COMMISSION ON MACROECONOMICS AND HEALTH
A WHO commission examining the interrelations among investments in health, economic growth and poverty reduction

CMH Working Paper Series

Paper No. WG5 : 6

Title

The Evidence Base for Interventions to Reduce Malaria Mortality in Low and Middle-Income Countries

Authors

S. Meek, J. Hill, J. Webster

Date: September 2001

The Evidence Base for Interventions to Reduce Malaria Mortality in Low and Middle-Income Countries

Working Group 5 of the CMH

Sylvia Meek
Malaria Consortium, London School of Hygiene & Tropical Medicine

Jenny Hill
Malaria Consortium. Liverpool School of Tropical Medicine

Jayne Webster
Malaria Consortium, London School of Hygiene & Tropical Medicine

2001

CONTENTS

Malaria Burden and Interventions

SUMMARY

This paper reviews evidence on the burden of malaria, presents evidence of effectiveness and cost-effectiveness of priority interventions, and briefly describes some of the key constraints which need to be overcome in order to obtain a real impact in malaria control. Malaria remains the leading cause of death in children under five in Africa, and is a major economic burden in all malaria endemic areas of the world. As part of Roll Back Malaria new efforts to quantify malaria burden should provide evidence of progress in control. There is good evidence that appropriately applied priority interventions can reduce morbidity and mortality. While evidence is strong for case management, use of insecticide-treated nets and intermittent treatment for pregnant women, further information is needed on indoor residual spraying in different operational settings and epidemic control. Evidence of the effectiveness of support interventions such as human resource development, information, education and communication, surveillance and operational research exists, but is patchy and related to delivery approaches.

Many of the constraints to better malaria control are not specific to malaria, and need to be addressed through comprehensive strategies. Examples of successful interventions show that longterm increased investment both by countries, for example through new debt relief opportunities, and by the international funding community has a good probability of high returns in reduction of mortality and disease. Priorities for investment for long term progress are human resource development, systems to improve access to quality care in facilities and the community and development of effective affordable antimalarials.

1 INTRODUCTION

The purpose of this paper is to review what is known of the burden of malaria and to describe priority interventions based on knowledge of what is effective or not, citing evidence where it is available. The paper also summarises the conclusions of recent cost-effectiveness studies of malaria control interventions. It provides data on existing coverage levels of interventions, and comments on constraints to scaling up the interventions.

2 BURDEN OF MALARIA

Introduction

Human malaria is a disease caused by a protozoal parasite of the genus *Plasmodium* and transmitted by mosquitoes of the genus *Anopheles.* Its main symptom is fever. Depending on factors including level of immunity, species of parasite and access to prompt and appropriate treatment, some cases develop severe disease and complications, and many of these will die without appropriate treatment. Of the four species of *Plasmodium* infecting humans the two most common are *P. falciparum* and *P. vivax*. *P. falciparum* is responsible for almost all malaria deaths and is widely distributed in tropical regions, whilst *P. vivax* is rarely fatal, but has a wider geographical distribution in tropical, subtropical and some temperate areas (1). General accounts of malaria include (2) and (3).

Good estimates of the mortality, morbidity and economic loss caused by malaria relative to other health and non-health problems are essential for decisions on health care provision and financing at all levels, from household to international. Clearly presented data on the extent of the problem are an important advocacy tool for raising resources. Ability to measure change in burden by time and place is essential for planning, monitoring and evaluation of malaria control efforts.

Methodological issues in estimating malaria burden

The pressure to have better estimates of morbidity and mortality has increased in response to increased global attention to malaria. The Roll Back Malaria initiative has set an ambitious target of halving the malaria burden by 2010. In order to track progress towards this target reliable estimates are needed. WHO has developed a set of key indicators for monitoring and evaluation of Roll Back Malaria, and aims to use a combination of the methods below to refine estimates of malaria burden (4).

Numerous efforts have been made to collect data on malaria burden, but much of the information is known to be very incomplete. Most estimates of morbidity and mortality derive from health facility data. The data from many health information systems are of limited accuracy, but also these estimates miss the high proportion of malaria cases which do not occur in the public health system.

There have been two comprehensive attempts to estimate burden of malaria recently (5, 6). Nájera and Hempel (5) discuss in detail the methodologies used in developing past estimates, which varied greatly in different geographical areas. Outside of Africa there was much reliance on records of microscopically confirmed cases, but these missed many clinically diagnosed cases and cases treated outside the public sector, particularly in the more remote areas, which in areas such as Southeast Asia have the highest transmission. In much of Africa microscopy is not possible, and most cases are diagnosed clinically at home or in health centres. In areas of high transmission detecting presence of parasites is of limited utility, where parasite prevalence rates are extremely high and often not associated with illness. Earlier estimates of morbidity were based on extrapolation from point parasitaemia prevalence surveys. Following the adoption of the global malaria control strategy in 1992 with its focus on case management, WHO attempted to estimate number of clinical attacks.

Snow *et al.*'s (6) estimates of malaria morbidity and mortality were based on the epidemiological associations between climate and the likelihood of stable *P. falciparum* transmission, empirical survey-derived estimates of disease risks linked to epidemiological features of acquired immunity and interpolated models of population distribution in Africa in 1995.

DeSavigny (7) describes the new opportunities through better information technology to measure burden of disease at a sufficiently local level to be useful for planning. He analyses the limitations of conventional sources of information including the biases and low quality of routine health services data, the lack of district specificity and contemporary relevance of Demographic and Health Survey data and the patchiness and low coverage of survey and research trial data. Two promising new approaches are spatial and environmental information systems, including use of geographic information systems to map populations at risk and health services (eg HealthMap at WHO) and use of satellite remote sensing data for epidemic prediction (MALSAT, NASA and MARA/ARMA). The MARA/ARMA collaboration is developing a continent-wide, spatial database of all malaria indices relevant to malaria burden in Africa (8, 9, 10). A second promising source of information is the network of Sentinel Demographic Surveillance Systems (INDEPTH), which can measure community-based burden of disease and trends.

There are two phenomena which complicate the quantification of malaria mortality (11, 12). The first is indirect malaria mortality, where more than one cause is responsible for a death, and malaria contributes to a death classified as due to other causes. This is revealed when malaria control results in a reduction in deaths greater than would be expected from preventing malaria deaths. This was noted in Guyana (13) and Sri Lanka (11) and in the trials of insecticide-treated nets in The Gambia and Ghana (14, 15). In Kenya, however, it was noted that there was a 41% reduction in paediatric admissions for malaria but no reduction in non-malaria admissions (16). The second phenomenon is competing risks when a major reduction in malaria mortality leads to a lower than expected

reduction in total mortality in infants and young children, as noted in the Garki project in Nigeria (17) and in the Gambia (18) suggesting that children saved from malaria died of other causes.

Morbidity

According to current WHO estimates (19) about 100 countries or territories in the world are malaria endemic, almost half of which are in sub-Saharan Africa. This has decreased from 140 in the mid-1950s, but more than 2400 million of the world's population are still at risk. The incidence rate of malaria worldwide is estimated to be 300 to 500 million clinical cases each year, with about 90% of these occurring in Africa, south of the Sahara. Most of these cases are caused by *Plasmodium falciparum*. The same estimates were used for 1991 to 1993 (5) and for 1994 (20). Snow *et al* (6) estimated over 200 million clinical attacks for 1995 in sub-Saharan Africa. It has been estimated that in 1995-1996 about 3 to 5 % of the clinical cases in Africa were due to *P. vivax* (about 6 to 15 million cases), whilst *P. vivax* accounted for about 56% of cases outside Africa (60 to 70 million cases) (1). A recent review (21) argues that the burden of malaria has probably often been underestimated, particularly because of the small percentage of cases using formal health services, and suggests that there may be 400 to 900 million febrile episodes per year in children under five in Africa, of which about half may be malaria (200 to 450 million). Worldwide, over 2 billion febrile episodes may occur annually in all age groups of which a substantial proportion may be malaria.

Geographical variation in incidence rate of infection, disease and death is great. Even within sub-Saharan Africa there is wide variability with lower incidence in Southern Africa and in highland areas than elesewhere in the region. Variable incidence of infection relates to variability of transmission rate by mosquitoes, which is determined by ecological factors (temperature, humidity, presence of breeding sites) and effectiveness of vector control where applied. Levels of transmission in turn affect the development of immunity which affects severity of disease, mortality rates and age

distribution patterns with most severe disease and death in young children where transmission is high. Severe disease risk and case fatality rates are also affected by access to prompt and appropriate treatment. The wide variation in population at risk of malaria by country is shown in WHO (22).

Actual numbers of cases reported by Ministries of Health through WHO offices in the 1990s were 8 to 27 times lower than the estimates. Table 1 shows the numbers reported to WHO headquarters each five years from 1982 to 1997 by continent. These figures are recognised to be gross underestimates and inaccurate, since there are inconsistencies of reporting, most countries only report cases in government health services, and many countries only report laboratory confirmed cases. They are, however, the only attempt to count global numbers directly.

In addition to acute febrile illness malaria has a range of other manifestations. Some cases develop into severe disease, of which common manifestations are cerebral malaria(23), anaemia, hypoglycaemia and metabolic acidosis presenting as respiratory distress. The proportion of cases becoming severe has been estimated at around 2% in one study (24). Malaria may have chronic effects including anaemia (25), (26), neurological (27), cognitive (28) and developmental effects. Snow *et al.* (6) estimated that 5.6% of children surviving cerebral malaria from Africa had neurological sequelae persisting at least 6 months. They also noted that the severe anaemia caused by malaria in young children often requires blood transfusion with associated risks of HIV infection. The incidence of some of the commoner manifestations in African children is reviewed in (29), and the estimates in this review are summarised in Table 2. The morbidity burden due to *P. vivax* is discussed in (1). The pathophysiology and epidemiology of malaria related anaemia are described in (30). A review of evidence of the impact of *P. falciparum* malaria on performance and learning (31) suggests that malaria in childhood is likely to have effects on general cognitive and behavioural development, but that more research is needed to quantify this burden. Several papers suggest some correlation of malaria infection and nutrition. For example, protein-energy malnutrition appears to

be associated with greater malaria morbidity and mortality, and vitamin A and zinc supplementation can reduce clinical malaria attacks. Iron supplementation may slightly aggravate malaria, but strongly improves haematological status (32).

The pattern of severe disease in non-immune adults is different from that in children with cough, hypoglycaemia and neurological sequelae of cerebral malaria being less common and jaundice, pulmonary oedema and renal failure more common (33).

Mortality

For children under five years in the WHO African region, malaria is the leading cause of death (34). Table 3 shows that malaria ranked globally as the fifth most common cause of death (all ages combined) due to communicable diseases in 1999 after respiratory infections, HIV/AIDS, diarrhoea and tuberculosis. It ranked third in the WHO African region, sixth in the Eastern Mediterranean, eighth in the Southeast Asia and the Western Pacific regions, eleventh in Europe and twelfth in the Americas. These estimates used a refinement of the methods of Murray and Lopez (35) to calculate the global burden of disease.

WHO estimates that malaria kills between 1.1 and 2.7 million people worldwide each year (19), of whom about 1 million are children under the age of 5 years in Africa, south of the Sahara. The WHO global estimate for 1992 to 1993 was 1.5 to 2.7 million deaths (5). Nájera and Hempel (5) estimate a total of 895,000 deaths per year in the early 1990s in Africa and 1 million worldwide. Snow et al. (6) estimated just under 1 million deaths in the non-pregnant population in sub-Saharan Africa with about 766,000 deaths in children under five years. Breman (21) and Murphy and Breman (29) suggest that earlier figures may be highly underestimated, as not all manifestations of malaria are taken into account.

Childhood malaria deaths, resulting mainly from severe anaemia, hypoglycaemia, cerebral malaria and metabolic acidosis presenting as respiratory distress (29, 33, 36, 37), constitute nearly 25% of child mortality in Africa (19). Case fatality rates of 10-30% are reported in children referred to hospital with severe malaria (19). Table 2 shows the case fatality rates and numbers of deaths due to different manifestations of malaria in African children. In highly endemic areas malaria is considered to be the main cause of severe anaemia-related death in children (38).

While most severe disease and deaths in sub-Saharan Africa are in young children before they acquire immunity, deaths from malaria in countries outside Africa, south of the Sahara, occur mainly in non-immune people of all age groups who become infected with *P. falciparum* in areas where diagnosis and treatment are inadequate. High risk groups are often related to occupation. *P. vivax* is rarely a direct cause of mortality, but may have been responsible for a significant burden of mortality in the past, for instance in England and in Sri Lanka, possibly through interaction with other conditions (1).

Health burden in pregnant women

Pregnant women are more susceptible to malaria infection than non-pregnant women due to altered levels of immunity. Malaria affects both the mother and the foetus. Effects on the mother include anaemia, placental infection and increased mortality due to severe malaria. Effects on the foetus include increased risk of abortion, foetal death, low birth weight (LBW) due to intrauterine growth retardation and premature birth, and congenital infection. Low birth weight is the single greatest risk factor for neonatal mortality and early infant mortality, mortality in low birth weight infants being four times higher than in normal birth weight infants (39, 40). In Malawi, where malaria transmission is stable, LBW contributes 80% of all neonatal deaths and 37.8% of infant mortality (41). A recent review estimated that each year 75,000 to 200,000 infant deaths are associated with malaria infection in pregnancy (42).

In Africa, at least 24 million pregnancies are threatened by malaria each year (43). The clinical features of *Plasmodium falciparum* maternal infection depend on transmission levels. In areas of high to moderate transmission (which include the majority of sub-Saharan Africa) adults develop a high level of immunity but this is altered in pregnancy. Maternal malaria infection is frequently asymptomatic but is associated with anaemia, which is most severe in the first pregnancy and decreases in subsequent pregnancies. A recent study in Papua New Guinea has shown that malaria was associated with over half of all LBW babies born to first pregnancies (44). Studies in The Gambia have shown that maternal chemoprophylaxis reduced the prevalence of LBW among the babies of primigravidae from 22% to 6% and of multigravidae, from 5% to 3% (45). Similarly, maternal chemoprophylaxis reduced mortality in the first year of life by one fifth among the children of primigravidae and by about 4% among children of multigravidae (46). The effects on neonatal mortality are likely to be even more marked. *P. vivax* has also been associated with anaemia and LBW among pregnant women and their babies in Thailand (47).

In areas of low transmission or epidemic malaria, where women have little or no immunity, malaria infection in pregnancy is associated with severe disease (symptoms may include hyperpyrexia, hypoglycaemia, severe haemolytic anaemia, cerebral malaria and pulmonary oedema) and very high risks of maternal and perinatal mortality. The risk of maternal and perinatal mortality is high in all pregnancies. HIV infected pregnant women of all parities have been found to have increased malaria parasite prevalence and density due to impairment of parity-specific immunity to malaria (48), and are therefore at greater risk of increased parasitaemia, severe disease including anaemia, and death. Infants of HIV infected women are therefore also at increased risk of death.

Malaria is estimated to cause up to 15% of maternal anaemia in Africa and 35% of preventable low birth weight babies (43). A recent review of the evidence on the coincidental risks of malaria and anaemia in Africa estimated that as many as 400,000 pregnant women may have developed severe

anaemia as a result of infection with malaria in sub-Saharan Africa in 1995 (49). A study in Kenya showing that intermittent presumptive therapy in primigravidae reduced severe anaemia by 39% illustrates that malaria is indeed an important cause of severe anaemia in malaria endemic countries (50). In holoendemic areas with a 5% severe anaemia prevalence, malaria is estimated to account for approximately 18% of severe anaemia related deaths in primigravidae (51); the rest are due to nutritional deficiencies (mainly iron, folate, vitamin A and vitamin B12 deficiencies) or HIV infection.

Changes in Burden of Malaria

In several malarious areas outside Africa there have been major reductions in mortality through the twentieth century. In the last ten years, for example, Vietnam, Thailand, China and Cambodia have shown a dramatic decrease in mortality. In Vietnam malaria mortality decreased dramatically by 50% from 1992 to 1996, and morbidity decreased by 20-30%. While incidence is now similar to the early 1980s when indoor residual spraying was the only vector control measure used, mortality rates are lower than ever before, possibly associated with wide access to artemisinin derivatives (52).Following years of conflict malaria control programmes have developed quickly in Vietnam and Cambodia, in addition to which the forest habitat of the vectors has diminished. Decreases in the mid twentieth century were often attributable to the global malaria eradication campaign, particularly in India and Latin America. In sub-Saharan Africa, however, the numbers of deaths are increasing (6, 53, 54, 55,56). Reasons for increasing mortality are likely to be complex, and may include combinations of deterioration in health systems where utilisation has in some cases decreased because of user fees, increasing drug resistance (57, 58, 59, 60, 61), climate change with increasing frequency and extent of epidemics in the East African highlands and changed rainfall patterns in southern Africa and large-scale population movements and complex emergencies (for instance, extremely high mortality rates were recorded in Eastern Democratic Republic of Congo in 2000).

Several countries in sub-Saharan Africa are suffering increased malaria burden due to political conflict, details of which can be found in country profiles on the RBM website (www.rbm.who.int). Conflicts may lead to high exposure of non-immune populations, when they flee from areas of low to high transmission, such as the highland population from Rwanda fleeing to Tanzania in the 1990s. Displaced populations (particularly internally displaced people, who stay in their own country) often have limited access to health services. In countries with long-term conflicts, such as Angola, Somalia and Sudan, only a small proportion of the population may have any access to Government health facilities (30% in Angola, 62).

Trends in childhood mortality from all causes are reviewed in (63), (64) and (65), showing a slowing decline in childhood mortality in the 1990s in most regions and an actual increase in southern Africa, where HIV prevalence is high.

Nájera *et al.* (66) explored patterns of change in malaria since the mid 1960s, and noted groups of countries as follows: those where malaria has declined had relative social stability and socioeconomic development, those with marked increases in certain areas were characterised by increased exploitation of natural resources or sociopolitical unrest. Others showed oscillating incidence with little overall trend, and the last group had suffered short but major epidemics. The striking point here is that many of the factors influencing change were not related to malaria control intervention strategies, but quality and quantity of implementation would be affected by the social and economic factors.

Climate change has been shown to shift the distribution of some insect species, but there is so far a lack of strong evidence of the impact of climate change on malaria (67, 68). New approaches to monitoring are needed. As climate is an important limiting factor of mosquito distribution, changes would be expected. While an apparent increase in epidemics in highland areas suggests an effect of

climate changes, the effects of altitude are complicated, and an important factor is lack of breeding sites. While an increase in malaria and temperature were noted in Ethiopian highlands, there were confounding factors such as reduced house spraying and increased chloroquine resistance. There is some evidence that malaria has decreased in association with decreased annual rainfall in countries just south of the Sahara desert.

There has been much debate in recent years on the effects of reducing malaria transmission on long-term burden of malaria in Africa. Carme (69), Snow and Marsh (70, 71), Snow *et al.* (72), Trape and Rogier (73) all suggested that malaria transmission control may not reduce overall mortality rates, as children in areas of higher transmission develop immunity earlier than those in areas of lower transmission. The clinical characteristics of severe malaria tend to be different under different levels of transmission with less cerebral malaria and more severe anaemia in areas of higher transmission (74). Molineaux (75) suggested that the long-term impact on all-cause mortality of reducing exposure to malaria is still likely to be beneficial, if indirect malaria mortality is important.

Rapidly increasing urbanisation may have an important influence on malaria burden in Africa. It has been estimated that in 2000 43% of the population of sub-Saharan Africa were living in urban areas. Whilst malaria transmission tends to be lower in developed urban centres than rural areas, there is considerable transmission in densely populated fast growing peri-urban areas (76). Malaria transmission in some Indian cities has increased. Urbanisation can also affect risk of disease, as people in areas of lower transmission develop less immunity.

The escalating burden of HIV infection in Africa has important implications for malaria burden. Evidence was very limited until recently of important interactions between malaria and HIV except in pregnant women, where HIV positive women have been shown to have higher malaria parasitaemia, and there is an association among placental parasitaemia, HIV and poor pregnancy

outcome. Appropriate recommendations for intermittent malaria treatment in pregnant women in areas of high HIV prevalence may be affected. There is now good evidence from Uganda, however, of increased susceptibility to malaria fever in HIV-infected adults in general, and there is an urgent need for more data in children (77, 78). The recent increased malaria mortality and incidence documented in Southern Africa coincides with increasing prevalence of HIV. In view of high prevalence of HIV in children under five, several countries in East and Southern Africa have now included HIV algorithms into their adaptations of the Integrated Management of Childhood Illness training in order to identify suspected symptomatic HIV-positive children and offer them appropriate counselling, testing and treatment.

Murray and Lopez (79) predict that malaria will fall from eleventh to twenty-ninth position in ranking of causes of death globally between 1990 and 2020. This projection is based on assumptions that socioeconomic development will decrease incidence and severity of communicable diseases, and that research and development will guarantee the availability of drugs effective against resistant strains.

Economic burden

Malaria is a major contributing cause of poverty in endemic areas. In 1997 an estimated US$1.8 to $2 billion was spent in Africa on both direct costs of malaria prevention and care, and on indirect costs such as lost productivity and time costs (80) and this figure was projected to rise to US$3.6 billion or more by the end of 2000. More recent estimates suggested that the economic losses due to malaria in Africa are actually about US$ 12 billion per year and the needs for malaria control have been estimated to be about US$3 billion (81). In Ghana, average direct and indirect costs of treating a malaria episode were US$8.67 (82), US$11.82 (in 1989) in Rwanda (83) and US$11.70 in Burkina Faso (84). In urban Burkina Faso families were found to spend on average $42 on treatment and $33

on prevention over the six months transmission season. This was nearly 5% of total family income over the period (85). Inpatient treatment for severe malaria has been found to cost $35 per admission in a typical Kenyan district hospital (86) compared to $1.10 for an outpatient visit in Malawi (87). In Cameroon, malaria was found to account for 31 % of annual family illness expenditures and costs (88), and an average of US$20 is spent annually by households on malaria costs in Malawi (89). In some areas such as urban Tanzania most people claim to use domestic mosquito control products, and many claim to use mosquito coils spend nightly, which would cost about US$1 per month (90). Malaria has been estimated to be responsible for reductions in gross domestic product from 0.6% to 6% in African countries (91, 92). It has been estimated that, taking into account initial poverty, economic policy, tropical location and life-expectancy, countries with intensive malaria had an economic growth between 1965 and 1990 1.3% lower per person per year than countries without, and that a 10% reduction in malaria was associated with 0.3% higher growth (93).

Further spread of drug resistance will result in higher costs to the health system and to families and communities, as potential new first line antimalarials are 4 to 40 times more expensive per treatment than currently recommended drugs.

Economic burden in pregnant women

There have been no analyses specifically addressing the economic burden of malaria in pregnant women. Direct costs of treating severe or complicated cases of malaria and malaria associated severe anaemia in pregnant women are assumed to be high. Where the quality of antenatal care services and/or access is poor, the outcome of malaria infection in pregnancy is likely to be poor. In turn, maternal death places a high economic burden on households (an indirect cost).

3 SUMMARY OF RECENT DEVELOPMENTS IN GLOBAL STRATEGIES

Before reviewing the interventions which are currently considered to be priorities, it is useful to consider how these were selected, and why the emphasis has changed over the last few decades. Bradley (11) reviews the evolution of malaria control.

In the early part of the twentieth century, following incrimination of mosquitoes as the vectors of malaria, there was great interest in environmental control to remove breeding sites (11, 94, 95).

1950s and 1960s

The first attempt to tackle malaria on a globally coordinated scale was the global malaria eradication campaign of the 1950s and 1960s (96, 97, 98). In order to achieve the goal of eradication the campaign aimed to end transmission by attacking the vectors and to eliminate the reservoir of infection by attacking the parasites. It did not aim to eradicate the vectors. There was little interest in treatment of individuals except as a form of transmission control. A time-limited campaign was envisaged to be carried out with sufficient perfection to avoid resumption of transmission.

Much was achieved by the campaign, although very little was done in Africa. By 1970 it had freed 727 million people from the risk of malaria (53% of those at risk before the programme). Eradication was achieved in large parts of North America, Southern Europe, the former Soviet Union, the Middle East and parts of Asia and South America. The progress in eradication saved many lives, and contributed to economic development in Asia, South and Southeast Europe and the Americas, and in India also reduced the prevalence of leishmaniasis and plague. It also stimulated the training of thousands of health workers, who became a significant part of general health services (96). Following the conversion to control in 1969 the situation deteriorated especially in southern

Asia, Latin America and Southeast Turkey. The number of reported cases doubled from 1974 to 1977.

Important lessons from the campaign apply to future malaria control efforts. Sustainability was limited due to: reliance on a single tool (resistance developed to DDT in some areas), difficulties in maintenance of quality of activities over extended periods (e.g. coverage of house spraying and quality of active case detection when slide positivity rates could be less than 1%), difficulties in maintaining faith and interest in the goal (by 1969 funding sources were already diminishing, as funders moved to other priorities) and pace of efforts (the importance of taking time to build a solid foundation for malaria control has been emphasised).

Many problems of malaria eradication have been attributed to inadequate planning. In particular, the needs for health services adequate to carry out surveillance in the consolidation and maintenance phases were often neglected. There was also no exit strategy. The global malaria eradication campaign was in existence for 14 years (1955 to 1969), but it was not until 1986 (99) that a true replacement strategy was articulated.

Such programmes are dependent on long term commitment. For example, the Indian National Malaria Eradication Programme (NMEP) was a gigantic effort, which initially achieved enormous success with a reduction of cases from an estimated 75 million in 1952 to 0.1 to 0.14 million in 1965-6, but progress was reversed in the latter part of the sixties leading to a peak of 6.47 million cases in 1976. According to NMEP the major cause was sudden withdrawal of assistance without consultation, especially for insecticide purchase.

The attitude to the public of the expert committees and failure to gain public support and ownership is thought to have contributed significantly to failure of the campaign.

1970s and 1980s

Following the end of this campaign, malaria control received little support for two decades, as there was a perception that disease-specific approaches were ineffective.

1990s

In response to the major burden of malaria in Africa and the concern of national authorities a Malaria Control Strategy for Africa was formulated in 1987. Difficulties in implementation and continued concerns of African countries expressed at WHO governing bodies led to the calling of the Ministerial Conference on Malaria Control in Amsterdam in 1992, which adopted the Global Malaria Control Strategy (100,101). The global strategy strongly emphasised case management through early detection and prompt treatment as its priority.

In addition to support from the US Agency for International Development and the UK Department for International Development (DFID) for strengthening capacity in the 1990s, WHO/AFRO received US$9 million from the WHO Director General's Special Fund for Accelerated Implementation of Malaria Control in 1997 and a further US$9 million in 1998 (102). 34 countries were supported under this scheme. Plans of Action of the targeted programmes were prepared in line with the Regional Malaria Control Strategy, and the main components of the planned country activities were: case management, community-based interventions, epidemic prevention and control, vector control, strengthening health information systems, monitoring and evaluation, operational research and programme support.

In June 1997 the Organisation of African Unity reviewed and endorsed the Global Malaria Control Strategy, and issued the Harare Declaration on Malaria Prevention and Control, and also in 1997 an African Initiative on Malaria Control (AIM) was developed by representatives of the World Bank,

WHO, UNICEF, selected countries and other interested parties to intensify efforts to control malaria with longer term commitment to the effort over 25 to 30 years (103).

In May 1998 the Summit of the Group of Eight industrialised countries agreed to support malaria control as part of a larger plan to combat infectious and parasitic diseases. At the World Health Assembly in May 1998 the newly elected WHO Director General proposed a major new movement to develop global and local partnerships to halve the burden of malaria by 2010: Roll Back Malaria (RBM) was launched in October 1998 by its four founding partners UNDP, UNICEF, World Bank and WHO, and received substantial support from DFID. Bilateral spending from various countries on malaria in several countries has increased in recent years (98). External contributions to malaria control are difficult to quantify, as some agencies increasingly provide unearmarked support to the health sector which supports malaria control according to national prioritisation.

The first decade of the 21st Century

Roll Back Malaria has been described as follows (104):

- The RBM partnership includes governments, development agencies, commercial organisations, professional associations, civil society, research groups and the media.
- RBM partners have set a 10-year target to halve the world's malaria burden by 2010. This will be achieved by creating a social movement that enables countries to take effective and sustainable action against the disease.
- RBM partners plan a massive, continuing attack on malaria. It aims to secure a 30-fold expansion in the proportion of people who can get effective treatment, ideally within two hours travel of the onset of symptoms, and in those who use treated mosquito nets. RBM particularly seeks to help pregnant women at risk.

- RBM partners aim to achieve this by strengthening countries' health systems; mobilising social movements to support local malaria control needs; evaluating results and monitoring progress; and developing new tools.
- Tracking the spread of drug resistance, improving access and use of quality anti-malarials and careful selection of treatment regimes help reduce the malaria burden.
- The Medicines for Malaria Venture aims to produce a new, affordable anti-malarial drug every five years.

RBM has prioritised four actions (34), which it considers evidence-based:

- Prompt treatment with effective drugs
- Insecticide-treated materials and other vector control methods
- Intermittent preventive treatment in pregnancy
- Emergency and epidemic preparedness and response

The evidence base can be considered in two ways. Firstly, these interventions have been shown to reduce morbidity and / or mortality if applied correctly, and secondly there is an ongoing need to collect evidence on the components of these actions in particular environments and over time (choice of drugs and insecticides, acceptability, accessibility and use by users and providers).

Progress in implementation of RBM in Africa up to September 2000 (i.e. in its second year) has been summarised as follows (105):

In April 2000 a conference of African Heads of State met in Abuja to adopt a strategy for implementation of RBM (106). A key step was the development of the framework for RBM

implementation in the African Region, which was adopted by the 50th Regional Committee meeting held in Burkina Faso in August 2000. The framework stated that:

- RBM builds on the foundation laid by the Accelerated Implementation of Malaria Control
- The goal is to reduce malaria burden to a level where it is no longer one of the major contributors to mortality and morbidity

There are 8 pillars in the implementation strategy:

1. ownership,
2. contributing to health sector reforms and socio-economic development activities,
3. integration of malaria control activities into primary health care,
4. increasing coverage of cost-effective interventions,
5. building and strengthening partnerships,
6. strengthening community participation,
7. strengthening health information systems and research
8. building and strengthening neighbouring countries' collaboration

It was concluded that new elements in RBM were:

- It is country specific and country driven
- It is linked to health sector development and poverty alleviation
- It aims to bring technical interventions to scale
- It focuses on development of multisectoral partnerships including opportunities such as Integrated Management of Childhood Illness (IMCI) and Bamako Initiative.

In other parts of the world the momentum of RBM has also increased. In particular an initiative in Cambodia, Laos, Myanmar, Thailand, Vietnam and Yunnan Province, China, known as RBM

Mekong with joint UNICEF/WHO support has developed a local strategy. This region is characterised by forest malaria in occupational risk groups and ethnic minorities, and malaria has been a particular problem in migrant populations (work-related and conflict-related). The focus of the strategies in the region is on appropriate treatment of multi-drug resistant falciparum malaria, which in parts of Thailand and Cambodia, requires combination therapy with mefloquine and artemisinin-derivatives. The role of rapid diagnostic tests in remote areas is being actively developed, and ensuring access to insecticide treated nets is a priority (52).

Following the G8 Summits in Okinawa in 2000 and Genoa in 2001 there is growing political commitment for a global health fund especially for TB, HIV and malaria, and further discussions are underway.

4 EVIDENCE OF EFFECTIVENESS OF PRIORITY INTERVENTIONS

This section lists the major interventions against malaria, and reviews evidence of their efficacy and effectiveness taking into account geographical variability in approach related to ecology, epidemiology and socioeconomic and political factors.

A consensus has built up in recent years that the priority interventions are as follows:

a) major direct interventions:

- Case management (diagnosis and treatment)
- Insecticide treated materials (ITMs)
- Indoor residual spraying in certain environments
- Protection of pregnant women
- Epidemic control

b) support interventions

- Human resource development
- Information, Education and Communication
- Surveillance
- Operational research

While these support interventions do not directly remove either the vector nor the causal agent, they are included in this review as essential components of malaria control with as much potential to reduce morbidity and mortality with adequate investment. IEC can have a direct effect on the host, if it leads to behaviour change. Surveillance can reduce blanket coverage of vector control by allowing the targeting of vector control based on information. HRD (in its broad sense of ensuring people have relevant skills and an enabling environment to use their skills efficiently) is essential for adequate quality application of interventions and increased scale of coverage. Operational research ranging from programme evaluation to invention, testing and refinement of new tools helps to adapt control strategies to changing biological, social and economic environments.

Protection of pregnant women and epidemic control have been included as direct interventions. While they incorporate elements of the other direct interventions, it is useful also to consider the set of interventions for these two purposes as single packages, as those responsible would need to address all the components. In addition, they include components not covered by the other basic interventions: intermittent presumptive treatment and chemoprophylaxis for protection of pregnant women and more sophisticated early warning systems for epidemic control. Control of malaria in complex emergencies is similarly a package of interventions for a specific risk group. It adapts a combination of the other interventions to the particular emergency, so is not classified as an intervention itself, although an argument could be made for doing so.

Interventions which have not been included in the list of priorities include those where there is less evidence of widescale effectiveness, such as environmental management and various forms of larviciding, but they may have an important role in limited areas, especially in urban settings. Environmental management may also be important against other disease vectors, and various examples including malaria control are reviewed in (107).

The potential of environmental management depends on the types of breeding sites used by the predominant vector species. In rural Africa the main vector is *Anopheles gambiae* sensu lato, which breeds in a very wide range of small temporary pools and puddles, which would normally be very difficult to remove over the long term. There are some exceptions, such as the leakage points on irrigation pipes in semi-arid areas such as northern Namibia, where better maintenance could potentially significantly reduce transmission rates and possibly shorten the transmission season. The other major African vector *A. funestus* inhabits fewer, larger and more permanent sites, such as large swamps and river edges, but even these would be difficult to remove. In peri-urban areas environmental management is more feasible, partly because the human population density reduces the per capita cost of engineering work. An example of successful malaria control through a combination of environmental management and other interventions in a Zambian copper mine in the 1930s to 40s has recently been reanalysed (108), suggesting that the very high initial costs reduced after a few years to the point where the interventions were cost-effective. As with many other interventions, however, affordability is likely to be a stronger driving force than cost-effectiveness. In West Africa rice fields in peri-urban areas are a breeding site, where some form of environmental management could be considered. In India the urban vector *A. stephensi* is a potential target for environmental control, and good control was achieved in Channai through improved design and maintenance of water tank lids. In much of Southeast Asia the major vectors *A. dirus* and to a lesser extent *A. minimus* are restricted to forest areas. Large scale deforestation had a temporary effect of increasing malaria risk for those involved in forestry, but in the long term has probably contributed

importantly to reduction in malaria prevalence, while bringing other environmental problems related to changing weather patterns.

While investments in environmental management for malaria control are difficult to justify in many situations on the basis of available evidence, the importance of health impact assessments should be emphasised as part of development projects to avoid creating new problems.

A particular aspect of environmental management, which has been widely recommended on the basis of no evidence, is the cutting of grass or clearing of bush around homesteads. The only published study provides evidence that this is not effective (109), yet it is a mainstay of health education messages to overworked communities.

Vector control with ultralow volume insecticide spraying and thermal fogging is expensive, and has limited use in very special conditions.

Malaria vaccines have not been included in the list, as there is as yet no effective vaccine to use. Investment in vaccine research is, however, increasing rapidly, and new possibilities offered through genomic research and DNA-based vaccine development may accelerate achievement of a usable multi-target vaccine (110, 111). A major issue will be the ability of vaccines to provide sufficiently long-term protection to make them operationally useful in populations living in endemic areas rather than only in short-term visitors. Reviews of pre-erythrocytic vaccine developments (112), merozoite surface protein vaccine candidates (113), progress and constraints in vaccine development including the risk of increasing severity and rebound mortality (114, 115) and the possible effects of transmission-blocking vaccines (116) provide an overview of current status. A Cochrane Review (117) reported that two types of vaccine, SPf66 vaccine against the asexual stages and NANP vaccines against sporozoite stages of *Plasmodium*, have been tested in randomised clinical trials in

endemic areas. Nine trials of the Spf66 vaccine and four trials of the NANP vaccines were reviewed, and showed no evidence of protection by SPf66 vaccines against *P. falciparum* in Africa . There was a modest reduction in attacks of *P. falciparum* malaria following vaccination with SPf66 in other regions. Trials to date have not been of sufficient size to evaluate the effect of malaria vaccines on mortality or on severe malaria requiring admission to hospital. There was not enough evidence to evaluate the use of NANP vaccines.

Where efficacious vaccines would fit into, and how they would influence, the combination of priority interventions against malaria will depend very much on the nature of the vaccine. It is clear, however, that their efficiency outside a research setting would, as for other interventions, rely on operational factors such as acceptability to users (education of providers and receivers), accessibility (delivery systems, human resources) and affordability. A new set of operational research questions will need to be answered, which can draw usefully on recent experiences with operationalising insecticide-treated nets.

Evidence of effectiveness of major direct interventions

4.1 Case management

Good case management is the foundation of effective malaria control, and many deaths and severe cases of illness could be avoided by better application of currently agreed procedures for case management. Introduction of some newer case management interventions could save further deaths. Case management includes recognition or diagnosis and treatment.

The evidence base for case management includes (1) evidence of the sensitivity and specificity of different diagnostic tools, (2) evidence of efficacy of different drugs at different doses, (3) evidence

of efficacy of different ancillary treatments and non-drug clinical interventions and (4) evidence of effectiveness of different service delivery systems, which are influenced by both providers and users.

Recommendations on range of diagnostic methods and drugs from which to choose, procedures for case management and systems for delivery vary according to the level of intervention (home, primary, secondary or tertiary facility in public and private sectors). Malaria cases are often distinguished as severe or uncomplicated with different procedures for each. WHO published a comprehensive review of issues and guidance on practice related to severe malaria (33) as well as a practical handbook (118). Management of uncomplicated malaria is described in (3) and (119).

4.1.1 Recognition and Diagnosis

Prompt and accurate diagnosis of malaria is a key element in effective case management. This includes initial recognition at home by the caretaker or patients and diagnosis by health workers. Many people who die from malaria never contact formal health services. For example, in Morogoro in Tanzania a survey showed that 90% of deaths in under five year olds take place at home, and 48% of these occur without any prior contact with a formal health facility (120). Of patients admitted to hospital with severe malaria a large proportion die within 24 hours (121). It is likely that more accurate and earlier recognition of malaria by patients and caretakers at home would significantly reduce mortality. The potential impact of programmes to educate people at risk on recognition of malaria and to provide diagnosis closer to the home is high but difficult to measure. Numerous systems have been developed to provide diagnosis closer to homes, particularly in Asia. Those with community volunteers have had mixed success often due to poor support of volunteers by the public health system. A successful programme (in terms of sustainability) in Sabah is described by Palmer *et al.* (127). Malaria incidence did decline in the area covered, but the relative roles of early

detection, treatment, treated nets and other factors are not known. In Thailand Ettling *et al*. (122, 123) investigated the role of central, peripheral and periodic mobile village level clinics in provision of microscopic diagnosis and treatment, and found that the periodic mobile clinics had lowest institutional costs per smear but highest costs per positive case, but reached women and children more than the other clinics. While they had the lowest travel costs and frequency of prior treatment, they did not reduce reported length of illness prior to attendance, and a large percentage (91%) of patients used none of the clinics, but spent more on treatment outside the public sector with longer illness times. In Tigray a scheme to educate mothers to recognise and treat malaria led to a 40% reduction in under five mortality and a significant reduction in malaria specific mortality (124). The relative importance of improved ability to recognise malaria symptoms compared to better access to chloroquine and awareness of treatment regimens is not known.

The major diagnostic approaches are clinical diagnosis, microscopic diagnosis, HRP2-based rapid diagnosis and pLDH-based rapid diagnosis. QBC and Acridine orange and PCR are less promising for widescale use. Table 4 compares the approaches.

Despite numerous attempts it has not been possible to develop highly sensitive and specific clinical algorithms (125, 126), so that accurate diagnosis requires detection of parasites by microscopy or with immunochromatographic rapid diagnostic tests (RDTs) detecting parasite antigen. Microscopy is often unavailable at peripheral levels of the health services, and requires good systems support and trained personnel, while RDTs are too costly for widescale use at present. The cost of malaria microscopy ranges from US$0.12 to $0.4 (127), while RDTs cost about US$1, although prices as low as $0.60 have been achieved for *P. falciparum* only tests.

The role of RDTs has been defined as being particularly promising in areas of low to moderate transmission (mostly in Asia and the Americas and in parts of Africa), where most infections are

symptomatic, and often there is multidrug resistance (128). While microscopy would be the tool of choice at more central levels, RDTs would be useful in peripheral and remote areas without the infrastructure for laboratories. There have been several small scale projects using RDTs, for instance in Cambodia, Thailand, India, Vietnam, Guyana, Brazil and Ethiopia.

In areas with high transmission rates, mostly in Africa south of the Sahara, the role of microscopy has been limited by inadequate health systems and the limited usefulness of detection of parasites where prevalence is very high and often not associated with illness. Use of RDTs has been extremely limited. Laboratory confirmation would be useful for suspected cases of severe malaria, suspected treatment failures, private sector care and multidrug resistance. RDTs also have a potential role in complex emergencies before microscopy can be established and in suspected malaria epidemics to determine the extent of malaria and for travellers, soldiers and migrant workforces.

To what extent could the number of deaths be reduced and acute cases be treated more effectively with better diagnosis? The greatest impact of any intervention would be realised in sub-Saharan Africa which accounts for 90% of cases, but this is where there are greatest reservations on the role of parasitological diagnosis. The impact of a given diagnostic approach depends on its influence on rational treatment. Could a well trusted diagnostic method be linked to more rational drug use? Could the concept be marketed that, once you have the result, you do not need a costly cocktail of drugs or injections? In several cases it has been noted that health care providers or patients will ignore the results of negative test results, and still treat for malaria, so that the diagnosis is of no use (129: for microscopy; 130: for RDTs). There is, however, potential to change this behaviour through education. In Solomon Islands it was noted that some patients refused treatment without a parasitic diagnosis (131). In Cambodia a programme is beginning for social marketing of RDTs with pre-packaged combined mefloquine artesunate treatment through private vendors (132).

Few studies have tried to assess directly the effect of diagnosis on morbidity or mortality. Sim (130) noted in three health centres in three provinces of Cambodia a large increase in cases diagnosed following introduction of RDTs, a reduction in case fatality (not statistically significant) and a reduction in the proportion of cases which were severe (statistically significant). A concern to be addressed in developing more widespread parasitological diagnosis is the risk of re-use of finger pricking devices with the associated risk of HIV transmission.

The role of diagnosis needs to be reviewed in response to major epidemiological changes in Africa. Rapidly increasing antimalarial drug resistance and increasing frequency and scale of epidemics may justify greater investment than before in diagnostic facilities.

4.1.2 Treatment: antimalarial drugs

Although the number of malaria cases and related deaths at the present time is enormous and unacceptable, it is widely agreed that the availability of cheap effective antimalarials has limited the burden. The rapid increase in resistance to the cheapest antimalarials threatens to cause great increases in disease and death, and is a major obstacle to achieving Roll Back Malaria's objective of halving malaria deaths by 2010.

Antimalarial drugs are used both for treatment of malaria and for prevention (chemoprophylaxis). Their use for prevention of malaria and pregnancy is discussed later. The other major use of drugs for prevention is for non-immune travellers to malaria endemic areas (119, 133), which is not discussed in detail here, as malaria in international travellers is a small proportion of the burden except in displaced populations, where chemoprophylaxis may not be practicable. In the 1980s there was considerable discussion on whether or not to recommend routine prophylaxis for children under five years living in high risk areas with WHO concluding that it was not advisable, whilst UNICEF

did advise it. It is currently not recommended because of difficulties in ensuring people follow prescribed regimens and increased drug resistance (119). A recent report has, however, shown a significant impact of intermittent sulfadoxine-pyrimethamine treatment of children in Tanzania at the time of routine vaccinations (134) on clinical malaria and the rate of severe anaemia. The rate of clinical malaria attacks during the first year of life was reduced to 0.15 compared to the control, and the rate of severe anaemia was 0.06 compared to the control of 0.11. Given the importance of anaemia, which is often not recognise, such a preventive approach is attractive if it can be administered easily.

Descriptions of the main drugs available for malaria treatment are found in (119), and an update will shortly be issued following an informal consultation on antimalarial drug use at WHO Geneva in November 2000. Table 5, which was prepared for this meeting, summarises the cost, treatment duration, likelihood of adherence, significance of side-effects and status of resistance of the major antimalarial drugs currently available. Commonly used drugs for uncomplicated malaria are chloroquine, sulphadoxine (or sulfalene) /pyrimethamine, amodiaquine, artemisinin and its derivatives (primarily artesunate and artemether). Less widely used drugs for uncomplicated malaria include quinine (with tetracycline or doxycycline where there is quinine resistance), mefloquine, halofantrine, lumefantrine combined with artemether, sulfamethoxazole/trimethoprim, and atovaquone/proguanil. Commonly used drugs for severe malaria are quinine and artemisinin derivatives. Combination drugs under development, where initial evidence of efficacy is promising, are chlorproguanil/dapsone, which may be combined with artesunate, a fixed dose combination of piperaquine, trimethoprim and dihydroartemisinin (DHA), a combination of pyronaridine and artesunate or DHA and finally a trial coformulation of naphtoquinone and DHA (135).

Numerous studies have tested the efficacy of antimalarial drugs both *in vitro* and *in vivo.* There have sometimes been problems in comparing data from different studies, as the methodologies have

varied. A standard *in vivo* test for chloroquine efficacy was developed by WHO (136), and widely used, but needed rethinking in the 1990s, as the range of drugs to be tested broadened to drugs with different dosage regimens and different elimination times. In addition it became clear that the initial *in vivo* test gave inadequate attention to clinical outcome, as it relied on parasitological follow up. There is now growing adoption of a new standard (137) for use in routine monitoring of drug efficacy, but some research projects collect other data. It is beyond the scope of this paper to review all evidence on drug efficacy, because the efficacy of each drug varies widely geographically and also with time. Attempts have been made to develop a continually updated database of current status of drug efficacy, accessible to all, but there have been constraints related to the issues of inconsistent methodology and of reluctance of some scientists to make data available before it is published. In the 1980s WHO had a database of *in vivo* and *in vitro* data, which for the *in vivo* studies only included those strictly adhering to WHO methodology. WHO African Region has more recently set up a database for Africa following discussions with the Centers for Disease Control, Atlanta and WHO headquarters. Useful summaries of drug efficacy by country are published each year for travellers by WHO (133). Some antimalarial drugs and combinations have been the subject of recent Cochrane systematic reviews, and conclusions from these and other reviews are summarised in Table 6.

Antimalarial drug resistance in *P. falciparum* is increasing faster than new antimalarial treatments are being developed to the point of widescale use. This is resulting in countries offering suboptimal therapy. Most of the newer antimalarials are much more expensive than chloroquine and sulfadoxine-pyrimethamine, which are the main drugs used in most of the world, and cost approximately US$0.1 per adult course. Table 5 shows the relative costs of different antimalarials. Areas of multidrug resistance in Southeast Asia have already had to rely on treatments costing approximately US$2 per adult course for several years. In some parts of Thailand and Cambodia

there is no affordable effective monotherapy, and treatment is with mefloquine-artesunate or mefloquine-artemether combination.

In Africa, which accounts for the majority of the world's malaria, chloroquine resistance is widespread, and has reached levels in southern and eastern Africa, where many countries are forced to abandon its use as first line therapy. SP used to be the obvious successor, but resistance to SP is developing quickly in some African countries, so that its useful therapeutic life is likely to be short, as it was in parts of Southeast Asia. The costs of changing first line drug are considerable (138).

Evidence of the role of effective treatment on malaria burden is patchy, as effective treatment is determined not only by drug efficacy, but also by access, treatment-seeking behaviour and drug quality. The association of increasing mortality with increasing drug resistance (57, 58, 59, 60) does confirm that use of effective drugs can lower mortality.

More direct evidence comes from Malawi where a reduction in mortality was recorded following the change of first-line treatment from chloroquine to sulfadoxine-pyrimethamine (139, 140). As noted earlier the widespread use of artemisinin derivatives in Vietnam may have contributed to the reduction in mortality in the early 1990s (52).

Relative incidence rates of *P. falciparum* and *P. vivax* are another indicator of the impact of effective drugs. In Thailand the proportions of the two species mirrored the development of resistance in *P.falciparum* and the introduction of more effective drugs (141), and in India the proportion of *P. falciparum* has increased from 15 to 40% in recent years (142). The introduction of mefloquine-artesunate combination therapy in Western Thailand was associated with a reduction in incidence (47, 143).

The importance of appropriate antimalarial drug policies taking account not only of drug efficacy, but also accessibility, affordability, acceptability, ease of use, safety and quality is increasingly emphasised (144, 145, 146). The need for efficient policy development processes in order to reduce the time when people are deprived of the best available and affordable treatment is also recognised. Some of the problems which delayed policy changed in Kenya are described in (147).

The primary goal of treatment policy is to treat the patient effectively (at a minimum to remove signs and symptoms and optimally to clear all parasites). Secondary goals are to avoid as far as possible the development of drug resistance and to reduce transmission. These goals do not necessarily suggest the same strategies, and a careful balance is needed in determining priorities. While the widest possible access to effective drugs would serve the primary goal in the short term, it could lead to a higher overall burden of malaria by leaving no appropriate drugs for use in the future.

Combination therapy

This dilemma has become particularly acute with the potential to combine highly effective artemisinin derivatives with other antimalarials

Measures to delay the development of resistance are essential, whilst still ensuring that safe, effective, usable and affordable treatment is accessible to those at risk. Resistance is due to mutations in genes controlling the structure and activity of the therapeutic target in the malaria parasite. Combination therapy is likely to delay development of resistance to component drugs, because the probability that a mutant will arise, which is simultaneously resistant to two drugs with different mechanisms of action is the product of the mutation rates to resistance to the respective drugs, multiplied by the number of cells exposed to the drugs (148).

The degree of protection will depend on the frequency of resistance genes already in the parasite population to the drugs in the combination. Where there is already high level resistance, the protection will be lower. This was a problem with the introduction of the mefloquine and sulfadoxine-pyrimethamine combination on the Thai-Cambodian border and in Thailand in the early 1980s. It has not, however, so far been a problem with the use of mefloquine-artesunate combination in Thailand despite high level mefloquine resistance (47). The mechanism of resistance is also likely to be important. For instance, complete resistance to SP depends on the presence of four dihydrofolate reductase (DHFR) mutations. Currently, only three are found in Africa, and the fourth is not yet reported, so combination of SP with a different effective antimalarial may still be valuable, as the other drug would kill most parasites where the fourth mutation arose, while the SP would still have enough efficacy to give some protection to the other drug, as most parasites exposed to the combination would at the most be triple DHFR mutants. The time remaining for useful introduction of SP combinations is limited.

Ideally the two drugs in a combination should have similar pharmacokinetic properties, and would not have long elimination half-lives, as there is an association between selective pressure and slow drug elimination. If one drug is eliminated more rapidly, the other one may encounter parasites from a second infection, when the first drug has been eliminated, and the second drug is at sublethal concentrations. This problem is more important in areas where frequency of infection is high. However, the most powerful resistance selection occurs during early treatment of an acute malaria attack, so drugs with different elimination half-lives can be effectively combined.

Evidence of the effectiveness of combination therapy in delaying the development of resistance is not yet available in Africa, but studies in an area of low, seasonal, unstable transmission on the Thai-Myanmar border have found that a combination of 25mg/kg split dose mefloquine and three days artesunate at 4mg/kg per day has maintained an efficacy of greater than 96% since introduction in

1994 despite less than 50% efficacy of mefloquine alone. An overall reduction in malaria incidence and significant *in vitro* reversal in mefloquine resistance were observed (47, 149)

The particular interest in combinations with an artemisinin derivative relates to its high efficacy, its very rapid parasite and symptom clearance times and its strong effect on reducing gametocyte carriage rate, which reduces further the transmission of resistant alleles . The value of artemisinine derivatives is great, so it is also important to use them rationally to protect them.

While there is urgency to offer more effective treatment whilst minimising the risks of developing further drug resistance, there are still many operational constraints such as (primarily) affordability, acceptability to, and adherence by, patients, providers and policy makers, access through public and private sectors, use in pregnancy, which may diminish the potential of combination therapies (150, 151). A more comprehensive operational research, information gathering and consultation strategy needs to be implemented as quickly as possible in order not to be too late to benefit from the range of antimalarials currently available.

4.1.3 Ancillary treatments

The three important ancillary treatments in cases of uncomplicated malaria are rehydration, fever reduction and treatment of anaemia (119, 152). In severe malaria, several ancillary treatments depending on what complications are detected, have been shown to increase the probability of survival. These include preventing convulsions with prophylactic phenobarbitone, treating hyperpyrexia and hypoglycaemia, correcting fluid electrolyte and acid-base imbalance, appropriate nursing care and avoiding harmful ancillary treatments such as corticosteroids and heparin. Details of these and evidence of their effectiveness are given in (33). Cochrane systematic reviews are available of evidence of the effects of antipyretic measures for treating fever in malaria (153), blood

transfusion for treating malarial anaemia (154), steroids for treating cerebral malaria (155) and iron chelating agents for treating malaria (156). Further discussion of blood transfusion is in (157, 158

4.1.4 Delivery systems for case management

In addition to the choice of the best drugs the means of provision of case management has a great impact on its effectiveness. Broad health systems policies can dramatically affect access to treatment. For example, user charges have been found to deter people from using public sector facilities (159), but there are examples where removal of user charges has exacerbated availability of drugs. In a study in Malawi only 7% of febrile children received optimal treatment, but children taken to the clinic were twice as likely to do so than non-attenders (160). The recognition of the importance of treatment providing and seeking behaviour is leading to useful ways of improving effective treatment (161, 162, 163, 164, 165, 166). A deterioration in seeking medical care for children with fever (64) is associated with slowing declines or even increases in child mortality.

Development of systems to ensure better quality of drugs is receiving much needed attention (167), but needs much more. Studies on pre-packaging of drugs have shown significant improvements in adherence to treatment regimens, although it is difficult to know how much of the improvement was attributable to the packaging, as the interventions often included patient education (168, 169, 170, 171).

Poor access to treatment is a major cause of avoidable illness and death, and different approaches to bringing adequate treatment closer to people at risk have been attempted. The level of the health services at which different drugs should be available is a subject of much debate, as parenteral treatment and use of second line antimalarials are often considered to be only appropriate at referral levels with trained staff, and yet referral is often impossible from first–line health facilities. Health

workers in many of these facilities will attempt to do what they can on the basis of their experience, often using drugs outside their normal authority, sometimes very successfully. The use of artesunate suppositories has recently attracted much interest as a potential treatment of severe malaria or potentially severe malaria, which can be administered with less skills and fewer risks than injections (172).

Given that a high proportion (approximately 80% in some areas) of patients seek health care outside the formal public sector, increasing attention is being given to working with the informal private sector (173, 174) and caretakers at home. In 1991 it was noted that only 25-30% of chloroquine distribution was through the public sector, while about half was distributed through unofficial drug sellers (175). Self-medication is often more accessible and acceptable than seeking treatment at a health facility, but is often incorrect (176). For instance, training of shopkeepers was shown to lead to a 62% increase in appropriate use of over-the-counter chloroquine (177). Home care is not always less correct than clinic care, and has the advantage of being less expensive. For example, studies in Nigeria (178) found tha all but one parent of 105 pre-school children sought treatment for a recent child illness. Most (88%) were judged to have suffered from malaria. Most parents (74%) took some treatment action under 8 hours, while nearly all (96%) acted within 24 hours. Only 14% of these actions were judged to have been appropriate. Attending a clinic during the course of the illness (44%) did not improve the chances of receiving and taking appropriate treatment but did result in significantly higher treatment costs.

There is increasing awareness that community- or home-based treatment may be essential in the efforts to roll back malaria. Engaging the community, providing training for parents and medicine shop owners, and making effective prevention and treatment commodities widely accessible and affordable to families are critical steps in reducing malaria morbidity and mortality. A major reduction in under-5 mortality was achieved in Ethiopia through training mother coordinators to

teach mothers to give under 5 year old children antimalarial drugs (124). A community-based programme to ensure prompt and adequate treatment of presumptive episodes of malaria in children in Burkina Faso was shown to be feasible, and was associated with a reduction in the proportion of severe cases in health centres (168). A survey of treatment seeking in a community-based malaria programme in Kenya showed that most people obtained chloroquine from the village health helpers chosen by the community (179).

One attempt has been made to define the public health significance of the clinical services provided by a district general hospital (180). It was noted that there was a higher than expected number of readmissions for malaria, a higher than expected number of readmissions with acute respiratory infection after an admission for malaria and a higher than expected mortality (not statistically significant) after discharge. It is assumed that a significant proportion of children would have died if they had not been admitted.

Integrated Management of Childhood Illness (IMCI)

This is covered in detail in a separate paper (65), so the evidence will not be reviewed here, but it is mentioned, as it has been adopted as a key strategy in Africa for provision of adequate treatment of malaria in peripheral facilities and at community level. At a meeting in November 2000 called by WHO/AFRO it was agreed that expansion of IMCI was too slow, and scaling up will require some shift of focus (181). All current components of IMCI need to be maintained but with a stronger focus on the community and systems components. Capacity building needs to be considered more broadly beyond the public health sector and beyond training. Finally more attention is needed to communications, broadening partnerships, updating policies and advocacy for political support and resource mobilization. A multicountry evaluation of IMCI effectiveness, cost and impact is underway, which should provide more evidence of effectiveness of the approach (182).

4.2 Insecticide treated materials (ITMs)/ insecticide treated mosquito nets (ITNs)

Impact

Insecticide Treated Mosquito Nets (ITNs) have emerged over the last 2 decades as a very promising intervention for reducing the risk of malaria infection in areas of both stable and unstable transmission. Intervention trials have been conducted in a wide number of countries, representing a range of transmission intensities. The majority of these trials have been randomised-controlled trials. Impregnated mosquito nets have been compared with no mosquito nets, and less commonly with untreated mosquito nets. The impact outcomes measured include all-cause child mortality (1-59 months), the incidence of severe malaria, the incidence of uncomplicated malaria episodes, prevalence of parasitaemia, mean haemoglobin level, splenomegaly and nutritional status. A Cochrane review (183) which included 18 such trials (11 of which were in Africa) excluded a further 47 trials from the analysis due to either non-randomisation, or the use of inadequate control groups. The conclusion of this review was that ITNs reduce overall mortality by about a fifth in Africa, (range from 14% to 29% (15, 16, 184, 185) and that for 1,000 children protected, about 6 lives can be saved per year in the age group 1-59 months. ITNs also reduce substantially clinical episodes of mild malaria from both *Plasmodium falciparum* and *P. vivax* infections, with a 50% reduction in episodes under most conditions. Parasitaemia is also reduced substantially, and decrease in anaemia, measured as increases in Packed Cell Volume (PCV) is variable (Table 7).

Personal protection or 'mass effect'

Whether the health impact of ITNs is due mainly to personal protection, to 'mass effect' or a combination of these, and what are their relative inputs to the efficacy measured is still under debate. Conflicting evidence has been found in the trials and studies that have sought to answer this question. The first evidence for the possibility of a 'mass effect' was from experimental hut studies

that showed a proportion of mosquitoes to be killed by permethrin (186). Magesa et al (187) in studies on the age structure of the vector population gave clear evidence of reduced survival of vectors due to ITNs, they found this to result in both a decreased sporozoite rate and a decrease in vector density. Studies in The Gambia (188) produced clear evidence that the protection offered by ITNs was due to personal protection rather than to a 'mass-killing effect' on the mosquito vector population. This is in contrast to studies in Tanzania (189) where personal protection by ITNs was low in comparison to the 'mass effect' observed. Children (particularly those <2) with no ITNs, but living in villages where the majority of the population did have ITNs had a lower prevalence of both parasitaemia and anaemia (190).

The relative role of personal protection and mass effect in bringing about a reduction in the survival rate of mosquitoes and subsequent health impact, thus appears to vary, and the factors that determine their roles are not yet fully elucidated. It is important, however, to recognise that mass effect is a positive externality and that this is due to the treatment of the net with insecticide. It is also clear that although no positive externalities are expected from untreated mosquito nets inadequate attention has been given to their possible impact through the degree of personal protection that they impart. An untreated mosquito net, by forming a barrier against biting, does provide an element of personal protection to its users. An inverse relationship between splenomegaly and the use of mosquito nets was found in Gambian children in 1986 (191). Further studies in The Gambia (192) found that children who slept regularly under an untreated mosquito net had lower parasite and spleen rates and higher mean PCV values than children without a net. Subsequent intervention trials concentrated on the impact of insecticide treated mosquito nets and paid less attention to the impact of untreated mosquito nets as compared with no mosquito nets.. The need for such an assessment of the impact of untreated mosquito nets on malaria mortality and morbidity is now recognised and recent data are presented in Table 8.

From efficacy to effectiveness

Efficacy is measured as impact under controlled trial conditions, that is, almost ideal conditions, as in the intervention trials above. That ITNs are efficacious in reducing child mortality and morbidity is no longer questioned. However, there has been much less success, until recently, in measuring the effectiveness of ITN interventions. Effectiveness is health impact under programme, rather than trial conditions, and there are many inherent difficulties in its measurement. Potential options for monitoring the effectiveness of ITN programmes include population–based active surveillance, health service based passive surveillance, repeated cross-sectional surveys and case control studies.

The first measure of effectiveness of insecticide treatment of mosquito nets was from surveillance of 5 sentinel sites through the Gambia National ITN Programme (192). The measure of effectiveness achieved against childhood mortality (25%, ranging from zero in areas where net use was low to >40% in areas of high usage) was 38% less than the efficacy of 63% previously measured under trial conditions. The two main operational factors identified as contributing to the difference between trial and operational impact were the fact that there were areas where net usage was low amongst children, and that the optimum dose of insecticide was achieved on <50% of nets.

Such population based surveillance is time consuming and hence expensive (particularly in human resources) to maintain and hence is not really an option for most projects/ programmes. Attempts have been made to find ways of using routinely collected data to monitor the effectiveness of ITN programmes. Two case-control studies were used to evaluate the effectiveness of The Gambia National Impregnated Bed Net Programme (193). The first of these had mortality as the outcome and used routinely collected mortality surveillance data, matched with healthy control children. The second used passively collected health facility data on children with fever and parasitaemia and compared them firstly with controls recruited at the health centre and secondly with village controls. The protective effect of ITNs on malaria morbidity detected using health facility controls,

disappeared when village controls were used. Whether this difference was due to a level of 'mass effect' in the village controls is not clear.

A similar study was undertaken in Pakistan (194), where febrile health facility patients were classified as cases when testing slide positive, and controls when testing slide negative for malaria. Here the effectiveness of ITNs against *Plasmodium falciparum* was 78% and against *P. vivax* 69%.

Although case-control studies using passively collected data offer an attractive way to assess the effectiveness of ITNs under programme conditions, they have many possible drawbacks. Only health facility users will be included, if they differ in their use of ITNs from non-attenders, then selection bias will be a problem. This is especially pertinent in areas that have a high level of self treatmentor treatment outside of the formal health sector. There is a great potential for the introduction of bias in the choice of controls. Both of the above studies used a simple question to assess ITN usage. Although this use of a simple question is open to bias, the alternative of observation of nets in households is certainly not feasible within such a design.

The KINET programme in Tanzania, a social marketing programme of treated nets and net treatment has made measurement of effectiveness a priority. Community-based cross sectional studies were used to measure parasitaemia, and anaemia amongst ITN users and non-users. The impact measured by the programme (195), 62% on the prevalence of parasitaemia and 63% on anaemia, is equivalent to that measured in efficacy studies. The design of the impact measures where individual users are compared with non-users results is a personal protection effectiveness measure.

These recent programmes have provided evidence of the effectiveness of ITNs under programme conditions (Table 9). However, they have not provided a model of a simple way in which to measure such effectiveness in other programmes. A lot of effort was made in the KINET programme to

control for confounding factors that would bias the measure of effectiveness, such a level of effort is unrealistic in the majority of projects/programmes. It is still recommended that ITN programmes concentrate their efforts on the measurement of process indicators and presume that high level coverage with regularly treated nets will result in a significant level of health impact.

Delivery mechanisms for nets

The history of ITN / mosquito net delivery has been one of many projects / programmes of varying sizes delivering nets and ITNs within their own focussed geographical areas. Actual delivery mechanisms, pricing policies, and funding mechanisms have varied but have included community-based delivery systems, social marketing, revolving funds, blanket subsidies, and cross subsidies. Some of these projects / programmes have had a sustainability focus, whilst for others the focus has been upon equity.

The options for delivering nets listed in Table 10, have been summarised in the context of

- "going to scale"
- the development of national ITN strategies
- a focus on the long term vision
- short-term projects / programmes contributing towards this long term vision
- partnerships for concerted effort
- the recognition that the cost of covering all those at risk of endemic malaria with an ITN is not achievable by governments and donors alone
- in most countries (although not all) there are nets available on the local markets
- in some countries (Table xx net coverage) there is relatively high household coverage with nets in areas where there are no ITN/net projects/programmes

- when projects/programmes sell nets for extended periods of time at prices below those of the local market there is a risk that they will ‘crowd-out’ (reduce commercial sales to a level that the market is destroyed) that market

Demand creation

The sale of nets and insecticide centres around issues of supply and demand, these have to reach a balance, the tipping of the scales towards either one is likely to be destructive. A demand creation strategy relies upon stimulation of demand by the public sector or other organisations such as NGOs, which is satisfied by the supply capabilities of the private sector. The aim is that an increase in demand will also serve to fuel an increase in supply, and in expanding the penetration of this supply in terms of geographical penetration and also penetration of different socio-economic levels. It is envisaged that the demand creation should need to be in the medium to long term, but that the market that it helps to develop would be permanent. It is possible to geographically target demand creation, however, any effect upon neighbouring areas would also be an advantage. Although messages about vulnerable groups are readily transferred during demand creation, the real aim is to stimulate growth of a sustainable commercial market, so that effective targeting of smaller sections of the population is not the aim. There is unlimited scope for scaling-up a demand creation intervention.

Sustainable subsidies for equity

By definition such a strategy needs to be permanent and needs to find ways of targeting the biologically vulnerable and / or the economically vulnerable. It is possible to target by geographical area within this strategy, and it may be necessary to do so, depending upon the level of funds and the numbers of the vulnerable in whichever group is being targeted. The nets distributed in this strategy should ideally be free, and at the least should be very highly subsidised. This strategy naturally complements an ongoing strategy of demand creation and development of the private market. It aims to cover those who are

excluded from private sector sales, who are mainly the economically vulnerable. However, in recognition of the difficulty of effectively identifying and targeting the very poor, a strategy of targeting the biologically vulnerable, in terms of pregnant women or children under 5 may be an alternative. If this strategy is implemented ineffectively, it is potentially damaging in two ways, firstly it will waste resources by making subsidies available to the none needy, secondly, misplaced subsidy will undercut the commercial market by diverting a potential sale. Effective targeting should not have adverse effects upon a commercial market, rather, it will be complementary in reaching those who are considered unreachable. It may also stimulate a degree of demand in non-target groups. The potential for scaling up this strategy is limited by the size of the target group and the related costs.

Revolving fund

The intended duration of a revolving fund is permanent, however, for this strategy to be truly sustainable, the prices of the nets and insecticide should cover all costs including materials, distribution, handling and administration, not solely the cost of the net and/or insecticide. Geographical targeting is possible, although targeting of vulnerable groups is possible, it may be undesirable as the programme will need a certain level of sales to cover its costs and to remain competitive with the commercial sector. If the revolving fund is truly covering all costs, then the programme will not be at an unfair advantage in undercutting the commercial sector. Although sales by the programme may substitute for commercial sales, the programme is directly competitive with the rest of the market. The potential for scaling-up of a project / programme using a revolving fund strategy is limited by the finances available.

Social marketing

Most social marketing programmes aim to be permanent, they are however, limited by the time span of funding from their donors, which is also a factor that limits their options for scaling-up. Prices are usually aimed at cost recovery this tends to put them at about the same level as those of the commercial sector, or more often slightly below. Socio-economic targeting may be the aim of

introducing higher subsidies and reducing the prices to substantially less than those of the commercial market, however, true socio-economic targeting is unlikely. Biological targeting however, is possible, and geographical targeting is the norm and is dependent upon delivery channels. Social marketing programmes have the aim of increasing demand in the commercial market ("crowding-in"), to increase sales of non-project nets together with their own branded nets. Subsidies through tax and tariff relief result in unequal competition between social marketing programmes and the private sector, and assessments of their expansion of the private market is lacking and where available the evidence is conflicting.

'Pump-priming'

The idea of 'pump-priming' is to stimulate demand in the commercial market. To do this, new customers are encouraged to buy nets / ITNs at slightly lower than market prices, with the aim being that they will use the product, like using it, and therefore be stimulated to replace it when needed. The hope is also that their neighbours will also be encouraged to buy. It is important for the commercial market that this strategy is short-term, a longer-term intervention of this kind would undercut and potentially damage the private market. Targeting by geographic area, and by vulnerable groups is possible.

Emergency relief

Although emergency relief should be temporary by definition, it may actually last for quite variable lengths of time, which may span several years in the case of chronic complex emergencies. It is likely that nets and ITNs are a more appropriate intervention in the chronic phase of emergencies. Geographical targeting of the affected area, or areas to which people have moved, is essential. It is possible that biologically vulnerable groups may be targeted, but economic targeting is not likely to be necessary, at least within the acute phase. Economic targeting may be desirable in the chronic phase of long protracted complex emergencies.

Alternative options for personal protection

A promising alternative option for personal protection which has been tested in Asia but not yet in Africa, is the use of impregnated blankets and items of clothing. In a randomised controlled trial in north-west Pakistan chaddars (a veil or wrap) impregnated with 1g/m2 permethrin reduced the odds of having a falciparum or vivax epidsode by 64% in children aged 0-10 years and by 38% in those <20 years. Incidence in those over 20 years, however, was not reduced (196). The possibility of impregnating plastic sheeting with insecticide for use in emergency where people are displaced, is also presently being explored.

4.3 Indoor residual spraying

There is ample evidence that spraying the inside of house walls and roofs with an efficacious residual insecticide is a very effective tool in reducing malaria transmission, disease and deaths (197, 198, 199, 200). It is therefore no surprise that hopes for a real impact on malaria were high with the discovery of DDT. So why has residual spraying lost favour in recent years, and attention turned to case management and insecticide-treated nets? Whilst resistance to DDT and concerns on its environmental effects together with the limited range of alternative insecticides of sufficient safety, longevity and affordability are important, the difficulties of maintaining the necessary high coverage and quality of spraying operations and the increasing reluctance of householders to accept it (201) have defeated the health systems of many countries.

Residual house spraying was a major component of many malaria control programmes outside Africa during the global eradication campaign, and resulted in major reductions in incidence. One of the most striking examples was in India where malaria incidence rate decreased from about 75 million cases per year to about 100,000 during the eradication campaign, then rose again to about 3

million per year (202). It has been widely believed that the transmission rates in sub Saharan Africa are so high that, without total coverage, house spraying would be unlikely to have a great impact, and was therefore not recommended. It has, however, played an important role in southern and highland areas of Africa, where transmission is lower. Even in the areas of highest transmission there are a few examples where house spraying was evaluated, and shown to be highly effective. These include Pare-Taveta on the borders of Kenya and Tanzania in the 1950s (11), the Garki project in Nigeria in the 1970s (17) and the Kisumu project in Kenya in the 1970s (203). In the Pare-Taveta trial mortality in infants and young children was halved, and, although it rose gradually after spraying was discontinued, it did not rebound to higher levels than before. In Kisumu a 96% reduction in transmission and a 40% reduction in infant mortality rate were associated with fenitrothion spraying, and in the Garki project there were even greater reductions in mortality rate.

Evidence of the effectiveness of residual house spraying under operational rather than research conditions is notoriously difficult to collect, as factors such as coverage and annual variation are difficult to control.

In Asia there is mixed experience with residual spraying. It is still widely used in several countries, but in many southeast Asian countries the major vectors *Anopheles dirus* and *A. minimus* rest mainly outdoors, and feed partially outdoors, so may have limited exposure to the insecticides (204). Insecticide resistance in these species is limited, whereas in India, there are high levels of DDT resistance in some states in the two major vectors *A. culicifacies* and *A. stephensi.* DDT spraying has continued in many parts of India on the basis that there still appeared to be an effect on malaria incidence (205, 206). It has been noted again recently (207) that, in areas where the amount of spraying has decreased, malaria incidence has risen. India is phasing out DDT and replacing it in some areas with pyrethroids, which cost more. Rowland *et al.* (208) demonstrated effectiveness of residual spraying with pyrethroids in Pakistan. Behaviour changes in time and place of biting of

several Asian vectors have been associated with use of insecticides (209), although a causal link would be difficult to prove. In some cases it is possible that the changes were due to replacement of one sibling species by another rather than change within a species.

In Africa physiological resistance to DDT is limited (210), although strong behavioural avoidance has been noted (211), but recently pyrethroid resistance has been reported in *Anopheles gambiae* sensu lato in West Africa (212) and in *A. funestus* in South Africa (213).

The role of indoor residual spraying has been played down in recent years for a number of reasons. It was not considered feasible in many of the poorest countries, as a well organised health system with functional transport, procurement, training, supervision and reporting is essential. It had also become unpopular with home owners in many countries where it was used. There was general consensus that limited resources would save more lives if targeted at improving case management. In addition, the promising results with insecticide-treated mosquito nets offered an alternative form of protection, which was more attractive. Finally, in recent years there has been considerable debate on the development of a convention for a worldwide ban of persistent organic pollutants including DDT. In December 2000 it was eventually agreed that DDT could continue to be used for malaria control until sustainable alternatives are found. The debate centred on the lack of affordable alternatives and the relative risks of DDT toxicity and malaria (214, 215, 216).

The relative efficacy and effectiveness of residual house spraying and insecticide-treated nets is currently the subject of lively debate. Curtis and Mnzava (217) recently carried out a review in which they noted that in 6 recent comparisons in Africa, Asia and Solomon Islands pyrethroid treated nets were at least as efficacious as house spraying with DDT, malathion or a pyrethroid. However, when earlier residual spraying trials in Africa are compared with recent ITN trials, the latter were

less efficacious. The operational and economic limitations of residual spraying are recognised, but further careful review of its role is needed.

In emergency situations where people have been displaced and are living temporarily in tents, these may also be sprayed with insecticide. Treatment may last for a year if the tent is double sheeted, less if single (218).

Novel Alternatives to Indoor Residual Spraying

Cattle-sponging, (the application of insecticide to livestock) has been proposed as an efficient way of using insecticide to control zoophilic mosquitoes (219). The treatment of domestic livestock with pyrethroid insecticide acts as a bait to attract mosquitoes to a toxic surface (220). A recent study of treated cattle (221) demonstrated a level of control better than that shown by ITNs or indoor residual spraying and at a fraction of the cost.

4.4 Protection of pregnant women

Treatment of symptomatic cases

WHO recommends that all pregnant women with clinical malaria receive prompt treatment with a safe and effective antimalarial. In addition, all pregnant women in malaria-endemic areas with severe anaemia are also to be treated with antimalarials, even if asymptomatic for malaria. The choice of antimalarials that are safe for use in pregnancy is limited, and in areas of multidrug resistance, the options are extremely limited.

The effectiveness of any drug used to treat a patient is dependent on a range of factors including drug sensitivity, completion of a full treatment course, severity of disease, stage of pregnancy, pre-pregnancy immune status and HIV status. Therefore the effectiveness of any one drug varies from

place to place and from person to person. A list of efficacious drugs commonly used for the treatment of malaria in pregnancy in malaria endemic countries around the world follows.

Treatment of non complicated malaria

Chloroquine (CQ) and quinine are safe for use throughout pregnancy and most probably also sulfadoxine-pyrimethamine (SP). The safety of SP use in the first trimester has not been monitored in trials though inadvertant use of SP for antimalarial treatment during the first trimester of pregnancy has shown no adverse effects/outcomes (222). Where there is CQ sensitivity, CQ is first line, and SP second line. Where there is SP resistance, quinine should be used. Other drugs that can be used to treat maternal malaria infection in the second and third trimesters are artemisinin derivatives, mefloquine and amodiaquine.

Treatment of severe or complicated malaria

Treatment of severe malaria is more complicated in pregnancy. Quinine is recommended for treatment of severe or complicated malaria. In areas of mutlidrug resistance, intramuscular artemether has been used to treat severe disease.

Case management of malaria cases is always important in endemic areas. However, case management alone is unlikely to be adequate for protecting pregnant women and their unborn babies from malaria because so many cases are asymptomatic and go undetected, hence infections continue to contribute significant morbidity to both mother and child.

Chemoprophylaxis

In 1993 WHO recommended that all pregnant women in malaria endemic areas receive regular chemoprophylaxis (100, 101). WHO currently recommends intermittent treatment with an effective, preferably one-dose antimalarial drug provided as part of antenatal care should be made available in

highly endemic areas to women in their first and second pregnancies. Such intermittent treatment should be started from the second trimester onwards and not be given at intervals of less than one month apart (19).

Drug regimens currently in use in Africa include CQ alone or in combination with proguanil, proguanil alone, or pyrimethamine alone, but the effectiveness of both CQ and pyrimethamine is now limited due to widespread resistance. Pyrimethamine-dapsone (Maloprim®) fortnightly has been effective in increasing birth weight and reducing anaemia in primigravidae in The Gambia (223). Weekly prophylaxis with mefloquine has been used effectively to prevent malaria infection in pregnancy in both Malawi (224) and Southeast Asia (225), though a recent report has found an increased risk of stillbirths in women taking mefloquine compared to women taking other antimalarials (226). Other reports find no indication that the risk of taking mefloquine in the first trimester of pregnancy is greater than from any other antimalarials studied (222, 227).

Factors affecting effectiveness of chemoprophylaxis are as for treatment (listed above), but adherence is far more complex and more difficult to achieve due to the need for repeated, frequent administration of drug(s) throughout pregnancy.

The Box below summarises the key findings of the Cochrane systematic review of prevention and treatment for malaria in pregnant women (228). Trials included in the review were: (223, 225, 229, 230, 231, 232, 233, 234, 235, 236, 237**,** 238, 239, 240, 248).

Key components of the Cochrane review of prevention and treatment for malaria in pregnant women

- *Participants:* Pregnant women living in endemic malarious areas.
- *Studies included:* Any trial during pregnancy in which an attempt was made to conduct a randomised comparison between routine preventive measures for malaria and treatment of symptomatic malaria; or between alternative prophylaxis regimens.
- *Studies reviewed:* Fifteen trials were included in the review. The studies were carried out Africa and in Thailand. Ten studies compared malaria chemoprophylaxis (either chloroqu pyrimethamine, proguanil, pyrimethamine/dapsone or mefloquine) with a placebo or notl Two studies compared different drug regimens and two tested permethrin-impregnated b nets.
- *Outcome measures:*

  Maternal: parasitologic, clinical illness, obstetric, anaemia

  Fetal: placental infection, birthweight, gestation, mortality
- *Data synthesis:* Meta-analysis: Using a fixed effects model and 95% Confidence Interval Relative Risk (RR) and Weighted Mean Difference (WMD).

  Effect of prophylaxis compared with placebo:

  In primigravidae

- fewer with severe anaemia at 34 weeks (Hb(8g)): RR 0.61 (0.48, 0.78); 1 trial (n=1132)
- mean packed cell volume in mother higher: WMD 2.6 (1.3, 3.9); 2 trials (n=118)
- mean birthweight higher: WMD 101 g (32, 171); 5 trials (n=683)
- fewer low birthweight infants; RR 0.59 (0.41, 0.85); 3 trials (n=614)

Multigravidae:

- no significant effects

Mortality:

- inconclusive, small studies (perinatal: 2 studies, n=555; neonatal: 1 study, n=349)

Any pregnant woman:

- fever episodes reduced: RR 0.42 (0.27, 0.66); 1 trial (n=227)

From: 228

Intermittent Presumptive Therapy

Intermittent presumptive treatment (IPT) applies to the periodic administration of antimalarials during pregnancy irrespective of the presence of parasites and/or clinical illness. The aim is to clear the placenta of parasites during the period of maximum foetal growth (24-36 weeks) and to clear peripheral parasitaemia allowing haematological recovery.

IPT with 2 doses of SP (one in the second and one in the third trimester) has been shown to be effective in reducing placental parasitaemia, improving birth weight (240, 241) and preventing severe maternal anaemia (50) in primigravidae. Both studies conducted in Kenya were important landmarks in that they provided the evidence on which to base changes in national policy for the prevention of malaria in pregnancy (228). IPT with 2 doses of SP has been policy for the prevention of malaria in pregnancy in Malawi since 1993 and in Kenya since 1999. Even in an operational setting (Malawi), with reduced adherence (see Table 12), women receiving SP during pregnancy had

significantly lower rates of placental infection (reduced from 32 to 23%) and low birth weight babies (reduced from 23 to 10%). Maternal anaemia rates were also reduced (242).

Chances of achieving good rates of adherence are vastly improved since the drug is administered only twice during 9 months of pregnancy (compared to approximately 36 doses of weekly CQ). This is reflected in cost effectiveness analyses. While improved adherence with IPT increases cost effectiveness against weekly prophylaxis, the use of drugs with a long half-life such as SP will potentially contribute to the spread of drug resistance and hence mitigate any health benefits. Effectiveness of 2 dose SP is impaired in HIV infected pregnant women, with three (243) or more (240) doses needed to achieve sufficient levels of effectiveness, though this remains a highly cost effective intervention even in HIV infected women (244). Safety of multiple doses of SP in HIV infected pregnant women requires further evaluation as does the evaluation of the safety of SP when used in combination with antiretroviral drugs (245)

No study has yet compared effective weekly malaria chemoprophylaxis with effective IPT (studies have always compared SP IPT with either a placebo or with weekly CQ chemoprophylaxis in areas of high CQ resistance). However, recent data from Mali indicate that, in places where chloroquine resistance is low, IPT with SP, IPT with CQ or weekly CQ chemoprophylaxis has a similar impact on mothers' health (246). The lowered efficacy of SP when given together with folic acid raises the question on whether these two drugs should be given together to pregnant women.

In low transmission areas, IPT may not be the best option because asymptomatic infection is likely to be very low in women without acquired immunity. Infection is likely to produce acute illness and foetal loss such that chemoprophylaxis, or possibly very active case detection and febrile case management, may be preferable though cost effectiveness has not been established.

Summary of drugs available for use in pregnancy

The following antimalarials are considered safe in pregnancy: chloroquine, proguanil, pyrimethamine, dapsone-pyrimethamine (Maloprim), SP, quinine and mefloquine. The following antimalarial drugs are contraindicated in pregnancy: tetracycline, doxycycline, primaquine, tafenoquine. The following drugs have limited data: amodiaquine, halofantrine, atovaquone (Malarone), chlorproguanil-dapsone (LapDap), artemisinin (alone or in combination with other drugs).

Insecticide Treated Nets to protect pregnant women

The role of ITNs in protecting pregnant women and their foetuses from the effects of malaria infection is inconclusive. ITNs had a significant effect on maternal anaemia and, while not significant, reduced premature births and LBW babies in a study in an operational setting in The Gambia (193, 247). In Kenya, use of IPT with SP in pregnancy had the same impact in both communities with and without additional protection from insecticide treated nets indicating that pregnant women should always use ITNs in conjunction with IPT (248). The differences seen between these trials are thought to be due to the different transmission settings with Kilifi, Kenya having more intense transmission than The Gambia. Preliminary analysis from a recent trial in a high transmission setting in Kisumu, Kenya showed that women who were protected by an ITN in their first three pregnancies delivered approximately 25% fewer babies who were either small for gestational age or born pre term compared with women who were not protected by ITNs (249). During pregnancy (all gravidae) mothers showed less parasitaemia and less anaemia.

Further research is required to establish the efficacy of ITNs in pregnancy. Meanwhile, it is recommended that all pregnant women use a combination of both chemoprophylaxis or IPT, and ITNs.

4.5 Epidemic control

In Africa about 110 million people live in epidemic prone areas (250), and outside of Africa the number is even greater. Most of these people have low immunity, as malaria is normally uncommon, so during epidemics severe disease and death rates are high. The key needs for epidemic control are rapid response, preventing spread and maintaining early warning systems in order to be prepared (251). Epidemic prone areas have a higher than normal reliance on good information and logistics systems including drug stockpiles. Epidemic early warning systems need data collection for indicators of vulnerability (eg low immunity, population movement, drug resistance), transmission risk (climatic factors) and early detection of increased cases (250). New methods of systematic information collection are being developed (252, 253). A meeting of the Highland Malaria Project, MARA and national malaria control programme managers in 1999 to develop new approaches for surveillance and control of malaria epidemics in East Africa proposed development of a system of nested surveillance, in which long-range forecasts, early warning and early detection could provide warning signals as a series of "flags", each of which is triggered by a specific set of indicators and in turn triggers a predefined response.

Evidence of the effectiveness of epidemic control interventions is extremely limited, as it would not be ethical to collect detailed data in epidemics without intervening. The quality of response can be evaluated, and this is systematically done in Southern Africa (264). Alternative interventions could be tried in different areas, but comparability of other factors would be limited. There is, however, strong justification for using epidemic control measures because of the high morbidity and mortality levels and suggestive evidence of effectiveness, such as the decline in outpatients by 90% in Madagascar following resumption of DDT spraying in response to the epidemic in the 1980s (198).

Evidence of effectiveness of support interventions

Fewer data are available in published literature on the impact of support interventions on malaria burden. This may be because they are less amenable to efficacy studies, as appropriate controls are difficult to devise for systems interventions which depend on interactions of several components. The results may be less generalisable and thus less interesting to academic researchers, and the quality of implementation can be difficult, though not impossible, to monitor. Where there is evidence of a health impact of the direct interventions, it is more useful to examine how the support interventions affect access, use, quality and cost-effectiveness of the direct interventions they support. Because these interventions are not specific to malaria, evidence of their effectiveness may be obtained from other fields.

4.6 Human resource development

Evidence of the effectiveness of human resource development is limited, partly because it has not been a research priority and it would be very difficult to measure except in individual contexts. Numerous attempts have been made to assess performance of health workers after training, and data from evaluations of IMCI training do suggest more appropriate treatment practice can be achieved (254). Training of shopkeepers in Kenya led to a significantly higher proportion of drug sales for children with fever including chloroquine and of children receiving an adequate dose (177). Other examples of the effect of training are disappointing with practice rapidly returning to previous levels after training ([255] Equally important in terms of providing effective health care is the provision of an environment which motivates health workers to provide good quality and quantity of work. This includes not only adequate remuneration but also reliable access to the necessary tools such as drugs

for treatment and transport for referral and supportive supervision mechanisms. Again there are many unpublished examples where incentives have enabled staff to stay at their work.

4.7 Information, Education and Communication

Much of the literature is not specific to malaria but still relevant. A review of more than five hundred articles on health education in developing countries in 1987 found only three with satisfactory evidence of behaviour change or health impact (256). An attempt to review the evidence on effects of maternal education is presented in Paper 9 of Working Group. A large hygiene promotion programme in West Africa has recently been shown to cause improved handwashing practices (257). A health education package to teach mothers to treat episodes of malaria in an area of The Gambia with no tradition of home-based treatment led to 67.9% of mothers dispensing complete chloroquine courses and mothers interviewed weekly gave 65% more chloroquine than those interviewed less frequently (258). Education of community, private practitioners and drug vendors on compliance with a treatment regimen of seven days' quinine and tetracycline in Cambodia showed that use of posters and videos featuring popular actors led to a 28% increase in number of patients buying full courses and 20% increase in the number completing the full course (259). Posters alone had less than half the effect. These examples support the role of education, but stress the importance of a suitable communication strategy.

4.8 Surveillance

The potential benefits of surveillance as an essential tool for planning and evaluating malaria control programmes and detecting outbreaks are obvious. Evidence of effectiveness is difficult to measure, as improved surveillance tends to detect more malaria. Some of the strengths and weaknesses of different surveillance systems were discussed earlier in the paper in relation to measuring burden.

Key issues for design of surveillance systems are the cost in time and money of different systems, their representativeness (community-based versus facility-based), quality (accuracy and timeliness) and the extent to which data collected is used by different levels (central and peripheral systems and community). A documented example of the use of a geographical information system to plan malaria control allowed development of a targeted approachto control (260).

4.9 Operational research

The effects of operational research in reducing malaria morbidity and mortality are indirect, and would be difficult to measure. It is, however, possible to link the changes in policy and practice related to interventions such as insecticide-treated nets to the developing operational research approaches which have influenced the changes. Similarly, changes in choice of first-line antimalarial treatment are primarily based on data from efficacy studies, but there has recently been increased realisation of the importance of research on a broader range of social, economic and operational factors which influence the effectiveness of a given choice of treatment (150). This increased interest was not yet reflected by 1994, when intervention trials and health services research did not show a change in their percentage contribution to total malaria publications between 1984 and 1994, although clinical management publications did increase (261). A great deal of operational research does not reach publication databases, as it is often of local relevance, so changes in the actual amount undertaken would be difficult to detect.

Global investment in malaria research in the late 1980s and early 1990s was very low compared with other disease areas, and appeared to be declining further (261), but increased in the late 1990s (98). The total identifiable global expenditure on malaria research in 1993 was approximately US$84 million. Expressed as investment in research per death, malaria research - at approximately US$42 per fatal case - received less funding, by one or two orders of magnitude, than other diseases such as

cancer, HIV/AIDS or asthma (261). The nature of operational research makes it less attractive to research funders than more basic research, as there is need for a large number of small projects, which are relatively costly to administer.

Research could have a greater influence on morbidity and mortality if more efforts were made to communicate results effectively to policy makers and implementers and to answer those questions that implementers and communities raise rather than setting agendas within scientific institutions.

Research to develop new drugs and insecticides is essential in order to keep up with development of resistance in parasites and mosquitoes respectively. The impact of introduction of new drugs has been mentioned earlier (decreased mortality in Vietnam with wide access to artemisine and decreased incidence in Thailand on introduction of mefloquine-artesunate combination).

5 COVERAGE

5.1 Case management

Access to government health facilities varies widely in different countries and at different times, but has been estimated at around 50% in developing countries (176). Other sources of treatment are formal and informal private providers including traditional healers and shops selling drugs for self-medication.

Diagnosis

Utilisation of different diagnostic methods varies greatly among countries and regions. In general clinical diagnosis is the most common method throughout most of Africa and in more remote areas of other continents. Microscopic diagnosis is widely used at health centre and hospital level in much of Asia, Oceania and the Americas in the public sector. Rapid diagnostic tests are still used on a very limited scale anywhere.

Treatment

Problems of access to treatment in the public sector are well-recognised as a key constraint to reducing the burden of malaria. It would be difficult to quantify coverage of effective treatment, as the situation varies very widely from country to country, and also fluctuates widely with time in relation to fluctuating funding sources. There is some evidence that countries with revolving drug funds such as the Bamako Initiative are less susceptible to ruptures in drug stocks in peripheral facilities than those countries with centrally controlled and financed systems.

Shops selling drugs are a more consistent and widely spread network of access to antimalarials in many but not all countries, although the quality is a problem in many places.

5.2 Mosquito nets and insecticide-treated mosquito nets

With continuing high levels of morbidity and mortality due to malaria and following from the evidence of high levels of efficacy of ITNs in the trials described above, the need to increase household level usage of ITNs has been recognised. Many programmes and projects have been established either with ITNs being their main foci, or with ITNs as one of their packages of intervention. The methods of promotion and distribution of ITNs used in these projects/programmes have varied, as has their degree of success. As it is quite clear that health impact is not measurable under routine programme conditions, the main measure of success of such ITN projects/programmes has been their ability to increase either the household coverage of ITNs, or coverage within their specific target groups.

Nets

In some countries, nets are not a new phenomenon but have historically had high levels of usage, such as in The Gambia. Nets were being used, mainly as a barrier to the biting of mosquitoes before

the advent of any project/programme that promoted their use. Household coverage levels of nets in different regions of The Gambia have varied between 51% and 86% (262, 263). These are coverage levels for rural areas and in general, net coverage tends to vary not only between regions, but also in the urban rural context. In other countries the situation is not so clear as it is in The Gambia. More and more evidence is being found that even in countries where the overall net usage is very low, there maybe pockets of very high level net usage, often around riverine areas where the mosquito biting nuisance is high.

Reported nation-wide coverage levels of mosquito nets (defined as percentage of households owning one or more nets) include: Angola <1%(264), Botswana >50%(264), The Gambia 58% (263), Malawi 7% (265, 266), Mozambique <1% (264), Tanzania 70% (urban), 7% (rural) (264), Zambia <10% (264), and Zimbabwe 2% (264) and 7% (267). This nation-wide data may mask wide regional variations (Table 11) as in rural areas of Tanzania, Dodoma 18%, Morogoro 53% and Mtwara 7% (268). Although generally net usage is felt to be higher in urban than rural areas, mostly due to availability and affordability, this is not always the case. In Accra rural coverage was found to be 93%, whilst in Accra urban it was only 16% (269).

The variations listed above emphasise the need for programmes to conduct a baseline assessment of net coverage before implementing an ITN programme. It should not be presumed that a low nation-wide net coverage can be translated directly to low coverage in a particular region or district. It should also not be presumed that the previous absence of an ITN programme ensures absence or low coverage of nets in the area. Nets are found for sale on many local markets throughout Africa and Asia.

ITNs

There is little available data on the coverage of ITNs at household level, where data is available it is usually post project/programme. In the Mekong countries coverage with ITNs has been reported as the percentage of the population at risk who are covered by ITNs, Cambodia 12%, China (Yunnan Province) <1%, Lao People's Democratic Republic 9%, Myanmar <1%, Thailand 3% and Vietnam 26% (52).

Methodological issues on net coverage

The methods used to assess net coverage have been very varied, they have included household surveys through questionnaires and through observation; Knowledge, Attitude and Practice (KAP) surveys; school surveys; bus-stop surveys. It is often difficult to compare data as there is such a variation in the methods used in its collection. Coverage has been reported as: percentage of households with one or more nets; number of nets per net owning household; percentage of children under 5 reportedly covered by nets in net owning households; percentage of children under 5 reportedly covered by nets in the total population of under 5s; percentage of pregnant women sleeping under a net; and coverage per capita. By far the most common measure is that of percentage of households with one or more nets.

Within the studies that have measured percentage of households with one or more nets there is variation in the standard of the sampling schemes. Sample size is obviously critical and has tended to be lower in KAP surveys that have asked a wide range of questions to a relatively small number of people. Also critical, given the way in which there may be great variations in net usage within a region and within a district, is the way in which the surveys have been randomised. Many of the published studies do not clearly state how the sample has been randomised – just that it has been. If randomisation is adequately considered within the sampling design then both methods of Cluster Sampling (as in EPI) and Simple Random Sampling, may give comparable measures of net coverage.

There have been debates about the possible biases involved in assessing both net ownership and net usage by asking a direct question such as ‘did you sleep under a net last night?’. Consequently some investigators have used observation of nets in the household to answer questions on both ownership and usage.

There is a need for more standardised survey protocols that will help programme managers to collect appropriate data for both an evaluation of their programmes and for the wider question of household coverage of nets. On the wider coverage, some of the most recent DHS surveys have included a malaria module with a question on nets, the data is not yet available, but promises to be a good way of measuring net coverage on a larger scale. Four recent surveys from which such data will shortly be available include Guinea in 1999, Malawi 2000, Rwanda 2000 and Uganda 2000.

Methodological issues on ITN coverage

Unlike nets ITNs are not a commodity which have been available and in common usage, they are a relatively new technology about which there are still many lessons to be learned, both technical and operational. Although the net is a visible commodity which can be counted and observed in households, this is not so for insecticide on the net. There are as yet, no practical field based tests for measuring the amount of insecticide on a net and therefore surveys have to rely on questions about treatment and re-treatment.

When a net is treated with insecticide, this insecticide will remain effective at repelling and killing mosquitoes for a limited period of time, usually 6 months to 12 months, depending upon the particular insecticide and the frequency of washing. When an ITN is purchased it will therefore be an ITN for a set period of time, after which, if not re-treated, it will revert to being just a net. There is a distinction to be made between nets that have been ‘ever treated’ and nets that have been ‘re-treated’. This distinction is not always made. Even when re-treatment data is carefully collected, without

knowing the frequency of washing or being able to measure the amount of insecticide remaining upon the net, it is not clear whether what is being counted is an effective ITN, or an ineffective ITN which is basically equivalent to an untreated net.

5.3 Indoor residual spraying

Comprehensive data on reported coverage of indoor residual spraying are not available, but some useful summaries are available for Southern Africa and the Mekong region (Table 12).

5.4 Pregnancy interventions

The data in Table 13 on coverage of malaria control interventions in pregnancy were collected through special surveys either as part of research on interventions (those which list a publication) or as part of national surveys (e.g. Nigeria).

6 COST-EFFECTIVENESS

Given the high economic burden of malaria described earlier, a strong case can be made for much greater expenditure on malaria prevention and control than there is at present. Data on the cost-effectiveness of malaria control interventions are limited. A review of fourteen studies of cost-effectiveness of malaria control measures (270) points out the limited data on costs and effects of residual spraying and IMCI and complete lack of data on epidemic and environmental control and treatment of severe malaria. Cost-effectiveness will also vary according to delivery strategy for a given intervention. Most interventions are not used in isolation, but as part of variable packages of complementary interventions, and it is very difficult to estimate the costs and effects of these. It was noted that the effects of

chemoprophylaxis combined with treated nets in the Gambia was less than the sum of the incremental effectiveness of the interventions when applied alone (271, 272), but there are potential cost-savings in combining interventions where resources are shared. In order to be useful to policy makers for resource allocation the cost-effectiveness of malaria control interventions needs to be compared with that of other health care interventions measured with a comparable methodology, which is rarely done (270).

In order to address the gap in evidence, a modelling approach has recently been used to estimate cost-effectiveness ratios for the main malaria prevention and treatment options in sub-Saharan Africa (273), and it showed that several interventions are cost-effective and an attractive use of resources (Figure 1). A cost-effectiveness range of entirely less than $150 per disability-adjusted life year (DALY) averted was considered attractive and entirely less than $25 was considered highly attractive in a very low income country(274). The authors point out, however, that high coverage with a package of cost-effective interventions, including intermittent treatment of pregnant women, insecticide treated nets and improved case management is not affordable by very-low-income countries, so that substantial financial support from external donors is needed.

6.1 Case management

Various approaches to improving case management are described earlier. Attempts have been made to model the cost-effectiveness of providing confirmed diagnosis (275), improving compliance, increasing access to second and third-line drugs and changing the first line drug (273).

6.1.1 Diagnosis

In areas of multidrug resistance the cost-effectiveness of confirmed diagnosis increases if it results in reduced use of more costly drugs for misdiagnosed cases (275, 276). If combination therapy is

introduced in order to avert multidrug resistance, where it has not yet arisen, confirmed diagnosis will also save substantial costs of the more expensive treatments. If rational use of drugs through better diagnosis actually delayed development of resistance to cheaper drugs, there would also be cost savings. In Malawi the restriction of antimalarial drugs in a hospital outpatient department to patients shown by microscopy to have parasites led to a dramatic reduction in drug use estimated to represent 3% of the hospital's drug budget. This cost saving was considered large enough to recommend a change in policy to requiring microscopic diagnosis (277). In Brazil significant cost savings (travel costs and lost wages) were achieved by establishing a community based programme for dipstick diagnosis and mefloquine treatment (278). The current reliance on clinical classification in the Integrated Management of Childhood Illness (IMCI) may need to be reviewed in some settings, as drug costs escalate, in order to reduce overtreatment.

6.1.2 Appropriate Drug Policies and Practice

Appropriate national drug policies and practice can enhance treatment efficacy and compliance, and minimise risks of rapid development of further resistance. They can thus limit costs to institutions, communities and families. Several elements of drug policy can influence cost-effectiveness. Improvement of compliance to chloroquine treatment through training, health education and drug pre-packaging was shown to be cost-effective in the model previously mentioned (273), the cost-effective range being $2-8 in a high transmission area with 30% clinical failure rates and less than $25 up to 77% chloroquine resistance. In low transmission areas the model showed a cost-effectiveness range of less than $25 up to 24% resistance and less than $150 up to 87% resistance. Improved availability of second- and third-line drugs had a cost-effectiveness range of $0.7 –3.0 in high transmission areas, becoming more cost-effective, as resistance increased.

Analysis of the cost-effectiveness of changing first-line treatment is more complex, as it needs to take account of the increase of drug resistance over time and trade-offs among higher drug costs, immediate decreases in mortality and morbidity and potential increases in resistance to replacement drugs which could increase mortality and morbidity in the future (138). A study in Tanzania modelled the costs and effects of changing first-line treatment from chloroquine to SP. It showed that, considering all drug and non-drug cost-savings the cost per operational failure averted would be $0.20, and the cost per death averted $14, even taking into account the high costs associated with changing policy. However, the authors emphasised that the results should be interpreted with caution, given the high degree of uncertainty involved (279, 280).

6.1.3 Integrated Management of Childhood Illness

RBM aims to control malaria in the whole population, while IMCI is addressing children under the age of five years for the five major childhood illnesses (diarrhoea, acute respiratory diseases, malaria, measles and malnutrition). IMCI can lead to efficiency gains by planning, budgeting and upgrading skills of health workers for all major childhood illnesses together rather than, for example, by continuing to conduct separate, disease-specific training courses and supervisory visits. Preventive care and the selective, appropriate referral of patients is far more cost-effective than late treatment of illness and haphazard referral. There are also synergies between the impacts of multiple community behaviour changes, as compared with their individual impacts. Reviews of IMCI implementation in various countries indicate potential cost-effectiveness of the approach. Many of the components of the approach have proved to be cost-effective as single interventions, and it is expected that their integration should increase cost-effectiveness. The Inter-Agency Working Group on IMCI has recently published an economic rationale for investing in IMCI which ranks IMCI among the 10 most cost-effective interventions in both low and middle income countries. Examples

of cost savings included a 1994 study in Kenya showing that IMCI reduced per child treatment costs from US$0.44 to $0.16 and data from Uganda showing that IMCI reduced the number of drugs in standard practice from 50 to 11, reducing the average cost per child from US$0.82 to $0.17. IMCI has been estimated as being able to avert 14% of the global burden of disease at a cost of $US1.60 per capita per year or $40 per DALY (281).

Data on actual as opposed to potential cost-effectiveness of IMCI are limited, as it has only been introduced on a small scale so far, but a multicountry evaluation of IMCI effectiveness, cost and impact is addressing the issue and should provide results in 2004 to 2005 with descriptive information on district level costs in Tanzania and Bangladesh in 2002 (182).

6.2 Insecticide treated materials

Preventing malaria is cost-effective through reduced expenditure on treatment and lives saved from ITN use (282). Economic losses from malaria could be reduced by 37.3% over a 3-year period in Malawi by extensive bednet use, and net use in Cameroon could result in reduction of malaria related costs by 9.3-11.2% (283).

With the use of mathematical models the cost-effectiveness range of insecticide treated nets treated once per year was estimated to be $19-85 or, if only the insecticide was needed , $4-10. If treatment was needed twice a year the ranges would $25-96 for treated nets and $9-23 for insecticide treatment only (273). If, however, there is rebound mortality later in childhood as a result of reduced exposure in early childhood from ITN use, the cost-effectiveness of ITNs could be reduced (284). The model showed that the age range over which rebound mortality might occur is a critical determinant of the thresholds at which one cannot be reasonably certain that ITNs are cost-effective in the long term. It is unlikely that the threshold rate of rebound would be reached if rebound occurs over the range of 5

to 9 years, but if rebound occurs over the ages of 3 to 6 years, the mortality rates required to reach this threshold are more probable.

6.3 Indoor residual spraying

Residual spraying with a pyrethroid was estimated to have a cost-effectiveness range of $16-29 for one round per year and $32-58 for two rounds per year in very low income countries (273).

6.4 Interventions to protect pregnant women

There are relatively few usable studies for cost effectiveness analysis (CEA) and only 3 for chemoprophylaxis in pregnant women (285). As with all CEA, there are significant variations in cost effectiveness from place to place depending on epidemiology, relative costs, existing infrastructure, scale of activity, compliance/ coverage, managerial capacity etc. (286).

One of the earlier studies in Malawi showed that two dose SP in first and second pregnancies was markedly more cost effective in preventing infant death than either SP treatment followed by weekly CQ prophylaxis or CQ treatment followed by weekly CQ - $75 per infant death prevented as compared to $ 481 and $ 542 respectively (287).

A more recent analysis which combined data from a meta analysis of strategies for preventing malaria in pregnancy with information on costs from a range of published and unpublished sources showed that chemoprophylaxis and intermittent treatment administered to primigravidae in subSaharan Africa is highly cost effective in terms of reducing neonatal mortality where antenatal care services already exist (244). The analysis excluded other health benefits associated with antenatal malaria chemoprophylaxis, namely increased survival in children older than 28 days and significant reductions in morbidity (number of malaria episodes in primigravidae and anaemia) and mortality in mothers. Also, it was not possible to analyse the variation in cost effectiveness in different epidemiological settings because the analysis was based on the Cochrane meta analysis

(241) which combined data from studies conducted under both perennial and seasonal transmission settings. Similarly, it was restricted to primigravidae because the Cochrane review only reported a significant impact on LBW in the first pregnancy.

The analysis shows the mean cost per DALY averted using 2 doses of SP in a low income country with no drug resistance was $12 and $21 when using weekly chloroquine throughout pregnancy. Both regimens are considered ‘highly attractive’ (options in this setting, falling below the threshold of $25 per DALY averted, SP being more cost effective than chloroquine due to improved compliance: 2 doses as opposed to weekly doses throughout pregnancy). Cost effectiveness decreases with decreasing drug sensitivity, though even with high levels of resistance (69% for CQ and 83% for SP) both drug regimens remain ‘attractive’ malaria interventions (falling below the threshold of $150 per DALY averted). Due to widespread chloroquine resistance in Africa, SP offers the most cost effective option for most parts of Africa today (even with SP resistance levels of over 40%, 2 dose SP would still be more cost effective than CQ with zero CQ resistance). IPT with SP remains cost effective even at three doses and one extra clinic visit ($21 compared to $12 per DALY averted) and so provides a cost effective strategy for HIV infected women. A more recent cost effectiveness study supports this finding (288). IPT with SP given to pregnant women with HIV seroprevalence rates greater than 10% (monthly SP regimen) and at HIV seroprevalence rates less than 10% (2-dose SP regimen) are both cost effective interventions when compared with two other SP regimens and febrile case management with SP.

The mean cost per DALY averted in middle income countries with no drug resistance was similar to low income countries - $13 for 2 dose SP compared to $12 for low income countries.

While the cost effectiveness analysis covers only primigravidae, it is desirable to offer antenatal malaria chemoprophylaxis to all pregnant women for a number of reasons. Firstly, while on an

individual level primigravidae are more susceptible to adverse effects of malaria in pregnancy in stable endemic areas, women of all parities are at risk of severe disease and death in areas of unstable or seasonal transmission and would benefit from IPT (289). In addition, HIV infection may increase malaria risk in multigravidae (290). In addition to reasons of biological vulnerability, there are several practical reasons that would complicate the application of different strategies to different groups. Both IPT with SP (2 doses) and weekly CQ are cost effective interventions when applied to all pregnant women ($32 and $60 per DALY averted respectively).

While malaria chemoprophylaxis for pregnant women is a cost effective intervention on its own, it provides an opportunity to combine antimalarial chemotherapy with micronutrient supplements (iron and folate), anthelmintics, and screening for and treatment of severe anaemia as a comprehensive package of antenatal care.

Cost effective analyses for malaria treatment specifically among pregnant women have not been undertaken, though CEA for treatment in all ages, for both inpatients and outpatients has been done (244).

7 APPROACHES TO ADDRESS CONSTRAINTS

Given that there is a set of cost-effective interventions the high toll of avoidable deaths and disease caused by malaria indicates that there are important constraints to their use. If Roll Back Malaria is to reach its ambitious objectives, there is an urgent need to scale up the use of interventions to reach much greater numbers of people quickly but also with adequate quality and attention to sustainability. The major constraints to scaling up tend to apply to all the priority interventions, although there are some specific issues for each.

Table 14 lists the key constraints related to each intervention and possible approaches to reducing them. Table 15 summarises priorities for addressing major constraints applicable to all interventions. Given comprehensive strategies to address these constraints, many of which are not specific to malaria, there is a high probability that increased investments will substantially reduce the burden of malaria.

Table 1: Malaria cases reported to WHO in selected years from 1982 to 1987 by continent

Year	Africa	Americas	Asia	Oceania	World Total
1982	8,045,746	713,878	5,580,381	190,332	14,530,337
1987	21,294,523	1,016,327	4,058,717	263,653	26,633,220
1992	21,371,102	1,186,053	3,939,559	193,103	26,689,817
1997	12,260,126	1,054,230	5,288,916	112,329	18,715,601

Source: 291 (original shows details by country).

Table 2: Estimates of malaria morbidity and mortality in African children under five years old (derived from (29))

Malaria manifestation	**Number cases***	**Incidence per 1,000 children at risk per year**	**Number deaths**	**Case fatality rate (%)**
Cerebral malaria (CM)	575,000	6.1	110,000	19.2
Neurological sequelae of CM lasting less than 6 months	47,000-75,000	0.5-0.8	-	-
Neurological sequelae lasting more than 6 months	9,000-19,000	0.1-0.2	-	-
Severe malarial anaemia	1.42-5.66 million	15-60	190,000-974,000	13.4-17.2
Respiratory distress	792,000	8.4	110,000	13.9
Hypoglycaemia	764,000	8.1	153,000-267,000	20-35
Malaria-associated low birth weight	167,000-967,000 live births	8-45 per 1,000 live births	62,000-363,000 live births	37.5
Malaria febrile episodes	150.9-509.5 million	1,600-5,400	0.9-2.3 million	0.2-1.5

* Numbers show all cases, including those from overlapping conditions

Table 3: Estimates for 1999 of relative burden of disease of global top six causes of death due to communicable diseases by WHO region

Cause	World	World	Africa	Americas	Eastern Mediterranean	Europe	Southeast Asia	Western Pacific
	000	% total	000	000	000	000	000	000
Total deaths (all causes)	55,965	100	10,436	5,687	4,218	9,057	14,270	12,297
Total deaths (communicable diseases)	14,025	25.0	6,309	635	1,100	452	4,440	1,091
Respiratory infections	4,039	7.2	1,086	299	343	275	1,523	514
HIV/AIDS	2,673	4.8	2,154	81	29	15	360	34
Diarrhoeal disease	2,213	4.0	765	74	300	30	978	67
Tuberculosis	1,669	3.0	357	59	112	60	723	359
Malaria	1,086	1.9	953	2	44	0	69	16
Measles	875	1.6	514	1	97	4	241	17
Population (000)	5,961,628		616,435	813,065	485,266	871,845	1,508,242	1,666,776

Source: 292

Table 4: Comparison of diagnostic approaches (293)

Diagnostic approach	Advantages	Disadvantages
Clinical diagnosis	• No special equipment, supplies nor extra staff • Relatively cheap	• Notoriously inaccurate in all settings • Where treatment fails no evidence of cause • Hidden costs to patient of repeat visits • Waste of increasingly costly drugs • Microscopic Diagnosis
Microscopic diagnosis	• Accurate if skilled staff • Diagnoses all species • Can monitor progress of parasitaemia • No capillary tubes • Labs have multiple uses	• Takes time and patient may not wait • Specially trained staff and costly equipment • Reagents needed • Quality control needed
Rapid Tests HRP2-based	• Less skilled staff. Results easy to interpret • Quicker than slide, so results available to patient on one visit • No high cost equipment/electricity	• Cannot follow parasitaemia • Positive result up to 2 weeks post clearance • Safety of sampling • Short shelf-life • Cost high
Rapid Tests pLDH-based	• Less skilled staff. Results easy to interpret • Quicker than slide • Negative result on parasite clearance • No high cost equipment/electricity	• Cannot follow parasitaemia • Safety of sampling • Short shelf-life • Cost high

Table 5. Summary of characteristics of common antimalarial drugs that should be considered in drug selection
Source: [294]

	CQ	SP	Q	AQ	ASU	MQ (25 mg/kg)	HAL	Q/D	Q/T	Q/SP	CQ/ SP	MQ/ ART	AT/ PR	ART/ LUM
Cost(US$) adult dose	0.07	0.08	1.35	0.15	2.16	3.22	4.75	1.47	1.6	0.66	0.15	5.38	42	<4?
Treatment Duration (days	3	1	7	3	5	1	2	3 or 7 /7	3, 5 or 7	3	3	3	3	3
Adherence probability	++	+++	+	++	+	++	++	+	+	++	++	++	++	++
Significant Side Effects	+	++	++	+++	+/++	++	+++	++	++	++	++	++	+?	+?
Evidence of Resistance	+	+	+	+	-	+	+	-(?)	-(?)	+	+	-	-(?)	-(?)

Legend

CQ	chloroquine	MQ	mefloquine
SP	sulphadoxine/pyrimethamine	HAL	halofantrine
Q	quinine	ART	artemisinin & derivatives
D	doxycycline	LUM	lumefantrine
T	tetracycline	AT/PR	atovaquone/proguanil
AQ	amodiaquine		

Table 6: Efficacy of currently used antimalarial drugs and some newer combinations

Drug	Efficacy	Reference
Chloroquine (CQ)	Very variable, resistance for years in Asia, Oceania and Latin America, efficacy declining in Africa, more rapidly in East and Southern Africa	133
Sulphadoxine (or Sulfalene) / Pyrimethamine (SP)	Variable, resistance developed quickly in Asia, and is doing so in E. Africa. In vitro sensitivity declined in Kenya from late 80s to mid 90s.	295, 296
Amodiaquine	Resistance present but less than chloroquine in same countries. Cochrane review included 40 of 72 trials identified from 1983 to 1994, 38 in Africa. Similar to SP on day 7 but less effective day 14 & 28. Severe adverse reactions only on prophylaxis.	297, 298
Artemisinin and Its derivatives	41 trials in uncomplicated malaria, mainly in SE Asia, in Cochrane review showed fast parasite clearance and high cure rate with adequate treatment duration. No worse than quinine in preventing deaths in 23 trials in severe malaria. Artemether as effective and better tolerated than quinine for severe malaria (9 randomised controlled trials -RCTs). All isolates tested *in vitro* in Thailand highly sensitive to artesunate, but IC_{50} higher in areas of multidrug resistance. One report of *in vitro* resistance to artemisinin derivatives in a patient infected in Mali.	299, 300, 301, 302, 303, 304
Quinine	Some reduction of efficacy in Southeast Asia	305
Mefloquine	Efficacy low in SE and E Thailand in early 1990s	306, 307
Halofantrine	High sensitivity with three day not one day treatment on Thai-Burmese border in early 1990s.	308
Non-artemisinin combinations		
Quinine / tetracycline or doxycycline	Addition of tetracycline or doxycycline restores efficacy where there is quinine resistance. Seven days quinine better than 3 days quinine with 7 days tetracycline.	309
Chloroquine/SP	2 studies vs SP and CQ alone. Shorter fever clearance time than SP. Parasite clearance not significantly different. Better than CQ not SP on day 28	310, 311
Amodiaquine/SP	Similar results toCQ/SP – 3 studies. Recent unpublished results in Uganda higher rates of clinical and parasitological cure than with S/P alone but not AQ alone.	310, (Kamya *et al*.)
Atovaquone/ Proguanil	High efficacy in Thailand and Gabon	312, 313
Chlorproguanil/ Dapsone	Studies in Kenya and Tanzania have shown high efficacy.	314
Artemisinin combination		
Lumefantrine-artemether	28-day cure rates with a 4-dose regimen were 95.1% outside Thailand and 76.5% in Thailand. 6-dose regimen gave a 28-day cure rate of 97.3%. In Africa the 28-day cure rate complemented by PCR studies to distinguish re-infections from recrudescences showed a corrected cure rate of 92.7%	315, 316, 317
SP/artesunate	High efficacy in The Gambia. Other countries to report very soon	318

Table 7: Impact of using ITNs on overall mortality, mild malaria disease, parasitaemia and anaemia, measured in RCTs

Country	Impact (Protective Efficacy[1])			Anaemia (Weighted mean difference in PCV [%]) Treated nets vs no nets/untreated nets	Source
	Overall Mortality	Mild disease (fever + parasitaemia)	Parasitaemia		
Burkina F.	14%		9%	1.5	184
Cameroon			28%		319
The Gambia	23%		7%	0.3	320
The Gambia		45%			14
The Gambia		43%	17%	0.6	321
The Gambia		72%	18%	2.7	322
Ghana	18%		4%	1.2	15
Guinea Bissau		29%			323
Kenya	29%		51%		16
Kenya		30%			324
Kenya		40%			325
Madagascar		21%			326
Pakistan		62%	42%		327
Sierra Leone		49%		5.4	328
Tanzania		55%		2.1	329
Thailand		46%			330
Thailand		22%			331

[1] Impact under trial conditions

Table 8: Impact of untreated nets in comparison with no nets under operational conditions

Country	Impact (Protective efficiency)		Source
	Parasitaemia	Anaemia	
The Gambia	37%	38.5%	332
Tanzania	51%	37%	195

Table 9: Impact of using ITNs on overall mortality, mild malaria disease, parasitaemia and anaemia, measured under operational conditions

Country	Study	Impact (Protective efficiency[2])				Source
		Overall mortality	Mild disease (fever and parasitaemia)	Parasitaemia	Anaemia	
The Gambia	Longitudinal surveillance	25 – 40%				192
The Gambia	Case control study	0%	59% [3] 0% [4]			193
Pakistan	Case control study		78% [5] 69% [6]			194
Tanzania	Cross sectional survey			62%	63%	195
Tanzania	Case control	27%[7]				333

[2] Impact under operational conditions
[3] Matched with health centre controls
[4] Matched with village controls
[5] *Plasmodium falciparum*
[6] *P. vivax*
[7] reduction in post-neonatal child death. Combined with coverage data this suggests that ITNs prevented 1 in 20 post-neonatal child deaths, if the effect of untreated nets is taken into account, then this increases to 1 in 10 post-neonatal child deaths prevented.

Table 10: Delivery options for nets

Strategies

	Operational characteristics and Indicators						
	Intended **Duration** of Intervention	Scope for scaling up	**Pricing Policy**	Targeting of delivery by **Geographical Area**	Targeting of delivery by socio-economic status **(the poor)** and/or by Biological vulnerability to malaria **(children & pregnant women)**	**Intended Impact on Commercial Market**	**Indicators of operational success**
Demand creation only - no supply/delivery	**Medium term**	**Unlimited**	Market forces	Possible – depends on size/scale of markets and reach of promotion	No	Stimulation of demand	• Commercial sales volumes • % coverage • Cost effectiveness of demand creation
Sustainable Subsidies for Equity	**Permanent**	**Limited** by size of target group	**Free or very cheap (Equity)**	Possible	**Essential**	**Complementary** (may stimulate demand in non-target groups)	• **% additional coverage in target groups** • effectiveness of targeting (leakage to non-target groups) • Cost per net delivered to target group
Revolving fund	**Permanent**	**Limited** by finances	Price must cover all costs (including distribution, handling, administration)	Possible	Usually undesirable - Selling to all helps to spread fixed costs, keeping prices down	**Competition** / substitution	• Project sales volumes • **Financial viability** (independence from subsidy) • **Cost per net delivered** • % coverage
Product based Social marketing	**Permanent**	**Limited** by finances	Similar or lower than the commercial market	Possible – depends on delivery channels	Some segmentation possible	Stimulation of demand "crowding-in" (avoid "crowding-out")	• Project sales volumes • Commercial sales volumes • % coverage • cost per net delivered • "crowding-in" versus "crowding-out"
"Pump-priming"	**Temporary**	**Limited** by time	Cheap (to encourage take-up) but not too cheap (to reduce perceived value)	Possible	Possible	Stimulation of demand	• **Increased sales in commercial market** (usually post-intervention) • **Cost effectiveness of demand creation**
Emergency Relief	**Temporary**	**Limited**	Free or very cheap (Equity)	**Essential**	Biological targeting possible, but economic targeting unlikely	Irrelevant	• No. ITNs delivered, • **% coverage in target groups**

Table 11: Net coverage data from project baseline surveys and non-project areas

Country	Region / District	Rural / Urban	Year	% HH with > / = 1 net	Source
Burkina Faso	Bobo-Dioulasso	Urban	1996	39%	334
Burkina Faso	Ougadougou	Urban	1996	52%	334
Burkina Faso	Ouahigouya	Urban	1996	45%	334
Cameroon	Doula	Urban	1990	48%	335
Cameroon	Yaounde		1989	14%	335
Congo-Brazzaville	Brazzaville	Urban	1990	73% (<10yr)	69
The Gambia	Nationwide	Rural	1991	58%	262
The Gambia	Eastern	Rural	1991	51%	262
The Gambia	Central	Rural	1991	76%	262
The Gambia	Western	Rural	1991	51%	262
The Gambia	Farafenni	Rural	1991	86%	263
Ghana	Accra	Rural	1992/93	93%	269
Ghana	Accra	Urban	1992/93	16%	269
Ghana	Accra	Urban	1996	9%	336
Ghana	Kumasi	Urban	1996	21%	336
Ghana	Tamale	Peri-urban	1996	17%	336
Ghana	Dangme West - Prampram	Rural	1995	17.8%	337
Ghana	Dangme West - Dodowa	Rural	1995	16.6%	337
Ghana	Navrongo	Rural	1990	4%	338
Guinea Bissau	Bissau Town	Urban	1986	69%	263
Kenya	Uriri (West Kenya)	Rural	1988	9%	324
Kenya	Bungoma (West Kenya)	Rural	1996	8.9%	339
Malawi	Nationwide	Urban + Rural	1992	7%	340 266
Malawi	Blantyre	Urban	1998	28%	341
Malawi	Blantyre	Rural	1998	14%	341
Mali	Gao	Rural	1996	69%	334
Mali	Kayes	Rural	1996	41%	334
Mali	Mopti	Rural	1996	53%	334
Sierra Leone	Bo	Rural	1990	6%	263
Tanzania	Dar es Salaam	Urban	1998	63%	268
Tanzania	Dodoma	Rural	1998	18%	268
Tanzania	Morogoro	Rural	1998	53%	268
Tanzania	Mtwara	Rural	1998	7%	268
Tanzania	Bagomoyo	Rural	1993	5%	342
Tanzania	Kilombero /	Rural	1996	37%	343

	Ulanga				
Tanzania	Kilosa	Rural	1996	21%	344
Zambia	Macha	Rural	1997	12%	345
Zambia	Mtendere	Rural	1997	16%	345
Zimbabwe	Nationwide	Urban / Rural	1996	7%	346

Source: 347

Table 12: Reported coverage rates of indoor residual spraying

Country	Population at risk	Number protected	%
Cambodia		0	
China (Yunnan Provinc	14,099,000	1,597,000	
Lao PDR		0	
Myanmar	36,400,000	295,000	
Thailand	44,414,000	930,000	
Vietnam	41,939,000	2,636,889	
Angola		1,196,700	10
Botswana		459,096	74
Malawi		NA	
Mozambique		1,450,620	9
Namibia		654,588	60
South Africa		7,087,283	80
Swaziland		265,335	95
Tanzania		NA	
Zambia		NA	
Zimbabwe		2,000,000	34

Source: 52 / 264

Table 13: Coverage of malaria control interventions in pregnancy

Intervention	**Coverage Rates**					
	Cameroon	Kenya	Malawi	Nigeria	Uganda	Africa Region
ANC		80% :348	87% :287	80% :349		
Chemoprophyl-Axis[8]	77% Cq or pyrimethamine :350	29% of primigravidae :351	1-18% with CQ :352			
Antimalarial Treatment					Less than half of 66% :353	Over 75%
Intermittent presumptive treatment			75% one dose SP 30% two doses SP[9]			

[8] Of the 24 million pregnant women at risk of malaria infection each year, less than 5% have access to effective interventions (SARA/USAID, 2001).

[9] Despite fairly low adherence with 2 doses, rates of placental infection and low birth weight babies were significantly reduced

Table 14. Constraints related to specific priority interventions

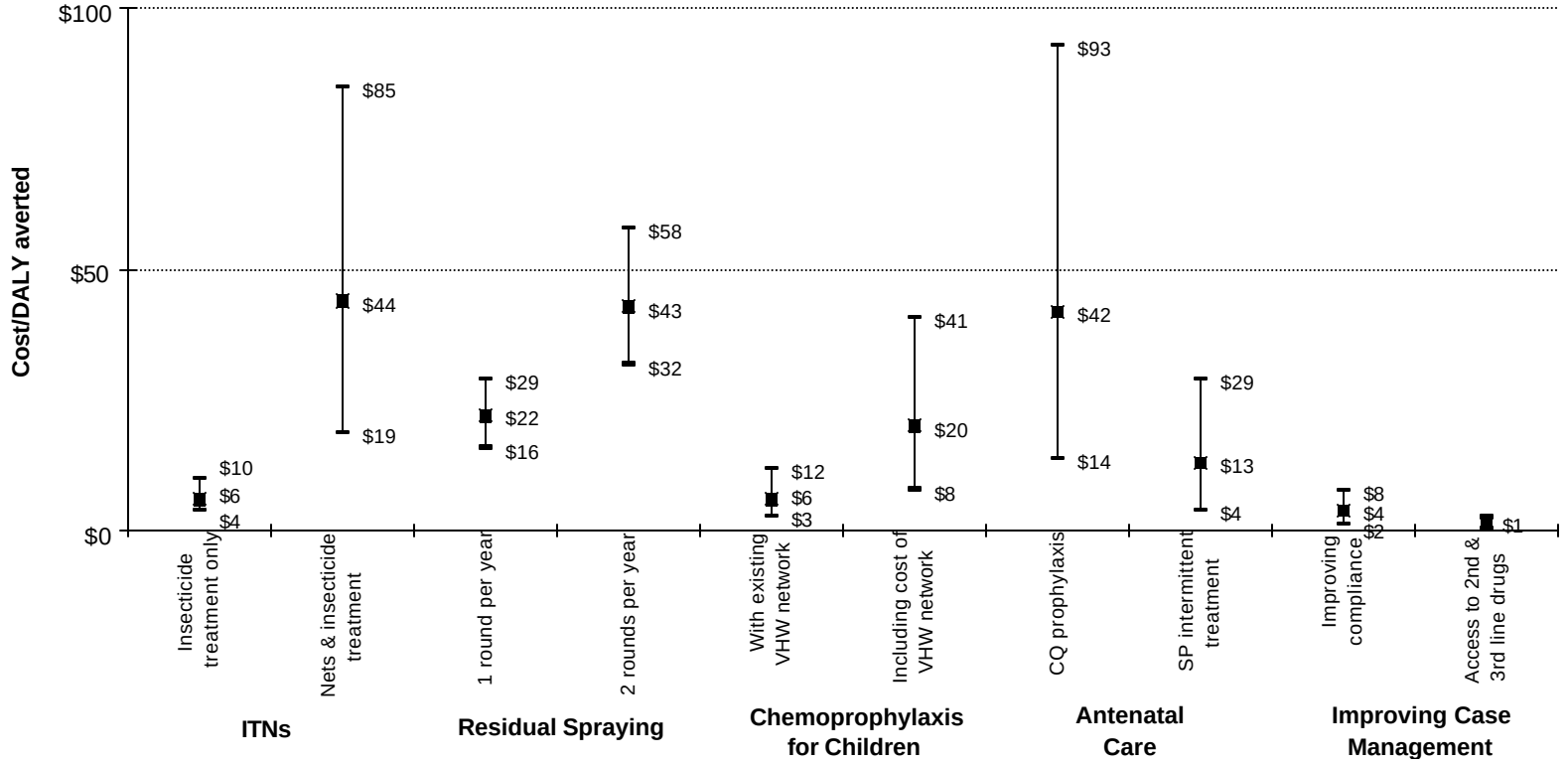
Intervention	Constraint			Approaches to removing constraints
	Technical	**Behavioural**	**Systems**	
Case management (diagnosis and treatment)	-Increasing drug resistance	- Poor quality of management at home - Health worker performance sometimes poor	-Cost of newer drugs -Poor quality of management in facilities -Limited access to public sector -Limited guidance of private sector	-Reduce drug prices -Invest in research -Increase priority to systems support to ensure access to high quality management, with IMCI -Invest more in home management
Insecticide treated materials (ITMs)	- Concerns on insecticide resistance -No alternative to pyrethroids identified	-Acceptability of nets -Willingness to retreat nets	-Access to high risk groups -Very poor retreatment rates -Cost	-Expand commercial markets through intense promotion and market environment while providing for the poorest -Improve technology for and ensure access to long lasting treatment -Develop new insecticides
Indoor residual spraying in certain environments	-Insecticide resistance in some areas -Limited alternatives	Low acceptability	-Cost of insecticides -Lack of infrastructure -Poor maintenance of quality	-Assess effectiveness in operational conditions -Develop new insecticides -Reduce prices
Protection of pregnant women	-Few drugs known to be safe -No clear alternative to SP for intermittent treatment	-Fear of drugs in pregnancy -Low utilisation of antenatal care in some countries	-Low involvement of reproductive health services -Drug supply issues	-Engage with reproductive health services -Test candidate drugs

Epidemic control	-Determinants of epidemics not always clear -Prediction inadequate	-Action is not always taken even with information	-Early warning systems not maintained -Cost of preparedness	-Develop better early warning systems -Develop supervised management systems
Human resource development	-Lack of management skills in programme managers -Lack of consensus on training methodologies	-Motivation low due to lack of enabling environment	-Working environments poor (salaries, incentives, working tools, supportive management)	-Develop long term capacity development plans -Increase resources -Explore incentives
Information, Education and Communication	-Information is not available to those who need it	-IEC is not always based on understanding of population	-Approaches to scaling up from local to national unclear and underresourced	-Greater investment in communications strategies
Surveillance	-Systems to collect community based as well as facility-based data poorly developed	-Motivation to collect data low where incidence low	-Quality difficult to maintain -Opportunities to use data at periphery limited	-General systems strengthening -Invest in population based data
Operational research			-Country relevant operational research poorly funded compared to basic research -Not a priority to industry -Management of OR cumbersome	-Develop local capacity -Introduce private sector incentives -Identify organisations which can manage operational research grants

Table 15. Approaches to addressing key constraints applicable to all interventions

Constraint	**Approaches to removing constraints**
Human resources	-HRD plans accounting for high attrition -Pre-service investment -Strategies to improve healthworker motivation
Funds	-Approach tailored to make best use of local resources -Longterm increased support
User behaviour	-Higher priority to communications strategies -Build on community priorities and ongoing activities through dialogue -Explore approaches to expand community approaches more efficiently
Systems	-Drug access: increase community control of cost recovery approaches -Supervision: improve quality assurance through increasing capacity of staff to identify and solve problems in their own working environment -Where referral is not possible improve access to limited treatment of severe disease
Practice-Policy-Research	-Link operational funds to operational research -Improve communications -Build experience of practitioners through exposure to successful new approaches
Tools	-Increase investment in research
Information	-Develop comprehensive communications strategies -Increase access to newer communication technology

Figure 1. Cost-effectiveness ranges and means in a very low income sub-Saharan Africa country with moderate to high malaria transmission (Source: 273 and Hanson *et al*., in press)



Notes

Figure shows mean and range within which 90% of cost-effectiveness estimates fall (1995 US$)
Acronyms: DALY: Disability-Adjusted Life Year; VHW: Village Health Worker; CQ:Chloroquine; SP: sulphadoxine-pyrimethamine
ITNs (insecticide treated nets): one treatment with deltamethrin a year, no insecticide resistance
Residual Spraying: lambdacyhalothrin, no insecticide resistance
Chemoprophylaxis for children: Maloprim®, perennial transmission, no resistance to Maloprim®
Antenatal Care: primigravidae only, 50% chloroquine RII/RIII resistance, 10% SP RII/RIII resistance
Improving Case Management: chloroquine as first line drug with 30% clinical failure

REFERENCES

[1] **Mendis K, et al**. The neglected burden of *Plasmodium vivax* malaria. *American Journal of Tropical Medicine and Hygiene,* 2001, **64** 1 (suppl.2): 97-106.

[2] **Wernsdorfer WH, McGregor IA (eds)**. *Malaria: Principles and Practice of Malariology*. London, Churchill Livingston, **1988.**

[3] **Gilles HM, Warrel DA (eds)**. *Bruce Chwatt's Essential Malariology Third Edition.* London, Arnold, 1993.

[4] **Remme JHF, Binka F, Nabarro D**. Toward a framework and indicators for monitoring Roll Back Malaria. *American Journal of Tropical Medicine and Hygiene,* 2001, **64** 1 (suppl.2): 76-84.

[5] **Nájera JA, Hempel J**. *The Burden of Malaria*. Malaria Unit, Division of Tropical Diseases, World Health Organisation, 1996. CTD/MAL/96.10.

[6] **Snow RW**, **et al**. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bulletin of the World Health Organisation*, 1999, **77** (8): 624-640.

[7] **De Savigny D.** Information for malaria control in Africa: are we ready? *Proceedings of the MIM African Malaria Conference, Durban, South Africa, March 1999.* Wellcome Trust 2000, 108-117.

[8] **Craig MH, Snow RW, le Suer D**. Reviews: A climate based distribution model of malaria transmission in sub-Saharan Africa. *Parasitology Today,* 1999, **15** (3): 105-111.

[9] **Snow RW, Marsh K, le Suer D**. The need for maps of transmission intensity to guide malaria control in Africa. *Parasitology Today,* 1996, **12** (12): 455-457.

[10] **Snow RW**, **et al**. A Preliminary Continental Risk Map for Malaria Mortality among African Children. *Parasitology Today,* 1999, **15** (3): 99-104.

[11] **Bradley DJ (Feachem R, Jamison D - eds)**. In: Disease and Mortality in sub-Saharan Africa. OUP, 1991: Ch. 12, Malaria, Ch.17, Morbidity and Mortality at Pare-Taveta, Kenya and Tanzania, 1954-66: the effects of a period of malaria control.

[12] **Molineaux L, et al**. The epidemiology of malaria and its measurement. In: Wernsdorfer WH, McGregor IA, eds. *Malaria: Principles and Practice of Malariology, volume two*. Churchill Livingstone, 1988: Chapter 36.

[13] **Giglioli G**. Changes in the pattern of mortality following the eradication of hyperendemic malaria from a highly susceptible community. *Bulletin of the World Health Organisation*, 1972, **46**: 181-202.

[14] **Alonso PL, et al**. A malaria control trial using insecticide-treated bednets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 6. The impact of the interventions on mortality and morbidity from Malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1993, **87** (suppl. 2): 37-44.

[15] **Binka FN**, **et al**. Impact of permethrin inpregnated bednets on child mortality in Kassena-Nankana district, Ghana: a randomized controlled trial. *Tropical Medicine and International Health,* 1996, **1** (2): 147-54.

[16] **Nevill CG, et al**. Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. *Tropical Medicine and International Health,* 1996, **1** (2): 139-46.

[17] **Molineaux L, Gramiccia G**. *The Garki Project; Research on the epidemiology and control of malaria in the Sudan Savanna of west Africa*. Geneva, World Health Organisation, 1980.

[18] **McGregor IA.** Measles and child mortality in the Gambia. *West African Medical Journal,* 1964, **13:** 251-257.

[19] **WHO Expert Committee on Malaria.** *Twentieth Report; Technical Report Series No. 892.* Geneva, World Health Organisation, 2000.

[20] **WHO**. World Malaria Situation in 1994. *WHO Weekly Epidemiological Record*, 1997, No. **36**: 269-274 / No. **37**: 277-283 / No. **38**: 285-290.

[21] **Breman JG**. The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. *American Journal of Tropical Medicine and Hygiene,* 2001, **64** 1 (suppl.2): 1-11.

[22] **WHO Division of Control of Tropical Diseases.** Malaria Control – Country Profiles. In: *Second Meeting of Interested Parties on the Control of Tropical Diseases, 1-2 April 1994.* Geneva, World Health Organisation, 1994. CTD/MIP/94.6.

[23] **Warrell DA.** Cerebral Malaria: clinical features, pathophysiology, and treatment. *Annals of Tropical Medicine and Parasitology,* 1997, **91**: 875-884.

[24] **Greenwood BM, et al**. Why do some African children develop severe malaria? *Parasitology Today,* 1991, **7:** 277-281.

[25] **Newton CRJC, et al**. Severe anaemia in children living in a malaria endemic area of Kenya. *Tropical Medicine and International Health,* 1997, **2**: 165-78.

[26] **Slutsker L, et al**. In-hospital morbidity and mortality due to malaria-associated severe anaemia in two areas of Malawi with different patterns of malaria infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1994, **88**: 548-51.

[27] **Brewster DR, Kwiatkowski D, White NJ.** Neurological sequelae of cerebral malaria in children (review). *The Lancet,* 1990: **330**: 1039-43.

[28] **Holding PA, et al**. Cognitive sequelae of severe malaria with impaired consciousness. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1999, **93**: 529-34.

[29] **Murphy SC, Breman JG**. Gaps in the childhood malaria burden in Africa: adding cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia and complications of pregnancy to the calculus. *American Journal of Tropical Medicine and Hygiene,* 2001: in press.

[30] **Menendez C, Fleming AF, Alonso PL**. Reviews: Malaria-related Anaemia. *Parasitology Today,* 2000, **16** (11): 469-476.

[31] **Holding PA, Snow RW**. Impact of *Plasmodium falciparuim* malaria in performance and learning: review of the evidence. *American Journal of Tropical Medicine and Hygiene,* 2001, **64** 1 (suppl.2): 68-75.

[32] **Shankar AH.** Nutritional modulation of malaria morbidity and mortality. *Journal of Infectious Diseases,* 2000, **182** (supp. 1): 37-53.

[33] **WHO**. Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 2000, **94** (1) suppl: s1-90.

[34] **WHO**. Roll Back Malaria: the first three years. In: *Presentation at the WHO Meeting of Interested Parties, 21 June 2001*. Geneva, World Health Organisation, 2001.

[35] **Murray CJL, Lopez AD (eds)**. *Global Burden of Disease Study*. Harvard, WHO, Harvard School of Public Health, World Bank, 1996: pp 1498 – 1504; Alternative projections of mortality and disability by cause 1990-2020.

[36] **Marsh K, et al**. Indicators of life threatening malaria in African children. *New England Journal of Medicine,* 1995, **332**: 1399-1404.

[37] **Molyneux ME, et al**. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Quarterly Journal of Medicine,* 1989, **71**: 441-59.

[38] **Brabin BJ, Premji Z, Verhoeff F**. Iron-Deficiency Anaemia: re-examining the nature and magnitude of the public health problem. An analysis of anaemia and child mortality. *Journal of Nutrition,* 2001, **2S-II**: 636s-648s.

[39] **MacCormick MC**. The contribution of low birth weight to infant mortality and childhood morbidity. *New England Journal of Medicine,* 1985, **312** (2): 82-90.

[40] **Bloland PB, et al**. Rates and risk factors for mortality during the first two years of life in rural Malawi. *American Journal of Tropical Medicine and Hygiene,* 1996, **55** (1) suppl: 82-90.

[41] **McDermott JM, et al.** The effect of placental malaria infection on perinatal-mortality in rural Malawi. *American Journal of Tropical Hygiene,* 1996, **55** (1 SS): 61-65.

[42] **Steketee RW, et al**. The burden of malaria in pregnancy in malaria-endemic areas. *American Journal of Tropical Medicine and Hygiene,* 2001, **64** 1 (suppl.2): 28-35.

[43] **SARA/USAID**. *Lives at risk: Malaria and pregnancy.* SARA / USAID, 2001.

[44] **Brabin P, Piper C.** Anaemia and malaria attributable low birthweight in two populations in Papua, New Guinea. *Annals of Human Biology,* 1997; **124**: 547-55.

[45] **Greenwood BM**, **et al**. The effects of malaria chemoprophylaxis given by traditional birth attendants on the course and outcome of pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1989, **83**: 589-594.

[46] **Greenwood AM**, **et al**. Malaria chemoprophylaxis, birth weight and child survival. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1992, **86**: 483-485.

[47] **Nosten F**, **et al**. Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study. *The Lancet*, 2000, **356**: 297-302.

[48] **Verhoeff FH**, **et al**. An analysis of the determinants of anaemia in pregnant women in rural Malawi – a basis for action. *Annals of Tropical Medicine and Parasitology,* 1999, **93**: 119-33.

[49] **Guyatt H, Snow RW**. The epidemiology and burden of *Plasmodium falciparum* related anaemia among pregnant women in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene,* 2001, **64** 1 (suppl.2): 36-44.

[50] **Shulman C**, **et al**. Intermittent SP to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo controlled trial. *The Lancet,* 1999, **353**: 632-6.

[51] **Brabin BJ, Hakimi M, Pelletier D**. Iron-Deficiency Anaemia: re-examining the nature and magnitude of the public health problem. An analysis of anaemia and pregnancy-related maternal mortality. *Journal of Nutrition,* 2001, **2S-II**: 604s-615s.

[52] **WHO**. Report on : *the Planning meeting for the implementation of Roll Back Malaria in the Six Mekong Countries. Ho Chi Minh City, Vietnam 2-4 March 1999.* Geneva, World Health Organisation, 2000. WHO/MAL/2000.1092. WHO/CDS/RBM/2000.15.

[53] **Alles HK, Mendis KN, Carter R**. Malaria mortality rates in South Asia and in Africa: implications for malaria control. *Parasitology Today,* 1998, **14** (9): 369-375.

[54] **Brinkman U, Brinkman A**. Malaria and health in Africa: the present situation and epidemiological trends. *Tropical Medicine and Parasitology,* 1991, **42**: 204-213.

[55] **Carter R**. A massive effort to Roll Back Malaria 2000; *WHO unpublished report,* 1999.

[56] **Root G**. In: *A review of malaria control activities in Southern Africa and the role of the World Health Organisation's Southern Africa Malaria Control Programme 1997-2000.* WHO/AFRO Draft 2000.

[57] **Greenberg AE et al.** Hospital based surveillance of malaria related paediatric morbidity and mortality, Kinshasa, Zaire. *Bulletin of the World Health Organisation,* 1989, **67**: 189-96.

[58] **Trape JF, et al**. Impact of chloroquine resistance on malaria mortality. *Comptes rendus de l'Académie des Sciences, Paris, Série III,* 1998, **321**: 689-697.

[59] **Trape JF.** Impact of drug resistance on morbidity and mortality in malaria infections in Africa. In: *Proceedings of the MIM African Malaria Conference, 15-19 March 1999,* Durban 2000: 38-44.

[60] **Zucker JR, et al**. Childhood mortality during and after hospitilisation in western Kenya: effect of malaria treatment regimens. *American Journal of Tropical Medicine and Hygiene,* 1996, **55** (6): 655-660.

[61] **Trape JF**. The public health impact of chloroquine resistance in Africa. *American Journal of Tropical Medicine and Hygiene,* 2001, **64** 1 (suppl.2): 12-17.

[62] **WHO.** Expert group meeting on malaria control in complex emergencies. Meeting Report Geneva, 1-2 December 1998.

[63] **Ahmad OB, Lopez AD, Inoue M.** The decline in child mortality: a reappraisal. *Bulletin of the World Health Organisation,* 2000, **78**: 1175-1191.

[64] **Rutstein SO.** Factors associated with trends in infant and child mortality in developing countries during the 1990s. *Bulletin of the World Health Organisation*, 2000, **78**: 1256-1270.

[65] **Gelband H, Nemer L, Stansfield S, Jha P.** The evidence base for interventions to reduce under-five mortality in low and middle-income countries. *CMH-WG5 Paper 9,* 2001.

[66] **Najera JA, Liese BH, Hammer J**. *Malaria New Patterns and Perspectives*. Washington, World Bank Technical Paper Number 183, 1992.

[67] **Kovats RS, et al.** Early effects on climate change: do they include changes in vector-borne diseased? *Philosophical Transactions of the Royal Society London B,* 2001, **356**: 1-12.

[68] **Cox J**, **et al**. *Mapping Malaria Risk in the Highlands of Africa*. MARA/HIMAL Technical Report, December 1999.

[69] **Carme B**, **et al**. Cerebral malaria in African children: socioeconomic risk factors in Brazzaville Congo. *American Journal of Tropical Medicine and Hygiene,* 1994, **50** (2): 131-136.

[70] **Snow RW, Marsh K**. New insights into the epidemiology of malaria relevant for disease control. *British Medical Bulletin,* 1998, **54**: 293-309.

[71] **Snow RW, Marsh K**. Will reducing *Plasmodium falciparum* transmission alter malaria mortality among African children? *Parasitology Today,* 1995, **11**: 188-190.

[72] **Snow RW**, **et al**. Relation between severe malaria morbidity in children and level of *Plasmodium falciparum* transmission in Africa. *The Lancet,* 1997, **349**: 1650-54.

[73] **Trape JF, Rogier C**. Combating malaria morbidity and mortality by reducing transmission. *Parasitology Today,* 1996, **12** (6): 236-240.

[74] **Snow RW, et al**. Severe Childhood malaria in two areas of markedly different *falciparum* transmission in East Africa. *Acta Tropica,* 1994, **57**: 289-300.

[75] **Molineaux L.** Malaria and mortality: some epidemiological considerations. *Annals of Tropical Medicine & Parasitology,* 1997, **91**: 811-825.

[76] **Warren M**, **et al**. *Malaria in Urban and Peri-Urban Areas in sub-Saharan Africa.* Environmental Health Project Activity Report No. 71, 1999.

[77] **Whitworth J, et al**. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in Uganda: a cohort study. *The Lancet,* 2000, **356**: 1051-56.

[78] **French N, Gilks C.** Royal Society of Tropical Medicine and Hygiene Meeting at Manson House, London,18 March 1999 – Fresh from the Field; some controversies in tropical medicine and hygiene: HIV and Malaria, do they interact? *Transactions of the Royal Society of Tropical Medicine & Hygiene,* 2000, **94**: 233-237.

[79] **Murray CJL, Lopez AD**. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study 1997. *The Lancet*, **349**: 1498-1504.

[80] **Foster S, Phillips M**. Economics and its contribution to the fight against malaria. *Tropical Medicine and Parasitology*, 1998, Jun **92** (4): 391-8.

[81] **WHO**. Economic Costs of Malaria are many times higher than previously estimated. In: *Press Release WHO/28 April 25th, 2000.*

[82] **Asenso-Okyere WK, Dzator JA**. Household cost of seeking malaria care. A retrospective study of two districts in Ghana. *Social Science & Medicine,* 1997, **45** (5): 659-67.

[83] **Ettling MB, Shephard DS**. Economic cost of Malaria in Rwanda. *Tropical Medicine and Parasitology,* 1991, **42**: 214-218.

[84] **Guiguemde TR**, **et al**. [An outline of a method for estimating the calculated economic cost of malaria cases. its application to a rural area in Burkina Faso]. [Article in French] *Tropical Medicine and International Health,* 1997, Jul **2** (7): 646-53.

[85] **Guiguemde TR, et al.** Household expenditures on malaria prevention and treatment for families in the town of Bobo-Dioulasso, Burkina Faso. *Transactions of the Royal Society of Tropical Medicine & Hygiene,* 1994, **88**: 285-287.

[86] **Kirigia JM, et al**. The cost of treating paediatric malaria admissions and the potential impact of insecticide treated mosquito nets on hospital expenditure. *Tropical Medicine and International Health,* 1998, **3**: 145-50.

[87] **Ettling M, McFarland DA**. Economic impact of malaria in Malawi. *Unpublished report 1992.*

[88] **Chambon R, et al.** [Part of health costs related to malaria in a Cameroon enterprise]. [Article in French] *Médecine Tropicale (Mars),* 1997, **57** (2): 169-73.

[89] **Ettling M, et al.** Economic impact of malaria in Malawian households. *Tropical Medicine and Parasitology,* 1994, Mar **45** (l): 74-9.

[90] **Stephens C,, et al**. Knowledge of mosquitos in relation to public and domestic control activities in the cities of Dar es Salaam and Tanga. *Bulletin of the World Health Organisation*, 1995, **73** (1): 97-104.

[91] **Shephard DS**, **et al**. The economic cost of Malaria in Africa. *Tropical Medicine and Parasitology*, 1991, **42**: 199-203.

[92] **Leighton C, et al**. *Economic Impacts of Malaria in Kenya and Nigeria*. Health Financing and Sustainability Project, USAID, Abt Associates, Bethesda, MD, 1993.

[93] **Gallup JL, Sachs JD**. The economic burden of malaria. *American Journal of Tropical Medicine and Hygiene*, 2001, **64** 1 (suppl.2): 85-96.

[94] **Bradley DJ**. Watson, Swellengrebel and species sanitation: environmental and ecological aspects. *Parassitologia*, 1994, **36**: 137-147.

[95] **Lines JD, Velayudhan R**. Bio-Environmental Control of Malaria Vectors: Myths and Realities. *Unpublished draft.*

[96] **Onori E, Beales PF, Gilles HM**. From malaria eradication to malaria control: the past, the present and the future. In: Gilles HM and Warrell DA, eds. *Bruce-Chwatt's Essential Malariology Third edition*. London, Arnold, 1993.

[97] **Litsios S**. *The Tomorrow of Malaria.* Pacific Press: Ecotrends, 1996.

[98] **Martínez J, Hill JA, Meek SR.** *Global co-ordination of malaria control efforts: issues and options for supporting country strategies.* Malaria Consortium, UK, 1998.

[99] **WHO**. *Expert Committee on Malaria Eighteenth Report. Technical Report Series No 735.* Geneva, World Health Organisation, 1986.

[100] **WHO**. *A Global Strategy for Malaria Control*. Geneva, World Health Organisation, 1993.

[101] **WHO**. *Implementation of the Global Malaria Strategy. Report of a WHO Study Group on the implementation of the Global Plan of Action for Malaria Control 1993 – 2000. Technical Report Series No. 839.* Geneva, World Health Organisation, 1993.

[102] **WHO**. *Roll Back Malaria Project for the accelerated implementation of malaria control in Africa, 1997-1998.* Geneva, World Health Organisation, 2000.

[103] **WHO/AFRO.** African Initiative for Malaria Control in the 21st Century, May 1998.

[104] **WHO**. *Roll Back Malaria Factsheet 2*. Geneva, World Health Organisation, 1999.

[105] **WHO/AFRO**. Final Report of: *Joint Meeting of the Roll Back Malaria and Integrated Management of Childhood Illness Task Forces, 25-28 September 2000, Harare, Zimbabwe*. World Health Organisation, 2000.

[106] **WHO**. The African Summit on Roll Back Malaria; Abuja Nigeria 25 April 2000, World Health Organisation, 2000. WHO/CDS/RBM/2000.17.

[107] **Ault SK**. Environmental Management: A re-emerging vector control strategy. *American Journal of Medicine and Hygiene,* 1994, **50** (6) suppl: 35-49.

[108] **Utzinger J, Tozan Y, Singer BH.** Efficacy and cost-effectiveness of environmental management for malaria control. *Tropical Medicine and International Health,* 2001, **6** (9): 1-11.

[109] **Ribbands CR.** Effects of bush clearance on fighting West African anophelines. *Bulletin of Entomological Research,* 1946, **37**: 33-41.

[110] **Carucci DJ**. Genomic Tools for Gene and Protein Discovery in Malaria: toward new vaccines. *Vaccine,* 2001, **19:** 2315-2318.

[111] **Doolan DL, Hoffman SL**. DNA based Vaccines Against Malaria: status and promise of the multi-stage malaria DNA vaccine operation. *International Journal for Parasitology,* 2001, **31:** 753-762.

[112] **Ballou WR, et al.** Malaria Vaccines; Triumphs or Tribulations? *Parassitologia,* 1999, **41**: 403-408.

[113] **Holder AA, et al.** Merozoite Surface Protein 1, Immune Evasion, and Vaccines Against Asexual Blood Stage Malaria. *Parassitologia,* 1999, **41**: 409-414.

[114] **Kwiatkowski D, Marsh K**. Development of a Malaria Vaccine. *The Lancet,* 1997, **350**: 1696-1701.

[115] **Brown GV**. Progress in the development of malaria vaccines: context and constraints. *Parassitologia,* 1999, **41**: 429-432.

[116] **Targett G**. Vaccine Efficacy, and Immunity Affecting Transmission. *Parassitologia,* 1999, **41**: 433-436.

[117] **Graves P, Gelband H**. Vaccines for Preventing Malaria (Cochrane Review). In: *The Cochrane Library,* 2001, **Issue 2**. Oxford: Update Software.

[118] **WHO.** Management of severe malaria: a practical handbook. 2nd edition. 2000, WHO, Geneva.

[119] **WHO.** Management of uncomplicated malaria and the use of antimalarial drugs for the protection of travellers. *Report of an Informal Consultation Geneva, 18-21 September 1995.* 1997, WHO/MAL/96.1075 Rev. 1. WHO, Geneva.

[120] **Ministry of Health, Dar es Salaam, Tanzania.** Policy implications of Adult Morbidity and Mortality: End of Phase 1 Report, 1997 unpublished report.

[121] **Greenwood BM.** What can be expected from malaria vaccines? *Annals of Tropical Medicine and Parasitology,* 1997, 91 (suppl. 1): s9-s13.

[122] **Ettling MB**, **et al**. Evaluation of malaria clinics in Mae Sot, Thailand: factors affecting clinic attendance. *Southeast Asian Journal of Tropical Medicine and Public Health,* 1989, **20**: 331-40.

[123] **Ettling MB**, **et al**. Economic analysis of several types of malaria clinics in Thailand. *Bulletin of the World Health Organisation,* 1991, **69**: 467-76.

[124] **Kidane G, Morrow RH**. Teaching mothers to provide home treatment of malaria in Tigray, Ethiopia: a randomised trial. *The Lancet,* 2000, **356**: 550-555.

[125] **Bassett MT et al.** Clinical diagnosis of malaria: can we improve? *Journal of Tropical Medicine and Hygiene,* 1991, **94:** 65-69.

[126] **Greenwood B.** The syndromic approach to malaria diagnosis. In: *Informal consultation on malaria diagnostics at the turn of the century 25-27 October 1999.* Geneva, World Health Organisation CDS/IC/WP 99.2.

[127] **Palmer K, Schapira A, Barat L.** The role of light Microscopy and Dipsticks in Malaria Diagnosis and Treatment. In: *Informal consultation on malaria diagnostics at the turn of the century 25-27 October 1999.* Geneva, World Health Organisation CDS/IC/WP 99.5.

[128] **WHO**. *Malaria diagnosis: new perspectives*. Geneva, World Health Organisation, 2000. WHO/CDS/RBM/2000.14.

[129] **Barat LM**, **et al**. Does the availability of blood slide microscopy for malaria at health centres improve the management of persons with fever in Zambia? *American Journal of Tropical Medicine and Hygiene,* 1999, **60:** 102-130.

[130] **Sim K.** The Experience of the National Malaria Control Programme in the use of Antigen Dipsticks for the Diagnosis of Malaria in Cambodia. In: *Informal consultation on malaria diagnostics at the turn of the century, 25-27 October 1999.* Geneva, World Health Organisation CDS/RBM/BP/99.16.

[131] **Palmer K.** In: *personal communication.*

[132] **Rozendaal J**. Pre-packaged antimalaria drugs project: rationale, design and evaluation. *Unpublished report May 1999.*

[133] **WHO.** International travel and health: vaccination requirements and health advice. 2001, WHO, Geneva.

[134] **Schellenberg D, et al.** Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomised, placebo-controlled trial. *The Lancet,* 2001, **357**: 1471-1477.

[135] **Schapira A.** Combinations in the pipeline. *Technical Consultation on Antimalarial Combination Therapy*, 4 – 5 April 2001, WHO, Geneva.

[136] **WHO.** Chemotherapy of malaria and resistance to antimalarials. Report of a WHO Scientific Group. *WHO Techical Support Series No. 529,* 1973 WHO, Geneva.

[137] **WHO.** Antimalarial drug policies: data requirements, treatment of uncomplicated malaria and the management of malaria in pregnancy. Unpublished document, 1994. WHO/MAL/94.1070.

[138] **Goodman CA, Coleman PG, Mills AJ**. Changing the first line drug for malaria treatment – Cost-effectiveness analysis with highly uncertain inter-temporal trade-offs. *Health Economics,* 2001; in press.

[139] **Kazembe P**. In: *personal communication.*

[140] **Nwanyanwu OC**, **et al**. Has the change in malaria treatment policy reduced mortality and morbidity in under five Malawian children? *Unpublished draft.*

[141] **Thimasarn, K.** *personal communication.*

[142] **Sharma VP**. Re-emergence of malaria in India. *Indian Journal of Medical Research,* 1996, **103**: 26-45.

[143] **Nosten F, Hien, TT, White NJ**. Use of artemisinin derivatives for the control of malaria. *Medicine Tropicale (Mars),* 1998, **58**: 45-49.

[144] **Barat LM**, **et al**. A systematic approach to the development of a rational malaria treatment policy in Zambia. *Tropical Medicine and International Health,* 1998, **3** (7): 535-542.

[145] **Bloland PB, et al**. Chloroquine in Africa: critical assessment and recommendations for monitoring and evaluating chloroquine therapy efficacy in sub-Saharan Africa. *Tropical Medicine and International Health,* 1998, **3** (7): 543-552.

[146] **Bloland PB, Ettling M**. Review: Making malaria-treatment policy in the face of drug resistance. *Annals of Tropical Medicine and Parasitology*, 1999, **93** (1): 5-23.

[147] **Shretta R**, **et al**. Using evidence to change antimalarial drug policy in Kenya. *Tropical Medicine and International Health,* 2000, **5**: 755-764.

[148] **White NJ**, **et al**. Viewpoint: Averting a Malaria Disaster. *The Lancet,* 1999, **353**: 1965-1967.

[149] **Price RN, et al.** Artesunate/mefloquine treatment of multi-drug resistant falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1997, **91**: 574-577.

[150] **Bloland PB, Ettling M, Meek S**. Combination Therapy for Malaria in Africa: hype or hope? *Bulletin of the World Health Organisation,* 2000, **78** (12): 1378-1388.

[151] **Wongsrichanalai C, Thimasarn K, Sirichaisinthop J**, Antimalarial drug combination policy: a caveat. *The Lancet,* 2000, **355**: 2245-47.

[152] **Warrell DA.**. Treatment and prevention of malaria. In: Gilles HM and Warrell DA, eds. *Bruce-Chwatt's Essential Malariology Third edition*. London, Arnold, 1993.

[153] **Meremikwu M, Logan K, Garner P.** Antipyretic measures for treating fever in malaria (Cochrane Review). In: *The Cochrane Library,* Issue 2, 2001. Oxford: Update Software.

[154] **Meremikwu M, Smith HJ**. Blood transfusion for treating malarial anaemia (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2001. Oxford: Update Software.

[155] **Prasad K, Garner P**. Steroids for treating cerebral malaria (Cochrane Review). In: *The Cochrane Library,* Issue 2, 2001. Oxford: Update Software.

[156] **Smith HJ, Meremikwu M**. Iron chelating agents for treating malaria (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2001. Oxford: Update Software.

[157] **Craighead I, Knowles J.** Prevention of transfusion associated HIV transmission with the use of a transfusion protocol for under five. *Tropical Doctor*, 1993, **23**: 59-61.

[158] **Obonyo CO, et al**. Blood transfusions for severe malaria-related anaemia in Africa: A decision analysis. *American Journal of Tropical Medicine and Hygiene*, 1998, **59**: 808-12.

[159] **Mwabu G, et al.** User charges in government health facilities in Kenya: effect on attendance and revenue. *Health Policy and Planning,* 1995, **10**: 164-170.

[160] **Slutsker L**, **et al**. Treatment of malaria fever episodes among children in Malawi: results of a KAP survey. *Tropical Medicine and Parasitology,* 1994, **45**: 61-64.

[161] **McCombie SC**. Treatment seeking for malaria: a review and suggestions for future research. *Resource Paper No. 2,* 1994, TDR/SER/RP/94.1 WHO Geneva.

[162]**Baume C, Kachur, SP.** Improving community case management of childhood malaria: how behavioural research can help. October 1999. Support for Analysis and Research in Africa project, Washington USA.

[163] **Baume C, Helitzer D, Kachur SP**. Patterns of care for childhood malaria in Zambia. *Social Science and Medicine,* 2000, **51**: 1491-1503.

[164] **Djimde A**, **et al**. Use of antimalarial drugs in Mali: policy versus reality. *American Journal of Tropical Medicine and Hygiene,* 1998, **59** (3): 376-379.

[165] **Espino F, Manderson L.** Treatment seeking for malaria in Morong, Bataan, The Philippines. *Social Science and Medicine,* 2000, **50**: 1309-1316.

[166] **Williams HA**, **et al**. A community perspective on the efficacy of malaria treatment options for chhildren in Lundazi District, Zambia. *Tropical Medicine and International Health*, 1999, **4** (10): 641-652.

[167] **Shakoor O, Taylor RB, Behrens RH**. Assessment of the incidence of substandard drugs in developing countries. *Tropical Medicine and International Health,* 1997, **2** (9): 839-845.

[168] **Pagnoni F, et al.** A community-based programme to provide prompt and adequate treatment of presumptive malaria in children. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1999, **91**: 512-517.

[169] **Shwe T, Lwin M, Aung S**. Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community-based treatment of non-severe falciparum malaria in Myanmar. *Bulletin of the World Health Organisation,* 1998, **76** (suppl. 1): 35-41.

[170] **WHO.** Advantages of pre-packaged antimalarials. Essential Drugs Monitor, 1998, **25&26**: 20.

[171] **Qingjun L, et al.** The effect of drug packaging on patients' compliance with treatment for *Plasmodium vivax* malaria in China. Bulletin of The World Health Organization, 1998, **76(Supp. 1)**: 21-27.

[172] **WHO**. Artesunate Rectocaps: a life-saving intervention, TDR News, 1997, **53**: 1-2.

[173] **Snow RW**, **et al**. The role of shops in the teatment and prevention of childhood malaria on the coast of Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1992, **86**: 237-239.

[174] **Foster SD**. Treatment of Malaria outside the formal health services. *Journal of Tropical Medicine and Hygiene,* 1994, **97**: 1-5.

[175] **Foster SD.** Pricing, distribution and use of antimalarial drugs. *Bulletin of the World Health Organisation,* 1991, **69** (3): 349-363.

[176] **Mwenesi HA.** The role of drug delivery systems in health care: the case of self-medication. *African Journal of Health Sciences,* 1994, **1**: 42-48.

[177] **Marsh VM**, **et al**. Changing home treatment of childhood fevers by training shop keepers in rural Kenya. *Tropical Medicine and International Health,* 1999, **4** (5): 383-389.

[178] **Breiger WR**, **et al.** Status of Malaria Control Interventions at the Community Level in Nigeria. In: *A study sponsored by the RBM programme of WHO in preparation for the technical discussions at the African Heads of State Summit on Malaria, 24-25 April, 2000, Abuja, Nigeria.*

[179] **Kaseje DCO, et al.** Usage of community-based chloroquine treatment for malaria in Saradidi, Kenya. *Annals of Tropical Medicine and Parasitology,* 1987, **81, Supp. 1**: 111-115.

[180] **Snow RW**, **et al**. Paediatric survival and re-admission risks following hospitalisation on the Kenyan Coast. *Tropical Medicine and International Health,* 2000, **5** (5): 377-383.

[181] **WHO/AFRO.** Making and Impact on Child Health. A framework for scaling up RBM and IMCI implementation in countries. Harare, January 2001.

[182] **WHO.** The multicountry evaluation of IMCI effectiveness, cost and impact (MCE) Progress Report May 2000 – April 2001. WHO/FCH/CAH/01.15.

[183] **Lengeler C**. Insecticide treated bednets and curtains for malaria control (Cochrane Review). *The Cochrane Library*, 1998, **Issue 3:** Oxford, Update Software.

[184] **Habluetzel A**, **et al**. Do insecticide-impregnated curtains reduce all-cause child mortality in Burkina Faso? *Tropical Medicine and International Health,* 1997, **2** (9): 855-62.

[185] **D'Alessandro U, et al**. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. *The Lancet,* 1995, **345**: 479-83.

[186] **Lines JD, Myamba J, Curtis CF**. Experimental hut trials of permethrin impregnated mosquito nets and eave curtains against malaria vectors in Tanzania. *Medical and Veterinary Entomology*, 1987, **1**: 37-51.

[187] **Magesa SM, et al**. Trial of pyrethroid impregnated bednets in an area of Tanzania holoendemic for malaria Part 2. Effects on the malaria vector population. *Acta Tropica,* 1991, **49**: 97-108.

[188] **Quinones ML**, **et al.** Permethrin-treated bed nets do not have a 'mass-killing effect' on village populations of *Anopheles gambiae* s.l. in The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1998, **92** (4): 373-8.

[189] **Curtis CF, et al.** A comparison of use of a pyrethroid either for house spraying or for bednet treatment against malaria vectors. *Tropical Medicine and International Health,* 1998, **3** (8): 619-31.

[190] **Curtis, C**. In: prep.

[191] **Bradley AK, et al.** Bed-nets (mosquito nets) and morbidity from malaria. *The Lancet*, 1986, Jul 26, 2 (8500): 204-7.

[192] **D'Alessandro U, et al**. A comparison of the efficacy of insecticide-treated and untreated bed nets in preventing malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1995, **89**: 596-598.

[193] **D'Alessandro U**, **et al.** The Gambian National Impregnated Bed Net Programme: evaluation of effectiveness by means of case-control studies. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1997, **91**: 638-642.

[194] **Rowland M**, **et al**. Sustainability of pyrethroid-impregnated bednets for malaria control in Afghan communities. *Bulletin of the World Health Organisation,* 1997, **75** (1): 23-9.

[195] **Abdulla S, et al**. Impact on malaria morbidity of a programme supplying insecticide treated nets in children aged under 2 years in Tanzania: community cross sectional study. *British Medical Journal,* 2001, **322**: 270-273.

[196] **Rowland, M, et al**. Permethrin-treated *chaddars* and top-sheets: appropriate technology for protection against malaria in Afghanistan and other complex emergencies. *Transactions of the Royal Society of Tropical Medicine and Hygiene,*1999, **93**: 465-472.

[197] **Kouznetsov RL**. Malaria control by application of indoor spraying of residual insecticides in tropical Africa and its impact on community health. *Tropical Doctor,* 1977, **7**: 81-91.

[198] **Mouchet, J.** La reconquête des Hautes Terres de Madagascar par le paludisme. *Bulletin de la Société des Pathologies Exotiques,* 1997, **90**: 162-168.

[199] **Ismail IAH, et al.** Studies on malaria and responses of *Anopheles balabacensis balabacensis* and *Anopheles minimus* to DDT residual spraying in Thailand. *Acta Tropica,* 1975, **32**: 206-231.

[200] **Garrett-Jones C, Grab B.** The assessment of insecticidal impact on the malaria mosquito's vectorial capacity from data on the proportion of parous females. *Bulletin of the World Health Organisation,* 1964, **31**: 71-86.

[201] **Hongvivatana T, et al.** An observational study of DDT house spraying in a rural area of Thailand. *Journal of Tropical Medicine and Hygiene,* 1982, **85**: 245-250.

[202] **Sharma GK**. A critical review of the impact of insecticidal spraying under NMEP on the malaria situation in India. *Journal of Communicable Diseases,* 1987, **19**: 187-290.

[203] **Payne D**, **et al**. Impact of control measures on malaria transmission and general mortality. *Bulletin of the World Health Organisation*, 1976, **54**: 369-77.

[204] **Meek SR**. Vector control in some countries of Southeast Asia: comparing the vectors and the strategies. *Annals of Tropical Medicine and Parasitology,* 1995, **89**: 135-147.

[205] **Sharma VP, et al.** Impact of DDT and HCH Spraying on Malaria Transmission in Villages with DDT and HCH Resistant *Anopheles culicifacies*. *Indian Journal of Malariology*, 1986, **23**: 27-38.

[206] **Bang YH**. Implications in the Control of Malaria Vectors with Insecticides in Tropical Countries of South East Asia. Part. I - Insecticide Resistance. *Journal of Communicable Diseases,* 1985, **17** (3): 199-218.

[207] **Bouma M**. In: *personal communication.*

[208] **Rowland M, et al**. Indoor residual spraying with alphacypermethrin controls malaria in Pakistan: a community-randomized trial. *Tropical Medicine and International Health,* 2000, **5** (7): 472-481.

[209] **Bang YH**. Implication in the Control of Malaria Vectors with Insecticides in Tropical Countries of South East Asia Region. Part II - Consequences of Insecticide Use. *Journal of Communicable Diseases,* 1985, **17** (4): 300-310.

[210] **WHO.** Vector Resistance to Pesticides. Fifteenth report of the WHO Expert Committee on vector biology and control. *WHO Technical Report Series,* 1992, **818**: Geneva.

[211] **Roberts DR, Andre RG**. Insecticide resistance issues in vector-borne disease control. *American Journal of Tropical Medicine and Hygiene*, 1994, **50** (6) suppl: 21-34.

[212] **Chandre F**, **et al.** Status of pyrethroid resistance in *Anopheles gambiae* sensu lato. *Bulletin of the World Health Organisation*, 1999, **77** (3): 230 – 234.

[213] **Hargreaves K**, **et al**. *Anopheles funestus* resistant to pyrethroid insecticides in South Africa. *Medical and Veterinary Entomology*, 2000, **14**: 181-189.

[214] **Attaran A, et al**. Balancing risks on the backs of the poor. *Nature Medicine,* 2000, **6** (7): 729-731.

[215] **Curtis CF, Lines JD**. Should DDT be banned by international treaty? *Parasitology Today,* 2000, **16**: 119-121.

[216] **Roberts DR, Manguin S, Mouchet J**. DDT house spraying and re-emerging malaria. *The Lancet,* 2000, **356**: 330-332.

[217] **Curtis CF, Mnzava AEP**. Comparison of house spraying and insecticide treated nets for malaria control. *Bulletin of the World Health Organisation,* 2000, **78** (12): 1389-1400.

[218] **Hewitt S**, **et al**. Pyrethroid-sprayed tents for malaria control: an entomological evaluation in Pakistan. *Medical and Veterinary Entomology,* 1995, **9** (4): 344-52.

[219] **Hewitt S, Rowland M**. Control of zoophilic malaria vectors by applying pyrethroid insecticides to cattle. *Tropical Medicine and International Health,* 1999, **4** (7): 481-486.

[220] **Rowland M**. Malaria control in Afghan refugee camps: novel solutions. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 2001, **95**: 125-126.

[221] **Rowland M, et al**. Control of malaria by applying deltamethrin insecticide to cattle: a community-randomised trial in Pakistan. *The Lancet*, 2001: in press.

[222] **Phillips-Howard PA, et al**. Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. *Journal of Travel Medicine,* 1998, **5**: 121-6.

[223] **Greenwood AM, et al**. The distribution of birth weights in Gambian women who received malaria chemoprophylaxis during their first pregnancy and in control women. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1994, **88**: 311-312.

[224] **Steketee RW**, **et al**. The effect of malaria and malaria prevention in pregnancy on offspring birthweight, prematurity and intrauterine growth retardation in rural Malawi. *American Journal of Tropical Medicine and Hygiene,* 1996, **55** (1): 33-41.

[225] **Nosten F, et al**. Mefloquine Prophylaxis Prevents Malaria during Pregnancy: A Double-Blind, Placebo-Controlled Study. *The Journal of Infectious Diseases,* 1994, **169**: 595-603.

[226] **Nosten F**, **et al**. The effects of mefloquine treatment in pregnancy. *Clinical Infectious Diseases,* 1999, **28**: 808-815.

[227] **Steketee RW**, **et al**. Malaria treatment and prevention in pregnancy: indications for the use and adverse event associated with chloroquine and mefloquine. *American Journal of Tropical Medicine and Hygiene,* 1996, **55** (1) suppl: 50-56.

[228] **Garner P, Gulmezoglu AM**. Prevention versus treatment for malaria in pregnant women (Cochrane Review). *The Cochrane Library,* 2001, **Issue 1**: Oxford, Update Software.

[229] **Cot M**, **et al**. Effect of chloroquine chemoprophylaxis during pregnancy on birth weight: Results of a randomized trial. *American Journal of Tropical Medicine and Hygiene,* 1992, **46 (1)**: 21-27.

[230] **Cot M, et al.** Increase of birth weight following chloroquine chemoprophylaxis during the first pregnancy: Results of a randomized trial in Cameroon. *American Journal of Tropical Medicine and Hygiene,* 1995, **53** (6): 581-585.

[231] **Schultz LJ, et al.** The efficacy of antimalarial regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental *Plasmodium falciparum* infection among pregnant women in Malawi. *American Journal of Tropical Medicine and Hygiene,* 1994, **51**: 515-522.

[232] **Morley D, Woodland M, Cuthbertson WFJ**. Controlled Trial of Pyrimethamine in Pregnant Women in an African Village. *British Medical Journal,* 1964, **1**: 667-668.

[233] **Nahlen BL**, **et al**. Lack of efficacy of pyrimethamine prophylaxis in pregnant Nigerian women. *The Lancet,* 1989, **2 II**: 830-833.

[234] **Fleming AF**, **et al**. The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Annals of Tropical Medicine and Parasitology,* 1986, **80** (2): 211-233.

[235] **Mutabingwa TK**, **et al**. Malaria chemosuppression in pregnancy I. The effect of chemosuppressive drugs on maternal parasitaemia. *Tropical and Geographical Medicine,* 1993, **45** (1): 6-14.

[236] **Mutabingwa TK, et al**. Malaria chemosuppression in pregnancy II. Its effect on maternal haemoglobin levels, placental malaria and birth weight. *Tropical and Geographical Medicine,* 1993, **45** (2): 49-55.

[237] **Hamilton PJS**, **et al**. The role of malaria, folic acid deficiency and haemoglobin as in pregnancy at Mulago Hospital. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1972, **66** (4): 594-602.

[238] **Mutabingwa TK, Malle LN, Mtui SN**. Chloroquine therapy still useful in the management of malaria during pregnancy in Muheza, Tanzania. *Tropical and Geographical Medicine,* 1991, **43** (2): 131-135.

[239] **Dolan G, ter Kuile FO, Jacoutot, V, White NJ, Luxemburger C, Malankirii L, Chongsuphajaisiddhi T, Nosten F**. Bednets for the prevention of malaria and anaemia in pregnancy. *Trans Roy Soc Trop Med Hyg*, 1993, **87**, 620-626.

[240] **Parise ME**, **et al.** Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. *American Journal of Tropical Medicine and Hygiene*, 1998, **59** (5): 813-822.

[241] **Gulmezoglu AM, Garner P**. Malaria in pregnancy in endemic areas (Cochrane Review). *The Cochrane Library*, 1998, **Issue 3**: Oxford, Update software.

[242] **Rogerson SJ, et al**. Intermittent sulfadoxine-pyrimethamine in pregnancy: effectiveness against malaria morbidity in Blantyre, Malawi, in 1997-99. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000, **94**: 549-553.

[243] **Verhoeff FH**, **et al**. An evaluation of the effects of intermittent SP treatment in pregnancy on parasite clearance and risk of low birth weight in rural Malawi. *Annals of Tropical Medicine and Parasitology*, 1998, **92** (2): 141-50.

[244] **Goodman CA, Coleman PG, Mills AJ**. *Economic analysis of malaria control in sub-Saharan Africa*. Global Forum for Health Research Strategic Research Series, 2000.

[245] **Okereke CS**. Management of HIV infected pregnant patients in malaria endemic areas: therapeutic and safety considerations in concomitant use of antiretroviral and antimalarial agents. *Clinical Therapy*, 1999, **21** (9): 1456-96: discussion 1427-8.

[246] **Brabin B.** *personal communication.*

[247] **D'Alessandro U, et al**. The impact of a national impregnated bednet programme on the outcome of pregnancy in primigravidae in The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1996, **90** (5): 487-492.

[248] **Shulman CE**, **et al.** A community randomized controlled trial of insecticide-treated bednets for the prevention of malaria and anaemia among primigravid women on the Kenyan coast. *Tropical Medicine and International Health*, 1998, **3** (3): 197-204.

[249] **ter Kuile F, et al.,** unpublished.

[250] **WHO.** Malaria Early Warning Systems. Concepts. Indicators and partners: a framework for field research in Africa. *WHO/CDS/RBM/2001.32*, 2001, Geneva.

[251] **Nájera JA, Kouznetzsov RL, Delacollette C**. *Malaria Epidemics: Detection and Control Forecasting and Prevention.* Malaria Prevention and Control Programme, WHO Division of Control of Tropical Diseases, 1998. WHO/MAL/98.1084.

[252] **Thomson MC, et al.** Mapping malaria risk in Africa – what can satellite data contribute? *Parasitology Today*, 1997, **8**: 313-318.

[253] **Thomson MC, et al.** Environmental information for prediction of epidemics. *Parasitology Today*, 2000, **16**: 137-138.

[254] **Ministry of Health, Uganda**, *personal communication.*

[255] **Ofori-Adjei D, Arhinful DK.** Effect of training on the clinical management of malaria by medical assistants in Ghana. *Social Science and Medicine*, 1996, **42** (8): 1169-76.

[256] **Loevinsohn BP.** Health education interventions in developing countries: a methodological review of published articles. *International Journal of Epidemiology*, 1990, **19**: 788-794.

[257] **Curtis V.** Evidence for behaviour change from a hygiene promotion programme in West Africa. 2001, (in press).

[258] **Menon A, et al.** Maternal administration of chloroquine: an unexplored aspect of malaria control. *Journal of Tropical Medicine and Hygiene,* 1988, **91**: 49-54.

[259] **Denis M.B.** Improving compliance with quinine + tetracycline for treatment of malaria: evaluation of health education interventions in Cambodian villages. *Bulletin of the World Health Organisation,* 1998, **76 Suppl 1**: 43-9.

[260] **Booman M, et al.** Using a geographical information system to plan a malaria control programme in South Africa. *Bulletin of the World Health Organisation,* 2000, **78** (12): 1438-1444.

[261] **Anderson J, MacLean M, Davies C**. Malaria Research: An audit of International activity. *PRISM Report*, September 1996, **No.7**. Unit for Policy Research in Science and Medicine, Wellcome Trust, London.

[262] **D'Alessandro U**, **et al**. Nationwide survey of bednets in rural Gambia. *Bulletin of the World Health Organisation,* 1994, **72** (3): 391-4.

[263] **Aikins MK, Pickering H, Greenwood BM**. Attitudes to malaria, traditional practices and bednets (mosquito nets) as vector control measures: a comparative study in five west African countries. *Journal of Tropical Medicine and Hygiene*, 1994, **97** (2): 81-6.

[264] **WHO/AFRO**. *A review of malaria control activities in Southern Africa and the role of the World Health Organisation's Southern Africa Malaria Control Programme 1997-2000*. WHO/AFRO Draft 2000.

[265] **Ziba C, Slutsker L, Steketee RW**. Use of malaria prevention methods in Malawian households. *Tropical Medicine and Parasitology,* 1994, **45:** 70-73.

[266] **Schultz LJ, et al**. A nation-wide malaria knowledge, attitudes and practices survey in Malawi: objectives and methodology. *Tropical Medicine and Parasitology*,1994, 45: 54-56.

[267] **Freeman T**. *Report for Special Programme for Research and Training in Tropical Diseases.* Geneva, World Health Organisation, 1996.

[268] **Hanson K and Jones CO**. *Social Marketing of Insecticide Treated Mosquito Nets, Tanzania: End of Phase 1 Social and Economic Analysis. Final Report*. London Malaria Consortium for PSI, 2000.

[269] **Agyepong IA, Manderson L**. Mosquito avoidance and bed net use in the Greater Accra Region, Ghana. *Journal of Biosocial Sciences,* 1999, **31**: 79-92.

[270] **Goodman, CA, Mills AJ**. The evidence base on the cost-effectiveness of malaria control measures in Africa. *Health Policy and Planning*, 1999, **14** (4): 301-312.

[271] **Picard J, Mills AJ, Greenwood BM**. The cost-effectiveness of chemoprophylaxis with Maloprim administered by primary health care workers in preventing death from malaria amongst

Gambian children aged less than five years old. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1992, **86**: 580-1.

[272] **Picard J, et al**. A malaria control trial using insecticide-treated bednets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 8.Cost-effectiveness of bednet impregnation alone or combined with chemoprophylaxis in preventing mortality and morbidity from malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1993, **87** (suppl. 2): 53-57.

[273] **Goodman CA, Coleman PG, Mills AJ.** Cost-effectiveness of malaria control in sub-Saharan Africa. *The Lancet,* 1999, **354**: 378-385.

[274] **WHO.** Investing in health research and development: report of the ad hoc Committee on Health Research relating to future intervention options. 1996, Geneva: TDR/Gen/96.1.

[275] **Goodman CA**. The economic evaluation of malaria diagnosis. In: *Informal consultation on malaria diagnostics at the turn of the century, 25-27 October 1999.* Geneva, World Health Organisation CDS/IC/WP/99.7.

[276] **Schapira A.** Chloroquine resistant malaria in Africa: the challenge to health services. *Health Policy and Planning,* 1989, **4:** 17-28.

[277] **Jonkman A, et al**. Cost-savings through microscopy-based versus presumptive diagnosis of malaria in adult outpatients in Malawi. *Bulletin of the World Health Organisation,* 1995, **73** (2): 223-227.

[278] **Pang LW.** Economic analysis of Brazil's community based malaria manaagment programme – lessons learned. In: *Informal consultation on malaria diagnostics at the turn of the century, 25-27 October 1999.* Geneva, World Health Organisation CDS/RBM/BP/99.1.

[279] **Goodman C**. Would replacing chloroquine with SP as first line drug be cost-effective in Tanzania? *EANMAT Newsletter,* Sept 2000, **No #7**.

[280] **Abdulla S. et al.** The costs, effects and cost-effectiveness of changing the first line drug for the treatment of malaria in Tanzania. Unpublished Report, 2000, Malaria Consortium, London.

[281] **The World Bank.** Health, Nutrition and Population Sector Strategy Paper, 1997, p. 61.

[282] **Binka FN, Mensah OA, Mills A**. The cost-effectiveness of permethrin impregnated bednets in preventing child mortality in Kassena-Nankana district of Northern Ghana. *Health Policy,* 1997, **41** (3): 229-39.

[283] **Brinkmann U, Brinkmann A**. Economic aspects of the use of impregnated mosquito nets for malaria control. *Bulletin of the World Health Organisation,* 1995, **73** (5): 651-8.

[284] **Coleman PG, Goodman CA, Mills AJ**. Rebound mortality and the cost-effectiveness of malaria control: potential impact of increased mortality in late childhood following the introduction of insecticide treated nets. *Tropical Medicine and International Health,* 1999, **4** (3): 175-186.

[285] **Mills AJ.**. Is malaria control cost-effective? *Proceedings of the MIM African Malaria Conference, Durban, South Africa, March 1999.* Wellcome Trust 2000, 92-107.

[286] **Goodman CA, Coleman PG, Mills AJ.** The cost-effectiveness of antenatal malaria prevention in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene,* 2001, **64** 1 (suppl.2): 45-56.

[287] **Schultz LJ, et al**. Evaluation of maternal practices, efficacy and cost effectiveness of alternative regimens for use in pregnancy: chloroquine and SP. *American Journal of Tropical Medicine and Hygiene,* 1996, **55** (1) suppl: 87-94.

[288] **Wolfe EB, Parise ME, Haddix AC, Nahlen BL, Ayisi JG, Misore A, Steketee RW**. Cost effectiveness of sulphadoxine-pyrimethamine for the prevention of malaria-associated low birth weight. *American Journal of Tropical Medicine & Hygiene,* 2001, **64**, 178-186.

[289] **Shulman C**. *personal communication.*

[290] **Steketee RW, Wirima JJ, Bloland PB**. Impairment of a pregnant woman's acquired ability to limit *Plasmodium falciparum* infection with HIV type 1. *American Journal of Tropical Medicine and Hygiene,* 1996, **55** (1) suppl; 42-9.

[291] **WHO**. Malaria 1982-1997. *WHO Weekly Epidemiological Record,* 1999, **74**: 265-272.

[292] **WHO**. *World Health Report 2000: health systems: improving performance.* Geneva, World Health Organisation, 2000.

[293] **Meek S.** Global malaria overview, focusing on local differences affecting diagnostic choices. In: *Informal consultation on malaria diagnostics at the turn of the century 25-27 October 1999.* Geneva, World Health Organisation CDS/IC/WP 99.1.

[294] **Shretta R**. The use of antimalarial drugs: policy implications for the treatment and prevention of malaria. *Report of an informal consultation,* WHO Geneva, 13-17 November, 2000.

[295] **Watkins WM**, **et al**. The efficacy of antifolate antimalarial combinations in Africa: a predictive model based on pharmacodynamic and pharmacokinetic analyses. *Parasitology Today*, 1997, **13** (12): 459-464.

[296] **Mberu EK, et al.** The changing *in vitro* susceptibility pattern to pyrimethamine/sulfadoxine in *Plasmodium falciparum* field isolates in Kilifi, Kenya. *American Journal Tropical Medicine and Hygiene,* 2000. **62:** 396-401.

[297] **Olliaro P, et al**. Systematic review of amodiaquine treatment in uncomplicated malaria. *The Lancet*, 1996, **348**: 1196-201.

[298] **Olliaro O, Mussano, P**. Amodiaquine for treating malaria (Cochrane review). In: *The Cochrane Library,* Issue 2, 2001. Oxford: update software.

[299] **McGready R, et al**. Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Transactions of the Royal Society of Tropical Medicine & Hygiene,* 1998, **92**: 430-33.

[300] **McIntosh HM, Olliaro P**. Artemisinin derivatives for treating severe malaria (Cochrane Review). In: *The Cochrane Library,* Issue 2, 2001. Oxford: Update Software.

[301] **Pittler MH, Ernst E**. Artemether for severe malaria: a meta-analysis of randomised clinical trials. *Clinical Infectious Diseases,* 1999, **28** (3): 597-601.

[302] **World Health Organisation**. *The use of Artemisinin and its derivatives as anti-malarial drugs.* Report of a joint CTD/DMP/TDR informal consultation, 1998 (Geneva) 10-12 June. WHO/MAL/98.1086.

[303] **Wongsrichanalai C, et al**. *In vitro* sensitivity of *Plasmdoium falciparum* to artesunate in Thailand. *Bulletin of the World Health Organisation,* 1999, **77** (5): 392-398.

[304] **Gay F, et al.** *In-vitro* resistance of *Plasmodium falciparum* to quinghaosu derivatives in West Africa. *The Lancet,* 1994, **343**:

[305] **Meshnick SR**. Why does quinine still work after 350 years of use? *Parasitology Today,* 1997, **13** (3): 89-92.

[306] **Ketrangsee S, et al.** Comparative trial of the response of *Plasmodium falciparum* to halofantrine and mefloquine in Trat Province, Eastern Thailand. *Southeast Asian Journal of Tropical Medicine and Public Health,* 1992, **23**: 55-58.

[307] **Fontanet AL, et al**. High prevalence of mefloquine-resistant falciparum malaria in eastern Thailand. *Bulletin of the World Health Organization,* 1993, **71**: 377-383.

[308] **Ter Kuile FO, et al.** Halofantrine versus mefloquine in treatment of multidrug-resistant falciparum malaria. *The Lancet,* 1993, **341**: 1044-1049.

[309] **Meek SR et al.** Treatment of falciparum malaria with quinine and tetracycline or combined mefloquine/sulfadoxine/ pyrimethamine on the Thai-Kampuchean border. *American Journal Tropical Medicine and Hygiene,* 1986. **35:** 246-250.

[310] **McIntosh HM**. Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine for treating uncomplicated malaria (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2001. Oxford: Update Software.

[311] **McIntosh HM, Greenwood BM**. Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine as a treatment for uncomplicated malaria – a systematic review. *Annals of Tropical Medicine and Parasitology* 1998, **93**:265-270.

[312] **Looareesuwan S, et al.** Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *American Journal of Tropical Medicine and Hygiene,* 1996. **54**(1): p. 62-6.

[313] **Radloff PD, et al.** Atovaquone and proguanil for *Plasmodium falciparum* malaria. *The Lancet,* 1996, **347**: 1511-1514.

[314] **Amukoye E, et al.** Chlorproguanil-dapsone: an effective treatment for uncomplicated falciparum malaria. *Antimicrobial Agents Chemother*, 1997; **41**: 2261-2264.

[315] **Looareesuwan, S., et al.,** A randomized, double-blind, comparative trial of a new oral combination of artemether and benflumetol (CGP 56697) with mefloquine in the treatment of acute Plasmodium falciparum malaria in Thailand. *American Journal of Tropical Medicine and Hygiene*, 1999. **60**(2): 238-43.

[316] **van Vugt, M., et al.,** Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug-resistant falciparum malaria. *Antimicrobial Agents Chemotherapy*, 1998. **42**(1): 135-9.

[317] **von Seidlein, L., et al.**, Treatment of African children with uncomplicated falciparum malaria with a new antimalarial drug, CGP 56697. *Journal of Infectious Diseases*, 1997. **176**(4): 1113-6.

[318] **Von Seidlein L, et al.** Parasitaemia and gametocytaemia after treatment with chloroquine, pyrimethamine/sulfadoxine, and pyrimethamine/sulfadoxine combined with artesunate in young Gambians with uncomplicated malaria. *Tropical Medicine and International Health*, 2001, **6**: 92-98.

[319] **Moyou-Somo R**, **et al.** Deltamethrin impregnated bednets for the control of urban malaria in Kumba Town, South-West Province of Cameroon. *Journal of Tropical Medicine and Hygiene*, 1995, **98** (5): 319-24.

[320] **D'Alessandro U, et al.** A malaria control trial using insecticide-treated bednets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa.. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1993, **87** (suppl. 2).

[321] **Snow RW,, et al**. A trial of permethrin-treated bed nets in the prevention of malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1987, **81** (4): 563-7.

[322] **Snow RW, et al.** Permethrin-treated bed nets (mosquito nets) prevent malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1988, **82** (6): 838-42.

[323] **Jaenson TGT, et al**. Control of endophagic *Anopheles* mosquitoes and human malaria in Guinea Bissau, West Africa by use of permethrin-treated bed nets. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1994, **88**: 620-624.

[324] **Sexton JD**, **et al**. Permethrin-impregnated curtains and bednets prevent malaria in western Kenya. *American Journal of Tropical Medicine and Hygiene*, 1990, **43** (1): 11-18.

[325] **Beach RF**, **et al**. Effectiveness of permethrin impregnated bednets and curtains for malaria control in a holoendemic area of western Kenya. *American Journal of Tropical Medicine and Hygiene*, 1993, **49**: 290-300.

[326] **Rabarison, P, et al**. Etude de l'impact de utilisation des rideaux impregnes de deltamethrine sur la morbidite palustre a Ankazobe, sur les hautes terres de Madagascar. *Medecine Tropicale*, 1995, **55** (suppl 4): 105-8.

[327] **Rowland, M, et al**. Pyrethroid-impregnated bed nets for personal protection against malaria for Afghan refugees. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1996, **90** (4): 357-61.

[328] **Marbiah NT**. *Control of disease due to perenially transmitted malaria in children in a rural area of Sierra Leone*. London, U.K, University of London PhD thesis, 1995: 315 pp.

[329] **Premji, Z, et al**. Changes in malaria-associated morbidity in children using insecticide treated mosquito nets in the Bagomoyo District of coastal Tanzania. *Tropical Medicine and Parasitology,* 1995, **46**: 147-153.

[330] **Kamol-Ratanakul P, Prasittisuk C**. The effectiveness of permethrin-impregnated bed nets against malaria for migrant workers in eastern Thailand. *American Journal of Tropical Medicine and Hygiene,* 1992, **47** (3): 305-9.

[331] **Luxemburger C, et al**. Permethrin-impregnated bed nets for the prevention of malaria in schoolchildren on the Thai-Burmese border. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1994, **88**: 155-9.

[332] **Clarke *et al* in prep.**

[333] **Armstrong Schellenberg JRM, et al**. Effect of large-scale social marketing of insecticide-treated nets on child survival in rural Tanzania. *The Lancet*, 2001, **357** (21): 1241-1247.

[334] **Centre Muraz.**

[335] **Desfontaine M, et al**. Evaluation of practice and costs of vector control on a family level in Central Africa. 11. Doula City (Cameroon). *Annals of Tropical Medicine,* 1990, **70** (2): 137-44.

[336] **Adongo PB**, **et al**. Rapid assessment of the coverage of mosquito nets using the Cluster Sampling Technique in the Kassena-Nankana District of northern Ghana. *Unpublished draft.* 1997.

[337] **Ahorlu CK, et al.** Malaria-related beliefs and behaviour in southern Ghana: implications for treatment, prevention and control. *Tropical Medicine and International Health*, 1997, **2** (5): 488-499.

[338] **Ghana VAST.**

[339] **CDC / KEMRI.**

[340] **Ziba C, Slutsker L, Steketee RW**. Use of malaria prevention methods in Malawian households. *Tropical Medicine and Parasitology,* 1994, **45:** 70-73.

[341] **PSI Malawi.**

[342] **Temu EA, et al.** Bedbug control by permethrin-impregnated bednets in Tanzania. *Medical and Veterinary Entomology*, 1999, **113**: 457-459.

[343] **Armstrong Schellenberg JRM**, **et al**. C. KINET: a social marketing programme of treated nets and net treatment for malaria control in Tanzania, with evaluation of child health and long-term survival. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1999, **93**: 225-231.

[344] **PATH Canada.**

[345] **CMAZ.**

[346] **Freeman T**. *Report for Special Programme for Research and Training in Tropical Diseases.* Geneva, World Health Organisation, 1996.

[347] **Webster J, Reed C, Lines J.** *Malaria Consortium.* Unpublished database.

[348] **Shulman C**. *Prevention of severe anaemia and malaria in pregnancy in Kenya 13-31 March*. London, Malaria Consortium, 2000.

[349] **FMOH / WHO SA 2000.**

[350] **Lemardeley P**, **et al**. Prevention and control of malaria in pregnant women in an urban area of Yaounde, Cameroon. *Cahiers d'Etude et de Researches Francophone/Sante*, 1997, **7** (4): 239-45.

[351] **Kaseje DC, Sempebwa EK, Spencer HC.** Malaria chemoprophylaxis to pregnant women provided by community health workers in Saradidi, Kenya. 1. Reasons for non-acceptance. *Annals of Tropical Medicine and Parasitology*, 1987, **81** (1): 78-82.

[352] **Steketee RW**, **et al**. The problem of malaria and malaria control in pregnancy in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene,* 1996, **55** (1) suppl; 2-7.

[353] **Ndyomugyenyi R, Neema S, Magnussen P**. The use of formal and informal services for antenatal care and malaria treatment in rural Uganda. *Health Policy and Planning*, 1998, **13** (1): 94-102.