been intercountry coordination meetings, starting in 1997 (Rabat, Morocco) for the five northern African countries; publication of WHO technical guidelines on malaria elimination and the prevention of re-introduction of malaria (WHO/EMRO, 2007a,b); intensive technical support to countries from WHO; and annual meetings of malaria control programme managers at regional level, most recently in a workshop on malaria elimination and malaria-free initiatives held in Dubai in June 2007.

Most countries of the region have adopted a phased approach to elimination, targeting *P. falciparum* first and gradually expanding the elimination programme areas. This approach is also being used in Tajikistan, the only country in the European region where *P. falciparum* malaria transmission still occurs. Yemen has adopted a successful local elimination programme

Table 2. **Malaria control activities in the Eastern Mediterranean and European regions**

Region	Country	Year of start of malaria elimination campaigns	Year since 0 local cases reported	Year of WHO certification
Eastern Mediterranean	United Arab Emirates	1990	1997	2007
	Oman	1991	2000	–
	Egypt	1997	1998*	–
	Morocco	1997	2005	–
	Syrian Arab Republic	1999	2005	–
	Yemen (Socotra Island)	2000	2006	–
	Saudi Arabia	2003	–	–
	Iran (Islamic Republic of)	2004	–	–
	Iraq	2005	–	–
European	Armenia	2006	2006	–
	Turkmenistan	2006	2006	–
	Azerbaijan	2007	–	–
	Turkey	2008	–	–
	Georgia	2007	–	–
	Kyrgyzstan	2006	–	–
	Uzbekistan	2008	–	–
	Tajikistan	2005 (*P. falciparum*)	–	–

* Concern has been raised about the accuracy of the surveillance systems.

at the important tourist destination Socotra Island. Country experiences show that, with intensive efforts, locally acquired malaria cases decline rapidly but that the residual burden (the last few cases) is the most difficult to control. In the European region, the peak of locally acquired malaria cases occurred during 1995–1996, when over 90 000 cases were reported annually. Since then, the number of cases has been reduced to only 1069 reported cases in 2007. Critical steps in the elimination approach in the region were: strong political will to achieve greater impact on malaria situation, intensive support from WHO, a high level of advocacy for action against malaria, a broad partnership action, particular focus on the malaria situations and countries' needs and annual inter-country coordination meetings, culminating in endorsement of the Tashkent declaration "*The move from control to elimination*" by all endemic countries of the region in 2005; and publication of the WHO/EURO regional strategy (WHO/EURO, 2006).

Increasingly, WHO/EMRO and WHO/EURO are facilitating close collaboration between countries in the border areas of their two regions (Tajikistan with Afghanistan, the Islamic Republic of Iran with neighbouring countries and Turkey with neighbouring countries) including joint fund-raising efforts.

A concern for the future of malaria elimination efforts in the European and Eastern Mediterranean regions is the shortage of national expertise and competence to guide programmes. A major focus of work in 2008–2009 will be to design training modules and interregional courses, strengthen national capacity and draw up a roster of experts on malaria elimination to support country activities. Rapid flare-ups of malaria remain possible, as shown by the major epidemic in Iraq after the first Gulf war and the recent large-scale exacerbation of the malaria situation in the European region after the political turmoil that followed the collapse of the former Union of Soviet Socialist Republics in the mid-1990s. Rapid response capability at national level must therefore be maintained to cope with emergency situations.

Another concern, particularly in less wealthy endemic countries in the European region, is the difficulty in raising funds and capturing and maintaining donor interest for malaria elimination at national and regional levels once the case load declines.

8. STRENGTHS AND LIMITATIONS OF AVAILABLE ANTIMALARIAL TOOLS IN THE CONTEXT OF MALARIA CONTROL AND ELIMINATION

Antimalarial medicines

Antimalarial medicines remain one of the most powerful tools in malaria control. Medication reduces morbidity and mortality by terminating a malaria infection in a patient and curtails malaria transmission by diminishing the parasite reservoir. One of the greatest challenges to malaria treatment is parasite resistance. Several medicines that have allowed nearly a century of malaria control, ranging from chloroquine, which was widely used in the Global Malaria Eradication Programme, to newer medicines, such as sulfadoxine–pyrimethamine and mefloquine, have sequentially fallen to resistance, in particular in the case of *P. falciparum* malaria, and have thus become ineffective for treatment in many parts of the world.

The most effective antimalarial medicines are now combinations which contain an artemisinin derived medicine given with a partner medicine to delay the emergence and spread of resistance. Artemisinin-based combination therapies are safe and highly effective in curing infection (exceeding 95% in most situations) and are also the most effective curative treatment yet for reducing parasite infectivity, owing to the anti-gametocyte activity of the artemisinin component. The disadvantages of these drugs are that they have a relatively short shelf-lives (often only two years), which makes supply chain logistics difficult, and that treatment is required for three days, which makes adherence to treatment schedules more challenging than with a single dose. As the anti-gametocyte effects of artemisinins are incomplete, malaria elimination programmes require that artemisinin-based therapies be combined with primaquine to block transmission more effectively.

The development and spread of resistance by *P. falciparum* threaten the usable lifespan of even artemisinin-based combination therapies, affecting both the artemisinin component and the partner medicine. Several studies at the Thai–Cambodian border, which has historically been the epicentre of resistance to all antimalarial medicines, have confirmed increasing failure rates of artesunate plus mefloquine. Prolonged parasite clearance times have also been recorded with artesunate, suggesting that parasites there have reduced susceptibility to artemisinins. These phenomena are being investigated in order to characterise the nature of this apparent tolerance to artemisinin. If artemisinins are lost to resistance in the near future, there are few, if any, alternatives to replace them.

Antimalarial medicines have applications beyond curing patients. Evidence shows that they could also be useful in prevention, particularly in high-transmission situations and in high-risk groups such as pregnant women, infants and children. Sulfadoxine–pyrimethamine is currently the only medicine available for use in intermittent preventive treatment in pregnancy, a strategy that is being used in high-burden countries in Africa, but its role is being compromised by widespread parasite resistance. Thus, at present, preventive treatment strategies are limited by the absence of suitable medicines to replace SP. Medicines for preventive use must have a long half-life and an extremely good safety profile, as they are given to normal, healthy subjects. They should, ideally, not be the same medicines as those used for curative purposes, so that the risk that parasites will develop resistance, which would be enhanced by their wide use in prevention, is minimized.

As increasingly better malaria control is achieved, populations, including those living in high-transmission areas, will be at lower risk for malaria; therefore, the relevance of preventive treatment is likely to diminish. As the world moves towards malaria elimination, however, there will be a greater demand for curative medicines, requiring, first, steady development of medicines to replace those that are lost to resistance, and, secondly, medicines that are highly effective for clearance of both asexual blood stages and gametocytes. These medicines will have to be safe, formulated as fixed-dose combinations, ideally be taken in no more than a single dose and have a shelf-life of at least 3 years. Ideally, antimalarial medicines must be strategic fixed-dose combinations of at least three medicines, each with a different mode of action, in order to delay parasite resistance. The components of such combinations should not be available on the market singly, as their use would predispose them to parasite resistance. As cross-resistance to related chemical compounds is common, new medicines should be based on unrelated families of compounds.

P. vivax is generally less susceptible to control than *P. falciparum* and even more difficult to eliminate, owing its highly efficient transmission and its ability to remain dormant in the liver and become active after varying lengths of time. The safety of primaquine, the anti-relapse medicine available today, is a concern because it causes potentially serious haemolysis in patients deficient in glucose 6-phosphate dehydrogenase. Primaquine must

be given in a long treatment regimen of 14 days, which could undermine adherence. Susceptibility of *P. vivax* to primaquine varies. Tafenoquine is a potential alternative to primaquine, although there is the same concern about its safety. *P. vivax* elimination and even its effective control will therefore rely on safer more effective anti-hypnozoite medicines becoming available.

WHO currently recommends that a diagnosis of malaria be confirmed before treatment, in all but two exceptional situations, children under 5 years of age in areas of high transmission and suspected severe malaria, in both of which clinical judgement on diagnosis must take precedence, even in the face of a negative test result, primarily because of the limitations of current diagnostic tools. Microscopy has now been supplemented by rapid diagnostic tests, which have vastly expanded the scope for diagnosis. There are at present 55 manufacturers of rapid diagnostic tests with named products known to WHO, and in 2005 endemic countries procured some 30 million of these tests for routine use. Both methods of diagnosis have limitations, however, and assuring the quality of the products and procedures is a major challenge. The sensitivity of different lots of many of the available rapid diagnostic tests varies considerably, and the stability of some under field conditions is questionable. Few rapid diagnostic tests are available for *P. vivax*, and their performance is more limited than those for *P. falciparum*. The cost of these tests at present is almost as high as that of a course of treatment.

As the malaria burden decreases, the demand for high-performance diagnostic tests will increase, because the disease will account for a lower proportion of febrile illnesses. Furthermore, in situations of high transmission, the age profile will shift from children to adults, in whom confirmation of the diagnosis is a prerequisite for treatment. Diagnosis is even more critical in the phases of malaria elimination and eradication than in the control phase because of the need for a higher degree of surveillance, and this will require simpler, more reliable diagnostic tools than are presently available.

Vector control tools

Mosquito control methods are available for preventing malaria and are being used widely; these take the form of insecticide-treated mosquito nets and indoor residual spraying. For these methods to be effective, high population coverage rates, exceeding 80%, are required. At such levels, they can reduce the risk for malarial disease by up to half, and, in low-transmission situations, they can have a similar or greater effect, including an impact on malaria infection rates. Thus, both of these preventive interventions can result in major reductions in malaria transmission and the related burden in all areas of the world, although there is no evidence that either one or the two in combination is effective enough to interrupt transmission in areas of high, stable transmission.

Insecticide-treated mosquito nets and indoor residual spraying are essential at early stages of vector control to reduce malaria prevalence and, especially indoor residual spraying, at the late stage of elimination to clear the last residual foci of transmission. Both methods have their limitations. Although spraying is very effective, it requires stringent planning, management and supervision. It can be delivered only by well-staffed and well-equipped vector control services, which currently do not exist in many countries. In the long term, indoor residual spraying tends to generate community fatigue, eventually resulting in increasing refusal. In areas with almost perennial malaria transmission, spraying would be difficult to conduct with existing insecticide formulations that have a short residual effect. The average total cost of indoor residual spraying is US$ 3.5 per person protected per year.

Insecticide-treated mosquito nets, especially long-lasting nets, are as effective as indoor residual spraying when full population coverage is achieved. The distribution of such nets is a logistical challenge, but experience has shown that they can be distributed rapidly in mass campaigns. Once high coverage has been achieved, as in campaigns, coverage has to be maintained as a long-term intervention by routine redistribution. Communication for behavioural change is essential to ensure effective use of the nets. The average total cost of long-lasting insecticidal nets is US$ 1 per user per year. Conventional treatment of ordinary nets is difficult to achieve and is twice as expensive as using long-lasting insecticidal nets.

Insecticide resistance, especially to pyrethroids, is a serious threat to sustained use of insecticide-treated mosquito nets and indoor residual spraying. The nets are impregnated with this class of insecticides, to which vectors are already resistant in some areas of the world. Although 12 insecticides are currently recommended for indoor residual spraying, they belong to only four chemical classes, and cross-resistance among insecticides is frequent. For public health use, it is essential that alternative insecticides belonging to new or different classes be developed if current scaling-up efforts are to be sustained and if local interruption of malaria transmission is to be achieved. Otherwise, recent advances will be rapidly jeopardized, especially in the case of indoor residual spraying, which tends to lose its efficacy as soon as vectors become resistant.

The existing methods of vector control will have to be improved if the ambitious targets for malaria control and elimination are to be reached. These will include new, longer-lasting (up to 1 year at least), user-friendly formulations of insecticides for indoor residual spraying, especially in areas of perennial transmission, and affordable, acceptable 5-year insecticidal nets made widely available by mass production. New tools are needed for malaria control in specific situations, such as in forests in Asia and Latin America where local vectors are exophagic and exophilic, and conventional vector control with existing tools is impossible.

These multiple constraints mean that vector control cannot, in the long term, rely solely on the two interventions. They will have to be supplemented progressively with other measures in the context of integrated vector management, which will be essential at an intermediate stage to enhance and sustain the achievements made with the existing interventions. It will also be relevant once elimination has been achieved, to maintain malaria-freed areas at a low level of vulnerability, to prevent rebound transmission from re-introduction of parasites by infected travellers.

Malaria vaccines

Several malaria vaccines are being developed, which are based on candidate antigens from the three main target stages of the life cycle of the malaria parasite: vaccines that target sporozoites, which will reduce human infection rates and, if highly effective, will prevent human infection; those that target the parasites in asexual blood stages, which will reduce the intensity of disease and mortality; and those that target the parasite in the sexual stages that develop in the mosquito, and which will reduce and interrupt the transmission of malaria. Vaccines are potential tools for the future. Their role in current malaria control will not be considered further in this report, other than to emphasize that, in situations where the burden of malaria is high, vaccines that reduce the rate at which infection or clinical disease occurs will be useful even if they have little effect on preventing infection or blocking transmission. As with increasing malaria control efforts, however, the malaria burden will decrease, and, when elimination and eradication become the goal, vaccines that prevent infection in humans and those that reduce or prevent transmission will become more relevant.

Conclusions

Effective mosquito control measures and medicines are the most potent weapons available today to reduce the malaria burden substantially. In areas where transmission is marginal, the disease has even been eliminated by judicious use of the currently available tools. Both categories are, however, heavily reliant on chemical entities insecticides and therapeutic agents which are vulnerable to the development of resistance by the mosquito vector and parasite, respectively. Alternative insecticides and medicines for malaria are far from optimal at this time, placing malaria control at considerable risk. Moreover, eliminating malaria from many parts of the world where the transmission intensity is high will require more effective and more innovative tools than are available today. The future of global malaria control and elimination will depend, therefore, on the success of research and development in delivering a steady stream of replacements for tools that are being lost to resistance. New, more effective tools are necessary to make elimination of malaria possible, especially in areas of high, stable transmission.

9. FUTURE DIRECTIONS

Feasibility of malaria control, elimination and eradication in various epidemiological situations

The experience of nearly a century of malaria control has shown that use of effective vector control measures and curative antimalarial treatment lowers malaria incidence and mortality in areas of all intensities of transmission. The deleterious consequences of subsequently relaxing intensive control efforts too quickly have been demonstrated repeatedly. The following assessment of the feasibility of various malaria control and elimination strategies is based on insights from past and recent country experiences and an assessment of the effectiveness of current tools.

In areas or countries with low intensities of malaria transmission, optimal use of current tools will have a strong impact and may reduce the parasite incidence to an extent that would allow interruption of local transmission. Complete interruption of local transmission will require that the tools remain effective and that a stringent course to malaria elimination is followed, including greatly strengthened monitoring, surveillance, and eventually vigilance (WHO, 2007). Failure to maintain the reduced levels of malaria thus achieved will lead to rebound epidemics, with high morbidity and mortality (in the case of *P. falciparum*) among populations who have now lost immunity and are living in areas that remain receptive due to the continuing presence of mosquito vectors and other factors favourable to resumption of malaria transmission. This risk is particularly high in geographically peripheral and isolated areas which are underdeveloped, with weak health systems, and in areas where systems have collapsed for socioeconomic reasons or political and civil unrest. It is therefore extremely important that temporary lapses in control, elimination and prevention of re-introduction are avoided for as long as areas remain receptive to resumption of transmission and are exposed to importation of parasites.

Malaria elimination will require strong government commitment, with sufficient domestic funding, and will require setting regional and intercountry targets with synchronized timelines and approaches across borders, to counter the effects of cross-border population and parasite movement and the importation of parasites through immigration from more distant endemic countries. Elimination efforts must be applied to all species of plasmodia that cause human malaria, with initial priority given to *P. falciparum*. A geographically phased approach within a country is often necessary.

As the malaria burden is reduced, the cost of maintaining the success of a well-executed malaria control or elimination programme and a strengthened general health services will increase: the cost per case averted becomes increasingly high. The positive economic and development fallout of eliminating malaria in low-transmission settings, however, due to increased productivity and enhanced tourism and trade, can help sustain the results of malaria elimination.

In areas of stable, high transmission of malaria, recent experience in some African countries confirms that substantial reductions in transmission intensity can be achieved by full-scale use of current tools. Thus, strong malaria control, leading to reductions in both morbidity and mortality, is possible in high-transmission areas, given a minimum of political stability and the right socioeconomic conditions. It can be achieved by scaling up current interventions to the full. Pursuing this rapidly by a front-loading approach will speedily reduce morbidity and save more lives. A vital requirement for this to occur is sustained funding and substantially more support for ongoing control and surveillance. There is no evidence that malaria transmission can be interrupted, nor that a 'malaria-free' status can be sustained in high-transmission areas, in the face of the unrelentingly high vectorial capacity, the current tools, the current resources and prevailing health-care systems.

Malaria eradication will require achieving and sustaining malaria elimination in countries and regions on a cumulative basis, over a period of decades rather than years. To achieve this, both endemic countries and international bodies will need an arsenal of highly effective tools for diagnosis, treatment and prevention; unprecedented efforts, a committed and empowered leadership and sustained funding; and unhindered, full access to the remotest corners of the malaria-endemic world, with the full cooperation of all the populations living there.

Artemisinin derivatives and pyrethroid insecticides are the backbone of our current arsenal for controlling malaria, and the loss of either of these without adequate replacement becoming available (which seems likely to be the case for the immediate future) will reduce the prospects for eradication. Thus, although there is good evidence that local transmission can be interrupted in countries with low intensities, the evidence and experience up to now do not support the view that global eradication of any of the four principal human malaria parasite species can be achieved with the existing tools, given the epidemiology of malaria today.

Antimalarial tools required for the next phase of malaria control and elimination

With the prevailing patterns of malaria epidemiology and health-care infrastructure, malaria eradication will not be possible without antimalarial tools of greater potency and effectiveness than those available today. The characteristics of the tools that might allow malaria elimination and possible eventual eradication are outlined below.

For prevention of malaria by mosquito control, new tools should include:

- new classes of rapid, long-acting insecticides, which do not induce excito-repellancy, for indoor residual spraying and long-lasting insecticidal nets;
- longer-lasting insecticidal nets;
- strategies to delay the onset of insecticide resistance, such as:
  - mosaic treatment or combination treatment of long-lasting insecticidal nets and for indoor residual spraying; and
  - combinations of tools, for example long-lasting insecticidal nets and indoor residual spraying combined with other approaches such as larviciding;
- insecticide-treated material for use by forest workers and dwellers, such as for hammocks, clothes and blankets; and
- new tools for the control of mosquito vector species that are not amenable to indoor residual spraying and long-lasting insecticidal nets.

New tools for the treatment of malaria should include:

- New classes of antimalarial medicines, with the following characteristics:
  - provide > 95% cure rates, with highly effective infectivity blocking efficacy (> 99% gametocytocidal activity) for both *P. vivax* and *P. falciparum*;
  - fixed-dose combinations with three medicines, each with a different mode of action and matched pharmacokinetic properties;
  - single-dose treatment regimen; and
  - high safety profile, including for children, infants and pregnant women;
- a new class of safe, effective antimalarials for radical treatment of *P. vivax*; and
- more robust and sensitive diagnostic tools, including tools to enable detection of parasite carriers (latent infections, asymptomatic infections and hypozoites).

The new and additional tools will include vaccines, especially those that block transmission and reduce infection rates.

Improvements to existing strategies are also needed, especially:

- encouraging behavioural change so that people comply fully with medication and use long-lasting insecticidal nets correctly; and
- monitoring and evaluation, specifically:
  - improved tools to assess entomological parameters;
  - new tools to monitor malaria infections, as substitutes for serological surveys; and
  - methods to allow targeting of interventions to high-risk areas and groups.

10. RECOMMENDATIONS

The following recommendations emerged from the meeting:

1. With rapid scaling up and sustained efforts, a major impact can be made on malaria morbidity and mortality in all epidemiological situations within a relatively short time. Malaria transmission can be interrupted in low-transmission settings and can be strongly reduced in many areas of high transmission. Global eradication cannot, however, be expected with the existing tools.

2. Failure to sustain malaria control and the resulting resurgence, as has happened in the past, must be avoided at all costs. Therefore, public and government interest in intensified malaria control and elimination must be sustained, even when the malaria burden has been greatly reduced.

3. Countries in areas of low, unstable transmission should be encouraged to proceed to malaria elimination. Before that decision is made, however, the malaria situation in neighbouring countries should be taken into consideration. Malaria elimination might require regional initiatives and support and strong political commitment.

4. In areas of high, stable transmission which have achieved a marked reduction in malaria transmission, a new consolidation period should be introduced, in which the control achievements are sustained even in the face of limited disease, health services are adapted to the new clinical and epidemiological situation, and surveillance systems are strengthened to be able to respond rapidly to new cases. This transformation phase precedes a decision to proceed with programme reorientation towards elimination.

5. Complete interruption of malaria transmission is likely to require additional tools, especially in areas of high transmission. As countries achieve marked reductions in the levels of transmission, they should review their malaria control strategies.

6. Because malaria control today relies heavily on a limited number of tools, in particular artemisinin derivatives and pyrethroids, which could be lost to resistance at any time, the development of new tools for vector control and other preventive measures, diagnosis, treatment and surveillance must be a priority.

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