MALARIA CONTROL TODAY

Current WHO Recommendations

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FOREWORD

One of the main functions of WHO is to issue guidelines and recommendations for the control of public health problems. As they are prepared in accordance with clear norms and excluding any influence by commercial or national interests, WHO guidelines are authoritative reference points in international cooperation. However, they are not mandatory. It is ultimately the decision of national authorities, whether WHO guidelines are followed in a given health programme. In case of disagreement between a donor and a recipient country, WHO recommendations are often invoked, and probably applied in most cases.

New international initiatives are enhancing the need for independent norms and standards, because it is recognized more and more that their funding decisions need to be guided by internationally accepted guidelines from a neutral body. This situation means that it is even more important than in the past that WHO guidelines are regularly updated, relevant to the needs and opportunities in endemic countries and easily accessible. The present publication is a summary presentation of current WHO guidelines and recommendations on malaria control. It is written for people involved in planning malaria control, who already have some practical experience. It is not a textbook on malaria control, but a guide to WHO recommendations.

It is hoped that this volume will serve as a practical reference for those who are involved in preparing malaria control plans and as a checking tool for those who review such plans. Users will be able to support the work of WHO by pointing out areas, where the guidance seems to be dated, unclear or lacking. It is the hope of the staff of WHO's Roll Back Malaria Department that this booklet will be widely used, and that the Department will receive ample feed-back, enabling it to steadily improve its service to malaria affected countries and other Roll Back Malaria partners.

Thanks are due to Dr Peter I. Trigg, former scientist, Malaria Control Unit, WHO, for preparing this compilation.

It is shared with members of the audience in early 2005 as a working document (not publication), because there is a need for it for the preparation of plans and project proposals. As a result of technical meetings, which took place in 2004, a number of new WHO guidelines and technical documents are currently under preparation for publication during 2005. It is therefore planned to finalize the document as a publication in 2005.

CONTENTS

1. INTRODUCTION

Malaria remains a leading cause of morbidity and mortality world-wide, especially in pregnant women and children, and particularly in tropical Africa, where at least 90% of the malaria deaths occur. Yet malaria is a curable disease and not an inevitable burden. Effective medicines and preventive measures are available. However, these effective and relatively inexpensive interventions reach only a small proportion of the populations in need, mainly because of insufficient financial resources. During the last decade, new medicines and approaches have been developed for malaria case management, for selective vector control and for epidemic detection and control. Malaria has become integrated into other health programmes and partnerships have been increased both internationally and nationally by the Roll Back Malaria (RBM) Initiative instigated by WHO's Director General in 1998. These developments have led to increased global awareness of malaria, and in 2002, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) started operations. By mid-2004, the GFATM has allocated nearly 2 billion US$ for malaria control over a five-year period. Although this remains far from covering the global needs, for the first time since the global malaria eradication campaign from 1956 to 1968, the international funding available for malaria control is making it possible to reduce the global burden.

WHO is the international organization whose mission it is to define standards for the prevention, control and possible elimination of major international disease problems. Since the creation of the global RBM partnership under WHO leadership, a large number of documents, consensus statements and advocacy materials on malaria control have been issued by WHO, other RBM partners and the RBM partnership.

On this background, WHO has decided to issue this document as a guide to current WHO recommendations for malaria control. The basis remains the Global Malaria Control Strategy, adopted in 1992 by a Ministerial Conference on Malaria and subsequently endorsed by the World Health Assembly and the UN General Assembly in 1993 (WHO, 1993a). This strategy is based on four basic elements:

- To provide early diagnosis and prompt treatment of malaria;
- To plan and implement selective and sustainable preventive measures, including vector control;
- To detect early, contain or prevent epidemics;
- To strengthen local capacities in basic and applied research to permit and promote the regular assessment of a country's malaria situation, in particular the ecological, social and economic determinants of disease.

The strategy recognizes that malaria varies throughout the world, with the consequence that cost-effective control must be based on local analysis. It calls for decentralization of decision-making, health sector development, community participation, integration of malaria control with other health programmes and for the involvement of other sectors such as education, agriculture and development.

This document summarizes the current WHO recommendations for malaria prevention and control based on the 1992 strategy, and evidence, which has since been generated on specific interventions and products. It provides the rationale and evidence-base for these recommendations, identifies both where evidence to support them is incomplete

and where there are constraints in implementing them. It also identifies future challenges and future priorities for securing a solid evidence-base for malaria control.

It is written to help:

- Regional and national health officials whose task it is to develop strategies and plans for the prevention and control of malaria;
- Partners in malaria control including managers of international and bilateral aid agencies and of Non-Governmental Organizations (NGOs).

The document is not a handbook of malaria control, but a reference for WHO recommendations and the source documents issued by WHO, where detailed guidelines can be found. For most planning and implementation purposes, health professionals and partners will probably need to look up details in these source documents; they are all available through the internet (www.mosquito.who.int) and they can be requested from WHO (rbm@who.int). The list of these WHO documents includes documents issued by WHO in cooperation with other organizations given in the reference section at the end of this document. Non-WHO references, which have been quoted in support of the WHO recommendations or to provide additional data, are given as footnotes.

2. THE MALARIA BURDEN IN THE WORLD

2.1. The present

Malaria remains one of the major tropical health challenges in the world today. However, assessment of the true scale of the disease burden is fraught with formidable challenges due to the focal and dynamic nature of the disease. Most of the current national surveillance systems are oriented towards trend assessment more than burden estimation. The number of malaria deaths in the world has been estimated at 1.1-1.3 million in World Health Reports 1999-2004. Based on reported malaria data and estimations of populations at risk and incidence rates, it is estimated that the malaria incidence in 2004 was between 350 - 500 million cases. [1]Malaria is considered to be endemic in 107 countries and territories.

2.1.1. Africa

Disease surveillance systems in Africa south of the Sahara are generally less developed than in other continents, where surveillance was a necessary part of eradication efforts. However, the relative uniformity of malaria transmission in tropical Africa outside highland and desert fringe areas makes extrapolation from surveys and focal studies relatively reliable. In contrast, the estimation of the malaria burden outside Africa is mainly based on surveillance data. About 90% of the world's malaria deaths are estimated to occur in tropical Africa south of the Sahara, where the majority of infections are caused by the most dangerous species, *Plasmodium falciparum*, which is predominantly transmitted by vectors that are highly efficient, widespread and difficult to control. Based on the data of the Africa Malaria report and other sources, WHO

1 Korenromp, E.L. for the RBM Monitoring and Evaluation Reference Group. Malaria Incidence Estimates at Country Level for the Year 2004 – proposed estimates and draft report. www.rbm.who.int/merg/

estimates that the number of malaria deaths in young children in sub-Saharan Africa in 2000 was 803,000 (precision estimate 710,000-896,000).[2] It is generally agreed that malaria causes around 20% of all deaths in children under 5 in Africa and that it is now the most important cause of death in this group (WHO and UNICEF, 2003). In malaria endemic countries in Africa, 25-40% of all outpatient visits and 20-50% of hospital admissions are for malaria (WHO and UNICEF, 2003).

Most of the people at risk of malaria in Africa live in areas where transmission is relatively intense and continuous, so that with increasing age some degree of immunity to malaria develops. In such areas, young children and pregnant women are at greatest risk of malaria infection and death due to their lower levels of malaria immunity. Malaria also causes anaemia in these groups and increases their vulnerability to other infections.

A smaller proportion of people in Africa live in areas of seasonal and less predictable transmission due to lower temperatures or rainfall in highland or desert fringe areas. Populations in these areas generally have lower levels of immunity and all age groups are vulnerable to highly seasonal transmission and epidemics. Such epidemics vary in their magnitude dependant on the situation and the causes. During the period 1997-2002, epidemics have been reported from Angola, Botswana, Burundi, Chad, Ethiopia, Kenya, Mali, Mauritania, Mozambique, Niger, Rwanda, Senegal, Somalia, South Africa, Sudan, Swaziland, Uganda, Zambia, and Zimbabwe (WHO, 2004a).

Malaria is also a major problem in peri-urban areas of most African cities, where, very often, the climate and the environment allows vector densities associated with intense transmission. In inner-city areas of larger urban agglomerations, anopheline breeding sites may be unevenly distributed, so that some urban populations are rarely exposed and therefore develop less immunity.
Malaria has been well controlled or eliminated in parts of South Africa, Namibia, Botswana and Zimbabwe in the southern fringe areas of Africa. In the five African countries north of the Sahara, i.e. Algeria, Egypt, Libyan Arab Jamahiriya, Morocco and Tunisia the disease, mainly caused by *P. vivax*, has been eliminated or persists in small isolated foci.

2.1.2. The rest of the world

With the exception of Papua New Guinea and focal intense transmission areas in forests of Southeast Asia and the Amazon Basin where malaria burdens may be as severe as in the savannah areas of Africa, malaria transmission in the rest of the world is from low to moderate. In tropical and subtropical areas, the disease burden may be due to both falciparum and vivax malaria, whereas in the temperate zones only vivax malaria is usually transmitted nowadays. In areas of low to moderate transmission, all age groups may be equally at risk.

Around 5 million confirmed cases of malaria are reported each year from countries outside Africa south of the Sahara, of which almost 3 million are from India and Pakistan, countries in which the malaria situation has remained more or less unchanged for the

2 Rowe, A.K., Steketee, R.W., Rowe, S.Y. Snow, R.W., Korenromp, E.L., Schellenberg, J.A., Stein, C., Nahlen, B., Bryce, J., Black, R.E. for the Child Health Epidemiology Reference Group (CHERG) (2004). Estimates of the burden of mortality directly attributable to malaria for children under 5 years of age in Africa for the year 2000. http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf

last decade (WHO, 2004b). However, it is generally assumed that the actual number of cases in the world is much greater.

Malaria risk is often occupational and related to population movements, particularly in the forest areas of Southeast Asia and South America. Some of these areas attract non-immune populations in search of economic opportunities, who use a variety of antimalarial medicines more or less rationally. These are the areas where resistance to multiple antimalarials was first documented. In some areas, development projects, war and civil disturbances have all increased the malaria burden. The effect of war and civil unrest is illustrated by the fact that in the WHO's Eastern Mediterranean Region, Afghanistan, Djibouti, Somalia, Sudan and Yemen represent 21% of the population of the Region but generate more than 90% of the malaria cases. All of these countries have had their health services and malaria control activities disrupted in the last decade[3]. In the Indian sub-continent, over the last two decades, malaria has become more and more common in urban areas such as Mumbai and Madras as a result of increasing adaptation of *Anopheles stephensi* to breeding in artificial containers and lack of environmental hygiene measures to accompany the growth of peri-urban slums.

Outside Africa, major epidemics have occurred during the last decade for example in Afghanistan, Azerbaijan, north-west India (Rajasthan), south-eastern Turkey, and Tajikistan (WHO, 2004a).

2.2. Trends

2.2.1. Monitoring Trends

Data from health facilities are potentially useful for monitoring trends in morbidity and mortality, as well as the impact of control measures, social and developmental changes and other factors that affect the malaria situation. However, they have severe limitations. Reporting varies in its quality, completeness and timeliness from country to country. It rarely includes data from non-governmental facilities or from the community where most cases of malaria illness and deaths occur. Less than 40% of malaria morbidity is seen in formal health services[4]. These factors are compounded with the difficulties in developing standardized case definitions for malaria morbidity and mortality (WHO, 2000a)

Mortality has always been considered the primary indicator of a serious malaria problem especially in vulnerable groups. However, as most malaria-associated deaths occur in the community, only special surveys or sentinel site monitoring based on verbal autopsies can provide reliable data, and even such methodologies are constrained by the limited accuracy of verbal autopsy diagnoses. The most reliable data available on trends in malaria deaths in Africa has been obtained from demographic surveillance systems (DSS)[5]. Recently such data from 28 DSS sites during 1982-1998 indicated that malaria mortality in children under 5 years almost doubled in eastern and southern Africa

[3] www.emro.who.int.rbm (2004).
[4] Breman, J.G. (2002). The ears of the hippopotamus: manifestations, determinants and estimates of the malaria burden American Journal of Tropical Medicine and Hygiene. 64 (1, 2 S): 1-11.
[5] INDEPTH network - International Network of field sites with continuous Demographic Evaluation of Populations and Their Health.

over the period 1990-1998 compared with 1982-1989[6]. Several factors may have contributed to this effect. The most important is resistance to antimalarials, but the emergence of HIV/AIDS as well as climate change may also have played a role although there is no hard evidence to support this hypothesis (WHO and UNICEF, 2003).

2.2.2 Re-emergence of malaria outside Africa

The re-emergence of malaria during the 1990s in the Korean peninsula and the Central Asian countries of the former Soviet Union has been disturbing. The former, due to *P. vivax*, arose in the early 1990s, after nearly 20 years of malaria-free status in the peninsula around the de-militarized zone between north and south for reasons that are not fully understood. The increase in malaria in countries of the former Soviet Union was due in part to the difficult economic situation, migration of populations, and the deterioration of the health services. Although the situation began to improve by the end of the 1990s, Kyrgyzstan and Tajikistan now face the resurgence and spread of falciparum malaria[7]

2.2.3. Improvements in malaria control

Successes in malaria control over the last decade have been few but significant and marked improvements in the malaria situation have occurred in particularly in Brazil, China, Ethiopia (Tigray Region), Thailand and Viet Nam but also in Cambodia, Malaysia, Mexico, the Philippines (during the 1990s), Solomon Islands and Vanuatu[8]. This was related predominantly to increased investments and specific malaria control interventions. The example of Viet Nam is particularly revealing. In 1990, malaria control was virtually paralysed due to lack of funding and antimalarial medicines for the health services. Investments from government revenue and to some extent from partners rapidly increased in 1991 followed by a dramatic reduction in malaria mortality and morbidity. A comparison of mortality data with other similar countries where the use of artemisinin and its derivatives are more restricted in the health services suggest that these antimalarials may have played some role in the reduction of mortality in Viet Nam (WHO, 2000b).

2.3. Economic burden

The economic burden of malaria to the country, the family and the individual is immense. It has been estimated that it causes a reduction of 1.3% in the annual per capita economic growth rate of malaria endemic countries and the long term impact of this is a reduction of the GNP by more than a half.[9] The economic effects of malaria are especially noticeable in rural areas where malaria strikes at the time of the year when

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[6] Korenromp, E.L. et al., (2003). Measurement of trends in childhood mortality in Africa: an assessment of progress towards targets based on verbal autopsy. Lancet, 3: 349-358

[7] www.euro.who.int/malaria (2004).

[8] Based on the three key indicators, confirmed cases, malaria incidence per 1000 population and malaria deaths. See www.wpro.who.int/themes-focuses and Interim Report of the Task Force Working Group 5 on Malaria Millennium Project. Commissioned by the UN Secretary General and supported by the UN Development Group, 8 June 2004.

[9] Sachs, J. and Malaney, P. (2002). The economic and social burden of malaria. Nature, 415: 680-685.

there is greatest need for agricultural work. Furthermore, the disease is a common cause of school absenteeism, reaching as high as 28% in some areas.

Especially in Asia and the Americas, the poor and often marginalized populations, such as ethnic minorities and people displaced as a result of civil unrest, are at greatest risk of malaria. Child mortality rates are higher among poor families, who live in dwellings that offer little protection against mosquitoes, and are less able both to afford protection measures and to seek health care when sick. Both direct and indirect costs of health care can be a substantial burden to poor households which may spend up to 34% of their total income on health care (WHO and UNICEF, 2003).

2.4. Resistance to Antimalarial Medicines

The worsening problems of resistance[10] in many parts of the world and the limited number of antimalarial medicines available have led to increasing difficulties in developing antimalarial treatment policies and the provision of prompt and effective treatment to all in need. There is a considerable amount of evidence demonstrating the relationship between increased resistance to first-line antimalarial therapy and increased morbidity and mortality. Drug resistance has also been implicated in the increasing frequency and severity of epidemics (WHO and UNICEF, 2003). A report on the global situation of antimalarial drug resistance will soon be published on www.mosquito.who.int.

Chloroquine resistance

Resistance of *P.falciparum* to chloroquine was first reported almost simultaneously at the beginning of the 1960s from areas on Thai/Cambodian and the Colombian /Venezuelan borders where uncontrolled use of the drug was rife among migrants working in isolation from routine medical services (WHO, 1965; 1973). It is now considered that the use of chloroquinized salt played a major role in Cambodia. In Africa, chloroquine resistance was first documented from Kenya in 1979[11].

It has now has spread throughout the world so that, at present, only falciparum strains from Central America north of the Panama canal and the island of Hispaniola (Haiti and the Dominican Republic) are still reported to be fully sensitive to the drug (WHO, 2001a). High levels of chloroquine resistance are found in East Africa, South Asia, South-East Asia, Oceania, the Amazon Basin and some coastal areas of South America.

In most countries of East Africa and Ethiopia more than 50% of patients are not cured by chloroquine. Moderate levels of resistance are now found in Central and Southern Africa whereas, in West Africa, reported levels vary widely but tend to be lower than in Central and Southern Africa (WHO, 2001a; 2003a).

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[10] Antimalarial drug resistance is defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal or higher than those usually recommended, but within the limits of tolerance of the patient (WHO, 1973). It is the result of spontaneously occurring mutations. Selection of mutants is thought to be enhanced by sub-therapeutic drug levels and by a flat dose response curve of the drug (WHO, 2001a)

[11] Fogh S, Jepsen S & Effersoe P (1979). Chloroquine resistant *Plasmodium falciparum* malaria in Kenya. Transactions of the Royal Society of Tropical Medicine and Hygiene, 73: 228-229.

2.4.2. Amodiaquine resistance

Although amodiaquine is generally more effective than chloroquine against chloroquine-resistant strains of *P. falciparum*, there is cross resistance. Moderate to high levels of amodiaquine resistance have been reported from Papua New Guinea, East Africa and the Amazon basin. However, the drug continues to be efficacious in most of West and Central Africa and the northern Pacific coast of South America (WHO, 2001a; 2003a).

Sulfadoxine-pyrimethamine (SP) resistance

High levels of resistance of *P. falciparum* are found in the Amazon Basin, and throughout South-East Asia, with the possible exception of focal areas of eastern Cambodia and northern Viet Nam (WHO, 1997). In Africa, resistance rates to SP are variable ranging from 10-50% in East Africa and <10% in Central and Southern Africa. They are generally low and focal in West Africa and in the coastal areas of South America and appear to be rising**.** (WHO, 2001a; 2003a). In Oceania, resistance is high in Papua New Guinea, moderate to high in the Solomon Islands and increasing in Vanuatu (K. Palmer, personal communication 2004).

2.4.4. Quinine

Decreasing sensitivity to quinine has been detected in areas of South-East Asia from border areas between Cambodia, Myanmar and Thailand and in some parts of South America, where it had been used extensively as the first line treatment for malaria. There is some cross-resistance between quinine and mefloquine, suggesting that the widespread use of quinine in Thailand may have influenced the development of resistance to mefloquine in that country. Strains of *P. falciparum in* Africa are generally highly sensitive to quinine (WHO, 2001a; 2003a).

2.4.5. Mefloquine

Recurrence of parasitaemia in over 50% of the patients treated with mefloquine has been reported from border areas of Cambodia, Myanmar and Thailand. Mefloquine resistance is uncommon in other areas of South-East Asia. It has also been reported from Brazil. Parasite isolates with reduced sensitivity to mefloquine *in vitro* have been reported from Central and West Africa although the drug has not been used operationally in these areas. This indicates that there is the potential for resistance to spread if mefloquine monotherapy is used on a wide scale in Africa (WHO, 2001a).

2.4.6. Artemisinin derivatives

Recrudescences are common when these drugs are used in monotherapy. In spite of reports of decreasing *in vitro* sensitivity, there is no confirmed evidence of *in vivo* resistance of *P. falciparum* to artemisinin and its derivatives (WHO, 1997; 2001a, b; 2002a).

2.4.7. *Plasmodium vivax* resistance

P. vivax resistance to chloroquine was first reported from Irian Jaya and Papua New Guinea in 1989. Now nearly 50% of strains from these areas show reduced *in vivo* susceptibility to this drug. Well documented reports of treatment failures in individual

patients or small case series have also been reported from Brazil, Guatemala, Guyana, India and Myanmar but resistance appears focal and much less intense than in Irian Jaya and Papua New Guinea (WHO, 2001a).

3. DISEASE MANAGEMENT

Early diagnosis and prompt treatment are the basic elements of malaria control. Early and effective treatment of malaria disease will shorten its duration and prevent the development of complications and the great majority of deaths from malaria. Access to disease management should be seen not only as a component of malaria control but a fundamental right of all populations at risk. As such, it must be an essential part of health care development.[12]

3.1. Treatment policy for malaria

It is the responsibility of national health programmes to develop a treatment policy for malaria which should ideally be part of the national malaria control policy, covering prevention as well as case management (WHO, 1994). Given the importance of the issues, the antimalarial drug policy should be given prominence within and supported by the National Drug policy (NDP) and National Malaria Control Policy (NMCP). The NMCP and the NDP should conform to the overall National Health Policy.

It is recognized that antimalarial treatment policies will vary between countries depending on the epidemiology of the disease, transmission, patterns of drug resistance and political and economic contexts. In addition, significant heterogeneity in the therapeutic response to first-line antimalarial drugs may exist in different geographical localities and regions of a country. Treatment policies in some countries have attempted to differentiate between localities with varying drug resistance. Such decisions depend on whether countries are able to implement different drug policies for different regions and whether the health system can deliver the required drug successfully to end-users. As the available drugs become more expensive or less safe, dual policies for vulnerable and less vulnerable groups may need to be considered (WHO, 2003a).

One key challenge facing the development of antimalarial treatment policies is achieving a balance between two essential purposes that:

- All populations at risk have access to prompt treatment with safe, good quality, effective, affordable and acceptable antimalarial drugs; and
- The approach should encourage rational drug use of currently available antimalarials in order to avoid unnecessary selection pressure favouring the development of drug resistance so as to ensure that antimalarial drugs have a maximum useful therapeutic life.

[12] These principles were agreed upon by the Ministerial Conference on Malaria in 1993. The recommendations based on these principles have been developed by a series of WHO Working Groups and Informal Consultations, to which specific references are made in the text.

3.1.1. Objectives

The objectives of an antimalarial treatment policy (WHO, 2003a) are to:

- ensure rapid and long-lasting clinical cure;
- reduce morbidity and mortality, including malaria-related anaemia;
- prevent the progression of uncomplicated malaria into severe and potentially fatal disease;
- reduce the impact of placental malaria infection and maternal malaria-associated anaemia e.g. through intermittent preventive treatment;

The period of clinical relief may be relatively short in areas of intense transmission compared to areas of low or seasonal transmission as re-infection may occur. In areas of intense transmission, reappearance of the infection (recrudescence) may be difficult to distinguish from re-infection. Other factors that influence the clinical response and duration of clinical cure include compliance and drug characteristics such as quality.

It must be noted that that these WHO recommendations differ from those made previously (WHO, I994) since long lasting clinical cure can only be achieved by parasite clearance with a highly effective blood schizontocide. It is no longer considered that countries should accept to use partially effective antimalarial drugs for the treatment of malaria. In general, the most difficult issue in antimalarial treatment policy has for long been the selection of the first line treatment for uncomplicated falciparum malaria. Over the last few years, there has been a paradigm shift in this area towards the universal adoption of artemisinin-based combination therapy (ACT) (see 3.3.1.)

3.1.2. Framework for malaria treatment policy

WHO has developed a framework for the development, evaluation and updating of malaria treatment policies by a series of consultation with countries and partners (WHO, 2003a and b). This framework is based on the WHO strategy for Essential Drugs and Medicines (WHO, 2003c) to ensure improved access of antimalarial drugs to those in greatest need, the main principles of which are that:

The selection of drugs is evidence-based;
The selected drugs are affordable;
The drugs are of good quality and the delivery supported by reliable health and supply systems that provide efficient procurement and rational use; and
Their delivery is sustainably financed.

The requirements for developing, evaluating and updating of antimalarial treatment policy are:

- a clear analysis of the technical, social and economic issues related to the provision of malaria treatment and antimalarial drug resistance such as the magnitude of resistance, potential interventions available and the consequences of action or inaction;
- an understanding of the health seeking behaviour of the populations at risk;
- analysis of the potential environment for decision making;

- consensus building and selection of treatment options among policy-makers, researchers, control staff and other relevant stakeholders (e.g. donors, private providers, industry and user representatives); and
- a supervisory body to oversee the development, implementation and revision of policy.

The framework proposes that the policy comprises the following essential components:

A definition of the criteria for diagnosis and the establishment of treatment algorithms;
An antimalarial drug list for the treatment of both uncomplicated and severe malaria selected on the evidence of their efficacy in reducing morbidity and mortality and, where appropriate, for chemoprophylaxis and intermittent protective treatment;
Guidelines on the rational use of drugs in both public and private sectors, including use in high risk groups such as pregnant women and young children;
Regulations for drug prescription and provision;
Pricing regulations and regulations on registration, supply, distribution and quality assurance of antimalarial treatments;
Definition of the system, norms and criteria for referral;
Definition of the criteria for improving home -based management of malaria; and
Strategies for financing the provision of early diagnosis and prompt treatment.

3.1.3. Selection of antimalarial treatments

In order to define which effective, affordable drug can be provided safely to satisfy the health care needs of the majority of the population, information is required on the epidemiological situation (e.g. malaria species, drug resistance), the characteristics of the available alternative treatments, human health seeking behaviour and their potential compliance with the treatments, the cost and cost effectiveness and the health capacity to deliver the treatments

3.1.4. Implementing the policy

The implementation of a national drug policy is faced with several constraints such as the logistics of distribution, the large number and variety of persons and institutions involved, and rising costs. Appropriate planning is, therefore, essential, particularly in the period of transition between the old and new policies.

Ministries of health will find it useful to arrange national collaborative mechanisms for implementation of the malaria drug policy to include not only malaria and general health services staff, but also partners, such as NGOs and the private sector. Such a mechanism is important for obtaining input from experienced staff and to create a sense of ownership in all who have a role to play in the implementation of the policy.

It is therefore recommended (WHO, 2003a) that the following important actions are undertaken:

- Develop a plan for the implementation of the policy;
- Ensure the policy can be implemented by both the public and private health sectors (see also 3.6. and 3.7);
- Register the selected drugs and regimens in line with national drug regulations;

- Incorporate changes in policy into national treatment guidelines and the essential drugs list;
- Define the responsibilities of health care at each level;
- Ensure adequate supplies of all necessary drugs at all levels of health care by a reliable distribution system;
- Consider financing implications;
- Develop a monitoring system for therapeutic efficacy, safety and quality assurance of the drugs selected;
- Train health workers, including drug vendors, in the implementation of the drug policy and the dissemination of new recommendations;
- Create public awareness and acceptance of the policy through the development and dissemination of communication materials;
- Monitor and evaluate the implementation of the policy;

Adequate supply of the second-line drugs is essential. Past restrictions of such drugs at the periphery compounded by difficulties in the accessibility of referral centres has often resulted in repeated first-line treatments. This has caused chronic malaria associated anaemia, particularly in children. The WHO Expert Committee therefore recommended that second-line treatment should be deployed at the most peripheral levels of the health services accompanied by effective instructions and monitoring (WHO, 2000a).

3.1.5. Monitoring the Drug policy

There is a need to maintain a method of continued monitoring of the efficacy of the present therapy and alternatives, preferably at the sites used for initial testing. There should also be monitoring of the availability, acceptability and affordability of effective drugs to the consumer. Through methods of social research, ranging from focus groups to interviews, consumers' use of antimalarial drug therapy, health-seeking behaviour, incentives for making their choice of therapy and compliance with recommendations can be elicited. The provider's opinion and adherence to the policy and quality of care should also be followed up.

Appropriate surveillance systems should be devised for monitoring adverse drug reactions. Such a system should address the issue that adverse effects and tolerance of the drug may compromise disease management by altering the provider and consumer confidence and adherence. In addition, the proportion of severe and life threatening events may influence whether the drug is appropriate for first-line therapy.

The impact of any possible change in policy also needs to be assessed using appropriate indicators in order to assist national policy-makers to review the policy and for countries.

3.1.6. Monitoring of drug resistance

3.1.6.1. Assessment of antimalarial drug efficacy in vivo

A new standard protocol for the monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria has been recently developed (WHO, 2003d). It is based on recommendations made by a WHO Informal Consultation (WHO, 2002b) [13].

This protocol is intended for the evaluation of range of antimalarial treatments, providing the minimum information essential for programme decision-making. Studies that follow this basic design, when conducted periodically in a number of appropriate sentinel sites, can also form a basis of a surveillance system capable of monitoring drug efficacy changes over time.

The design is a simple, one-arm, prospective evaluation of the clinical and parasitological response to observed treatment of uncomplicated malaria, allowing the evaluation of both the first-line treatment as well as one or more of the potential replacement treatments. However, the protocol is not designed to assess drug regimens administered over periods longer than 3 days.

In all areas, regardless of the intensity of transmission, the evaluation should emphasize treatment efficacy in children 5 years with clinically apparent malaria. The rationale for this requirement is that, even in populations with little immunity (as occurs in areas of low or highly seasonal transmission) younger children often have a less favourable therapeutic response to antimalarial drugs than do older children or adults. It is recommended that a sufficient number of patients be enrolled, wherever possible, to allow the stratification of results based on age (WHO, 2002b; 2003d).

The recommended duration of follow-up for areas of intense transmission is 14 days and for areas with low or moderate transmission 28 days. These are the minimum requirements and programmes that have the capability to maintain the quality of the study for longer periods and have access to molecular markers are encouraged to do so. Studies with shorter follow-up (i.e. <14 days) will underestimate overall failure rates. This is especially true with drugs with longer elimination half-lives. Follow-up periods longer than 14 days are appropriate for amodiaquine, chloroquine and sulfadoxine/pyrimethamine (26 days), artemether/lumefantrine (28 days) and for mefloquine (63 days) to allow drug levels in the blood to fall below the minimum therapeutic threshold. Longer-duration assessments have substantial logistic and cost implications that should not be taken lightly. Even, short-duration assessments are prone to invalidation due to high rates of defaulting and loss to follow-up (WHO, 2002b; 2003d).

[13] The first standardized tests for monitoring the response to antimalarial drugs were developed in 1965. These tests measured drug failure only on the basis of parasite response. The methods were demanding, requiring a 28 day follow up of all patients who were kept in a mosquito free environment. Further modifications offered a 7-day follow and then new methods were developed to measure drug failure in symptomatic patients, based on both clinical and parasitological parameters. Separate protocols, based on these parameters, were developed for areas of intense transmission (WHO, 1996a) and of low and to moderate transmission (WHO, 1998b; 2001b). The presence of two "official" protocols led to some confusion.

3.1.6.2 In vitro tests

In vitro tests to determine the susceptibility of *P.falciparum* to antimalarial drugs can be used (WHO, 2000a; 2002b) to:

- Assess patterns of cross-resistance between different drugs:
- Assess the base-line susceptibility to new drugs before they are introduced into malaria control; and
- Monitor parasite susceptibility to drugs both temporally and geographically.

They, therefore, have a role to play in the surveillance of drug resistance at country or regional levels but the results of such tests should not be used to determine the treatment of an individual patient. *In vitro* tests should only be carried out by centres with adequate resources and expertise because of the technical difficulties in carrying them out and their cost (WHO, 2002b).

There is a need to for standardizing the methodology, especially cultivation procedures and the reporting of results. Threshold levels defining resistance must be validated by clinical studies in non-immune patients specifically for each type of *in vitro* test. A quality control system should be established and should include reference clones (WHO, 2002b).

3.1.7 Changing the policy

The primary indicators to consider as evidence that there may be a need to revise existing malaria drug policy are:

- A systematic increase in the routine notification of treatment failures either based on clinical or clinical and laboratory criteria;
- Evidence of reduced therapeutic efficacy from routine monitoring using the WHO standard protocol (see also Section 3.1.8.1);
- An increase in malaria-associated mortality and morbidity;
- Consumer and service provider dissatisfaction with the policy or the drugs.

There is no fixed point of the proportion of clinical failures to the currently used first-line antimalarial beyond which change is necessary. The decision should be country-based, and the speed of change will depend on several complementing factors and conditions including the:

level and geographical distribution of clinical failure rate;
effect of failure rate on morbidity and mortality as well; and
availability of acceptable, affordable and effective alternative drugs.

However, it has been generally accepted that a 25% failure rate of the first line therapy should not be exceeded (WHO, 2000a).

A consultation convened by WHO's Regional Office for Africa in 2003 recommended that clinical failure rates of 15% and parasitological failure rates of 25% should not be exceeded. (WHO/AFRO, in press).

3.2. Diagnosis

A diagnosis of malaria must precede treatment with antimalarial drugs and is made first on a clinical suspicion of the disease based on fever and other signs and symptoms. A confirmatory diagnosis requires evidence of the presence of parasites.

3.2.1. Clinical diagnosis

Determination of a patient's clinical history and symptoms is an acceptable basis for the management of malaria disease. Although the signs and symptoms of malaria, such as fever, chills, headache and anorexia, are generally non-specific, some signs and symptoms, especially in combination, have diagnostic value in specific epidemiological and operational situations[14]. However, it is not possible to apply any one set of clinical criteria to the diagnosis of all types of malaria in all patient populations. Experience has shown that the appropriateness of particular clinical diagnostic criteria vary from area to area according to the intensity of transmission, the prevalent malaria species, the incidence of other causes of fever, the qualifications of the health care staff and the health service infrastructure (WHO, 2000a).

With these considerations in mind, the Twentieth WHO Expert Committee on Malaria recommended (WHO, 2000a) that;

In general, **in settings where the risk of malaria is low** (i.e. in areas of low endemicity or where malaria is seasonal during the low-transmission season, clinical diagnosis of uncomplicated malaria should be based on a history of fever alone[15] ; and

In settings where the risk of malaria is high (i.e. in areas where malaria transmission is stable or during the high transmission season of seasonal malaria), the accepted criteria for the treatment of malaria disease in young children[16] and pregnant women should be a history of fever or the presence of detectable anaemia, for which pallor of the palms appears to be the most reliable sign in young children (WHO, 2000a). In older children, adult males and non-pregnant women, the sole criteria is a history of fever. The incidence of malaria disease in these age groups is low and therefore the absence of an alternative explanation of fever may be useful. (WHO, 2000a).

Clinical diagnosis offers the advantages of ease, speed and low cost. In areas where malaria is endemic, it usually results in all patients with fever and no other apparent causes of malaria being treated for malaria. This approach can identify most patients that really need malaria treatment but is also likely to misclassify many who are not. Over-diagnosis can be considerable and contributes to the misuse of antimalarial drugs. Considerable overlap exists between the signs and symptoms of malaria and other

[14] Marsh, K. *et al*., (1996). Clinical algorithm for malaria in Africa. Lancet, 347: 1327-1329;
Redd, S.C. *et al*., (1996). Clinical algorithm for treatment of *PlasmOdium falciparum* in children. Lancet, 347: 223-227;
Olaleye, B.O. *et al.* (1998). Clinical predictors of malaria in Gambian children with fever or a history of fever. Transactions of the Royal Society of Tropical Medicine and Hygiene, 92: 300-304.

[15] History of fever is defined as the presence of fever and/or a history of fever within the past 4 days.

[16] Generally children below 5 years are defined as young children but this depends on the level of endemicity (WHO, 2000a).

frequently occurring diseases, especially respiratory tract infections. In areas of high transmission of malaria, parasitaemia is likely to occur concurrently with other diseases. Children with a clear clinical diagnosis of pneumonia often may also require antimalarial treatment while demonstration of malaria parasitaemia does not exclude other aetiology.

In order to address these issues, WHO's Integrated Management of Childhood Illnesses (IMCI) programme has developed an algorithm to improve diagnosis and treatment of the common childhood diseases, relying upon health care workers without access to laboratories or special equipment. This algorithm recommends that, fever, without runny nose or measles and no other apparent cause of fever are acceptable clinical criteria for the treatment of malaria in children in low risk settings (WHO, 1998a). In high risk areas for malaria[17], every febrile children child should be considered to have malaria and be treated for such.

3.2.2. Light Microscopy - Confirmatory Diagnosis

Evidence of the presence of parasites can be made by the examination of a stained blood smear by light microscopy or by the detection of parasite products by rapid diagnostic techniques (RDTs). However, in areas with intense transmission, it is of limited value for children and to some extent for adults, as asymptomatic parasite carriers may be common. However, in these areas, the WHO Expert Committee recommended that confirmatory diagnosis is desirable to detect treatment failures, confirm severe disease, and diagnosing complicated malaria during a low transmission season (WHO, 2000a).

If light microscopy is available, the diagnosis of uncomplicated malaria should be based on a history of fever and a positive blood slide. Malaria disease may exist despite a negative blood slide but unless the patient has already started treatment and there is a high clinical suspicion of the disease, treatment for uncomplicated malaria should not be given as long as the blood slides are negative (WHO, 2000a).

(i) Advantages of light microscopy

Given the low specificity of all clinical case definitions, there is a compelling need to make parasite detection more widely available. Basic microscopy has many advantages. It:

- Has low direct costs if the infrastructure to maintain the service is already available;
- Can be sensitive if the quality of microscopy is high;
- Can be used to differentiate between species;
- Can determine parasite densities;
- Can be used to diagnose many other conditions.

[17] High risk is defined in the IMCI Adaptation Guides as any situation where as little as 5% of febrile children between the age of 2 and 59 months are parasitaemic (WHO, 1998a). This definition is likely to lead to significant over-diagnosis of malaria in areas with low to moderate transmission (Boland, P.B., 2001. Drug resistance in malaria. WHO/CDS/CSR/DRS/2001.4).

(*ii)* *Constraints with light microscopy*

However, experience in malaria endemic areas has shown that it can be difficult to maintain good microscopy at the periphery of the health services where most patients are treated because of the:

Poor quality of microscopists, particularly at the peripheral level;
Difficulties in maintaining microscopical facilities in good order;
Logistic problems and high costs of maintaining adequate supplies and equipment;
Lack of adequate training and retraining of laboratory staff;
Delays in providing results to clinical staff; and
Lack of quality assurance and control of laboratory services

This can be overcome by ensuring that:

- Slide collection staining and reading are timely and linked to clinical diagnosis;
- Results are quickly provided to the clinicians;
- Logistic support for supplies and equipment; and
- Constant training, supervision and quality control.

(iii) *Extension and integration of laboratory services*

With the increasing problems of drug resistance and the need to use more expensive therapies such as artemisinin combination therapy (see Section 3.3.1.), it is becoming more important that confirmatory diagnosis is made available closer to the periphery of the health services. As a consequence the WHO Expert Committee recommended that, as far as possible, the extension and strengthening of laboratory facilities should be integrated with efforts of other disease control programmes and the up-grading of the general health services (WHO, 2000a).

3.2.3. Rapid diagnostic tests (RDTs)

When parasite-based diagnosis is essential, RDTs[18] may be an alternative to light microscopy in situations where normal laboratory services are non-existent or overworked.

(i) *Advantages and disadvantages*

A review of the current evidence on the use RDTs by WHO informal consultations (WHO, 2000c; 2003e) identified that these tests have many potential advantages such as:

[18] RDTs are immuno-chromatographic tests that detect parasite specific antigens in a finger-prick blood sample. Some tests detect only one species (*Plasmodium falciparum*), others detect one or more of the other three species of human malaria parasites (*P.vivax*, *P. malariae* and *P.ovale*) (WHO, 2000c; 2003e; 2004c). RDTs are commercially available in different formats, as dipsticks, cassettes or cards. Cassettes and cards are easier to use in difficult conditions outside health facilities.

producing rapid results. This is useful in clinical care as well as rapid epidemiological assessments;
needing a lower level of training/skilled personnel;
requiring lower capital costs than light microscopy (but they can be more costly when case numbers are high);
reinforcing patient confidence in the diagnosis and the health service;
identifying patients that do not have malaria for which another source of fever should be sought; and
permitting rational use of high-cost drugs, thus reducing costs in areas where artemisinin-combination therapy is required for *P. falciparum* based solely on clinical diagnosis. This may not apply if parasite prevalence is very high, in which case the additional costs of improved diagnosis may provide little benefit in terms of savings on drug costs.

Certain disadvantages were also identified such as:

where prevalence (and host immunity) is high, RDT test results may erroneously suggest a positive diagnosis in patients with parasitaemia incidental to another illness (WHO, 2000c).
RDTs detect antigens and not parasites: results may therefore reflect recent and not current parasitaemia. However, antigen detection may be a better indication of parasite load than light microscopy (WHO, 2003e).
sensitivity in the field may be unpredictable. Published sensitivities for *P. falciparum* range from comparable to good field microscopy (>90 % at 100-500 paratsites/µl) to very poor (40-50 %) for some widely used products. Sensitivities are generally lower for non-falciparum species (WHO, 2003e).

Reasons for poor sensitivity are not clear. They may include: poor manufacture, damage due to temperature or humidity exposure, incorrect handling by end-users, possible geographical variation in the test antigen and poor comparative microscopy (WHO, 2003e).

(ii) Recommendations for RDT use

More recent experience with RDTs led WHO informal consultations (WHO, 2003c; 2004a) to conclude that:

they are useful for case management where microscopy is absent, if sufficiently stable, simple to perform, detect local parasite species, and there is evidence of benefit in terms of public health and cost savings.
they are useful for confirming the cause and end-point of malaria epidemics;
they should not be the sole basis for treatment;
they should be backed up with adequate quality assurance, including temperature stability testing;
there must be adequate training and monitoring of health workers; and
negative test results should not preclude treatment (a clear management algorithm must be in place).

If used, WHO recommends that RDT transport and storage should be based on the following principles (WHO, 2003e, 2004a,c):

avoid heat exposure of the tests, e.g. at airports and in vehicles;
ensure stockpiles are stored in central locations which are kept as cool as possible (e.g. an air-conditioned area) in readiness for use, with quality testing every few months to ensure that the RDTs remain in good condition. Proper storage extends the shelf-life;
seek to maximize the length of time RDTs are kept under such conditions. They should be then rapidly deployed to the field for short-term use; and
consider simple methods to reduce the temperature at an outlying site (e.g. evaporative cooling of the products, work under thatched roofs).

(iii) Constraints

Variable field performance and sensitivity to damage through heat exposure underline the importance of quality control testing and careful monitoring of RDTs. It should also be noted that there are no uniform international standards for RDT specifications, and many endemic countries have no national regulations covering the quality and use of diagnostics. No malaria RDTs have been approved by the US-FDA. It is therefore important to monitor the sensitivity of RDTs after purchase (WHO 2003e, 2004c).

3.3. Treatment of Uncomplicated Falciparum Malaria

3.3.1. Combination therapy

As a response to the antimalarial drug resistance situation, WHO now recommends that treatment policies for falciparum malaria in all countries experiencing resistance to monotherapies, such as chloroquine, sulfadoxine/pyrimethamine and amodiaquine, should be combination therapies[19], preferably those containing an artemisinin derivative (ACT - artemisinin-based combination therapy). This is a change from previous recommendations (see also above Section 3.1.1). It is now considered that an effective first-line antimalarial treatment would have a greater impact on reducing mortality than merely improving second-line treatment or the management of severe malaria. Therefore, combination therapies must be available and affordable to communities for use in the first-line treatment of malaria. These conclusions are the rational culmination of the recommendations of a series of WHO informal consultations with countries and partners ((WHO, 2001a, c; 2003b; 2004a and d).

The advantages of artemisinin derivatives that make them ideal combination partners (WHO, 2001a; c) are:

[19] The concept of combination therapy is based on the synergistic or additive potential of two or more drugs, to improve therapeutic efficacy and also delay the development of resistance to the individual components. Combination therapy with antimalarial drugs is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets in the parasite (WHO, 2001c).

- Rapid reduction of parasite densities;
- Rapid resolution of clinical symptoms;
- Effective action against multi-drug resistant *P.falciparum*;
- No documented resistance as yet with the use of artemisinin and its derivatives;
- Few clinical adverse reactions; and
- Reduction of gametocyte carrier rate which may reduce transmission.

The following are the combination therapies currently recommended[20], [21](WHO, 2001c; 2003b; 2004a and d):

- Artemether/lumefrantrine;
- Artesunate (3days) plus amodiaquine (in areas where amodiaquine efficacy remains high);
- Artesunate (3days) plus sulfadoxine/pyrimethamine (in areas where S/P efficacy remains high);
- Artesunate (3 days) plus mefloquine (reserved for areas of low transmission); and
- Amodiaquine plus sulfadoxine/pyrimethamine (SP) (as an interim policy in areas where amodiaquine and S/P efficacy remains high if countries, for whatever reason, are unable to move to ACTs).

It should be noted that there are limitations with the use of the combination of amodiaquine plus SP listed above. These are:

- As both amodiaquine and SP are currently in wide usage as monotherapies it is unlikely that the adoption of this combination therapy will significantly delay the spread of resistance to either drug. Therefore, the adoption of combination therapy with amodiaquine plus SP is likely to be a short-term solution;
- Even in areas where the efficacy of both amodiaquine and SP remain high, their combined use will compromise the useful therapeutic life of both, and thus endanger their potential use as partner drugs for artesunate in ACTs;
- There is currently no replacement for SP as a drug for Intermittent Preventive Treatment (IPT) in pregnancy. Rather than compromise its therapeutic life by using it as a component of combination therapy, SP should be reserved for IPT (see also Section 6.1.2.below); and
- As the process of drug policy change and implementation is resource- and time-intensive (experience shows this might take from one to three years), all efforts for improving access to treatment should be directed towards implementing the most effective and durable treatment policy.

[20] Artemether/lumefrantrine is a fixed single tablet formulation. Artesunate plus amodiaquine, artesunate plus mefloquine and artesunate plus sulfadoxine/pyrimethamine are available as multiple-dose therapy or as co-blistered packed. Amodiaquine plus sulfadoxine/pyrimethamine is only available as multidrug therapy.

[21] The following combinations are not recommended: chloroquine-based combinations (such as chloroquine plus sulfadoxine/pyrimethamine and chloroquine plus artesunate); one day artesunate plus sulfadoxine/pyrimethamine, all mefloquine-based combinations in areas of high transmission, and one day artesunate plus mefloquine.

There are major challenges to the deployment and use of ACT, particularly in Africa. These include the:

- Cost and affordability; and
- Operational obstacles to implementation, such as registration and marketing, supply, and drug quality.

There are also potential constraints, such as the:

- Limited knowledge and use of ACT outside South-East Asia;
- Potential misuse of artemisinin derivatives, risking to compromise their therapeutic efficacy for the treatment of severe malaria;
- Problems with adherence to co-administered (non-fixed) combinations, particularly at the household level;
- Lack of evidence of its effectiveness in delaying development of resistance in areas of high transmission;
- Resource requirements for changing and implementing new treatment policies; and
- Drug supply management, related to limited shelf-life and availability of multiple course therapy packs;
- Concerns regarding safety of artemisinin and its derivatives in pregnancy (see 6.1.2(bi).

3.3.2. Strategies for Improving Access to Combination therapy[22]

3.3.2.1 Drug regulation

Although over the last 3 years around 40 countries, including 22 in Africa, have registered artemisinin derivatives and updated their treatment policies to include ACT as first or second line treatment of uncomplicated malaria, others will follow. New registration may be required, even for drugs that have been used previously and registered as monotherapies, if they are to be co-packaged or co-administered as combination therapies or even in different doses (WHO, 2001b, 2003b and f).

3.3.2.2. Supply and quality

Current production levels of ACTs are insufficient to meet current needs and there is an urgent need to increase production. This will depend on increased demand, requiring governments and donors to indicate their willingness to procure ACTs. There are also only a limited number of producers. Generic substitution, stimulation of domestic production of quality generic medicines should not only increase production but also lead to lower prices through market competition (WHO, 2003b, c and f).

The presence of counterfeit drugs is a major problem in South-East Asia and the marketing of sub-standard drugs, particularly of artemisinin derivatives, is increasing (WHO, 2003b, 2004a). This highlights the need for countries to develop and improve

[22] Access to essential drugs is a key priority for WHO. Four enabling factors need to be firmly in place to increase and sustain access. They are: 1. The rational selection based on a national essential drugs list; 2. Affordable prices for governments, health care providers and consumers; 3. Sustainable financing through equitable funding mechanisms such as government revenues or social health insurance; and 4. Reliable systems incorporating a mix of public and private supply services.

their mechanisms for quality control. In this context, WHO in collaboration with other UN agencies has begun a pilot procurement, quality and sourcing project for artemisinin based antimalarial products in which product dossiers are reviewed and manufacturing sites are inspected to assess compliance with Good Manufacturing Practices (GMP)[23].

3.3.2.3. Affordability and financing

The antimalarial combination therapies are over ten times more expensive than those drugs currently used in Africa as monotherapies. Thus, adoption of combination therapy without increased external financial support will involve higher direct and indirect costs to health services and will be out of reach for many developing countries, especially those on Africa, south of the Sahara.

A WHO Informal Consultation concluded that no single strategy is likely to solve the problem of access to ACT and that a pluralist approach using several strategies to serve different needs and different groups is likely to achieve the best results. These strategies included price regulation, price competition, bulk purchasing, differential pricing for low income countries, and price negotiations. Options need to be evaluated and a careful mix of strategies selected according to the specific situation (WHO, 2003f).

The first strategy for ensuring equal access to antimalarial drugs, including ACTs, is to optimize government funding and avoid that the major part of the health budget serves only urban centres and better-off populations. However, government financial strategies alone are unlikely to be sufficient for malaria control and external support will be needed to help finance antimalarial drug supplies.

3.3.3. Monotherapy

Monotherapy with chloroquine is recommended for the treatment of uncomplicated falciparum malaria in areas of Central America and Hispaniola where *P.falciparum* is still sensitive to the drug. (WHO, 2001a ; see also Section 6.5. below). It also remains the treatment of choice for vivax malaria, in the majority of areas where this parasite is prevalent (see section 2.4.7. for *P.vivax* resistance and Section 6.5. 2. For management of vivax malaria).

3.4. Management of severe malaria

3.4.1. The Principles

Malaria can progress to a catastrophic disease in a short time and, to date, it is not possible to predict which patients are at risk. Severe malaria disease is not readily distinguishable from other severe diseases, such as severe pneumonia, meningitis, bacteraemia, that require very different therapies.

Optimal care for severe malaria, therefore, requires well developed diagnostic facilities and intensive care. Centralizing these capabilities may be logical in a managerial sense but will not benefit the people at greatest risk. The WHO Expert Committee on Malaria therefore concluded that it was important to enable peripheral health services to provide

[23] see <www.who.int/medicines/organization/qsm/activities/pilotproc/malaria/pilotprocmal.shtml>

emergency treatment by means of guidelines, training, and the regular supply of medicines and diagnostic supplies and equipment (WHO, 2000a).

At the periphery, the priority requirement is the rapid recognition of the signs and symptoms of severe malaria that should lead to emergency care or referral to a higher level of care. These are a history of fever plus at least one of the following: prostration, altered consciousness, lethargy or coma; respiratory distress; severe anaemia; convulsions; inability to swallow; persistent vomiting, dark or limited urine (adults only).

3.4.2. Choice of drugs

Data indicates that the efficacy of intravenous (iv) quinine and intramuscular (im) artemether is similar under hospital conditions (WHO, 2000d; 2004a). However, the more complicated dosing schedule of iv quinine and the requirement for the monitoring of both cardiac function and glucose levels make im artemether the drug of choice for severe malaria in areas where intravenous drug administration is impossible. Intramuscular artemether is included in the WHO complementary model list of Essential Drugs as a reserve antimalarial (WHO, 2003g).

Artesunate suppositories have now been produced according to Good Manufacturing Practice. Experience with these products is limited but their use may be appropriate for emergency treatment prior to referral at health facility and community levels in severely ill patients who are unable to swallow oral medication when im artemether (or iv quinine) is not available (WHO, 2000d; UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, 2004). If artesunate suppositories are used, patients should be moved, as soon as possible, to a facility where im or iv therapy can be commenced. In situations where the patient can not be moved, continued treatment with rectal artesunate is considered appropriate (at least in epidemic situations) until the patient can take oral medication (WHO, 2004a). As evidence of the efficacy and safety of suppository formulations during operational use is limited, this formulation should only be considered when alternatives are not available.

3.5. Referral systems

The WHO Expert Committee recommended that, in general, referral systems should be strengthened to ensure that referred patients receive prompt care at facilities with more specialized facilities. It has to recognized, however, that referral to higher levels of the health services may be costly both in time and money. Referral of patients with minimal resources to another level of the health service may result in no further treatment being given since patients may not reach the next level of care. Wherever feasible, capacity to manage severe illness should be available as close to the periphery as possible (WHO, 1993b; 2000a).

3.6. Home treatment

Home based treatment of malaria is extremely common in all malaria endemic countries. In Africa, more than 70% of malaria episodes in rural areas and > 40% in urban areas are self-treated with drugs bought from local private drug sellers. Help from the public health services is only sought if the home based treatment is ineffective (WHO, 1998c,

2003h). The main reasons are inaccessibility of the health services and limited time, transport or funds to visit them.

Although mothers and health providers are able to recognize symptoms associated with uncomplicated malaria, fewer than 15% of episodes are treated correctly. Malaria patients often receive ineffective, inappropriate or expired drugs in incorrect doses (2003h).

The following approaches have been shown to improve home-based management of malaria in research settings (WHO, 1998c; 2003h) and have the potential for improving the rational treatment of malaria close to the home (WHO, 2004e). They have not yet been widely used operationally:

- Unit dose packaging of full course therapy, and pictorial labelling;
- Training of local communities, especially mothers and other community resource persons;
- Training of shop keepers, drug vendors, chemical sellers and drug shop owners; and
- Community-targeted IEC for behavioural change.

Implementation of these measures places heavy demands on resources, planning and management. It requires intensive support from the health services, particularly those at the periphery. The community health workers or their equivalents have a major role to play in improving treatment close to the home but unpaid volunteers are frequently lost to the system. Increased investments are required to make community based antimalarial treatment programmes sustainable.[24]

A number of malaria endemic countries are now in the process of scaling up these approaches as a means of improving access to effective antimalarial medicines.

3.7. The role of the private sector

It is widely accepted that governments can not be the sole provider of health care. In many malaria endemic areas, it is common practice that national and district health administrations are contracting NGOs for health care delivery for malaria and this is actively encouraged by international and bilateral agencies. The private profit-making sector also plays a significant role in health care delivery and is, in some communities, the sole provider of life-saving medicines through drug sellers and pharmacies[26]. Although it is an important channel of delivery of antimalarials, this informal sector is a source of some of the major challenges to malaria control. As it comprises a large number of unregulated and unregistered drug sellers, investment in their training may be costly. More importantly, control over drug quality and price is difficult to impose. Promoting rational prescribing in the private sector is also notoriously difficult as prescribers are influenced by many factors, including patient demand, drug advertising

[24] Mendis, K., Bosman, A., Olumese, P., Ringwald, P., Ondari, C. and Were, W (2003) Effective delivery methods for malaria treatment. In Reducing Malaria's Burden: Evidence of Effectiveness for Decision Makers. Global Health Council Technical Report - December 2003 pp39-45.

and drug quality. Thus where health systems are weak, the private sector is both part of the solution and problem.

While their motive is profit, the private sector offers the best option for accessing treatment to some communities. It is therefore imperative to engage and train local medicine vendors and retail shopkeepers about disease recognition, appropriate treatment and referral practices, making them an integral component of home management of malaria. However, the public sector's stewardship role is critically important to ensure that medicines and services delivered in the informal private sector are of good quality. There is therefore a need for an efficient regulatory authority that critically reviews all applications for market approval, with strong inspection and enforcement. Such a system can exclude many irrational therapeutic alternatives from the market (WHO, 1993a and b).

4. PREVENTION

4.1. Use of antimalarial drugs for prevention

The role of chemoprophylaxis in malaria control has been considerably reduced in the last two decades. In the past, WHO recommended that pregnant women and young children in malaria-endemic areas should receive a full antimalarial treatment on their first contact with the antenatal and postnatal services, followed by weekly chemoprophylaxis with chloroquine (WHO, 1986). The implementation of this policy was limited by a number of factors, including: (i) spread of chloroquine resistance, (ii) poor compliance with a weekly regimen throughout pregnancy and childhood, (iii) adverse drug effects; (iv) the contraindication of alternative drugs during different stages of pregnancy and childhood and (v) cost (WHO, 1994).

Chemoprophylaxis is now only recommended, as a short term measure for international travellers to malaria endemic areas (see Section 6.6. below) and for soldiers, police and labour forces serving in highly endemic areas. It is no longer recommended for young children or pregnant women (WHO, 1996b, 2000a, 2001a). For the latter group, intermittent preventive treatment (IPT) is now the strategy of choice (see Sections 6.1.2. and 6.2.2 below).

4.2. Vector Control

Vector control remains the most generally effective measures to prevent malaria transmission, and as such it is one of the four basic technical elements of the Global Malaria Control Strategy. There are basically two kinds of mosquito vector control. Those directed against the adult and those against the aquatic stages. As a process for managing vector populations to reduce or interrupt transmission of disease, WHO recommends integrated vector management (IVM). IVM is a systematic approach to planning and implementing disease vector control in an inter-sectoral context (see 4.2.6.) It entails the use of a range of interventions of proven efficacy, separately or in combination for the implementation of locally cost-effective control.

The control options against the adult mosquito are:

Indoor residual spraying (IRS) with insecticides;
Insecticide-treated material such as mosquito nets (ITNs); and
Ultra-low volume space spraying (fogging) (generally not recommended for malaria control, see section 4.2.5. below).

These vector control methods vary considerably in their applicability and cost, as well as the sustainability of their results.

Currently, indoor residual spraying (IRS) and insecticide treated nets (ITNs) are the mainstay in malaria prevention. As vector control interventions, both are effective in preventing malaria morbidity and mortality in a range of epidemiological settings. In reducing densities and infectivity of malaria vectors, they reduce overall transmission and protect all individuals within a community.

4.2.1. Indoor residual spraying (IRS).

IRS is a powerful method of vector control and is especially effective for the prevention and the control of malaria. Its use in the last 50 years has played a major role in the elimination of malaria from southern Europe and the Mediterranean, Russia, large parts of Asia and Latin America and in many areas of South Africa. Conversely, the interruption of spraying in Latin America, Sao Tome and Madagascar had a demonstrable detrimental effect on the malaria situation[25].

WHO recommends the use of IRS provided that it is timely, selectively targeted according to the local environmental situation, and where there is documented evidence that it can be successful. The non-selective coverage of IRS, as used during the eradication era is no longer a recommended strategy (WHO, 1993a, b; 2000a; 2004f).

The conditions for the success of IRS are that:

The population lives in huts or houses with sprayable walls;
The local vector species enters and rests inside the dwellings often enough and for long enough to absorb the insecticide;
The vector species is susceptible to the insecticide being used;
The insecticide is applied safely;
Spraying is targeted according to local environmental factors, including topography and seasons;
The proportion of houses and rooms sprayed is high enough (>80%) to ensure that the majority of mosquitoes are exposed to the insecticide, thus, producing the phenomenon known as "mass effect" where the small proportion of the targeted community not covered by the intervention also benefits because of the overall reduction in the risk of transmission;

[25] Lengeler, C. and Sharp, B. (2003). Indoor residual spraying and insecticide-treated nets, In Reducing Malaria's Burden: Evidence of Effectiveness for Decision Makers. Global Health Council Technical Report - December 2003 pp17-24; and
Mouchet, J., Carnevale, P., Coosemans, M., Julvez, J., Manguin, S. Richard-Lenoble, D. and Sircoulon, J (2004). Biodiversité du paludisme dans le monde. John Libbey Eurotext, Montrouge, France

It is supported by adequate planning and, an infrastructure that allows timely delivery and application of the insecticides by well trained and supervised workforce; and
Activities are monitored and evaluated.

(i) Choosing the insecticide

WHO[26] has produced guidelines to assist countries in the choice of the insecticide to be used. This choice should be based on the following criteria:

The surface to be sprayed;
An adequate residual effect that covers the entire transmission season;
High susceptibility of the vectors to the selected insecticide. In the absence of data on insecticide resistance, one should be chosen that is being or has not been used locally for agricultural purposes and is among the 12 insecticides recommended by WHO for IRS[28];
Good stability for storage, easy formulation and application;
Acceptable cost;
Safety for humans and domesticated animals is an absolute requirement;
Good acceptability by the population (e.g. lack or minimal odour and lack of staining on household surfaces); and
Effectiveness against other household pests such as bed-bugs, fleas, cockroaches is a major advantage as it will lead to greater acceptance by the population.

DDT meets most of these criteria. It is the only organochlorine insecticide that is still recommended for indoor residual spraying. It is highly persistent and has a long residual effect of over 6 months on most household surfaces. It is currently cheaper than the alternatives but the relatively high transport costs may make it a costlier option in some circumstances. It leaves a white residue on the sprayed surface that has led to high refusal rates in some areas.

DDT has been banned for agricultural use in many countries on the grounds of environmental pollution and potential toxicity for humans. However, WHO recommends its use[28] (WHO, 2000a; 2004f, g, h) for disease vector control provided it is:

Used only for indoor spraying;
Proven to be effective;
WHOPES product specifications are met; and
The necessary safety precautions are taken for its use and disposal.

Any of the insecticides recommended for IRS by WHO can be an alternative to DDT, if they are affordable and found to be effective against the mosquito vector. The choice will

[26] Najera, J.A. and Zaim, M. (2001) Malaria Vector Control: Insecticides for Indoor Residual Spraying. WHO/CDS/WHOPES/2001.3; and
Najera, J.A. and Zaim, M. (2002) Malaria Vector Control: Decision making criteria and procedures for judicious use of insecticides. WHO/CDS/WHOPES/2002.5

depend on the local situation and should be based on WHO guidelines and specifications[28].
Certain synthetic pyrethroids provide an effective alternative to DDT as they have a residual action of 2-6 months, are safer to apply than most other insecticides, resistance to them is limited at present, and they are less bulky to store and transport. Some organophosphates (malathion, fenitrothion and pirimiphos-methyl) and carbamates (bendiocarb and propoxur) are also recommended by WHO. The residual action varies between 2-6 months dependant of the insecticide and surface being sprayed. The organophosphates are more costly and, as acetyl-cholinesterase inhibitors, generally more toxic than DDT to humans. Fenitrothion is the most toxic of the insecticides currently used for indoor residual spraying and its use requires protective clothing and regular monitoring of cholinesterase activity in the spray-men.

(ii) Constraints to IRS implementation

The key constraint to implementing IRS programmes is the need for long-term human and financial resources for regular spraying campaigns. This is especially true where the level of transmission is so low that it becomes increasingly difficult to justify funds for this purpose. There are recent examples from Mozambique and Zambia of successful IRS activities being funded by commercial companies for the benefit of their employees and local communities[27]. This model may be applicable in other countries.

IRS is relatively demanding in terms of planning, logistics, infrastructure, skills required, and coverage levels that are needed for a successful operation. Reaching areas without roads, particularly in the rainy season may be exceedingly difficult.

Other major constraints are mosquito resistance to insecticides and the resistance of populations to having their homes sprayed.

4.2.2. Insecticide Treated Nets (ITNs)

(i) Impact on morbidity and mortality

During the last 15 years a large body of evidence has been compiled on the key technical and managerial aspects of ITNs as well as on their efficacy and effectiveness. A systematic review of 22 randomized controlled trials showed a consistently high impact of ITNs[27],[28] in preventing malaria episodes. The measured impact was substantially, but not significantly, higher when the control group had no nets at all. In

[27] Lengeler, C. and Sharp, B. (2003). Indoor residual spraying and insecticide-treated nets, In Reducing Malaria's Burden: Evidence of Effectiveness for Decision Makers. Global Health Council Technical Report - December 2003 pp17-24;
Mouchet, J., Carnevale, P., Coosemans, M., Julvez, J., Manguin, S., Richard-Lenoble, D. and Sircoulon, J (2004). Biodiversité du paludisme dans le monde. John Libbey Eurotext, Montrouge, France

[28] Lengeler, C (2003) Insecticide-treated bednets and curtains for preventing malaria. Cochrane Database of Systematic Reviews.

areas of unstable malaria transmission, the impact against *P. falciparum* appeared to be higher than against *P. vivax episodes*.

Only one randomized controlled trial studied severe disease as an outcome.[29] A reduction of 45% in the frequency of severe malaria was observed following the introduction of ITNs. These findings highlight the potential for ITNs to reduce malaria case-loads in hospitals in endemic areas. Evidence on impact on childhood mortality is presented in section 6.2.2.

ITNs have been shown also to reduce the burden of malaria and anaemia in pregnant women and young children (see below sections 6.1., 6.2., and 6.3.).

(ii) Implementing ITN programmes

In contrast to IRS, many ITN implementation models exist although so far there is limited experience with large-scale distribution of free ITNs through the public health services, except during complex emergencies. In contrast, there is long experience in East Asia of insecticide treatment of nets owned by householders being provided as a free public service with high coverage. Therefore, the Roll Back Malaria Partnership developed in 2002 a strategic framework for scaling up of ITN programmes in Africa (WHO, 2002c).

This strategy includes the development and support of:

- A commercial market for ITNs within a public-private partnership. For the public sector, this requires creating an "enabling environment " including adequate legislation, removal of taxes and tariffs on nets, netting materials and insecticides, and a vigorous campaign to create a demand for generic ITNs;
- Sustained targeted subsidies for vulnerable groups (primarily pregnant women, infants and young children), either through the direct subsidy of the products or through a voucher system which enables targeted groups to access subsidized ITNs from local commercial distributors;
- Public sector implementation, when required, to reach defined target populations e.g. in cooperation with immunization programmes; and
- The need for a high level of national co-ordination between all stakeholders (the commercial sector, public sector, NGOs, researchers, as well as bilateral and multilateral organizations) involved in ITN interventions. Such co-ordinated action has led already to a highly successful and widespread implementation of ITNs in the United Republic of Tanzania[27].

[29] Neville, C.G., Some, E.S., Mung'ala, V.O., Mutemi, W., New, I., Marsh, K. *et al.* (1996). Insecticide-treated bednets reduce mortality and severe morbidity from malaria in children on the Kenyan coast. Tropical Medicine and International Health, 1: 139-146.

4.2.3. Challenges

The major challenges to the implementation of ITN programmes are:

- The creation of the "enabling" environment by the public sector;
- The provision of an improved supply of affordable ITNs to the majority of rural populations;
- The need to regularly treat nets every 6-12 months with insecticide. This has been a problem in many programmes to date. The development and commercialization of long lasting insecticidal nets offers considerable promise; and
- Resistance of mosquitoes to the pyrethroids used to impregnate the nets. Some degree of resistance is found in West Africa but also in South Africa and southern Mozambique where selection is considered to be a result of agricultural use. Although there is so far no evidence that insecticide resistance has reduced the effectiveness of ITNs for malaria prevention, this is a subject of growing concern.

4.2.3. Comparing the impact of IRS and ITNs

In recent years, a number of trials have been conducted to compare the health impact of IRS and ITNs, particularly related to their cost-effectiveness[27, 29]. Both IRS and ITNs were found to be effective in a large number of epidemiological settings. Overall, the health impact of ITNs was slightly better than IRS, although the differences were not great in most settings and cannot be used to justify one approach over the other[27]. The difference in costs of IRS and ITNs was not large. However, all studies analysed included the cost of providing nets. If the cost of the nets was borne by the users, ITNs would be more expensive to the end-user and less expensive than IRS for a government provider. Recently, the prices of long-lasting insecticidal nets (LLINs), which retain insecticidal activity for about four years, have come down, and it may well be that in many settings, these will prove cheaper than both IRS and conventional ITNs.

Choosing between IRS and ITNs is therefore largely a matter of operational feasibility and availability of local resources rather than one of malaria epidemiology or cost-effectiveness. In general, ITN would be the preferred intervention in areas of intense transmission, where it is not possible to envisage a time limit of the operations.

4.2.4. Larval control (control of aquatic stages)

Larval control can be achieved by environmental management and, the use of larvicides or larvivorous fish. A variety of larvicides are or have been used for malaria control, including chemicals and insecticides of biological origin varying in their modes of action, efficacy, safety, formulations, cost and availability. The evidence base of the impact and cost-effectiveness of this strategy is limited. Larval control is indicated only for vectors which tend to breed in permanent or semi-permanent water bodies that can be identified and treated with relatively short cycles and where the density of the human population to be protected is sufficiently high to justify the treatment of all the breeding places (WHO, 2000a; 2004f). These prerequisites practically reduce the indications for larval control to some urban areas, labour or refugee camps, and development projects. Such programmes may be complementary to environmental measures aimed at controlling malaria and other mosquito-borne diseases or nuisance mosquitoes within integrated vector management.

4.2.5. Ultra-low volume space spraying (fogging)

ULV space spraying (fogging) is generally not cost-effective as a means of malaria vector control because:

Operational costs are high;
The residual effects are low;
Other more cost-effective methods are available; and
It is more often than not used as a cosmetic measure without proper technical evaluation of its appropriateness or impact (WHO, 2004a).

It may however, be considered for use in exceptional circumstances such as emergency situations in refugee camps. In this case, if the target mosquito species is exophilic, treatment is applied outdoors wherever the mosquitoes rest. If the vector is endophilic, treatment is applied both indoors and outdoors. Suitable insecticides are applied as cold aerosol sprays or as thermal fogs. Where possible, applications should coincide with the flying times of the local vector.

4.2.6. Integrated Vector Management

(i) The Rationale

Although vector control has a proven record of reducing the burden of malaria and other vector borne diseases by preventing, reducing or eliminating transmission, its benefits are far from being realized because:

- The skills to manage and implement vector control, remain scarce, particularly in those poor countries that are most need of vector-borne disease control. This has led to unsuitable and poorly targeted interventions with insufficient coverage and wastage of resources;
- The use of insecticides in agriculture and poor management of insecticides in public health have contributed to insecticide resistance in disease vectors; and
- Development programmes, including irrigation and dam construction, road building, forest clearance, housing development and industrial expansion have increased the risk of vector-borne diseases. Co-operation between these sectors and those of health have been poor or in-existent.

(ii) WHO Strategic Framework

In response to this situation, WHO has developed a Global Strategic Framework for Integrated Vector Management (WHO, 2004i). This approach is based on the premise that effective control is not the sole preserve of the health sector but requires the collaboration of various public and private agencies as well as community participation (WHO, 1993a).

Characteristic features of integrated vector management include:

- Evidence based decision making that allows the adaptation of strategies and interventions to local ecology, epidemiology and resources, guided by operational research and subject to routine monitoring and evaluation;
- The use of a range of interventions, often in combination and synergistically;

- Collaboration within the health sector and with other public and private sectors that impact on vectors, particularly the development sector;
- Engagement of local communities and other stakeholders working nationally as well as within the community;
- A public health regulatory and legislative framework; and
- The development of an infrastructure, financial resources and adequate human resources to manage and implement integrated vector control programmes at the national and local levels.

Monitoring insecticide resistance

The assessment of vector susceptibility to insecticides is a basic step in the planning and the epidemiological evaluation of any malaria control programme including vector control. Such testing should be carried out to:

Assess the base-line susceptibility of the different vectors in the area:
Monitor the possible changes throughout the period of insecticide application;
Assess the vectors' susceptibility to potential alternative insecticides if there is a need for change; and
where possible identify the mechanisms of resistance and cross resistance patterns.

WHO has developed a practical test to detect resistance in mosquitoes (WHO, 1998D) and organizes the production and distribution of standard kits and insecticide impregnated papers[30]. Tests exist for all insecticides recommended for malaria control by WHOPES i.e. DDT, malathion, fenitrothion, propoxur, bendiocarb, alpha-cypermethrin, permethrin, deltamethrin, lambda-cyhalothrin, cyfluthrin and etofenprox.

Baseline information on susceptibility requires the determination of dose-response regression lines from tests with a range of insecticide concentrations. In a normal susceptible population the distribution of the logarithms of the doses required to kill individual insects is normally distributed. Hence the mortalities of samples of insects give a straight line when plotted on probit mortality-log concentration paper. Such a line gives the concentrations which would produce specified mortalities, e.g. $LC_{50,}$ $LC_{90,}$ $LC_{99.9.}$ Low mortality in the controls is an indication of the validity of the test. Tests with control mortality exceeding 20% are considered invalid. When the control mortality is between 5-20%, the test mortalities should be corrected using Abbott's formula (WHO, 1998d).

For practical purposes, it has been found useful to establish a "discriminating concentration", i.e. a concentration that would kill all susceptible individuals. Survivors at such a concentration would clearly be resistant. This discriminating concentration has been commonly established as double the estimated $LC_{99.9}$ as determined for a given species in different areas of its distribution. The discriminating concentration of insecticides have no relationship to the field application rates. They are only used for monitoring insecticide resistance in the mosquito population.

The tests should be carried out indoors in premises which are free from contamination with insecticides, avoiding low relative humidity and extremes of temperature. Female mosquitoes used for the test should ideally be non-blood fed of known age (24-48 hours

[30] These tests can be obtained through Strategy Development and Monitoring for Parasitic Diseases and Vector Control, WHO, Geneva, Switzerland.

post-emergence) issued from larvae and/or pupal collections or first generation from wild caught females. When only field-collected females can be used, their physiological state (unfed, blood-fed, semi-gravid, gravid) should be recorded (WHO, 1981; 1998d). Although it is recommended to use female mosquitoes only, it is recognized that there is seldom a large difference in susceptibility between the sexes.

5. CONTROL OF MALARIA EPIDEMICS AND MALARIA IN COMPLEX EMERGENCIES

5.1. The Rationale

Malaria epidemics are among the most serious public health emergencies with which health officials have to deal. Typically, they occur with little or no warning in areas where the health system is unprepared. In most situations, epidemic conditions take some weeks to build up, theoretically allowing time for preventive action. Even when an epidemic occurs, it takes several weeks to reach its peak, so that some effective control is possible if implemented in the early stages of epidemic development.

The most important factor in reducing the impact of an epidemic is a timely response with the implementation of effective control measures once it has been detected. The longer the epidemic goes undetected, the higher will be the cost in terms of morbidity and mortality. Control measures are inherently costly. If they are implemented around the epidemic peak, there is little or no benefit in terms of the deaths averted. Implementation of control measures with a short delay after the epidemic has been detected will have some benefit. The maximum impact is however, when measures are implemented at the very early stages. This requires the development of a cost-effective monitoring system that includes forecasting, early warning and detection that leads to either: the very early recognition of epidemics and immediate implementation of control measures; or the implementation of preventive control measures before the epidemic starts.

It is therefore essential that national authorities in epidemic-prone countries develop a strategic plan for epidemic prevention and control that can be used as a basis for a preparedness plan of action to be developed by the regional/provincial health services in epidemic-prone areas. The key to be able to react decisively and rapidly to prevent and control a malaria epidemic is "be prepared".

The following recommendations are the result of a series of WHO informal consultations held from 2000-2003.

5.2. Preparedness Plan of action

The objectives of the preparedness plan of action (WHO, 2004a) should be to:

- Identify the epidemic-prone areas and the populations at risk to allow the prediction and detection of epidemics, the targeting of rapid response and the planning of the logistics of this response;

- Where feasible, forecast and prevent malaria epidemics by vector control measures; and
- Detect the early appearance of the epidemic and to control it by rapid case management and, where possible, vector control.

5.3. Identification of epidemic-prone areas and populations at risk.

Geographical information systems (GIS) are increasingly being used and currently evaluated for estimating populations at risk and decision-making in malaria epidemic-prone areas. GIS are resource demanding. Therefore careful consideration should be given as to how GIS should be used in a country, and by whom, and what level of GIS development would be required to meet the immediate control programme requirements (WHO, 2002d). In their absence, hard copy and sketch maps based on local expert opinion should be used to delimit the epidemic area, and plot the distribution of cases, the local population, the availability of health services and any environmental changes (WHO, 2004a).

5.4. Long range forecasting (LRF), early warning (MEWS) and early detection (EDS).

The continuum of LRF-MEWS-EDS has the potential to measure the build-up towards a possible epidemic with decreasing lead time (10-14 months to 1-2 weeks) but increasing accuracy and spatial resolution (continental-country-district-local) of prediction. The information provided by these three surveillance mechanisms is sequential and complimentary, allowing health services to prepare for and mobilize appropriate prevention and control activities in a timely manner (WHO, 2001d, 2002d, 2004a). Guidelines to establish, plan and implement these systems have been developed by a WHO informal consultation (WHO, 2002d)

However, many programmes will not have the resources implement all stages of the continuum. Few countries are able to collect and analyse the relevant data and report in a timely manner to implement effective control or prevention. The key to success will be capacity building, realistic planning and community awareness.

It is more realistic in such situations, to start simply by giving priority to improving surveillance with a limited number of validated indicators and increase the complexity of the system as staff capabilities improve, new information and techniques become available from research and collaboration with other partners, and sources of information are established (WHO, 2004a).

Climatic indicators can be used to predict the timing of an impending epidemic. Excessive rainfall is usually associated with epidemics in arid and semi-arid areas where the limiting factor for malaria transmission is the absence of breeding sites. The combination of increased rainfall and higher temperatures are indicators for malaria epidemics in highland and desert-fringe areas.

Vulnerability indicators predict the potential severity of epidemics, not the timing. These include:

Prolonged drought;
The migration of non-immune populations into malaria risk areas
Poor nutritional status of the population;
High incidence of other diseases that may compromise health status e.g. HIV/AIDS;
Breakdown of control activities;
Drug resistance of the parasite;
Environmental change that increases the risk of transmission, such as the construction of dams, agricultural projects, and flooding or drying out along river margins.

(i) Long-range forecasting[31] still remains predominantly research-based. While more accurate prediction models and systems continue to be developed, simple and crude methods of warning can already be used to advantage, allowing prospective monitoring and validation. For instance, in Southern Africa, SAMC is translating seasonal climate forecasts into seasonal malaria forecasts.

(ii) Early warning systems (MEWS) are based on monitoring of climatic indicators, population vulnerability factors and operational and environmental factors to detect when conditions suitable for an epidemic have already appeared at a given time and place. They have the potential of predicting epidemics weeks to months in advance, allowing surveillance to be enhanced and preventive and control measures to be directed to specific areas.

Although MEWS have started the transition from research projects into public health application, their full practical potential has not yet been achieved. Such systems are showing good promise in Southern Africa where some countries are routinely using rainfall, temperature and population vulnerability as indicators for early warning of malaria epidemics, and others are also making regular assessments of drought and food security status.

(iii) Early Detection Systems (EDS) attempt to detect the beginning stages of an epidemic by measuring changes in the incidence of malaria morbidity and mortality. They offer very little lead-time (days to weeks) for preparation of control measures.

However, such data can only be used for the early detection of a potential malaria epidemic if:

Data collection and notification are timely;
Data collection is representative;
Data analysis is timely; and
Data interpretation provides an accurate indication of an epidemic occurring.

In most countries, the health information system routinely collects and reports health data, including the incidence of malaria, on a monthly basis and sometimes even on a quarterly basis. The time taken to report this data to the higher level (e.g. from health

[31] Long range forecasting is based on El Niño Southern Oscillation (ENSO) indices and climate forecasting.

care facilities to the district management team) is at least 10 days and most of the time significantly longer. Experience shows that malaria epidemics develop relatively quickly and have an average duration of 3-4 months. It is obvious, therefore, that a monthly reporting system cannot capture, at an early stage, an increase in suspected malaria cases that is indicative of an emerging epidemic. This situation is compounded by the fact that peripheral health workers are not trained to analyse the data they are generating and, as a consequence, do not usually take any decision based on it. As a result, the health services can not mobilize the resources needed to control the epidemic in a timely manner.
The WHO Informal Consultation in 2003 (WHO, 2004a) therefore recommended that, where possible, a weekly system of reporting should be introduced. However, it was recognized that not all countries are currently in a position to do this. In these cases, it may be more appropriate to begin with monthly reporting and ensure that quality of the data and its reporting is improved.

In countries where laboratory diagnostic facilities are poorly developed, it may be cost-effective in epidemic-prone areas to select health centres with laboratory facilities as sentinel sites for surveillance. Data from these centres could then be provided to the district and provincial authorities on a weekly basis (WHO, 2004a). Complete reliance should not be placed on surveillance by such centres since it is recognized that epidemics may develop in areas outside their reach.

Integration of malaria EDS into more general disease surveillance systems should be encouraged as it is likely to be beneficial in terms of improving the quality of data and the efficiency of the system. This is contingent on (i) appropriate training being provided at the peripheral level and (ii) surveillance approaches being consistent with malaria control needs.

Attempts have been made to identify epidemic thresholds[32] that can clearly define normal variations and abnormalities in malaria incidence against the previous experiences of the disease in a particular area. Given the uncertainty of the appropriateness of these thresholds, the area of threshold development and evaluation should be a priority for further review (WHO, 2004a)

5.5. **Case management** (WHO, 2004a)

The drugs used to treat malaria in epidemics should be highly efficacious (at or above 95%), safe and offer good patient compliance. Complete treatment should be given in all circumstances

Currently, ACTs are considered the only appropriate drugs[33] for the treatment of uncomplicated malaria in *P. falciparum* epidemics and in mixed *P. falciparum/P.vivax* epidemics (with the limited exception of Central America and Hispaniola where *P.falciparum* remains sensitive to chloroquine and sulfadoxine/pyrimethamine).

[32] This is relatively easy in areas with functioning health information systems, good health care coverage, historical epidemiological data for several years, a history of epidemics and stable population.
[33] Although currently ACTs is the only drug treatment that meets the criteria for use during malaria epidemics, experience of their use in these situations is relatively limited.

Chloroquine remains the drug of choice in vivax only epidemics. Anti-relapse therapy with primaquine should only be considered once the epidemic subsides.

Intramuscular injectable artemether is the drug of choice for the management of severe disease because quinine use is impractical in most epidemic situations. If injectable artemether is unavailable, the use of artesunate suppositories is recommended for emergency use in the periphery when severely ill patients are unable to swallow oral medication. In conditions where referral is not possible, continued treatment with rectal artesunate is recommended until the intake of oral drugs is possible.
Mass treatment of fever cases (MFT) with ACT as a strategy to reduce mortality is appropriate once malaria has been established as the cause of the epidemic. However, there is no evidence to support the use of mass drug administration (MDA)[34].

5.6. **Vector control** (WHO, 2004a)

Whilst the first priority in an epidemic is the prompt and effective diagnosis and treatment of people with malaria, vector control if well planned, targeted and timely, can make an important contribution to reducing the risk of infection and saving lives.

Anti-vector measures for epidemic prevention and control can only be implemented effectively if supported by an infrastructure of well-trained personnel, adequate supplies and equipment, preparedness planning, and supervision and evaluation. Creating such an infrastructure during an epidemic is not feasible but epidemic-prone countries that do not have this infrastructure should plan to develop this capacity

Implementation of anti-vector measures in epidemic situations is most cost-effective when used for (i) prevention, and (ii) control at the very beginning of an epidemic, and if high (>85%) coverage can be obtained. It can be used preventively in situations such as (i) against a resurgence of malaria in controlled areas, (ii) to prevent a gradual build-up of transmission over years and/or a surge in seasonal transmission, and (iii) when targeted to communities where an epidemic is expected soon.

5.6.1. Indoor residual spraying (IRS)

IRS is especially well adapted to epidemic prevention and response. The criteria for using IRS and the choice of insecticides in epidemic and emergency situations are the same as those described in Section 4.2 1 above.

5.6.2, Insecticide treated mosquito nets (ITNs)

There is limited evidence on the impact of treated mosquito nets for epidemic prevention and control. The community use of ITNs in most epidemic-prone areas is limited and the distribution of ITNs might not be practical given the urgency of implementing epidemic control measures. The effectiveness of ITNs is dependent on behavioural change. This requirement limits their suitability in most epidemic situations as ITNs (or untreated nets) are often not used in the long non-transmission periods.

[34] Mass Drug Administration (MDA) is the indiscriminate distribution of treatment to all of the population at risk.

However, in some circumstances the use of ITNs for prevention and control may be quicker to implement than IRS, such as (i) where ITNs are readily available and staff experienced in implementing ITN are already in place, (ii) where a high level of coverage of untreated nets has already been achieved and the infrastructure for timely treatment (ideally free of charge) exists, (iii) in refugee camps together with other personal protection measures; and (iv) in emergencies with scattered displaced populations where IRS is impracticable.

5.6.3. Larval control and UV fogging (WHO, 2004a)

Larval control is unsuitable for the control of epidemics but it may be useful for prevention in exceptional circumstances, where breeding sites are few, permanent, identifiable and accessible. There is no evidence to support the general use of UV space spraying (fogging) as a means of epidemic prevention and control except for the limited use in refugee camps.

6. SPECIAL PROBLEMS

6.1. Pregnant women

6.1.1. The burden

(i) Plasmodium falciparum

In areas of *P. falciparum* transmission, pregnant women are at high risk of malaria illness and death. In Africa alone, it is estimated that approximately 25 million become pregnant each year and are at risk (WHO 2004j)

Malaria's ill effects on pregnant women differ according to transmission and immunity levels. In areas of stable and intense transmission, the principal effects are associated with malaria-related anaemia in the mother and with the presence of parasites in the placenta. The resultant impairment of foetal nutrition contributes to low birth weight (LBW), which is a leading cause of poor infant survival and development in Africa (WHO, 2000a, 2004j).

Pregnant women who reside in areas of low or unstable malaria transmission have little or no immunity to malaria, and their risk of developing severe disease as a result of malaria infection is two to three times greater than that of non-pregnant women living in the same area. In these areas, pregnant women may die as a direct result of severe malaria or as an indirect result of malaria-related severe anaemia. In addition, malaria infection of pregnant women may result in a range of adverse outcomes, including spontaneous abortion, neonatal death and LBW (WHO, 2000a; 2004j).

Even asymptomatic infections frequently worsen anaemia which is more common in pregnant women than non-pregnant women.

HIV infection diminishes a pregnant woman's ability to control *P. falciparum* infections. (for details see Section 6.4 below).

(ii) Other malaria species

The effects of the *P. vivax, P. malariae* and *P. ovale* in pregnancy are less clear. A study among non-immune pregnant women in Thailand reported that *P. vivax* malaria during pregnancy is associated with maternal anaemia and LBW but to a lesser extent than *P. falciparum*[35]. Studies are needed to better define the effects of these parasites on the health of pregnant women and new-borns.

6.1.2. Policy for malaria prevention and control

The following recommendations are based on the conclusions of a series of WHO informal consultations, the 20th Expert Committee and the policy framework for malaria prevention and control developed by WHO/AFRO in 2004 (WHO, 2004j).

(i) Chemoprophylaxis

Chemoprophylaxis in pregnant women is no longer recommended (WHO, 2000a: 2001b¸2004j). For the rationale see Section 4.1.1. above.

(ii) Intermittent preventive treatment (IPT)

IPT, based on the directly observed administration during antenatal visits of a fully effective treatment dose of an antimalarial drug at predefined intervals after quickening, has been shown to reduce the burden of malaria in pregnant women in Africa. Such a strategy has been shown to be widely acceptable and coverage of up to 80% can be achieved (WHO, 2000a, 2003i, 2004j).

In areas of stable (moderate to intense) transmission, it is recommended that all pregnant women should receive at least 2 doses of IPT. Where *P. falciparum* is sensitive, the most effective drug for IPT is sulfadoxine-pyrimethamine (SP) because of its safety for use during pregnancy, its effectiveness in reproductive-age women and the feasibility for its use in programmes, as it can be delivered as a single-dose treatment under observation by the health worker.[36] IPT-SP doses should not be given more frequently than monthly (WHO, 2004j). Unfortunately, SP is currently the only drug that has been shown effective for IPT and the spread of resistance to SP is affecting its

[35] Nosten, F. et al. (1998). Effects of *Plasmodium vivax* malaria in pregnancy. Lancet, 354: 546-549.

[36] Current scientific evidence suggests the following: 1) At least 2 IPT doses are required to achieve optimal benefit in most women; 2) One study of IPT in HIV-infected pregnant women has demonstrated that monthly dosing of IPT (with most women getting 3-4 doses) was necessary to achieve optimal benefit; 3) In settings with HIV prevalence in pregnant women greater than 10%, it is more cost effective to treat all women with a 3-dose regimen than to screen for HIV and provide this regimen only to HIV-infected women; 4) There is no evidence that a third dose of IPT causes any additional risk, that more than 3 IPT doses during pregnancy offers additional benefit, or that receiving 3 or more doses of IPT with SP will result in an increased risk of adverse drug reactions. Research to assess the safety, efficacy and programme feasibility of other antimalarial drugs for use in IPT is ongoing (WHO, 2004j.

efficacy. There is, therefore, an urgent need to evaluate other drug regimens for IPT (See Section 10.3).

There is no evidence to support the use of IPT in areas of low transmission of falciparum malaria (WHO, 2004j).

(iii) Insecticide-Treated Mosquito nets (ITNs)

The use of ITNs can be extremely beneficial as a preventive measure for pregnant women living an all areas where malaria is transmitted (WHO 2000a, 2003i; 2004j) In highly malarious western Kenya, studies indicate that women who were protected by insecticide-treated nets every night in their first four pregnancies delivered approximately 25% fewer babies who were either small for gestational age or born prematurely than women who were not protected by ITNs.

The use of an ITN by a pregnant woman benefits the woman as well as her family. The demonstrated impact of ITNs on reducing the risk for LBW and maternal anaemia is important. Further, the infant who sleeps under the net with the mother will also have marked benefits: reduced malaria exposure, decreased incidence of anaemia, decreased risk of death and enhanced development (WHO, 2004j)

(iv) Delivery of preventive measures

As recent surveys in Africa confirm, at least two thirds of pregnant women have access to, and use antenatal care, and most of them attend at least twice. The high level of antenatal care coverage and use provides a unique opportunity to deliver prevention packages of IPT and ITNs to pregnant women. Although there are examples of the successful delivery of such packages (WHO, 2003i), large scale programmes are only now being developed and so data on coverage is limited.

Challenges to their implementation are ensuring timely antenatal attendance, improving antenatal coverage in the poor, and increasing the current low use of ITN in women of reproductive age.

(v) Cost-effectiveness of prevention

Malaria prevention during pregnancy using a package consisting of IPT and ITNs can be highly cost-effective. IPT with either SP or CQ has been estimated to cost in the range of $12 to $21 per disability-adjusted life year prevented, a very favourable cost[37].

ITN use by children in several settings has been shown to be very cost-effective (WHO, 2004k). More pregnant women are using ITNs, and the cost-effectiveness of ITN use by pregnant women is likely to be similar to that for children. The antenatal prevention package (of IPT and ITNs) is expected to produce comparable enhanced cost-effectiveness. As regional coverage attains the 60% target, the estimated annual infant

[37] Goodman, C.A., Coleman, P.G. and Mills, A.J. (1999). The cost-effectiveness of antenatal malaria prevention in sub-Saharan Africa. American Journal of Tropical Medicine and Hygiene, 64 (1-2 Suppl): 45-56.

deaths (75 000-200 000) attributable to maternal malaria infection should be significantly reduced (WHO, 2004j).

(vi) Management of malaria disease during pregnancy (see also Section 6.5 below)

Falciparum malaria in pregnancy is a grave risk since uncomplicated malaria in pregnant women can progress rapidly with severe manifestations and complications. The aim of treatment of malaria in pregnancy must be both clinical cure and elimination of all parasites since any level of parasitaemia is of consequence to both mother and foetus. The recommended drugs for both uncomplicated and severe malaria must, therefore, be highly efficacious (at or above 95%) and safe to both mother and foetus (WHO, 2004j).

The recommended drugs for the treatment of uncomplicated malaria are chloroquine (in areas where *P.falciparum* is fully sensitive, SP in areas of chloroquine resistance where the parasite is sensitive to SP, quinine, mefloquine and artemisinin combinations. Sulfadoxine-pyrimethamine, mefloquine and artemisinin[38] are, however, contraindicated during the first trimester of pregnancy (it should be noted that women rarely report to the antenatal services during the first trimester) (WHO, 2001a; 2003j). The following drugs should not be used during any stage of pregnancy: doxycycline, halofantrine, primaquine and tetracycline (WHO, 2001a).

Where conditions allow intensive care monitoring, quinine may be used safely for the treatment of severe malaria in all stages of pregnancy. Intramuscular artemether is the drug of choice in the second and third trimesters.

Malaria Treatment Guidelines currently (2005) being prepared by WHO include the following summary recommendation for the treatment of falciparum malaria in pregnancy:

1st trimester

Quinine 10mg salt three times daily +/- clindamycin (10mg/kg twice daily) for 7 days.

2nd trimester

1. ACT known to be effective in the region or,
2. artesunate plus clindamycin (10mg/kg twice daily) for 7 days or,
3. quinine plus clindamycin - both drugs given for 7 days.

Each country in malaria endemic areas needs to develop and implement a policy that guides effective management of malaria in pregnant women. Collaboration between malaria control and reproductive health staff will facilitate the development of systematic management protocols and drug supply strategies (WHO, 2000a).

[38] There is a lack of data regarding the use of artemisinin derivatives during the first trimester of pregnancy

6.2. Infants and young children

6.2.1. The burden

Young African children infected with *P. falciparum* account for over 75% of the more than 1 million deaths from malaria that occur worldwide each year. In areas of intense perennial malaria transmission, clinical episodes occur from the age of approximately 3 months, with the highest burden of severe disease and death falling on children between the ages of 6 months and 3 years who have not yet acquired adequate clinical immunity. Anaemia, low birth weight, and the neurological sequelae of cerebral malaria are, in addition, complications of malaria that may compromise the health and development of millions of children throughout the tropical world.

6.2.2. Strategies for prevention

Randomized controlled trials in Kenya, Ghana, The Gambia, and Burkina Faso have demonstrated that wide-scale use of ITNs can reduce all-cause child mortality by around one-fifth, saving an average of 6 lives for every 1,000 children aged 1-59 months protected each year[39]. In an area of intense perennial transmission in western Kenya, ITN use reduced episodes of clinical malaria and anaemia in infants by >60%[40], and reduced by nearly one third the incidence of sick child visits to peripheral health facilities[41].

There are, at present, only a limited number of published studies on the use of IPT in infants (IPTi). A randomized controlled study in Tanzania showed that a single dose of sulfadoxine-pyrimethamine (SP) given to asymptomatic infants, attending for routine vaccination at 2, 3, and 9 months of age, reduced episodes of clinical malaria by 59% and episodes of Anaemia by 50% during the first year of life [42]. Similar results were obtained from a study conducted in northern Tanzania using amodiaquine[43]. IPTi is a particularly attractive strategy, since sustainable delivery may be achieved through the Expanded Programme on Immunization (EPI), but the following important questions need to be addressed before it can be considered for inclusion in national malaria control policies:

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[39] Lengeler C. (2002). Insecticide-treated bednets and curtains for preventing malaria (Cochrane Review). The Cochrane Library. Oxford: Update Software.

[40] ter Kuile FO, Terlouw DJ, Kariuki SK, et al. (2003). Impact of permethrin-treated bed nets on malaria, Anaemia, and growth in infants in an area of intense perennial malaria transmission in western Kenya. American Journal of Tropical Medicine and Hygiene. 68 (4 Suppl)**:** 68-77.

[41] Phillips-Howard PA, Nahlen BL, Wannemuehler KA, et al. (2003). Impact of permethrin-treated bed nets on the incidence of sick child visits to peripheral health facilities. American Journal of Tropical Medicine and Hygiene 68 (4 Suppl)**:** 38-43.

[42] Schellenberg D, Menendez C, Kahigwa E, et al. (2001). Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomized, placebo-controlled trial. Lancet. 357**:**1471-1477.

[43] Massaga JJ, Kitua AY, Lemnge MM, et al. (2003). Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomized placebo-controlled trial. Lancet*,* 361:1853-1860.

Is IPTi applicable in a range of epidemiological settings?
Is it safe?
What is the impact on serological responses to EPI vaccines and on the development of malarial immunity?
What are the alternatives to SP and amodiaquine?
Is it operationally feasible and cost-effective?

A consortium of WHO, UNICEF, and research groups in Africa, Europe and the USA, has been established to address these outstanding research issues.

6.2.3. Case management in infants and young children

Amodiaquine, artemisinin derivatives, artemether/lumefantrine[44], chloroquine and quinine are all safe to use in infants and children of all ages for the treatment of uncomplicated malaria. Clindamycin is apparently also safe in all ages but the data is limited. Sulfadoxine/pyrimethamine is contraindicated in infants under 2 months of age, mefloquine in infants under 3 months, primaquine in children under 4 years, and tetracycline and doxycycline in children under 8 years[45] (WHO, 2001a).

Administration of antimalarial drugs to infants and young children may be problematic and dosages should be based preferably on body surface area. However, given the absence of pharmacokinetic data in young children and infants and the narrow therapeutic ration of many antimalarial drugs, most recommendations are based on the assumption that children need the same mg/kg doses amounts as adults.

6.2.4. Breast feeding

Antimalarial drugs may be excreted in the milk and passed to the infants during breastfeeding. Amodiaquine (limited data), artemisinin derivatives, chloroquine, SP, mefloquine, quinine, primaquine and clindamycin (limited data) are all safe for the breast-fed infant. Tetracycline is contraindicated because of the risk of bone disorders and teeth discoloration. There is no data on the safety of artemether/lumefantrine in breast-feeding mothers and its use can not, therefore, be recommended (WHO, 2001a).

6.3. Anaemia

6.3.1. The burden

Anaemia is extremely common, affecting more than half of all pregnant women and children <5 years in Africa, but it frequently goes undetected, both in the community and

[44] Artemether/lumefantrine is not currently licensed for use in children under 5 kg

[45] These drugs are contraindicated in the specific age groups for the following reasons: Sulfadoxine /pyrimethamine because of the fear of kernicterus in small infants (There is little evidence to support this concern); mefloquine because of lack of data; primaquine because infants are G6PD-deficient; tetracycline and doxycycline because of the risk of bone disorders and teeth discolouration in young children (WHO, 2001a).

by health care workers[46]. Severe anaemia is associated with an increased risk of death, while iron deficiency and anaemia may impair cognitive and motor development, growth, immune function, and physical work capacity. Despite this, many children with mild to moderate anaemia receive no treatment. Prevention is clearly of critical importance.

Anaemia is usually caused by several factors, although malaria plays a key etiological role in endemic countries. Sequestration of malaria parasites in the placenta, deficiencies of iron, zinc, and other micro-nutrients during pregnancy and the first year of life, HIV infection, intestinal helminth infections and haemoglobinopathies are all associated with an increased risk of anaemia in pregnancy and during the first year of life.

In areas of intense transmission, most cases of severe malarial anaemia and related deaths occur in infants and young children. A single overwhelming episode of malaria, or repeated episodes due to re-infection or failure to adequately clear parasitaemia as a result of antimalarial drug resistance may result in life-threatening anaemia, metabolic acidosis, and, if untreated, death. Severe anaemia is thought to account for more than half of all childhood deaths from malaria in Africa, with case fatality rates in hospital of between 8-18%.

6.3.2. Interventions to prevent malaria anaemia

The risk of malaria-related anaemia can be reduced by effective malaria control using ITNs, intermittent preventive treatment and early diagnosis and prompt treatment of malaria episodes. A recent review of 29 community-based studies of insecticide-treated nets (ITNs), antimalarial chemoprophylaxis, and indoor residual spraying demonstrated that the relative risk for anaemia in children under 5 years was significantly reduced by up to 50% after 1-2 years of malaria control[47]. In other studies in areas of intense transmission, ITNs have been shown to reduce the incidence of both clinical malaria and anaemia by 60%, the greatest reduction being in infants 1-3 months of age. When used by women during their first four pregnancies, ITNs reduced maternal and placental parasitaemias and increased significantly haemoglobin levels[44].

Studies in areas of Kenya and Malawi with low resistance to sulfadoxine-pyrimethamine have shown that Intermittent Preventive treatment (IPT) with sulfadoxine-pyrimethamine in pregnancy reduces maternal anaemia, placental malaria, and low birth weight by approximately 40%[38].

The role of iron in the prevention and treatment of anaemia in malaria-endemic regions remains a highly contentious issue as there are concerns that the administration of iron for the treatment of anaemia may exacerbate malaria and other infectious diseases. In a

[46] Crawley, J (2004). Reducing the burden of anaemia in infants and young children in malaria-endemic countries of Africa: From evidence to action. American Journal of Tropical Medicine and Hygiene, 71: (2 Suppl.): 25-34.

[47].Korenromp, E.L., Armstrong-Schellenberg, J.R.M., Williams, B.G., Nahlen. B.L. and Snow, R.W. (2004). Impact of malaria control on childhood anaemia in Africa - a quantitative review. Tropical Medicine and International Health, 9: 1-16.

recent systematic review, administration of iron had a beneficial, though variable, impact on haemoglobin levels, but was associated with an increased risk of diarrhoea. The risk of malaria parasitaemia was not increased by iron supplementation, once baseline parasitaemia was taken into account. The risk of exacerbating infectious disease with iron supplementation needs to be balanced against the benefits of preventing iron deficiency.

6.3.3. Implementation

The complex, multifactorial nature of anaemia in malaria-endemic regions of Africa means that it is best tackled by means of an integrated, non disease-specific approach. This approach is more likely to be successful if interventions are targeted at the groups at highest risk of anaemia, namely pregnant women and their infants, and if sustainable systems, namely antenatal clinics and the Expanded Programme on Immunization, are used for their delivery[52].

Although prevention is of utmost importance, there are additional challenges that must be addressed. More emphasis needs to be placed on increasing awareness of malaria related anaemia in the community and by health care workers, since mild and moderate degrees of anaemia may, if unrecognized and untreated, progress to severe, life-threatening anaemia.

6.4. Patients with HIV/AIDS

6.4.1. The burden

Malaria and HIV/AIDS are among the two most important global health problems of our time. Together, they cause more than four million deaths per year, the great majority in Africa south of the Sahara where more than 29 million people live with HIV/AIDS and 90% of the global burden of malaria occurs.

HIV/AIDS and malaria are highly endemic, and there is wide geographic overlap in Africa south of the Sahara. Among the most severely affected countries are Cameroon, Central African Republic, Malawi, Mozambique and Zambia where more than 90% of the population is exposed to malaria, and HIV prevalence (among adults 15-49 years of age) is above 10 per cent. Outside Africa, the two diseases overlap in certain at-risk groups in South-East Asia and South America, and in several Indian cities such as Mumbai.

Malaria and HIV/AIDS are both diseases of poverty and causes of poverty and they share determinants of vulnerability. Given the wide geographic overlap in occurrence of HIV and malaria in Africa and the resulting co-infection, the interaction between the two diseases clearly has major public health implications.

6.4.2. Evidence of interaction malaria and HIV/AIDS

There is a growing body of knowledge on the interactions between HIV/AIDS and malaria[48]. The consequences are particularly serious for reproductive health. Co-infected pregnant women are at very high risk of anaemia and malarial infection of the placenta. As a result, a considerable proportion of children born to women with HIV and malaria infection have low birth weight and are more likely to die during infancy. There is no clear evidence that malaria during pregnancy increases the risk of HIV-transmission from the mother to her child (mother to child transmission, MTCT), as studies examining this relationship have shown conflicting results. Among adult men and non-pregnant women, HIV/AIDS may augment the risk of malarial illness, especially in those with advanced HIV-related immunosuppression in areas of unstable malaria transmission. HIV-infected adults with low CD4 counts may also be more susceptible to treatment failure of antimalarial drugs. On the other hand, acute malaria episodes temporarily increase viral replication and hence HIV viral load. As an important cause of anaemia, malaria frequently leads to blood transfusions, which is a potential risk factor for HIV infection.

As yet, there is no direct evidence or data available to demonstrate that (i) HIV in children increases the risk of malaria infection and malaria parasite density, or compromises the response to antimalarial treatment; and (ii) malaria increases the HIV viral load in children or the risk of HIV transmission between mother and child (WHO, 2004j).

In addition, research on the interactions between antiretroviral and antimalarial medicines is needed urgently

6.4.3. Integrated approach to health service delivery

In order to reduce the lethal consequences of dual infection with HIV/AIDS and malaria, prevention and treatment programmes of the two diseases must mutually reinforce each other. There is immense potential for such synergism, in particular at a time of growing political and financial commitment to effectively reduce the burden of HIV/AIDS, malaria and tuberculosis. A technical consultation convened by WHO in 2004 agreed on the following key recommendations (WHO, 2004k):

[48] ter Kuile, F.O., Parise, M.E., Verhoeff, F.H., Udahayakumar, V., Newman, R.D., van Rijk, A.M., Rogerson, S.J. and Steketee, R.W. (2004). The burden of co-infection with human immunodeficient virus type 1 and malaria in pregnant women in sub-Saharan Africa. American Journal of Tropical Medicine and Hygiene, 71 (2 Suppl.): 41-54;
Grimwade, K., French, N., Mbatha, D., Zungu, D.D., Dedicoat, M. and Gilks, C.F. (2003). Childhood malaria in a region of unstable transmission and high human immunodeficiency virus prevalence. Paediatric Infectious Diseases Journal, 22: 1067-1073;
Mwapasa, V. and French, N. (2004). HIV and malaria: interactions in non-pregnant adults including clinical presentation and case management issues. Paper presented at WHO informal consultation on HIV/AIDS and malaria interactions and policy implications. 23-25 June 2004 Geneva , Switzerland;
Bates, I., Fenton, C., Gruber, J., Lallo, D., Lara, A.M., Squire, S.B., Theobald, S., Thomson, R. and Tolhurst, R. (2004). Vulnerability to malaria, tuberculosis, and HIV/AIDS infection and disease. Part 1: determinants operating at individual and household level. Lancet, (in press).

- As people living with HIV/AIDS in areas of malaria transmission are particularly vulnerable to malaria, their protection by insecticide-treated nets has high priority;
- HIV-positive pregnant women at risk of malaria should always be protected by insecticide-treated nets, and in addition - according to the stage of HIV-infection - receive intermittent preventive treatment with sulfadoxine-pyrimethamine (at least three doses);
- Programmes for control of the two diseases should collaborate to ensure integrated service delivery, in particular within the framework of reproductive health services, and at peripheral health services, where the provision of better diagnostic tools for both diseases, antiretroviral treatment and more effective antimalarial medicines should be undertaken in cooperation; and
- Additional research on interactions between antiretroviral and antimalarial drugs is needed urgently.

6.5. Vivax malaria

6.5.1. The burden

P.vivax is the predominant malaria species in most of Asia, (including the Indian sub-continent), Europe, Oceania, North Africa, and Central and South America and is estimated to account for about 55% of the total malaria incidence outside Africa south of the Sahara (WHO, 1999).

Unlike falciparum malaria, vivax malaria is relapsing malaria found in the temperate as well as tropical and subtropical regions. Vivax malaria is rarely fatal but anaemia may become severe in children. It is important because of the debility that it causes as a result of relapses. The incubation period and pattern of relapses vary geographically. In tropical vivax malaria the incubation period is short[49] with frequent relapses. In subtropical and temperate regions the incubation period may be short with prolonged latency[50] followed by one or several relapses at frequent intervals[51]. In most areas, the incidence is bimodal with a peak in the spring and another in the summer. The first peak is a result of long-term relapses or of delayed primary attacks of those infections contracted in the previous summer whilst the second peak in the summer consists primary attacks of recent infections. These factors influence the way that vivax malaria is managed.

[49] 12-20 days
[50] 7-13 months
[51] North of latitude 57° in Russia , strains of vivax malaria occur that have incubation periods of 6 months or longer, he primary attack is succeeded by a series of relapses at short intervals and by second long latency and relapses

6.5.2. Management of vivax infections

The aim of the treatment of vivax infections is two-fold to eliminate:

- both clinical symptoms and parasites from the blood with a safe and effective blood schizontocide; and
- prevent relapses with an effective tissue schizontocide in areas of low transmission where re-infection is rare and in temperate areas where relapses occur 6-12 months after the primary attack.

It is not necessary to provide antirelapse treatment routinely to patients living in endemic areas of high vivax transmission. In such cases, a relapse can not be distinguished from reinfection and such patients should be treated with an effective blood schizontocide for each symptomatic recurrence of parasitaemia. In areas of seasonal transmission, antirelapse treatment can be delayed and all persons at risk can be treated at the end of the transmission season. This will save time and will also catch reinfections in patients who have already been treated. Pregnant patients in whom primaquine, the recommended anti-relapse treatment, is contraindicated should be treated after delivery (WHO, 2001a).

(i) Blood Schizontocidal Treatment

Chloroquine remains the drug of choice for the treatment of uncomplicated vivax malaria since the parasite remains sensitive to this drug in most areas of the world. Resistance of *P.vivax* to chloroquine has been reported from SE Asia and Oceania but is probably limited. There is insufficient knowledge at present to make specific treatment recommendations for *P.vivax* in areas of suspected resistance (WHO, 2001a) but amodiaquine and mefloquine have been shown to be effective against drug sensitive *P.vivax.* Sulfadoxine/pyrimethamine is not recommended since it is not totally effective for vivax infections.

(ii) Anti-relapse Treatment

P.vivax strains differ in their sensitivity to primaquine, currently the only widely used anti-relapse drug.

For strains from Papua New Guinea, Solomon Islands, Vanuatu and parts of Indonesia, a total dose of primaquine base of 7 mg/kg, given as 30mg base daily for 14 days is required to give 100% cure rates. Strains from China, South East Asia, central Asia, the Middle East, northern Africa and South and Central America can be cured with half this dose (i.e. 15mg/kg given over 14days) (WHO, 2001a). The previously recommended course of 15mg primaquine base/kg for 5 days for vivax infections in the Indian subcontinent (WHO, 1996b) has now been shown to be inadequate[52].

Primaquine may cause haemolysis in glucose-6-phosphate delydrogenase (G6PD) - deficient patients and, whenever possible, this condition should be excluded before

[52] Rowland, M. and Durani, N. (1999). Randomized controlled trials of 5 and 14 primaquine therapy against relapses of malaria in an Afghan refugee camp in Pakistan. Transactions of the Royal Society of Tropical Medicine and Hygiene, 93: 642-643.

treatment. However, G6PD deficiency alone should not necessarily preclude treatment as in most cases haemolysis is mild and self-limiting. Although tests for G6PD deficiency exist, there is a need to develop simpler ones for use in field conditions.

(iii) Constraints

The major constraints to the implementation of a drug policy for the management of vivax malaria are:

- Lack of compliance with anti-relapse treatment due to side effects of primaquine and the length of treatment. Compliance problems can however, be overcome with simple health messages even when the majority of individuals are illiterate and without formal education[53]
- Limited information on the extent of chloroquine resistance in *P.vivax* and the efficacy of alternatives. This is hampered by the lack of a suitable method for the monitoring of drug resistance of this parasite.

6.6. International Travellers

6.6.1 The principles

During the transmission season in malaria-endemic areas, all non-immune travellers exposed to mosquito bites, especially between dusk and dawn, are at risk of malaria. The risk for travellers of contracting malaria is highly variable from country to country and even within areas of each country. Travellers and prescribers should therefore ascertain the risk before travelling and consult the detailed recommendations for the protection of travellers against malaria that are published annually by WHO in *International Travel and Health: Vaccination Requirements and Health Advice* (WHO, 2004l).

Each year many international travellers fall ill while visiting malaria-endemic countries and well over 10 000 fall ill after returning home. Fever occurring in a traveller within 3 months of leaving a malaria-endemic area is a medical emergency and should be investigated immediately. Most cases of malaria in travellers occur because of poor compliance with drug regimens or inappropriate prophylaxis.

Travellers and their advisers should note the four principles of malaria protection:

- Be aware of the risk;
- Avoid being bitten by mosquitoes. Individual protection between dusk and dawn is the first line of defence against malaria;
- Take antimalarial drugs (chemophylaxis) to suppress infection when appropriate; and
- Immediately seek diagnosis and treatment if a fever develops one week or more after entering an area where there is malaria risk and up to 3 months after departure.

[53] Leslie, T., Rab, M.A., Ahmadzai, H., Durani, N., Fayaz, M., Kolaczinski, J. and Rowland, M. (2004). Compliance with 14-day primaquine therapy for radical cure of vivax malaria - a randomized placebo-controlled trial comparing unsupervised with supervised treatment. Transactions of the Royal Society of Tropical Medicine and Hygiene, 98: 168-173.

6.6.2. Choice of Antimalarial medicines for prophylaxis

No prophylactic regimen gives complete protection.

Depending on the area to be visited and the local patterns of drug resistance, the recommended drug may be chloroquine, chloroquine plus proguanil, mefloquine, or doxycycline. Chloroquine on its own can only be recommended for areas where malaria is due exclusively to *P. vivax* or chloroquine-sensitive *P. falciparum.* In areas where mefloquine is the prophylactic drug of choice, doxcycline or atovaquone/proquanil can be used as an alternative that can be started the day before travel: chloroquine/proquanil would offer less protection. Atovaquone/proquanil for travellers on short trips to chloroquine-resistant areas who can not take mefloquine or doxycycline (WHO, 2004e).

All antimalarial drugs have specific contraindications and possible side effects. Adverse reactions attributed to chemoprophylaxis are common but most are minor and do not affect the activities of the traveller. Serious adverse reactions are rare. The risk of drug associated adverse events should be weighed against the risk of malaria and local drug resistance patterns. Because of the risk of side-effects, chemoprophylaxis should not be prescribed in the absence of malaria risk.

6.6.3. Stand-by emergency treatment.

Most travellers who experience a fever one week or more after entering an area of malaria risk will be able to obtain prompt and reliable medical attention. However, a minority at risk of infection may be unable to seek such care within 24 hours after the onset of symptoms, particularly if they are in isolated situations far from competent medical services. In such cases, it is advised that prescribers issue antimalarial drugs to be carried by the traveller for self- administration, i.e. stand-by emergency treatment.

Such people should be given clear and precise written instructions on the recognition of symptoms, when and how to take the treatment, the treatment regimen, possible adverse reactions and the action to be taken in the event of drug failure. They should be made aware that stand-by treatment is a first aid measure, and not an alternative to proper medical care which they should seek as soon as possible.

Depending on the area to be visited and the chemoprophylaxis regimen taken, one of the following stand-by treatments can be recommended: chloroquine (*P.vivax* areas only), mefloquine, quinine or quinine plus doxycycline. Artemether/lumefantrine been registered in Switzerland for use as stand-by treatment for travellers to areas where the parasite is resistant to other drugs (WHO, 2001a, 2004l).

The use of RDTs with stand-by treatment has been suggested, but studies have shown that travellers experience major difficulties in the performance and interpretation of these tests. Major technical modifications are required before these tests can be recommended for use by travellers. (WHO, 2000c, 2003e).

6.6.4. Protection against mosquito bites

All travellers should be told that individual protection from mosquito bites between dusk and dawn is their first line of defence against malaria. They may protect themselves by means of insect repellents[54], (such as DEET, IR3535® or Bayrepel®[55]), mosquito coils, aerosol insecticide sprays, protective clothing and/or insecticide-treated mosquito nets (ITNs). Mosquito nets are excellent means of protection while sleeping and can be used either with or without insecticide treatment. However, treated nets are much more effective. Screening of windows, doors and eaves reduces exposure and accommodation with these features should be sought. Air condition is also an effective means of keeping mosquitoes out of rooms so that in air-conditioned buildings other precautions are not necessary indoors.

Details of these personnel protection methods can be found in *International Travel and Health: Vaccination Requirements and Health Advice* (WHO, 2004l).

6.6.5. Special Groups

(i) Pregnant women and infants

Pregnant women and infants should be advised to avoid travelling to areas where chloroquine-resistant *P. falciparum* occurs since these groups are at greatest risk and the drugs available to protect them are limited. When travel can not be avoided, it is essential that effective preventive measures are taken and they are extra diligent in using measures to protect against mosquito bites, when travelling to areas with only vivax malaria transmission. Breastfed as well as bottle fed babies should be given chemoprophylaxis since they are not protected by their mother's milk.

In the few areas with exclusive *P. vivax* transmission or where *P. falciparum* is fully sensitive to chloroquine, chloroquine alone can be used as chemoprophyaxis in both pregnant women and infants. In areas with chloroquine-resistant *P. falciparum,* prophylaxis with chloroquine/proquanil can be safely prescribed during pregnancy and infants but its efficacy may be severely limited. Mefloquine may be more effective and can be given in the second and third trimesters but should be used with caution in the first trimester. Other drugs are either dangerous to the foetus or have been insufficiently studied to be prescribed during pregnancy. Mefloquine may be given to infants of more than 5 kg body weight. Atavoquone /proquanil to those of more than 11kg. Doxycycline is contraindicated in children below 8 years of age.

(ii) Women who may become pregnant during or after travel

Both mefloquine and doycycline prophylaxis may be taken but pregnancy should be preferably avoided during the periods of drug intake and for 3 months after mefloquine and one week after doxycycline prophylaxis is stopped. If pregnancy occurs during prophylaxis with mefloquine or doxycycline, this is not considered to be an indication for pregnancy termination.

[54] Repellents should be used in strict accordance with the manufacturers' instructions and the dosage must not be exceeded especially for young children.
[55] Bayrepel® = 1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-, 1-methylprphlester.

7. MONITORING AND EVALUATION

An effective system for monitoring progress and evaluating outcomes and impact will be critical for efforts to reach the Millennium Development Goals (MDGs). This information will be crucial for identifying areas where modifications may be needed in relation to the intervention strategies and for allocation of resources at local, national and global levels. In this section, we describe briefly the key issues related to monitoring and evaluation at *global and national* levels in relation to the MDGs.

In 2003 the RBM partnership established a monitoring and evaluation reference group (MERG) to promote the consensus on a comprehensive monitoring and evaluation system to track progress towards the core indicators of RBM and the Millennium Development Goals. The RBM-MERG brings together the concerned UN agencies, key bilateral donors, such as USAID, DFID and the Global Fund, the RBM regional networks and representatives of national malaria control programmes, as well as research organizations. The MERG focuses on harmonizing and coordinating all work related to monitoring of malaria targets, and provides guidance to the RBM partnership on specific technical issues related to monitoring and evaluation. The RBM-MERG has established several task forces to address specific technical and methodological issues, including the relevance and feasibility of monitoring malaria-specific mortality at country level, the importance of Anaemia as an indicator for malaria, and country level capacity building in monitoring and evaluation for malaria. Two additional task forces address the coordination of household survey activity and malaria morbidity measurement. Summaries of the discussions and recommendations from the general MERG meetings as well as task force meetings are available on-line (http://www.rbm.who.int/partnership.

7.1. Monitoring and evaluation systems

Monitoring is the routine tracking of the key elements of programme/project performance, usually inputs and outputs, through record-keeping, regular reporting and surveillance systems as well as health facility observation and client surveys. Monitoring helps programme or project managers determine which areas require greater effort and identify questions that might contribute to an improved response. In a well-designed monitoring and evaluation system, monitoring contributes greatly towards evaluation. Indicators selected for monitoring will be different depending on the reporting level within the health system. At the global level, monitoring primarily focuses on outcome indicators to monitor trends in coverage of the recommended interventions.

Evaluation is the periodic assessment of the change in targeted results that can be attributed to the programme or project intervention. In other words, evaluation attempts to link a particular output or outcome directly to a particular intervention after a period of time of implantation of a particular programme has passed. Evaluation helps programme or project managers determine the value or worth of a specific programme or project.

The following sections summarize framework and issues related to the development and issues of a monitoring and evaluation system for malaria prevention and control. Further details can be found in the Global Fund's Monitoring and Evaluation Toolkit published in June 2004 (available at (http.www.the globalfund.org/en/about/policies_guidelines/) (see also WHO, 2000e), and guidelines for Core Population Coverage Indicators (Roll Back Malaria, et. al., 2004)

7.2 Malaria-Related Millennium Development Goals, Targets and Indicators

Millennium Development Project has two goals, #6 and #4, relevant to malaria control. Goal #6 includes the following malaria-specific targets and indicators:

Goal 6:	**Combat HIV/AIDS, malaria and other diseases**
Target 8: Have halted by 2015, and begun to reverse, the incidence of malaria and other major diseases	21a. Malaria prevalence rate in the general population. 21b. Malaria related death rate in children under five. 22a. Proportion of children under five in malaria risk areas that sleep under insecticide treated nets. 22b. Proportion of children under five with malaria who are appropriately treated.

In most countries, malaria prevalence (indicator 21a) can be measured by the number of malaria cases reported annually, with or without confirmed diagnosis, provided by the routine Health Information System (HIS). Malaria parasite prevalence surveys are not routinely conducted as part of monitoring and evaluation activities. WHO uses a morbidity model which incorporates country reports to generate country-level estimates of malaria cases and deaths.

Since it is estimated that 90% of all malaria deaths in the world today occur in Africa south of the Sahara, and 90% of deaths from malaria in Africa are among children less than 5 years of age, the key objective of present malaria control efforts in Africa is to reduce mortality from malaria in young children. This links directly to the Millennium Development Goal #4 below:

Goal 4:	**Reduce Child Mortality**
Target 5: Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate	13. Under-5 mortality rate 14. Infant mortality rate 15. Proportion of under 1-year olds immunized against measles

In most African countries it is unlikely that Goal #4 can be met without substantial reductions in childhood deaths due to malaria. However, malaria-specific mortality (Indicator 21b) is difficult to measure routinely and reliably in most malaria-endemic

areas. WHO and the RBM-MERG have, therefore, recommended that the primary indicator for measuring the impact on mortality (Indicator 21b) in highly malaria endemic situations, such as those in Africa, should be *all-cause, under-5 mortality* (per 1000 live births per year, Indicator 13). This can be measured by nationally-representative, household surveys. It should be reported together with malaria intervention coverage (Indicators 22a, 22b and others) for use both as proxy measures and in modelling of child mortality reduction attributable to malaria-specific interventions.

7.3 Regional differences in monitoring and evaluation

Monitoring of progress to reduce the burden of malaria globally should be based on the impact on mortality and morbidity in relation to the coverage of interventions. However, monitoring needs and opportunities are not the same in all countries because of differences in the availability of existing monitoring and measurement systems (based largely on differences in economies) and in the epidemiology of disease.

Two major categories exist:

- ***Highly endemic* settings** where generally, *P. falciparum* malaria predominates, this includes most tropical African countries, Papua New Guinea, and foci of intense transmission outside Africa, especially in South-east Asia.

- **Other malaria-endemic settings** where malaria transmission intensity tends to be low or epidemic. In some of these areas, *P. vivax* predominates or contributes to a substantial proportion of malaria transmission. Systems and resources may be more developed allowing for higher rates of vital registration and systematic disease reporting with higher rates of confirmation of diagnoses.

As a consequence, priorities for use of specific measures to monitor malaria burden may differ in these situations. They are:

	Highly endemic malaria	Other malaria settings
Mortality measures		
All-cause under-5 mortality rates	X	X
Malaria-specific mortality count/rates	X	X
Morbidity measures		
Malaria infection prevalence	X*	
Malaria case rates		X
Malaria-associated morbidity measure e.g., anaemia	X**	

* May be useful for surveys conducted during peak malaria transmission.

** In areas of stable malaria transmission, haemoglobin measurement among children 6 -24 months of age is recommended to track improvements in child health resulting from increasing coverage of effective prevention and treatment for malaria.

The Millennium Development Goals above are both relevant in the above two settings. Goal #4 is highly relevant to malaria and is the recommended measurement for monitoring and evaluating malaria control activities i.e. achieving (and therefore measuring) a reduction in all-cause child mortality. This should be measured in both types of malaria settings. It is likely that for highly endemic settings, substantial changes in malaria-specific mortality will be reflected in the all-cause child mortality measure. In the other malaria settings, malaria may contribute to child mortality to a variable and usually limited degree.

Goal #6 is relevant, but is both general (it applies to malaria and "other diseases" such as TB) and is not expressed in a clearly measurable way. "Malaria incidence" is an ambiguous term and could mean either the rate of new clinical disease or the rate of new infections. Neither of these rates is easily or currently measured in populations, although the reported incidence of confirmed and probable malaria can serve as indicators, provided the quality of surveillance is good.

7.3.1. Mortality Indicators

While it might be ideal to measure malaria-specific child mortality, this is not currently done widely or in a consistent manner in most high-burden endemic areas. The most widely used method to measure malaria-specific mortality involves a "verbal autopsy". This measure has limitations in sensitivity and specificity, and while it has been of some value in specific study settings and in demographic surveillance sites (DSS), it is unlikely to be available for repeated or continual use at national levels. Verbal autopsy, HIS-data on malaria mortality and vital registration will tend to underestimate the impact of malaria control, because they pick up only a subset of true malaria deaths (those with fever and seizures) and miss other malaria deaths (such as those due to malarial anaemia).

In some countries with a lower malaria burden, vital registration and health facility records may provide a stable and reliable count of malaria deaths, and reporting from these sources may be useful for monitoring trends.

Thus, greater emphasis must be placed on process (input and output) indicators and outcome monitoring, before embarking on impact evaluation. It is important to note that mortality measured from cross-sectional surveys always reflects the level of interventions carried out in previous years. An impact on mortality can only be detected several years after coverage has increased. It is, thus, unrealistic to expect to demonstrate convincing reductions in malaria-specific mortality within a year of increasing intervention coverage. Given the limitations of methods available at present, an impact on the malaria-specific mortality may be best estimated from the measured trend in all-cause under-5 mortality rate in combination with the measured coverage of the three key interventions.

Morbidity indicators

In most highly endemic settings, there is no current system for systematic collection of morbidity data (e.g., numbers of malaria cases, malaria infection rates, malaria-associated anaemia rates, etc.). The RBM-MERG is encouraging/supporting the evaluation of early childhood anaemia as a possible measure of morbidity in Africa south of the Sahara. It is also possible to consider sentinel site evaluation of child parasite prevalence, however current and past data indicate that the parasite prevalence rates in

populations will not decline dramatically until multiple interventions have been applied at high coverage. Thus, this measure may respond slowly despite progress in malaria control. For areas with lower malaria endemicity, case reporting may be reliable and can be used for MDG indicators.

7.3.3 Coverage indicators

In high endemicity settings, the RBM-MERG recommends evaluating the coverage rates for the three core interventions including household use of ITNs, intermittent preventive treatment in pregnancy, and prompt and effective treatment of febrile/malaria illness in young children. In other settings, measurement of the coverage of the locally applied vector control intervention (if any) and that of prompt and effective treatment of febrile/malaria illness in children or for all cases will be the relevant measure.

7.4 Health Information Systems (HIS)

Routine Health Information Systems (HIS) are the usual source of national data on malaria cases and deaths seen in health facilities. Data from HIS are crucial for monitoring of health facility needs for antimalarial drugs and other commodities. Where facility data has been most useful is with regard to understanding dynamics of severe disease and case fatality rates in in-patients where the population of interest is those who arrive at the health facility. Although data available from health facilities are potentially useful for monitoring time trends in the number of cases and deaths, HIS date have limitations. In principle, these data are national, but in practice not all facilities and districts report. Reporting from health facilities to districts and from districts to the ministry of health varies in its completeness and timeliness and often does not include nongovernmental facilities or military health services. The numbers of cases and deaths reported are therefore less than the actual malaria burden. More importantly, most malaria patients either do not seek treatment or are treated outside the formal health sector.

Other limitations of malaria data available through HIS in most endemic countries include the fact that most cases of malaria at the peripheral health facility level are based on clinical (not confirmed) diagnosis. Common malaria-associated symptoms and signs (such as fever) are non-specific. In highly endemic areas, malaria parasitemia is common among clinic attendees, and a positive laboratory result does not necessarily mean that the patient is ill with malaria. Besides, many deaths, in most countries the majority, do not occur in hospitals and are not routinely recorded in HIS. These deaths occurring at home are recorded by vital registration systems in some countries, however, such systems are usually incomplete and not very specific.

Improvement in the quality of health information systems is generally required before they can be relied on for monitoring epidemiological trends. In some countries, enhancement of HIS may include randomly selected in-patient and out-patient formal health service providers recruited to act as sentinels for changing disease presentation risks. Changing case-fatality, clinical presentation and defined treatment failures will provide important data. These sentinels could form part of enhanced HIS services and should be guaranteed adequate diagnostics and capacity to track changing disease burdens.

Community and Household Surveys

Community-based information on prevention and treatment practices is critical for monitoring the effect of malaria control. The greatest burden of malaria and the greatest need for prevention and control efforts tend to occur in isolated rural settings, where a large proportion of cases are managed at home and where, similarly, most malaria deaths occur outside the formal health care setting. Household surveys will, therefore, be required to report on trends in increasing coverage of insecticide-treated nets and appropriate treatment for malaria. Such surveys are time-consuming and relatively costly and are best conducted at intervals (e.g., every 2-3 years).

Presently there are three major tools for conducting community surveys which are highly relevant to malaria control:

- **Demographic and Health Surveys (DHS).** DHS are nationally representative household surveys that focus on reproductive and child health. Typically, DHS consist of interviews with between 4000 and 12000 women aged 15-49 years living in households that are sampled in a multiple-stage cluster design. Because the questionnaires are standardized and structured and change little between surveys, DHS results are comparable between countries and over time. Since 1998 specific questions on malaria prevention and treatment have been included in DHS, where relevant. These questions were grouped in 2001 into a standard malaria module added to DHS conducted in malarious countries. In addition to providing information on the major outcome indicators, the DHS are a primary source of information on under-5 all-cause mortality rates, obtained by the direct estimation technique , e.g, from birth histories. Recent DHS also measure the prevalence of anaemia by haemoglobin measurement in children under 5 years. DHS are organized by MACRO International, Calverton, MD, USA and are funded primarily by the United States Agency for International Development (USAID). Questionnaires and survey results are available on the internet approximately 1 year after completion of field work (http://www.measuredhs.com).

- **Multiple Indicator Cluster Surveys (MICS).** Multiple Indicator Cluster Surveys (MICS) were conducted between 1999 and 2001 in 67 countries with support from UNICEF. MICS are nationally representative, with an average sample of around 6000 households sampled through a two-stage cluster design. In the 24 African countries where MICS was conducted, the survey included a malaria module with questions related to prevention and treatment. MICS also provides data on all-cause mortality among children under 5 years. Survey results and questionnaires are available on the internet (http://www.childinfo.org). The next round of MICS surveys planned for 2004-2005 will include questions on malaria prevention and treatment.

- **Malaria Indicator Survey (MIS).** Recently the RBM-MERG has worked with MACRO International to develop a Malaria Indicator Survey (MIS) which may be used at a national or sub-national level. The sample sizes are smaller than for the DHS and MICS since the primary use for the survey is to monitor progress in improving coverage of ITNs and effective treatment and not all-cause child mortality. The MIS is less expensive to conduct than DHS or MICS and can be conducted at a sub-national level if needed. In addition, for operational reasons, both DHS and

MICS are conducted during the dry season and, therefore, outside of the peak malaria transmission season, whereas the MIS can - and should - be targeted to the peak transmission and combined with measurements of haemoglobin and parasite prevalence, where relevant. The entire MIS package (questionnaire, training manual, guidance on sampling and sampling sizes with costing, etc) has become available in 2004, (Roll Back Malaria et. Al., 2004)

7.5 Demographic Surveillance Systems

At present the most reliable data on trends in malaria deaths in children under 5 years is obtained from continuous prospective surveillance such as sentinel demographic surveillance systems (DSS). DSS measure deaths and possible causes prospectively in populations of known size and composition. The DSS use methods which have either total sampling or representative sampling methods that avoid the self-selection bias seen in the HMIS and IDS data. DSS sites have recently formed a network called INDEPTH that makes it easier to harmonize and strengthen methods, and answer questions across multiple sites (http://www.indepth-network.org). There are presently 30 DSS sites in 13 countries in Africa producing continuous, cause-specific mortality data. Establishment of additional DSS sites in malaria-endemic areas would enhance the ability to track changes in cause-specific mortality, among children as well as adults.

8. CAPACITY DEVELOPMENT

8.1. The need

A major constraint in reducing the burden of malaria is the lack of capacity at all levels of the health system to prevent and control the disease effectively. Although a cadre of malaria control managers has been developed over the years and considerable training carried out on the technical aspects of malaria control, investments in capacity building have been fragmented and inadequate to meet the needs. The new strategies for malaria control, the changing organization of health systems in many countries and increasing recognition of the importance of the private sector and the community in malaria control all require knowledge and new skills. In the past, the impact of investments in capacity development have been limited by the lack of both technical support, e.g. information, provision of supplies and supervision, and an enabling environment e.g. political commitment, effective policies, adequate institutional strengthening, for trained staff to apply new skills.

This situation has stimulated WHO/RBM to develop a Strategic Plan for Capacity Development (WHO, 2004m) as a guide for countries and partners to plan, conduct and evaluate capacity development for malaria prevention and control. This has been supported by documentation on standardized best practices for all levels of health care and national and international training courses.

8.2. The strategic approach

8.2.1. Provision of an enabling environment including systems for human resource development.

Policy makers and health programme managers have the responsibility for providing an "enabling" environment and developing systems for human resource development. This requires the development of regulatory, supervisory and institutional support that will allow the identification of training needs, the planning of relevant training activities, and the training of adequate numbers of personnel at all levels, the deployment of the personnel to areas of greatest need, and the managerial support to allow the trained workforce to work effectively. Career structures for trainees and monitoring and evaluation of the activities are essential.

8.2.2. Strengthening managerial skills

The target groups are national malaria programme and general health service managers, medical officers at hospitals and health centres and technicians co-ordinating malaria programmes at the district level. The challenge is to balance both managerial and technical skills at all levels. Specific skills in partnership building with the private sector, NGOs and other partners in malaria control, as well as fund-raising and financial resource management are required. The re-evaluation of the responsibility of programme managers in the context of health service reform and the competencies in malaria control of general service staff will need to be addressed.

8.2.2. Improving clinical and technical skills

The targets in the public sector include health care providers at district and community levels, health information and surveillance staff, vector control specialists, sanitary and civil engineers, community health workers and volunteers. Approaches for reaching the private sector are also needed. These should address private practitioners, private industry which provide anti malaria health services to their staff, the commercial sector (drug companies and pesticide manufactures), pharmacists, traditional healers and drug sellers.

The aims are to increase competence in surveillance, prevention and control, particularly the epidemiological analysis of the local malaria situation in epidemic-prone areas; the rapid diagnosis and treatment of uncomplicated and severe malaria; the planning, implementation and evaluation of vector control using IRS and ITN programmes; and targeted operational research. This entails not only instruction in new skills but also some redirection away from certain ingrained practices.

There is a particular need to strengthen and in many cases restore training in malaria in pre-service curricula for schools of medicine, nursing, pharmacy and laboratory technology. These curricula should be periodically reviewed to ensure that training is according to current norms and government policies.

8.2.3. Strengthening community capability

The objectives of capacity building at the community level are to improve family, household and community practices in health seeking behaviour, the quality of treatment in the home and in the community at large by the informal services. The target groups include mothers and caregivers, community leaders (political and religious), drug sellers/shopkeepers, traditional healers, schools (teachers and students), community-based organizations including women's groups and national and international NGOs. Information, education and communication (IEC) materials are required on the causes of malaria, its symptoms, how to prevent the disease with a focus on the use of effective prevention measures such as ITNs and IRS, and what to do when people have malaria disease. Specific IEC materials need to target drug sellers since mothers/carers usually get their information where they buy their drugs. Particular attention should be given to ensure that drug sellers provide antimalarial drugs within the framework of the national drug policy.

9. COMMUNITY MOBILIZATION (WHO, 2002e)

9.1. The principles

The coverage of public health services is currently unacceptably low in many malaria endemic countries where the most vulnerable groups may live in remote areas not reached by health services. As the resources for the accelerated expansion of health facilities to these areas are beyond the financial capabilities of most countries, it is necessary that many antimalarial interventions are undertaken by the communities themselves. In order to be successful, these community-based activities have to be an integral part of the national efforts to control malaria and the public health system will need to take major role in stewardship to ensure that community based activities are supervised, guided and assured of quality.

9.2. The objectives

Objectives that can be achieved with community participation include improving:

- Recognition of malaria illness and provision of appropriate treatment by caregivers within 24 hours of onset of illness;
- The capacity of health systems, particularly at the periphery, to support malaria control including access to antimalarial drugs and referral mechanisms;
- Health seeking behaviour of caregivers, family and the community so that they can recognize signs of severe illness and seek appropriate care quickly when referral is indicated;
- Access to insecticide-treated mosquito nets and promotion of their regular and proper use and re-treatment;
- Promotion of measures to reduce the burden of malaria in pregnant women and infants; and promotion of other vector control wherever appropriate.

9.3. Building community-based malaria prevention and control programmes

The implementation of community-based malaria control programmes needs to be based on the following basic principles:

- *Assessing the community* by identifying local capacities, resources, information needs and other local priorities in order to prepare an plan of action that can be effectively implemented;
- *Understanding local practices and beliefs*. Communities have local practices and beliefs that may be both for and against malaria prevention and control. These have to be taken into account to develop successful community based action.
- *Community participation* should be part of the inception and planning of new interventions, whenever possible. Participation promotes self awareness of the problems, increases a sense of control, increases demand for services, leads to ownership and builds sustainable systems;
- *Broadening partnerships.* Local participants need to be linked to other partners working within the community e.g. civil society, schools, the private sector and governmental agencies to actively promote community-based malaria control;
- *Building on experiences*. Many communities will have development or health committees with the leader of the village acting as chairman. In addition, there may be one or more health or development activities going on at any one time, such as IMCI, safe motherhood or DOTs. These may be relevant to community based malaria control;
- *Developing community-level intervention channels.* The initial phase in developing community-based programmes is to identify community leaders or other key persons who can be involved in the implementation of the antimalarial programmes. Community development/health committees may need to be strengthened or established;
- *Improving linkage between communities and the district health system*. Communities must be linked to the district health facilities which will serve as referral centres as well as sources of expertise, correct information and supplies;
- *Communication strategy*. This essential to the success of community based control and to changing people's behaviour. It requires information exchange among community members, local authorities and service providers. The population needs to be aware of the malaria risk, the antimalarial services available to them and their usefulness, and the role that they can play in preventing/minimizing the malaria risk to their family and the community as a whole. Advocacy, information and social mobilization are all important elements a communication strategy; and
- *Strengthening self-monitoring and decision making*. Communities need to take more responsibility for malaria prevention and control by developing a system to monitor and evaluate their resources, activities and performance according the local plan of action. (See also Section 8 above);

10. PRIORITY OPERATIONAL RESEARCH ISSUES

The following high priority areas for operational research were identified by the TDR Scientific Working Group on Malaria (UNDP/World Bank/WHO, 2004).

10.1. Improved tools and strategies for malaria treatment

10.1.1. Case management

- Evaluation of the efficacy impact of ACTs in areas of high transmission in Africa;
- Studies on the safety and efficacy of existing antimalarial drugs in HIV positive and negative malaria patients;
- Effective incorporation of malaria treatment guidelines within Integrated Management of Sick Child programmes; and
- Improved access to antimalarial drugs, including studies on the effectiveness of drug distribution systems and the preferences for and barriers to the choice of malaria health care.

10.1.2. Severe malaria

As severe malaria results largely from late or inadequate treatment, priorities are to:

- Improve and accelerate the recognition of severe malaria and to distinguish it from other severe diseases, particularly in children;
- Evaluate the delivery and use of artesunate suppositories for the emergency treatment at the periphery;
- Develop and evaluate the impact of a standard care package for emergency use at the periphery, containing treatment protocols, appropriate drugs, fluids, an anti-convulsant, fixed standards for appropriate interventions and other adjunct therapies; and
- Improve and accelerate referral to facilities with the capability to manage severe malaria disease;

10.1.3. Home management

High priorities in home management include how to:

- Expand training of drug sellers and traditional healers to ensure that good quality effective antimalarial drugs are given to carers/patients in accordance with national drug policies;
- Develop appropriate packaging of antimalarial drugs to ensure patient compliance with the full treatment dose; and
- Understand the way economic decisions are made about the purchase of health interventions for common diseases such as malaria; and
- Develop methods for health promotion with emphasis on the role of health care person, dispensers and cares

10.2. Disease prevention

10.2.1. Indoor residual spraying

- Determination of the comparative advantages of IRS and ITNs in different epidemiological situations; and
- Determination of the role of IRS in epidemic response.

10.2.2. Insecticide treated mosquito nets

- Determination of the relationship between coverage and impact (mass effect versus personal protection);
- Development of standardized methods to determine the efficacy of ITNs especially long lasting insecticidal nets;
- Determination of the most efficient, equitable and sustainable methods to scale-up ITN use;
- The impact of ITNs for malaria prevention on the development of pyrethroid resistance in mosquitoes; and
- Multi-disciplinary social research evaluating the scaling-up and targeting of ITNs.

10.3. Prevention and control in pregnancy and infants

- Safety of existing antimalarial drug combinations to treat malaria in pregnancy particularly those based on artemisinin derivatives;
- Safety and efficacy of new antimalarial drugs in pregnancy;
- Safety and efficacy of antimalarial drug combinations in HIV positive women;
- Assessment of the mechanism of action of IPT in pregnancy and of the safety and efficacy of alternatives to SP;
- Optimization of operational use of IPT in pregnancy;
- Assessment of interactions between SP and other drugs (e.g. folate, co-trimoxazole) and vaccines (e.g. tetanus toxoid) in pregnancy;
- Feasibility and cost-effectiveness of IPT and ITNs for malaria prevention in pregnancy in areas of low to moderate transmission; and
- Determination of the safety and efficacy of IPT in infants and young children in a range of epidemiological settings.

10.4. Policy Related Issues

- Analyzes of country situations where there has been policy change to understand the process of change, the prerequisites for success and the barriers to implementing a change of policy;
- Economic analysis of the impact of changing an antimalarial drug policy;
- Determination of the impact of large scale economic processes and policies e.g. trade agreements and globalization on social and health policies related to malaria and on the availability of tools for the prevention and control of malaria e.g. drugs, diagnostics, insecticides and ITNs;

10.5 Community Participation

- Studies to determine the poor and marginalized populations cope with malaria risk in the context of other risks and priorities faced by households/individuals trying to maximize their welfare;
- Development and application of a common methodology for measuring malaria vulnerability by social and economic strata such as gender, ethnicity and other determinants of inequality;

11. WHERE ARE WE GOING?

This report has summarized the current WHO guidelines and recommendations for the prevention and control of malaria, highlighting the importance of a scientific evidence base for decision making and the need to build and diversify partnerships to put these decisions into practice. It is heartening that international organizations, pharmaceutical companies, research institutes, NGOs, bilateral agencies and national governments are now working together to address the burden of malaria but much more needs to be achieved.

Although successes in malaria control in the last 40 years have been few, experience indicates that where there is a political will, sufficient financial and human resources, and a good health infrastructure, malaria can be controlled with the tools that are currently available. Unfortunately, these conditions are not met in the majority of malaria endemic countries where health care systems are weak and resources scarce.

At present, many malaria control efforts particularly in Africa, are carried out as small projects with limited coverage. In order to scale up these initiatives to the national level, greater human and financial investments, improved access to essential medicines, diagnostics, ITNs and insecticides, greater coverage of the public health services, improved community involvement and improvements in the monitoring and evaluation systems will all be required.

The report also highlights the operational research issues that need to be addressed before potentially useful strategies can be fully deployed. Investment in operational research is crucial to the long term sustainability of malaria prevention and control and should complement the basic and applied research needed to develop new antimalarial medicines, improved diagnostics, vaccines, insecticides and novel approaches to vector control. Although, malaria is the 13th leading cause of death and of disability-adjusted years of life lost globally, it consumes barely 0.1% of the annual global health research budget of US$73 billion[56]; there is clearly a need to increase investments in fundamental applied malaria research in parallel with the increased investments in malaria control Implementation.

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ANNEX 1 LIST OF ACRONYMS AND ABREVIATIONS USED

ACT	Artemisinin-based combination therapy
ANC	Antenatal Care
AIDS	Acquired immune deficiency syndrome
API	Annual parasite index
CQ	Chloroquine
CT	Combination therapy
DDT	Dichlorodiphenyltrichloroethane
DEET	N,N-diethyl-m-toluamide
DHS	Demographic and health surveys
DOTS	Directly observed therapies
DSS	Demographic surveillance systems
EDS	Early detection system
ENSO	El Niño southern oscillation
EPI	Expanded Programme on Immunization
EW	Emulsion, oil in water
FDA	Federal Drug Administration (USA)
FEWS	Famine early warning system
GIS	Geographical information system
GNP	Gross national product
G6PD	Glucose-6-phosphate dehydrogenase
HIS	Health information systems
HIV	Human immunodeficiency virus
HMIS	Health management information systems
IDS	Integrated disease surveillance
IEC	Information, education and communication
im	Intramuscular
IMCI	Integrated management of childhood illnesses
INDEPTH	International Network of field sites with continuous Demographic Evaluation of Populations and their Health
IPT	Intermittent preventive therapy
IPTi	Intermittent preventive therapy in infants
IR3535®	(3-[N-acetyl-N-butyl]-aminopropionic acetyl ethyl ester)
IRS	Indoor residual spraying
iv	intravenous
ITN	Insecticide-treated mosquito net
LBW	Low birth weight
LRF	Long range forecasting
MDA	Mass drug administration
MDG	Millennium development goals
MERG	Monitoring and evaluation reference group
MEWS	Malaria early warning system
MICS	Multiple indicator cluster survey
MIS	Malaria indicator survey
MTCT	Mother to child transmission (of HIV/AIDS)
NDP	National Drug Policy
NGO	Non-Governmental Organization

NMCP	National malaria control programme
RBM	Roll Back Malaria
RDT	Rapid diagnostic test
SAMC	Southern Africa Medical Council
SP	Sulfadoxine- pyrimethamine
TDR	UNDP/World Ban/ WHO Special Programme for Research and Training in Tropical Diseases
UN	United Nations
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization
WHOPES	World Health Organization Pesticides Evaluation Scheme