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From malaria control to eradication: The WHO perspective

Kamini Mendis[1], Aafje Rietveld[1], Marian Warsame[1], Andrea Bosman[1], Brian Greenwood[2] and Walther H. Wernsdorfer[3]

1 *Global Malaria Programme, World Health Organization, Geneva, Switzerland*
2 *Department of Medical Parasitology, London School of Hygiene and Tropical Medicine, London, UK*
3 *Institute of Specific Prophylaxis and Tropical Medicine, Medical University of Vienna, Vienna, Austria*

Summary Efforts to control malaria have been boosted in the past few years with increased international funding and greater political commitment. Consequently, the reported malaria burden is being reduced in a number of countries throughout the world, including in some countries in tropical Africa where the burden of malaria is greatest. These achievements have raised new hopes of eradicating malaria. This paper summarizes the outcomes of a World Health Organization's expert meeting on the feasibility of such a goal. Given the hindsight and experience of the Global Malaria Eradication Programme of the 1950s and 1960s, and current knowledge of the effectiveness of antimalarial tools and interventions, it would be feasible to effectively control malaria in all parts of the world and greatly reduce the enormous morbidity and mortality of malaria. It would also be entirely feasible to eliminate malaria from countries and regions where the intensity of transmission is low to moderate, and where health systems are strong. Elimination of malaria requires a re-orientation of control activity, moving away from a population-based coverage of interventions, to one based on a programme of effective surveillance and response. Sustained efforts will be required to prevent the resurgence of malaria from where it is eliminated. Eliminating malaria from countries where the intensity of transmission is high and stable such as in tropical Africa will require more potent tools and stronger health systems than are available today. When such countries have effectively reduced the burden of malaria, the achievements will need to be consolidated before a programme re-orientation towards malaria elimination is contemplated. Malaria control and elimination are under the constant threat of the parasite and vector mosquito developing resistance to medicines and insecticides, which are the cornerstones of current antimalarial interventions. The prospects of malaria eradication, therefore, rest heavily on the outcomes of research and development for new and improved tools. Malaria control and elimination are complementary objectives in the global fight against malaria.

keywords malaria, control, elimination, eradication, transmission

Introduction

During the past 5 years, there has been a substantial increase in international funding for malaria control through major international financing mechanisms such as the Global Fund to fight HIV, TB and Malaria, the US President's Malaria Initiative and the World Bank's Booster Programme (WHO 2008a). This, together with a high level of political commitment in endemic countries, has resulted in increased coverage of malaria interventions in endemic areas, and a reduction in malarial disease and death in several countries, including several in sub-Saharan Africa where the burden of malaria is greatest. Inspired by these achievements and by the momentum created by global advocacy, the possibility of malaria eradication has been placed again on the agenda of international health

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Box 1 Definitions (WHO 2006a)

Malaria control is reducing the disease burden to a level at which it is no longer a public health problem.

Malaria elimination is interrupting local mosquito-borne malaria transmission in a defined geographical area, i.e. 0 incidence of locally contracted cases.

Malaria eradication is the permanent reduction to 0 of the worldwide incidence of malaria infection caused by a specific agent; i.e. applies to a particular malaria parasite species.

(Feachem & Sabot 2008; Okie 2008; Tanner & de Savigny 2008). WHO convened a panel of experts[1] in January 2008 to examine the technical issues underpinning malaria control and to review the feasibility of eradicating the disease. Based on the current knowledge and tools available to control malaria, and hindsight from the malaria control and eradication experiences of the past century, the meeting outlined the scientific basis for malaria control and elimination and helped define the prospects for malaria eradication (Box 1; WHO 2008b). This paper describes the outcomes of that meeting in the current context of malaria elimination efforts.

Historical perspectives

Since first recognized as a distinct disease, the distribution of malaria has contracted progressively (Figure 1). Until the mid-19th century, malaria was endemic in most countries its distribution in the northern hemisphere reached as far as the arctic circle, and an estimated 90% of the world's population lived in malarious areas; countries that did not have malaria included the Pacific islands east of the longitude of Vanuatu (the Buxton line). In the second half of the 19th century, large areas of northern and central Europe and North America became malaria-free, probably mainly as a result of changes in agricultural land use and improved housing. Key events in the latter part of the 19th century, including the discovery of the malaria parasite in 1880 and its mode of transmission in 1897, led to most northern countries in western Europe virtually eliminating malaria before the second World War through the use of focal mosquito control and by making diagnosis and treatment widely available. When the potent tools DDT and chloroquine became available, WHO launched the Global Malaria Eradication Programme in 1955, which led to a campaign to interrupt transmission in all endemic areas outside tropical Africa where the intensities of transmission were low to moderate (WHO 1956). As a result of this campaign, 37 of the 143 countries that were endemic in 1950 were free from malaria by 1978, including 27 in Europe and the Americas (Wernsdorfer 1980).

In many other countries, the burden of disease and deaths from malaria were greatly reduced. For example, in India, the number of malaria cases declined from an estimated 110 million in 1955 to less than a million reported in 1968, and reported malaria mortality dropped to 0. Sri Lanka reduced the incidence of malaria from an estimated 2.8 million cases in 1946 to a reported 18 cases in 1966. However, failure to sustain the programme led to a resurgence of malaria in many countries (WHO 1969). Thus, in 1969, the goal of malaria eradication was abandoned in favour of malaria control. In the ensuing years, malaria control went into further decline following increasing parasite resistance to chloroquine and its replacements, mosquito resistance to DDT and dwindling investments in malaria control. Malaria incidence increased throughout the world, as did child malaria deaths in Africa (Trape *et al.* 1998). The adoption of the Global Malaria Control Strategy at the Ministerial Conference in 1992 marked the beginning of a renewed interest in malaria control (WHO 1993). The launch of the Roll Back Malaria initiative by WHO in 1998 (Nabarro & Taylor 1998; Nabarro & Mendis 2000) stimulated increased financial investment in malaria control, the adoption of artemisinin-based combination therapies for the treatment of malaria patients and the large scale deployment of insecticide-treated nets and, to a lesser extent, house spraying as mosquito control measures.

[1]**Expert panel:** Dr Abdullah Suleiman Ali (National Malaria Control Programme, Zanzibar, United Republic of Tanzania); Dr Karen Barnes (University of Cape Town, South Africa); Prof. John Beier (University of Miami, USA); Dr David Brandling-Bennett (Bill and Melinda Gates Foundation, Seattle, WA, USA); Prof. Marc Coosemans (Institute of Tropical Medicine, Antwerp, Belgium); Prof. Brian Greenwood (London School of Hygiene and Tropical Medicine, UK); Prof. Stephen L. Hoffman (Sanaria Inc., Rockville, IN, USA); Dr Corine Karema (National Malaria Control Programme, Rwanda); Dr Anatoly Kondrashin (Moscow, Russian Federation); Dr Giancarlo Majori (Istituto Superiore di Sanità, Rome, Italy); Dr Jose Nájera (Crans-près-Céligny, Switzerland); Dr Ibrahim Ousmane (Health Ministry Malaria Programme, Niger); Dr Wichai Satimai (Ministry of Public Health, Thailand); Dr V. P. Sharma (New Delhi, India); Dr Duong Socheat (National Centre for Parasitology, Entomology and Malaria Control Programme, Cambodia); Prof. Awash Teklehaimanot (Columbia University, New York, NY, USA); Prof. Walther Wernsdorfer (University of Vienna, Austria); Prof. Nicholas White (Mahidol University, Bangkok, Thailand) and Prof. Christopher Whitty (London School of Hygiene and Tropical Medicine, UK). **Other contributors (WHO Secretariat):** Dr Hoda Atta, Dr Mikhail Ejov, Dr Richard Cibulskis, Dr Ibrahima Soce Fall, Dr Peter Olumese, Dr Kevin Palmer, Dr Pascal Ringwald, Dr Raman Velayudhan and Dr Wilson Were.

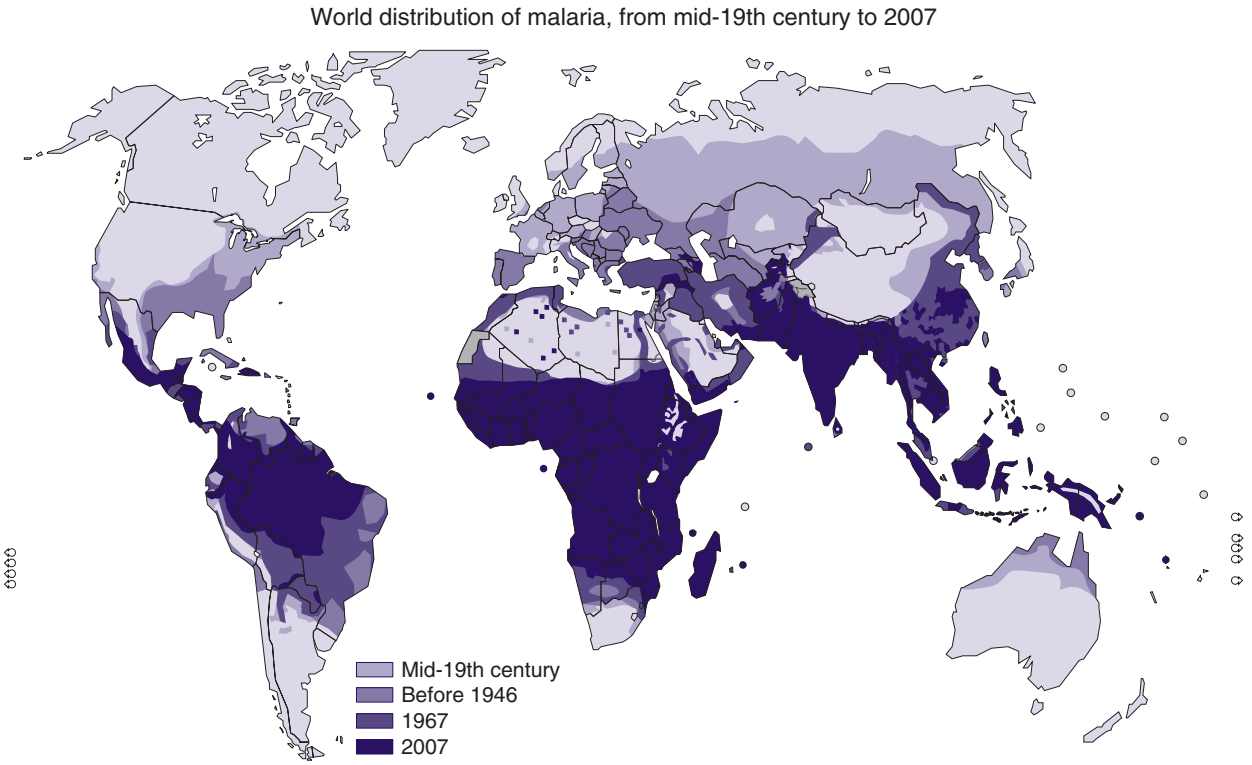

Figure 1 Malaria risk areas of the world from mid-19th century to the present. The boundaries and names shown and the designations used in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Recent progress and current status of malaria control

During the past few years, several high-burden countries in Africa, including Eritrea, Rwanda, Sao Tome and Principe, and Zanzibar (United Republic of Tanzania) have provided a high proportion of their at-risk populations with effective mosquito control interventions and access to artemisinin-based combination therapies (Bhattarai *et al.* 2007; WHO 2008a,b). The health information systems of these countries have shown a significant decline in the incidence of clinical malaria, malarial anaemia, hospital admissions by reason of malaria and/or malaria mortality as these interventions were scaled up (WHO 2008a). Other African countries such as Ethiopia, Gambia, Kenya, Mali, Niger and Togo (WHO 2008a) have achieved or are on their way to achieving high coverage with these effective malaria control interventions.

Enhanced malaria control efforts over the last 15 years are showing an even greater impact in other parts of the world, with clear downward trends of reported cases in 22 countries (WHO 2008a). Following the malaria elimination successes of Tunisia (1979) and the Maldives (1984), a further seven formerly endemic countries reported 0 locally acquired cases: Mauritius (1998), the United Arab Emirates (1998), Egypt (1998), Morocco (2005), Syrian Arab Republic (2005), Armenia (2006) and Turkmenistan (2006). Countries in the WHO Eastern Mediterranean and European regions were the first to approach malaria elimination from the 1990s onwards, starting with individual countries and progressing to blocks of neighbouring countries. In 1997, the five Northern African countries launched a sub-regional malaria elimination programme (WHO/EMRO 1997); by 2006, only one locally acquired malaria case was reported in Africa north of the Sahara, in Algeria (WHO 2008c). On the Arabian Peninsula, the United Arab Emirates was certified by WHO as malaria-free in 2007 (WER 2007). Oman reduced local transmission to only four reported cases in 2007 (WHO 2008c), and Saudi Arabia and other Gulf countries are assisting Yemen in an effort to jointly eliminate malaria from the peninsula (WHO 2006a; Meleigy 2007). Iraq reported only two cases in one area of local transmission in 2007. Iran is

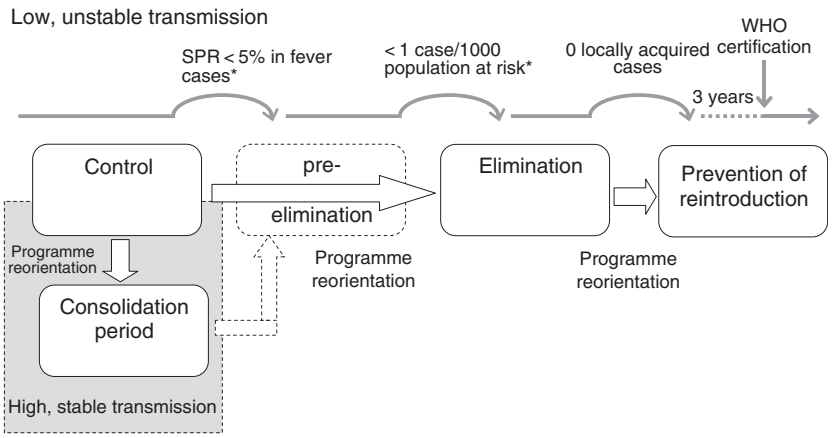

Figure 2 The malaria control to elimination continuum in high- and low-transmission settings. *These milestones are indicative only: in practice, the transitions will depend on the malaria burden that a programme can realistically handle (including case notification, case investigation, etc.).

progressively freeing its territory of falciparum malaria transmission. Even the high-burden countries Afghanistan, Sudan and Yemen showed a combined 40% reduction in reported cases, with estimated cases declining from 15 to 10.5 million over the period 2000–2006 (WHO/EMRO 2008).

The WHO European Region, which includes Central Asia, the Caucasus and Turkey, has successfully overcome the resurgence of malaria seen in the 1990s, with locally acquired cases down from 90 000 in 1992 to <1000 in 2007. In 2005, the Region adopted a joint strategy of malaria elimination (WHO/EURO 2006). In Central and South America, malaria incidence and mortality have fallen: the incidence of malaria has fallen in 15 of the 21 malaria endemic countries in the Americas over the past 5 years, including reductions of >50% in eight countries (WHO 2008a). In the WHO Southeast Asia and Western Pacific regions, reported malaria incidences and mortality have decreased steadily during the past decade, with the exception of Myanmar, Papua New Guinea and the Solomon Islands, which have made limited progress and/or experienced an increased malaria burden (WHO 2008a). The Philippines and Sri Lanka have reported substantial successes, declaring an increasing number of islands and provinces/districts 'malaria-free'. In all these countries, as the total malaria incidence decreases, the relative proportion of *Plasmodium vivax* malaria has increased, confirming that *P. vivax* transmission is more resilient to interruption (WHO 2008c).

Worldwide, 82 countries are now in the phase of malaria control; 11 are making the programme transition to elimination; 10 are operating malaria elimination programmes and 6 are actively battling a reintroduction of malaria (Figure 2, Box 2). Those moving to elimination, with the exception of El Salvador, are all located along the outer margins of the world malaria distribution map.

The biological basis of malaria transmission and its implications for elimination

The intensity of malaria transmission depends on two factors: (1) the vectorial capacity, defined by the density, longevity and bionomics of the mosquito vector prevalent in a particular area and the climate suitability for the particular species of malaria and (2) human ecology including the health systems dimension, which influences exposure of humans to mosquito bites, and access to effective treatment, which in turn would determine the magnitude of the parasite pool in humans (Wernsdorfer & McGregor 1989). Mosquito bionomics that are critical to transmission include the feeding frequency on humans, the daily survival rate and the duration of the parasite's development in the mosquito. For malaria to be eliminated, its basic reproduction rate must be reduced to be <1, i.e. on an average over the duration of infection, each case should produce less than one new case. Current antimalarial interventions lead to a reduction in the basic reproduction rate by reducing human infectivity through early and effective treatment, and to a reduction in vectorial capacity through mosquito control measures. Vectorial capacity is particularly sensitive to changes in the daily survival rate of the mosquito, and less so to changes in their density and human biting frequency. Indoor residual spraying (IRS) with insecticides reduces the daily survival rate of the mosquito; insecticide-treated mosquito nets (ITN) reduce the human biting rate of the mosquito and its daily survival rate. Critical pre-requisites for these effects are, in the case of IRS, walls of dwellings being sprayable, and mosquitoes resting indoors and being sensitive to the insecticide used.

Box 2 Moving from malaria control to elimination in moderate- and low-transmission settings: when to change approach?

A reorientation from malaria control towards an elimination approach, the *pre-elimination programme*, can be considered in areas where the malaria case load has been reduced to a level that would allow individual follow up for each and every malaria patient. This level will in practice fluctuate with the availability of peripheral health services resources and competent staff, and depend on competing public health demands, available communications, infrastructure, transport, etc. It will rarely be possible to introduce the stringent requirements of an elimination approach in districts where more than 5% of all people with fever (i.e., current fever or fever within the last 24 h) at any given time are diagnosed with malaria, and/or where more than 500 cases occur annually in a district of 100 000 people. Most countries made the programme transition much later, when only a few hundred cases remained nation-wide. From the start of the pre-elimination programme onwards, 100% diagnosis by Giemsa-stained microscopy needs to be phased in and case management should aim to reduce the parasite (and gametocyte) reservoir through early diagnosis and treatment and use of efficacious medicines. During this first programme reorientation, the following needs to be accomplished:

- Strengthening the health information system, including entomological surveillance and immediate notification of all malaria cases
- Improving the effective coverage of good-quality curative and preventive health services in all transmission areas. This implies that the whole population, either nationals or foreigners, is easily accessing and using private and/or public health-care facilities, whatever their citizenship or conditions (refugees, displaced, temporary workers, etc.)
- Reorientating public and private health service staff towards the new goals of malaria elimination;
- Establishing the national malaria elimination monitoring committee
- Developing the elimination programme
- Setting up the elimination database
- Setting up a national register of foci (well-defined areas where malaria transmission can occur)
- Strengthening the programme in terms of personnel, resources and logistics
- Establishing a programme of joint activities in international border areas
- Mobilizing domestic funding and necessary assistance from international and bilateral partners
- Advocacy to assure political commitment and continuous funding for remaining transmission foci (especially in the decentralized political and budget context that many countries are experiencing)

Elimination programme

This phase usually starts once malaria cases have been considerably reduced further to 100 or less cases per district of 100 000 people annually, where local transmission is limited to clearly defined foci, and the activities of the first programme reorientation has been achieved. The latter implies that the following programme changes have been completed:

- Training and reorientation of personnel has taken place
- The organization and physical facilities for the programme have been set up
- Drug policy change to include primaquine treatment for *P. vivax* (radical treatment) and artemisinin-based combination therapy plus 1 day gametocyte treatment for *P. falciparum* has been implemented
- All malaria cases are microscopically confirmed and treated according to national policy, including cases diagnosed and treated in the private sector
- Microscopy quality-assurance systems are fully operational
- All malaria cases are notified, epidemiologically investigated and centrally registered
- Malarious areas are clearly delimited and an inventory of foci has been made
- An elimination database has been set up, including geographic information systems-based data on foci, cases, vectors, parasite isolates and interventions

Source: *Malaria elimination – a field manual for low and moderate endemic countries (*WHO 2007).

In the case of ITNs, they require the consistent use of the nets by humans whenever and wherever people are exposed to mosquito vectors.

The tenacity of malaria transmission lies largely in the heterogeneity of contact between humans and mosquitoes, resulting in a small proportion of people receiving a large proportion of parasite inoculations. This is largely because of such factors as the proximity of dwellings to mosquito breeding places, living in poorly constructed houses which encourage mosquito entry, occupations such as forest-related work and behaviour patterns which increase contact with mosquitoes, especially where the vector is exophilic. Furthermore, only some of those who are inoculated become infected because humans differ in their susceptibility to malaria as a result of genetically determined resistance factors and acquired immunity. The resultant clustering, i.e. the lack of uniformity in the distribution of malaria inoculations confers a high degree of resilience to the cycle of malaria transmission (Carter *et al.* 2000; Smith *et al.* 2005, 2007). Although heterogeneity in the spatial distribution of malaria prevails across all malaria landscapes, the application of interventions through a blanket approach will have a considerable impact on malaria transmission in areas where transmission intensities are high (Table 1). However, where transmission intensities are closer to the threshold

Table 1 Classification of malaria endemicity levels

Criterion	Hypoendemic	Mesoendemic	Hyperendemic	Holoendemic	Sources
Parasite prevalence/spleen rate children 2–9 years	0–10%	11–50%	50%+	75%+*	WHO 1963
Endemicity	Low	Moderate	High	High	Boyd 1949; Molineaux 1988
Stability	Unstable		Stable		WHO 2006
Types of epidemic	True	Exaggerated seasonal transmission			WHO 2002
EIR	<0.25	0.25–10	11–140	>140	Beier 1999; R. Cibulskis (unpublished)

Source: adapted from Systems for the Early Detection of Malaria Epidemics in Africa, WHO 2006c.
*The 75%+ parasite prevalance applies only to <1 year (infant) age group.
EIR, entomological inoculation rate.

level below which transmission cannot be sustained, interrupting the cycle will require a targeted approach, identifying all foci of transmission, applying focal vector control measures and precisely diagnosing and treating all infected individuals to prevent the onward spread of the disease. It is for this reason that the move from malaria control to elimination demands a significant change in strategy: from an emphasis on the coverage of interventions towards an emphasis on effective surveillance systems to detect, investigate and classify every case of malaria, avert disease outbreaks and prevent reintroduction from endemic areas. WHO has elaborated guiding principles for assessing the feasibility of malaria elimination (WHO 2007). Although a low case load is necessary for programme transition to elimination, feasibility is determined by financial, geographical, political, socio-economic and technical factors, as well as epidemiological issues and health systems strengths.

The resurgence of malaria in many areas in Europe, Asia and Latin America from which malaria was (almost) eliminated during the Global Malaria Eradication Programme serves as a reminder that vigilant surveillance systems need to be sustained for as long as the mosquito vectors, a suitable climate and other conditions exist to sustain transmission. Even after the successful elimination of malaria, most countries remain susceptible to the re-establishment of transmission. The risk of resurgence is determined by the prevailing vectorial capacity (receptivity) and the number of infected individuals moving into the area (vulnerability). Therefore, malaria elimination, once achieved, is more likely to be sustained where vectorial capacities are naturally low or brought down by human development, and in geographically isolated areas with limited cross-border population movement and importation of parasites. Natural and man-made disasters have often resulted in re-establishment of malaria transmission.

There is no evidence to-date to indicate that malaria transmission can be interrupted in areas of high (intensity), stable transmission, nor that malaria elimination can be sustained in such areas with existing tools. Some important insights into the feasibility of interrupting transmission in areas of high, stable transmission were obtained in a population-based WHO study in Garki, Nigeria in 1972–1973 (Molineaux & Gramiccia 1980). In this area, near-complete coverage with IRS with propoxur combined with bi-weekly mass administration of sulphalene and pyrimethamine led to a marked reduction in parasite prevalence over the 2-year project period, and almost certainly to a major reduction in malaria morbidity and mortality, but transmission was not interrupted.

The way forward and recommendations from the meeting

The achievements of the past few years and the experiences of the Global Malaria Eradication Programme in the last century confirm that, with strong national leadership and a rapid scale up of effective antimalarial interventions, a major impact can be made on malaria morbidity and mortality within a relatively short period of time in all epidemiological situations, including areas of high and stable transmission in tropical Africa. Current tools will permit the interruption of malaria transmission in low-transmission countries, particularly in those with a robust institutional infrastructure and well-functioning health systems, and in those neighbouring malaria-free areas. In order to avoid failure to sustain malaria control, and elimination where it has been achieved, with the resulting resurgence of infection as seen many times in the past with

devastating effect, public and government interest in intensified malaria control and elimination must be maintained even when the malaria burden has been greatly reduced. Despite a considerable increase in the past few years, global funding for malaria control still falls short of the estimated requirements to provide complete intervention coverage to those at risk in endemic regions (Kiszewski *et al.* 2007). Elimination programmes will require additional resources not only during the elimination phase, but also to sustain strong health systems to prevent the re-introduction of malaria.

In areas with unrelenting high vectorial capacity resulting in high, stable transmission, countries which have achieved a marked reduction in the burden of malaria face the challenge of maintaining high coverage of vector control interventions despite the reduced public health importance of the disease and competing demands on scarce resources. These countries should consolidate their control achievements over a period of time in which their health services adapt to the new clinical and epidemiological situation inherent to reduced population immunity, and during which surveillance systems are strengthened to detect unusual increases in cases and mount a rapid outbreak response if needed. This consolidation period should precede a possible decision to proceed to elimination.

Global eradication of malaria cannot be expected with existing tools. Interruption of transmission in situations with ongoing high vectorial capacities will require more effective tools than are available today. In forested areas of Asia and the African savannah where outdoor-resting and outdoor-biting mosquito vectors prevail, the elimination of malaria has not been possible, so far, with existing strategies of ITN and IRS. Current successful antimalarial interventions are under threat from the ability of the parasite and its mosquito vector to develop resistance to medicines and insecticides, respectively. Data from the Thai–Cambodian border suggest that *P. falciparum* parasites there have developed reduced susceptibility to the latest medicines, artemisinins, as indicated by prolonged parasite clearance times to artesunate (Wongsrichanalai & Meshnick 2008). Likewise, malaria vectors in several countries display some degree of resistance to pyrethroids (Chandre *et al.* 1999). There are no new medicines in advanced stages of development to replace artemisinins, nor are there alternative insecticides. This places even current malaria control and elimination efforts at considerable risk, and so despite current recent successes in malaria control, the drive to develop new antimalarial drugs and insecticides must be sustained.

In summary, both the goal of greatly reducing the malaria burden in high-transmission areas and of eliminating malaria from low-transmission countries are feasible with existing tools, for as long as these remain effective. They must be pursued diligently and in parallel. The world malaria map is shrinking through the progressive elimination of malaria from countries and regions at the margins of distribution. This would enable the global effort to be increasingly focused on areas of high transmission; it may also limit the potential for dangerous parasite polymorphisms such as those which confer resistance to medicines. Elimination of malaria from high-transmission countries is a long-term goal, which will depend on the success of research and development to deliver a more robust arsenal of tools than those available today – tools of greater potency and effectiveness, especially those with an impact on transmission, and replacements for medicines and insecticides that are being lost to resistance.

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Corresponding Author **Aafje Rietveld,** Global Malaria Programme, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel.: +41 22 7913753; E-mail: rietvelda@who.int