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Malaria: Burden and Interventions

Evidence Overview

A Working Paper (Version 1.0)

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Contents

Foreword

What this evidence paper is and what it is not

This paper, written by staff members of DFID, with some chapters written by academic colleagues, provides a summary of current evidence on malaria, concentrating on those areas where policy or practical decisions will have to be made. It aims to help inform decision-making, mainly by DFID and its development partners. For this reason there is relatively little information on regions such as Latin America where DFID does not have a major presence or on important scientific areas where direct implications for policy or practice are limited.

The authors do not attempt to prescribe policy conclusions, which, for DFID, will appear elsewhere; nor do they intend formally to classify or grade the evidence. In some areas, reliable evidence of positive impact is limited to the context or particular delivery approach which cannot be generalised more widely. Other areas are well established with high quality studies and a lower risk of bias or confusion and are widely generalisable. In some areas, such as case management and insecticide treated nets, there is sufficient evidence from systematic reviews for a more formal grading of evidence. Recognising that many of the issues are context-specific, this paper will be supplemented by country profiles which will be available in early 2011, and should be read in conjunction with the country data published in the World Malaria Report and updated by the World Health Organization (WHO).[1]

The paper is divided into sections and is not designed to be read cover-to-cover. The idea is to signpost the reader to the sections which are useful for particular decisions. Wherever possible the authors have tried to refer to good reviews which are freely available or accessible through HINARI where readers will find more detailed information, major original studies, and recent papers which refer to earlier studies. The report should be seen as a 'portal' to more detailed information if needed rather than being a definitive document.

Every effort has been made to give a fair and balanced summary; the paper has been peer-reviewed by leading experts in the field. In some areas where the evidence base is not clear-cut there is inevitably a subjective element. If readers consider that the evidence on any issue is not accurately described or misses important studies which may change the balance please let us know by emailing malaria-evidencefeedback@dfid.gov.uk so that we can consider it when correcting or updating this evidence paper.

Please note that this evidence overview was produced by the UK Department for International Development (DFID). The interpretation of the evidence expressed in this report are entirely those of the named authors and do not necessarily represent those of DFID as an institution. This is not a policy document, and is not meant to represent DFID's policy position.

Executive Summary

This evidence paper summarises evidence relevant for DFID advisers and policy makers and other decision makers in DFID target countries.

Epidemiology and Burden

The majority of human clinical malaria is caused by *Plasmodium falciparum* and the great majority of deaths are caused by this species. *Plasmodium vivax* malaria remains a significant health problem in much of Asia and Latin America. Quoted evidence of the rate of transmission of malaria around the world depends on direct observation and modelling. Using these two approaches there are now a number of maps of malaria, at a global and country level. These demonstrate the *very wide range of transmission* of malaria from areas where clinical cases are only occasional to those, particularly in West and Central Africa, where unprotected people can receive several infected bites a night and have several clinical episodes of malaria a year. There is therefore a *wide divergence between population at risk, and burden of disease.* The majority of the deaths occur in Africa, particularly West and Central Africa, due to a combination of very high transmission and weaker health services. There is considerable variation in transmission even within countries with many countries in Africa and Asia having areas of very high transmission and low or no transmission within short distances of one another. *Data quality* on which existing maps and graphs of malaria transmission are based is variable however, and in particular in many of the poorest areas reliable evidence of malaria transmission is hard to come by. *P. vivax* malaria is the predominant form of malaria in parts South and Central Asia. In those areas, as malaria control improves, the proportion (although not the absolute amount) of vivax malaria is likely to increase because vivax malaria is more difficult to control. Epidemiological mapping of vivax malaria incidence is generally less good than falciparum malaria as vivax has generally received less attention.

Recent trends in malaria show that *malaria burden has dropped substantially* both in terms of transmission and clinical burden in a number of countries in Africa which have effective malaria programmes. Evidence for this is strong, although mainly from health service data. In other countries, generally where health systems (and data) are weaker, there is no evidence of a decline in malaria. In Asia malaria has been improving over many years, probably in large part due to improvements in socio-economic factors and urbanisation, but pockets of significant malaria transmission continue. There is an on-going debate about the importance of malaria in India. In low transmission settings, particularly settings where control has been good but then ceases to be, there is a risk of *epidemic malaria* affecting whole populations over a short period of time.

Malaria is a significant burden on health systems and on the wider economy and, particularly in Africa, represents a *substantial economic burden* on households having to pay for prevention and treatment. Community, age, nutritional status and some aspects of economic socio-economic status have an impact on the probability of individuals both acquiring malaria and dying from it.

In *fragile/conflict affected states* where malaria control and other public health services break down malaria can often have a significant resurgence. Examples of this include Afghanistan and Burundi.

There is an on-going debate on the effects of *climate change* on malaria. Malaria is likely to be transmitted higher up in highland areas and may spread into some areas it was previously not found due to global warming, but this effect is probably modest and it is changes in rainfall patterns that are likely to be the main driver of changes in transmission; the effects of climate change on rainfall are currently unpredictable in most malaria-endemic

countries. Climate change will therefore move malaria around. It is unclear whether this will lead to an overall increase (or decrease) in malaria all other things being equal. Changes in water management and sanitation, agricultural practices, urbanisation and deforestation all have significant impact on malaria transmission.

Certain groups are at significantly higher risk acquiring malaria, or once acquired, having a poor outcome. Pregnant women are a particular risk group. Malaria causes significant risks to both the pregnant mother and the unborn child. Recently, the affect of HIV infection on increase in the risk of malaria have become much clearer.

A number of recent changes may complicate our ability to control malaria. These include *artemisinin drug resistance* which has emerged in South East Asia. The extent of the spread of this is currently unclear. If this spreads outside South East Asia it would have significant negative implications for malaria control in Africa and elsewhere. There is drug resistance to the majority of other anti-malarial drug classes; the importance of this varies by geographical regions. *Insecticide resistance* to all the existing classes of widely used insecticides already exists (particularly in Africa) and is likely to spread as control efforts scale up.

Interventions and Delivery

Vector control.

There is *strong evidence for the use of insecticide treated bednets* (ITNs), long lasting insecticide treated nets (LLINs) and indoor residual spraying (IRS) in areas where the predominant mosquito species bite and rest indoors. This is in the majority of Africa and a number of other areas in Asia, although in areas of Asia and Latin America much or most transmission is outdoors. Evidence that ITNs, LLINs and IRS work under trial conditions is very clear. *Evidence to what is the best delivery mechanism for insecticide treated bed nets is less strong* and more context specific. There is a long standing debate around the role of free net distribution vs vouchers vs subsidy to increase coverage levels from their current low rates particularly in Africa. A mixed delivery method is probably appropriate in most settings. IRS has generally had to be delivered by vertical programmes. A number of novel methods of delivering insecticides such as curtains or blankets and tarpaulins in emergencies have been shown to work.

There are a number of non-insecticide based approaches to *vector control* including larvae control, changed water management and building out malaria. These have an established place in certain environments although they are generally less useful across Africa where major vectors have many breeding sites. Novel methods including genetically modified mosquitoes are being considered but are a long way from deployment.

Case Management: Diagnosis and Treatment

Diagnostic Tests for Malaria

Whilst light microscopy remains the most widely used form of malaria diagnosis, *rapid diagnostic tests* (RDTs) are becoming increasingly used. These are sensitive and specific and increasingly heat stable. They have advantages in certain situations particularly where there is low throughput of tests and where electricity is not available, for example peripheral areas. Deploying tests *without training* however does not lead to improve diagnosis as the *results are often ignored*. There is good evidence that malaria is significantly over-diagnosed in formal health care settings in Africa and possibly in Asia. At the same time malaria is often not diagnosed because people do not reach formal health care. Improving diagnostic tests and training can help with the first but not second of these. The role of rapid diagnostic tests in the private sector is currently unclear.

Drugs for malaria

There are a wide range of potential drugs for malaria. A major limitation of available drugs is drug resistance. There is now some drug resistance to almost all the older anti-malarial drugs used either alone or increasingly in combination.

Broadly there is extensive *drug resistance* throughout South East Asia and to the lesser extent the rest of Asia. In this area artemisinin combination drugs (ACTs) are the only realistic option. Early evidence of artemisinin resistance exists in South East Asia. In Africa combinations of older drugs may still have some role but ACTs remain the drugs of choice and have additional benefits including a greater impact on reducing transmission. There are particular concerns around the use of *drugs in pregnancy* because of the risk of teratogenicity (damage to the foetus) but evidence is reassuring that ACTs are safe in the second and third trimester and there is no evidence that they are dangerous in the first trimester. There is however a need for new drug classes since drug resistance to malaria is a matter when, not if. New and more effective drugs including ACTs *cost more* than older drugs and this causes significant problems of willingness to pay in areas where the majority of care is through the informal private sector (shops and drug-sellers); the informal private sector is the predominant source for antimalarials in much of Africa and Asia.

Whilst evidence for which drugs work under control trials is a very strong, *evidence on what is the most effective ways to get drugs to those who need them is much more variable*. Highly effective drugs that reach only a fraction of those who need them have relatively limited operational impact. There are *multiple steps* along the pathway between a child or adult first having symptoms and their receiving effective drugs where they can fall off. This includes: failure to seek care of any kind; physical barriers to access to formal health care (e.g. distance, mountains); poor diagnosis in the private, informal or formal sector; absent drugs; unaffordable drugs; poor quality and fake drugs; and failure to take a course completely. Each of these requires different possible solutions, and testing of these is only beginning in many areas. Solutions to failure to seek care are likely to be largely around education and awareness campaigns. Reducing the impact of physical access to antimalarials includes community health workers, home base delivery of care, and improving transport in rural areas. All of these have some evidence but it is mixed and likely to be locally specific. For those seeking care in the private sector there is reasonable evidence from a very limited range of studies that interventions with shops and other drug providers can significantly improve the quality of care provided. Improving adherence to drugs is likely to revolve around drug packaging and training of health care workers and other providers. Management of the epidemic of fake drugs is likely to require a combination of improved detection and law enforcement but in particular it is likely to involve reducing the cost of effective drugs to end users (although formal evidence that this works is so far limited).

For *severe malaria* recent trial evidence suggests that in both children and adults artesunate drugs are superior to quinine.

Drugs can be used to *prevent* malaria. There is now strong evidence to support intermittent preventive treatment in pregnancy (IPTp), intermittent preventive treatment in infancy (IPTi) and intermittence preventive treatment in children (IPTc). There are however operational questions with all of these. In particular the level of transmission at which they cease to be effective is currently unclear. Which drugs to use, particularly in pregnancy, remains a difficult question on which evidence is limited.

Different methods of delivery also have to be considered, particularly in areas where malaria is seasonal. Mass treatment for malaria to kill gametocytes has been considered. There is evidence that it works under ideal conditions but how to make it operational it remains unclear in many settings.

Whilst evidence that vector control methods and drugs work is very strong under ideal conditions, *evidence around delivery channels and how cost effective these are is much more variable and context specific*. This applies to drugs, diagnostics, insecticide treated bed nets, and other vector control measures. Sustainability and affordability in particular are unclear for several of these, and evidence of how best to engage the private sector is in most areas sketchy.

Whilst nutrition does appear to be associated with increased severity of malaria, evidence that nutrition interventions have a significant impact on malaria is limited or absent.

Interventions in high-risk groups: pregnancy, HIV, conflict affected/fragile states

Malaria in pregnancy requires specific interventions. Evidence for providing insecticide treated bed nets for pregnant women in high malaria transmission settings is very strong. Evidence for intermittent preventive treatment is also strong with the caveats mentioned above.

Evidence that intervention in HIV positive individuals is moderate but there are theoretical reasons for thinking that the current advice to give HIV positive individuals insecticide treated bed nets is sensible. Cotrimoxazole prophylaxis, which is already recommended for HIV positive individuals with more advanced disease, provides significant protection against malaria.

Conflict-afflicted and fragile states present all the same problems as other malaria endemic countries but additional problems of their own. These include breakdown of public health services, bottlenecks and constraints to all interventions and that non-immune populations may be displaced through areas of high malaria transmission. They also provide opportunities for positive change. A number of interventions have been devised specifically for these settings with a reasonable evidence base behind them.

Malaria vaccines

There is a great deal of work on malaria vaccines from several different directions. Some vaccines have shown promise in early studies although only one to date (RTS'S) has shown significant advantages when deployed in early clinical trials. RTS'S is now in advance stage 3 studies and results should be available within 3 years. If initial results are confirmed it will produce significant (but incomplete) protection. Its cost-effectiveness compared to other interventions remains to be determined. There is a large number of other potential pre-erythrocytic, blood stage, transmission blocking, pregnancy and vivax vaccines but all are some way from advanced stage clinical trials.

Approaches to health systems

In much of Africa and Asia the problem is not that there are no preventive measures and drugs which are proven to work, but rather that they do not get to the people who need them. This is a failure of health systems which in many countries is extreme. Usually this is due to multiple stages. Evidence suggests that independent activities need to be undertaken to address each of the individual steps rather than assuming that a single intervention will achieve significantly stronger health systems. Research on this area has been variable and sometimes context specific. Areas where there is some evidence of interventions under operational deployment include: improved physical access; supply chain management; quality drug formulation and packaging; training in case management and rational treatment; community case management and home management of malaria; health worker and work force planning; human resource management; and information systems and health worker motivation. Involving both public and private health care for malaria is in many countries

essential since much health care is currently provided by the informal private sector (mainly shops) especially for the poorest. Reducing the cost of antimalarials, and possibly diagnostic tests, is likely to be a necessary but not sufficient part of the response to this. Initial studies of subsidised antimalarials through the private sector are encouraging although they are relatively small scale.

Malaria eradication and elimination

There is renewed interest in eradication of malaria globally, and elimination locally in specific countries. There is a technical consensus that global eradication using the existing tools is not currently possible. There are however a number of areas of the world where local elimination is technically feasible, although less good evidence that it is operationally or politically feasible. The areas where most deaths occur and where elimination is possible are geographically different; if a country cannot reduce deaths to very low levels elimination is not realistic. There is an increasingly systematic approach to considering those areas for which elimination of malaria makes practical and economic sense; there are places (e.g. Zanzibar) where elimination may be technically feasible but not cost effective at this point in time. New tools, socioeconomic development and the response to enhanced malaria control mean that areas where elimination is not currently possible may become so in the future. The technical and geographical factors involved in the possible elimination efforts are reviewed.

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Acronyms

ACT	Artemisinin Combination Therapy
AFRO	WHO Regional Office for Africa
ANC	Antenatal Care
AMF-m	Affordable Medicine Facility-malaria
AS-AQ	Artesunate-amodiaquine
CAFS	Conflict affected and fragile states
CCM	Community case management
CMH	Commission for Macro-economics and Health
CHWs	Community Health Workers
DALY	Disability Adjusted Life Years
DCPP	Disease Control Priorities Project
DDT	Dichloro-Diphenyl-Trichloroethane
DFID	Department for International Development
DP	Displaced Person
EIR	Entomological Inoculation Rate
ENSO	El Niño southern oscillation
Fanta	Food and Nutrition Technical Assistance
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
HMIS	Health management information systems
HMM	Home malaria management
HRM	Human resource management
IMCI	Integrated Management of Childhood Illness
IPCC	Intergovernmental Panel on Climate Change
IPT	Intermittent Preventive Treatment
IRS	Indoor Residual Spraying
ITC	Insecticide-treated curtains
ITNs	Insecticide Treated Nets
IVCC	Innovative Vector Control Consortium
LiST	Lives Saved Tool
LLINs	Long Lasting Insecticidal Nets
M and E	Monitoring and Evaluation
MDG	Millenium Development Goals
MERG	Roll Back Malaria Monitoring and Evaluation Reference Group
MICS	Multiple Indicator Cluster Surveys
MMV	Medicines for Malaria Venture
PCR	Polymerase Chain Reaction (Diagnostic Test)

PMI	President's Malaria Initiative
RDT	Rapid Diagnostic Tests
R and D	Research and Development
RBM	Roll Back Malaria
SEARO-WPRO	WHO Regional Office for South-East Asia/ WHO Regional Office for the Western Pacific
SSA	sub-Saharan Africa
U5	Under 5 years of age
UNICEF	United Nations Children's Fund
WHO	World Health Organization

1. Introduction

Malaria is one of the major diseases of poor people in developing countries and one of the leading causes of avoidable death, especially in children and pregnant women. The UK government has made a major commitment to fight malaria. This paper by DFID staff summarises current evidence relevant to the work of DFID, the UK government and its development partners in combating malaria.

The paper sets out the background epidemiology and the determinants of infection and high risk groups, and then reviews the evidence for various interventions and approaches.

One theme which emerges throughout the paper is that there is strong evidence for many interventions currently used in the fight against malaria including insecticide-treated nets (ITNs), Long Lasting Insecticidal Nets (LLINs), indoor residual spraying (IRS), drugs, diagnostic tests and less widely known anti-vector methods. In other words, we know what works.

There is also good evidence that where these have been systematically applied in countries the impact on malaria cases and deaths can be dramatic. There is, however, additional clear evidence that in many settings these highly effective interventions are not getting to more than a small proportion of those who need them.

The evidence base on how best to *deliver* effective interventions is weaker, sometimes conflicting, and inevitably more context specific than the evidence base supporting the interventions themselves. For operational decisions this lack of a clear cut evidence base for delivery mechanisms must be taken into account when planning interventions.

2. Epidemiology and disease burden

2.1. Population at risk

Malaria is a complex disease caused by protozoan parasites belonging to the genus *Plasmodium*. Four species account for almost all human infections *(P. falciparum, P. vivax, P. malariae and P. ovale)*, of which *P. falciparum* is responsible for most severe disease and mortality, and *P. vivax* accounts for most cases (although not for most deaths) outside Africa.[2] *P. knowlesi*, a newly recognised 5th species is important in a small geographical range in Oceania.

During the past 100 years, the area of malaria risk has reduced from around 50% to 25% of the Earth's land surface,[3] with the number of countries exposed to some level of malaria risk falling from 140 to 106, with 9 classified as pre-elimination, 10 in the elimination phase and 7 preventing reintroduction of malaria.[4] However, because of demographic changes, the number of people exposed to malaria has increased substantially over the same time.

In order to make informed policy decisions, a more detailed understanding of transmission is needed. Malaria-endemic countries range from those with minimal transmission (sporadic and generally seasonal) to intense year-round transmission.[5] (See Figure 1). Various descriptions of transmission are used, one common one ranges from holoendemic (intense transmission occurs all year long, with spleen rates over 75% and parasite prevalence >60-70% in children under 5), through hyperendemic (intense, but with periods of lower transmission during dry season, parasite prevalence >50% <70%), mesoendemic (regular seasonal transmission) and hypoendemic: very low or intermittent transmission, parasite and spleen rate prevalence <10% in children under 5 years).

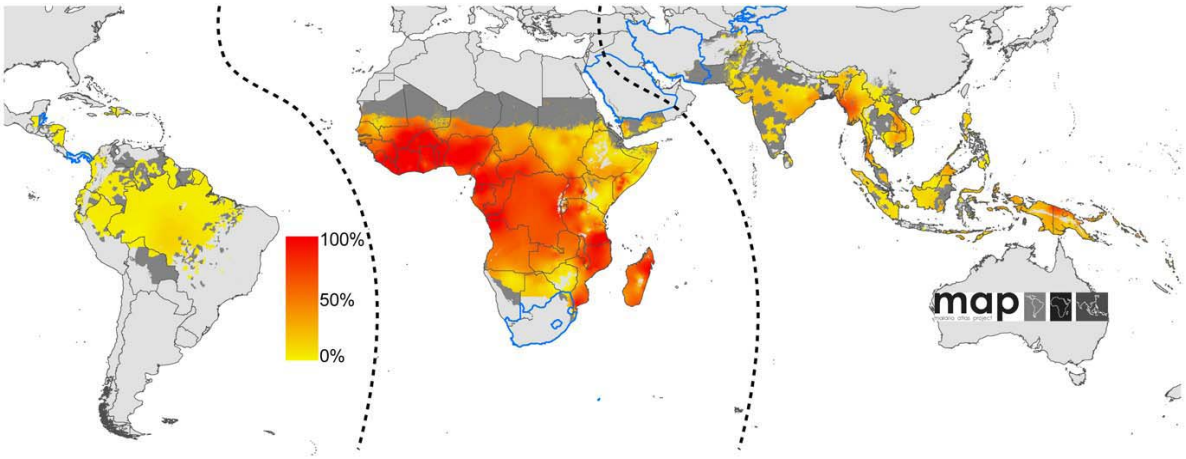


Figure 1: *P. falciparum* transmission.[6] Global limits and endemicity of *P. falciparum* in 2007. The land area was defined as no risk (light grey), unstable risk (medium grey, where PfAPI, 0.1% PA), and stable risk (where PfAPI .0.1% PA) [40] with endemicity (PfPR in the 2- up to 10-year age group, PfPR2–10) displayed as a continuum of yellow to red between 0% and 100%. The dashed lines separate the Americas, Africa+, and central, south and east Asia, respectively, from left to right. The seven countries with thick blue borders have very a low *P. falciparum* burden and reliable national health information systems.

Even in high-transmission countries, transmission rates vary considerably in different geographical areas, with factors such as height above sea-level[7], rainfall patterns and urbanisation having a significant impact.[8] In many countries, falciparum malaria is highly

seasonal, including many parts of Africa[9] and Asia.[10] The practical importance of this variability includes the fact that the peak age of malaria burden (the more intense the transmission the younger the peak age of severe disease), clinical presentation,[11,12] and the most effective tools and cost-effective delivery mechanisms for control often vary with transmission intensity. There are several examples of this in Section 5, Interventions and delivery, including intermittent preventive treatment[13] and community case management (CCM) of fever with antimalarials,[14] both of which are more cost-effective and probably more appropriate in high-transmission settings. Other interventions are more effective or cost-effective at lower transmission settings, such as diagnostic tests[15] and treatment specifically to reduce malaria transmission.[16] Who, where, what and when to focus malaria control activities therefore depends on the local transmission pattern. Within a single country malaria transmission can change from an area where the average person gets clinical malaria several times a year to one a couple of hours drive where there is no malaria transmission at all. In some countries, such as China, the great majority of the population are at no risk from local transmission of malaria with a small part of the population living in malaria-endemic areas.

Mapping malaria has become increasingly sophisticated with several initiatives such as the MARA-map[17] (see Figures 2 and 3 below for examples of regional and country level mapping of transmission) and more recently the Malaria Atlas Project (MAP),[18] although many more detailed maps are derived from models which have relatively geographically limited reliable data points. In particular, real data from many of the high-burden countries such as the Democratic Republic of Congo (DRC) or Sudan cannot be confirmed. Recent studies by Guerra et al have attempted to chart the global spatial distribution of *P. falciparum.*[19]

In 2007, 2.37 billion people were estimated as being at risk of *P. falciparum* malaria worldwide, with 26% located in the WHO AFRO region compared to 62% in the combined SEARO-WPRO regions.[20] It is important to differentiate, however, between being at risk, in the sense of living in a country where some malaria is transmitted and having a high lifetime risk of malaria. Of this total population at risk 42%, almost 1 billion people, lived under unstable or extremely low malaria risk. Almost all populations at medium and high levels of risk were in sub-Saharan Africa (SSA), where the burden of disease from *P.falciparum* is high[21]. An even higher proportion of the deaths occurred in Africa due to the combination of higher transmission and lower access to effective healthcare.

Figure 2: MARA map of endemic and epidemic prone areas of *P. falciparum* in Africa (geographical and temporal variation)

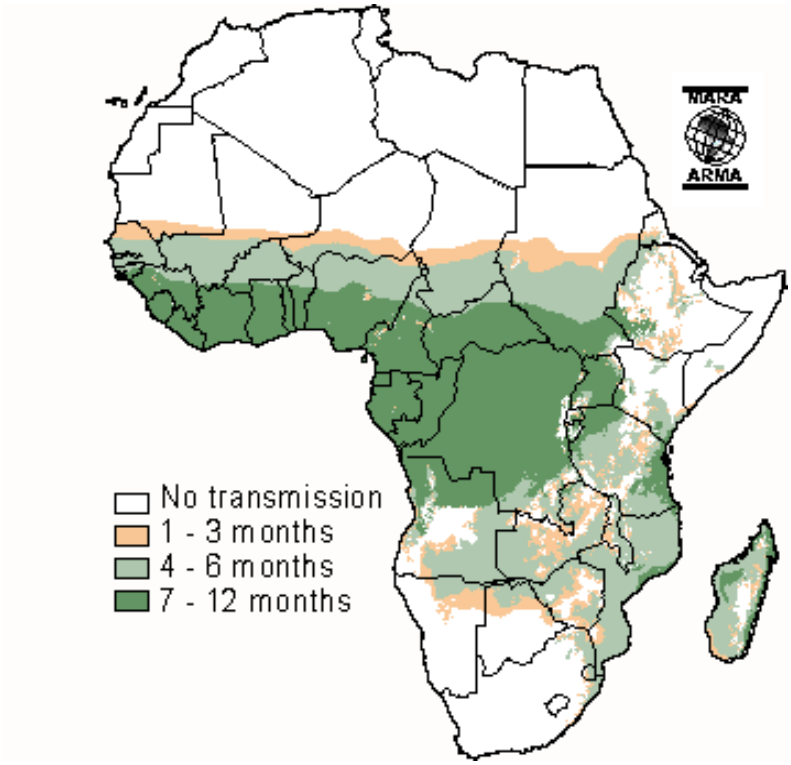
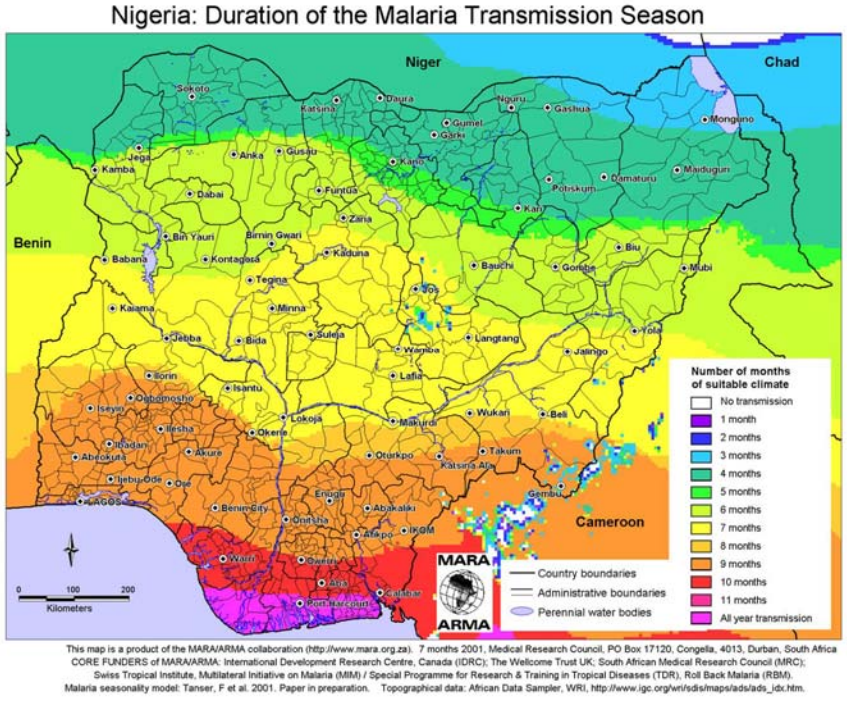


Figure 3: MARA map of seasonality in Nigeria (temporal variation)



P. vivax malaria

P. vivax is widely distributed and transmitted in 95 countries in tropical, sub-tropical and temperate regions.[22] It was estimated that 2.85 billion people were exposed to some risk of transmission in 2009, most of who were living in the tropical belt of central and south-east Asia, which has very high populations. The probability of infection is reduced substantially across Africa, probably mainly due to the frequency of the Duffy negative trait;[23] it is still seen across the continent[24] but currently considered a significant problem only in Ethiopia.[25] The ten countries with the highest estimated population at risk, in descending order, were India, China, Indonesia, Pakistan, Viet Nam, Philippines, Brazil, Myanmar, Thailand and Ethiopia.[26]

As with many diseases the reliability of official statistics on both falciparum and vivax malaria numbers varies widely. In part this is because malaria diagnosis is often haphazard with both over- and under-diagnosis, (see Section 5.2 Case management: diagnosis and treatment).[27] Decision-makers should therefore try to get as accurate an estimate of the range of epidemiology in their country of interest based on real, recent data as possible so as to target resources effectively. Annex B discusses some of the issues in estimating malaria burden. As a general point, estimates of malaria tend to be least accurate (in the sense of being based on reliable data) in the areas where the most transmission is thought to occur. This is to some extent inevitable as countries with sophisticated malaria information tend to be very roughly correlated with those which are either wealthy, have good control, or both.

2.2. Clinical disease burden

Estimating the disease burden posed by malaria remains an important public health challenge. Disease burden has been measured using metrics ranging from incidence of clinical cases, malaria attributable mortality and disability adjusted life years (DALYs). Several factors confound our ability to make accurate estimates of the true burden of disease, including:

1. In areas of stable transmission with high levels of immunity, malaria parasites may be present in those with illness from another cause (and in the general healthy population).
2. Symptoms of fever do not distinguish between malaria and other infections leading to an overestimation of the incidence malaria on the basis of fever. This becomes more of a problem as malaria incidence drops.
3. Many fevers are self-medicated or treated outside the formal health system.
4. Inaccurate diagnoses may be reported and national reporting systems may be incomplete.[28]

Figures for disease burden vary widely, reflecting disparity in the data sources and analysis used to derive different estimates. The WHO estimated there were 250 million (5^{th}–95^{th} centiles [189–327]) clinical cases of malaria in 2006, of which about 90% were due to *P. falciparum*.[29] However, Hay et al, using newer cartographic techniques based on models, have reported much higher case numbers and estimated 451 million (95% credible interval 349-552) clinical cases specifically of *P.falciparum* malaria in 2007.[30] Neither approach would claim to be based on perfect data.

Most falciparum cases, estimated between 60 and 87%, originated from Africa.[31,32] Nineteen countries in Africa – Rwanda, Angola, Zambia, Guinea, Chad, Mali, Malawi, Cameroon, Niger, Burkina Faso, Côte d'Ivoire, Ghana, Mozambique, Uganda, Kenya, United Republic of Tanzania, Ethiopia, Democratic Republic of the Congo and Nigeria – accounted for 90% of

all WHO estimated cases in 2006.[33] Hay et al reported that more than half of all estimated *P. falciparum* clinical cases occurred in Nigeria, the DRC, Myanmar (Burma) and India.[34]

The intensity of transmission varies considerably between these countries. For example, India features mainly because its population is large and so absolute numbers are correspondingly large, but most people in India will never have malaria. A small proportion of febrile illness is malaria and this is largely concentrated in four states (although in these states it is a significant cause of morbidity, and possibly mortality, although the methodology on which this claim is based is flawed).[35] In contrast, in savannah Ghana a child may have up to seven clinical attacks of malaria a year;[36] similar rates are not uncommon elsewhere in Africa.

Measuring malaria-specific mortality rates remains a significant challenge in low-income countries. Routinely collected data on vital events provide complete and representative information for only about 40% of the world's countries and 25% of its population.[37] In SSA, fewer than ten countries have death registration systems that produce usable data.[38] Thus, in many malaria-endemic countries information on malaria mortality has been derived primarily through the post-mortem questionnaire technique which is not specific in differentiating between deaths from malaria and deaths from other acute febrile illnesses.[39]

Most estimates suggest that malaria directly causes just fewer than one million deaths per year or 3,000 deaths a day and that most of these deaths are African children. However, exact figures vary; for example a recent systematic analysis with wide support suggested that 0.732 million children under five died of malaria.[40] The WHO estimates that 85% of all malaria-related deaths occur in children under five years.[41]

The Global Burden of Disease analysis uses a summary measure of disease burden, disability adjusted life year (DALY), which combines information on mortality and non-fatal health outcomes into a single time based metric. The 2004 estimates rank malaria as the fourth leading cause of burden of disease in low-income countries,[42] but this varies widely by country.

Table 1: Leading cause of burden of disease (DALYs) in low income countries, 2004[43]

Rank	Disease or injury	DALYs (millions)	% of total DALYs
1	Lower respiratory infections	76.9	9.3
2	Diarrhoeal diseases	59.2	7.2
3	HIV/AIDS	42.9	5.2
4	**Malaria**	**32.8**	**4**
5	Prematurity and low birth weight	32.1	3.9
6	Neonatal infections and other	31.4	3.8
7	Birth asphyxia and birth trauma	29.8	3.6
8	Unipolar depressive disorders	26.5	3.2
9	Ischaemic heart disease	26	3.1
10	Tuberculosis	22.4	2.7

Malaria also has negative impacts on other health indicators. In addition to its direct role in morbidity and mortality, malaria is thought to have a significant indirect effect on morbidity and mortality by predisposing to other infectious diseases such as non-typoidal salmonella infections and pneumonia and by contributing to malnutrition, although the extent of the indirect impact is not well understood.[44]This is important for malaria control, however: in high-transmission settings a consistent finding, dating back to the first malaria eradication attempt, is that reducing malaria also reduces non-malaria deaths, sometimes significantly.[45] It may also lead to a reduction in morbidity from diseases associated with malaria such as salmonella.[46] Older estimates suggest that the *indirect* impact of malaria on mortality can be up to four times as important as the direct effects,[47] although this is not always the case, and in certain circumstances the reduction of mortality due to reducing malaria is actually less than predicted.[48]

2.2.1 Malaria in Africa: recent trends

Most falciparum malaria cases and a high proportion of malaria deaths originate from the Africa region. However, there have been encouraging declines in the disease burden of malaria in some countries in sub-Sahara Africa over the last five years.[49] In the Horn of Africa, country-wide surveillance in Ethiopia and Eritrea has shown a 70% reduction in malaria morbidity. Similar patterns have been reported in East Africa; for example paediatric malaria admissions in the coastal area of Kenya declined by as much as 75% between 2003 and 2007,[50] although this varies across the country.[51] In West Africa, surveillance from five healthcare facilities in Gambia showed a 50-85% decline in prevalence of slide confirmed malaria between 2003 and 2007,[52] a trend that has continued through to 2009.[53] Zanzibar, Tanzania, Zambia, South Africa, Mozambique, Ethiopia and Rwanda have also had reliable reports of malaria cases dropping, sometimes dramatically.[54,55,56,57] Whilst evidence of a decline is strong, some caution should be used in interpreting its exact extent however, as many reports are based on health attendance data which have a number of obvious and less obvious flaws, including that there are changes in patterns of referral over time, that many cases do not reach formal healthcare, and that as diagnosis has improved so the number of non-malaria cases attributed to malaria has declined.[58] Nevertheless recent reports do provide solid evidence that, where effective anti-vector methods are combined with Artemisinin-based antimalarials in countries that are developing economically, significant reductions in malaria can be achieved in previously high-burden African countries.

In contrast, limited data from Central Africa shows little change in the malaria burden in Brazzaville-Congo and the DRC.[59,60] In central and western parts of SSA, where the greatest burden of disease falls, there is no evidence of any decline in malaria cases, although this is largely due to the absence of any evidence, rather than good evidence that a decline (or increase) has not occurred.

In Africa north of the Sahara, Malaria is, for practical purposes, no longer a public health problem. In most countries in this region, Malaria has either been eliminated or is awaiting certification of elimination.[61]

2.2.2 Malaria in Asia

In Asia, there are around 24 million cases of malaria each year and 40,000 malaria deaths, which account for around 4.6% of the global mortality due to malaria.[62] Malaria used to be the leading cause of under five mortality in much of south and south-east Asia; the picture is now more mixed. Whilst malaria remains a significant public health problem in several Asian countries it is one of the leading causes of mortality in relatively few. The bulk of deaths are probably in India, Burma, Bangladesh, Indonesia and Papua New Guinea, and within these countries deaths tend to be highly concentrated geographically, although reliable numbers are not easy to determine.

The fringe areas of other countries, such as Thailand and Vietnam, have border areas where malaria remains a problem especially for migrants.[63] *P. vivax* accounts for approximately 50% of malaria cases, but the proportion varies widely over Asia – for example contributing very few cases in Laos[64] and Yemen[65] where falciparum predominates but most cases in Pakistan and Afghanistan.[66] The difference between the large population at risk (living in malaria-endemic countries) and the relatively low contribution to global mortality compared to Africa is explained by a combination of the much lower incidence of malaria (due to much more efficient malaria mosquito vectors in Africa), the greater proportion of vivax malaria, and generally better access to health services in Asia. This means that those who get malaria are more likely to be treated early and are therefore unlikely to die; evidence for the relative contribution of these is limited. There are caveats to this, however. Recent evidence demonstrates that vivax malaria can cause appreciable mortality in some areas such as Papua,[67] and the burden of malaria mortality may have been underestimated in other settings.[68] As with malaria elsewhere, the data are least reliable where the burden is probably highest, for example in rural Burma.[69] Countries where complex emergencies, relatively higher poverty, or relatively weaker health systems exist are more likely to have significant morbidity and mortality from malaria than neighbouring countries with potentially similar epidemiology, which is often under-appreciated; examples include Papua New Guinea,[70] Lao PDR,[71] Afghanistan,[72] Yemen,[73] Cambodia (reducing as Cambodia develops)[74] and Burma.[75] There is mixed evidence from studies in Asia about whether poverty is an independent factor for the higher incidence of malaria in individuals.[76,77,78] Because there is so much variation in Asia it is even less easy to generalise about the epidemiology of malaria in Asia than in Africa. One consistent finding, however, has been that as countries have developed economically, malaria has tended to decline – often rapidly.[79] The extent to which this is caused by better prevention and early effective treatment, changes in the environment and working and living conditions which make transmission more unlikely, and other factors (ranging from nutrition to pollution) remains debated with little compelling evidence, although all these factors are likely to contribute.

Because malaria transmission is lower in Asia than in SSA, immunity to malaria is generally not acquired during childhood (Papua New Guinea is an exception) and all age groups, men and women, are at risk of significant disease – contributing to the larger population at risk in these regions.

It has also been shown that, historically, South-east Asia has been the cradle of multi-drug resistance (see Section 7 Insecticide resistance). The spread and intensification of antimalarial drug resistance represents a serious challenge to global malaria control and is discussed in more depth later in this paper.

India, with a higher population than malaria-endemic Africa, has malaria in most regions, but significant malaria is largely confined to the poorest states. In India as elsewhere, malaria is most common in areas where reliable data are least available so exact numbers are not easy to determine.[80,81]

2.2.3 *Plasmodium vivax*: additional reasons to be cautious

Study of *P. vivax* is a relatively neglected area of research in comparison to *P. falciparum,*[82,83,84,85,86] largely because mortality is much lower so that absolute numbers of malaria deaths are lower. Increased interest in vivax malaria has emerged with evidence of the considerable burden of morbidity and perhaps mortality caused by this parasite, and because of practical and mathematical evidence showing it is less amenable to elimination than is falciparum malaria in low-transmission settings. This is due to the ability of this parasite, and *P.ovale,* to cause repeated relapses after an initial infection because of the persistence of resting stages of the parasite (hypnozoites) in the liver, the early appearance

of gametocytes and the greater transmission of this parasite at low parasite densities.[87] There is also recent evidence that severe, drug resistant and fatal cases of vivax malaria are more common than has sometimes been assumed.[88,89,90,91,92]

Epidemiological data on the contribution of vivax to the overall disease burden of malaria is scarce in many areas,[93] as malaria diagnoses are made on clinical grounds alone, without recourse to diagnostic tools,[94] indeed, 'almost 95% of the burden is inferred from laboratory-confirmed cases representing less than 5% of the total'.[95] Where such data do exist their accuracy is potentially compromised by the availability, specificity and sensitivity of diagnostic tests capable of *P. vivax* detection although that is improving. (See Section 5.2 Case management: diagnosis and treatment.)[96,97,98] These issues are compounded by aspects of the biology of the *P. vivax* parasite itself that make it difficult to detect, especially the low parasite density in vivax malaria compared to falciparum malaria.[99]
The limited data mean that the estimates that the number of people at risk of vivax transmission of approximately 2.85 billion[100] are more robust than estimates of the annual number of *P. vivax* infections which are popularly quoted to be 132–391 million cases per year.[101,102] The WHO south-east Asia region (which includes India) has been estimated to account for more than 80%[103,104] of this disease burden (90–248 million)[105].

2.2.4 Epidemics

Whilst most malaria morbidity and mortality occurs in high transmission settings (often called hyper-endemic or holo-endemic regions) malaria epidemics are a risk in low-transmission settings since in such situations the entire population, of all ages, is susceptible to malaria. Malaria epidemics occur throughout the world, frequently affecting highlands and semi-arid areas surrounded by areas of high transmission,[106] Factors which may precipitate a malaria epidemic predominantly fall into two categories: natural (climatic variations, natural disasters), and man-made (conflict and war leading to breakdown of public health and population displacement, agricultural projects favouring malaria vectors, dams, mining and logging).[107] In addition, there is good historical evidence that epidemics can also occur when populations with limited exposure to malaria move into endemic regions as refugees or economic migrants. The burden of epidemic malaria is difficult to assess. Its impact can be significant, but the cost-effectiveness of interventions to predict and respond to epidemics is uncertain.[108,109]

In Africa, areas of unstable malaria transmission at risk of epidemics include highland areas of Ethiopia, Eritrea, western Kenya, south-west Uganda, highlands of Tanzania and Rwanda and Burundi. Ethiopia has a long history of recurrent malaria epidemics. In the 1958 epidemic in Ethiopia, an estimated 3.5 million people were infected, resulting in 150,000 deaths and the 1998 epidemic was similar in intensity and breadth.[110] In Asia, epidemics have long afflicted parts of India, Sri Lanka and Pakistan; in east and southern Africa epidemics are in part explained by variation in the monsoon brought on by the El Nino southern oscillation and probably the Indian Ocean Dipole.[111,112,113] Epidemic malaria and pattern of malaria transmission and intensity is very diverse across Asia due to a wide array of mosquito vectors and environments.

Attempts to estimate the disease burden caused by epidemics have proven challenging due to the lack of clarity in definitions of epidemics and the lack of data describing the morbidity and mortality in epidemic situations. No standard thresholds for the declaration of epidemics are used, as local epidemiological situations can vary greatly.[114]

Two systematic studies have described the disease burden due to epidemics in Africa.[115] Worrall et al estimated that about 4% of annual malaria cases and 12–25% of deaths worldwide are attributable to epidemics in Africa[116]. However, their methodology has not been validated and the sensitivities of the implicit assumptions have not been tested.[117]

The welcome reduction in the transmission of malaria in many parts of previously high and stable transmission Africa increases the potential for malaria epidemics. Over time it is to be expected (and hoped) that a cohort of children not exposed to *P. falciparum* will come to make up a significant minority, and eventually most of the population, unless vaccine-induced immunity has replaced natural immunity; (see Section 5.7 New technologies) this cannot be assumed on current evidence. Mosquitoes with the potential for significant transmission will still exist, however. Any breakdown in public health services (e.g. during economic or political turmoil), or mosquitoes developing widespread resistance to insecticides which currently control malaria could lead to epidemics in a non-immune population and this has to be anticipated.

2.3 Economic burden of malaria

2.3.1 Burden on health systems

Malaria has a major burden on individuals, health systems and infrastructures throughout many developing parts of the world. Despite very low levels of care-seeking behaviour malaria still accounts for 25–35% of all outpatient visits, 20–45% of hospital admissions and 15–35% of hospital deaths in endemic African countries.[118] The African Leaders Malaria Alliance estimates that in Africa, as much as 40% of healthcare spending in endemic countries goes on malaria, costing the continent around $12 billion a year.[119]

The costs of malaria in terms of strains on health systems are substantial. In endemic countries, as many as three out of ten hospital beds are occupied by patients with the disease.[120] However, there is limited information on the burden malaria places on the health system, especially with regard to human resources and finance. A study in Malawi[121] found that treating 65% to 85% of cases would result in using 8.9% to 12.2% of the national health budget or 22.2% to 33.2% of the national drug budget. Furthermore, having 65% to 85% of cases treated at a health facility would consume 55.5% to 61.1% of full-time equivalents of all the clinicians registered in the country. Malaria exacts a heavy toll on the health system in Malawi. In this situation, the national recommendation of self-medication with the first-line drug for uncomplicated malaria is justified as there are not enough clinicians to provide clinical care for all cases.

The direct costs of malaria to the Rwandan Ministry of Health were also substantial, with an estimated 19% of the recurrent budget directed to malaria.[122] Up to 39% of total health expenditure in Tanzania is directed to malaria prevention and care,[123] with the government spending more money on malaria than on any other disease – 3.4% of Gross Domestic Product.[124] The government of Uganda spends about 10% of its total health budget on fighting malaria.[125]

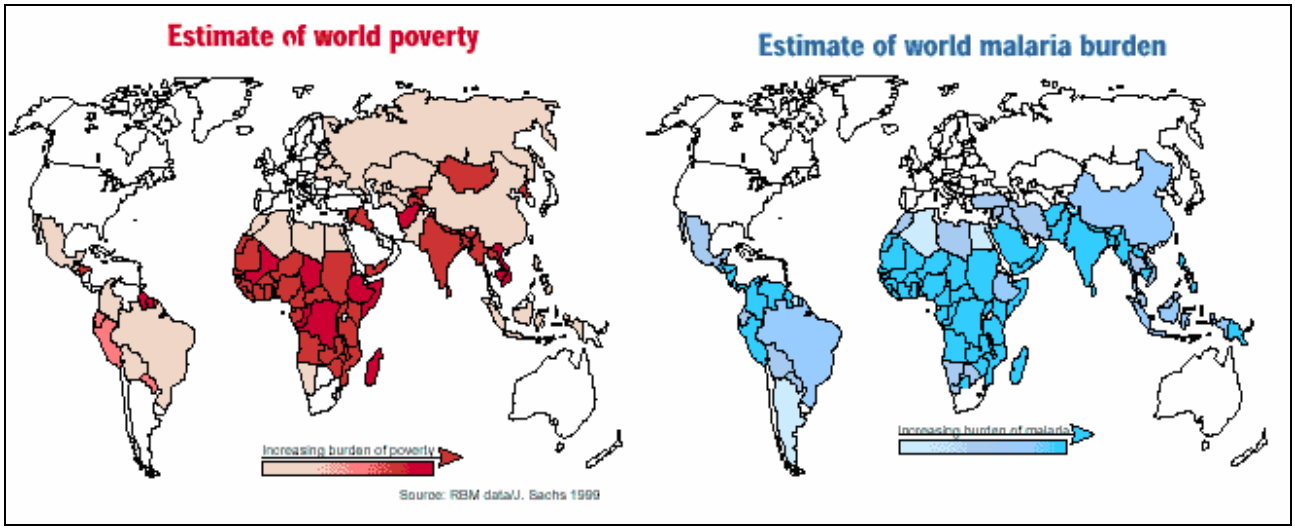
2.3.2 Burden on the wider economy

Measuring the economic burden of malaria carries a number of methodological challenges.[126] These include: defining a suitable measure of the health burden that takes into account febrile illness episodes and other consequences such as anaemia and severe illness; the generally poor data available on earnings and days lost from illness and the ways in which firms and households cope with illness; and the general difficulty of capturing the opportunity cost of anticipatory or risk mitigation strategies. Most estimates must, therefore, be interpreted with caution as reflecting the lower boundary of the economic burden of malaria.

Macroeconomic impact

The map of the global burden of malaria mirrors that of poverty and malaria is considered both a cause and consequence of poverty; 58% of malaria cases occur in the poorest 20% of the world's population[127] and those who are least likely to have access to treatment and to be able to afford preventive and treatment interventions (see Figure 4).

Figure 4: Correlation between poverty and malaria[128]



The macroeconomic impact of the disease is thought to be significant. Malaria's impact on premature mortality, the direct and indirect costs of illness, fertility rates, population growth, migration patterns, technology adoption, savings and investment, and worker productivity all impede economic development. Malaria reduces foreign direct investment, tourism, and trade, and 'the transmission of ideas, techniques and the development of transportation systems'.[129] In a survey of 8,000 business leaders conducted in over 100 countries[130] over a fifth of all business leaders reported that malaria affects their business with 10% reporting serious impacts. In Sub-Saharan Africa, 72% of respondent firms reported deleterious effects, with 39% reporting serious impacts through absenteeism, lower productivity, increased costs, education and skills, cognitive abilities, poor skill matching, increased labour turnover, and hiring and training costs.

One widely-cited study estimated that in malaria endemic countries, economic growth was 1.3% less per person per year over the period 1965 to 1990 compared with findings in countries without malaria but matched for many other socio-economic variables.[131] McCarthy et al, using a similar methodology, explored the impact of malaria on average per capita growth in three five–year periods and found a significant negative association between malaria and economic growth, though smaller than that found by Gallup and Sachs, averaging 0.55% per year for countries in SSA.[132] There is evidence to suggest that the impact of malaria on growth is due to the effects on total productivity with a 1% increase in the incidence of malaria reducing total factor productivity by 0.58%–0.75%.[133]

Microeconomic impact

The microeconomic impact of malaria can be divided into the direct costs of expenditure on treatment and prevention (see below) and the indirect consequences of time lost to illness or caring for sick household members, reduced productivity, and consequences of the ways in which households cope with risk.

Indirect costs

The mechanisms through which malaria is linked to poverty include the effects of lost time, either through illness or caring for sick family members. In rural areas, the rainy season is often a time of intense agricultural activity when poor families earn most of their annual income. A bout of non-fatal malaria will typically last for ten to fourteen days including four to six days of total incapacitation with the remainder characterised by headaches, fatigue and nausea. The extent to which this lost labour time reduces output depends on whether it coincides with harvest time in agricultural areas, and whether other family members can compensate.[134] Estimates of the average indirect cost per malaria episode range from $0.68 for children under ten years of age in Malawi to $23 per adult episode in Ethiopia.[135] Various authors have examined the indirect cost burden of malaria, estimating this to be 2.6% of annual household income in Malawi,[136] 2–6% of gross domestic product in Kenya, and 1–5% in Nigeria.[137]

One challenge in estimating the impact of malaria on output is that households may anticipate risks of seasonal labour shortages by planting crops that are less labour intensive, or take other precautionary decisions that make it difficult to identify the economic impact.[138] Only one study has demonstrated a clear and negative relationship between malaria (measured as parasitaemia) and labour efficiency, in a study on cotton production in Cote d'Ivoire.[139]

Malaria also results in reduced accumulation of human capital and associated lost productivity in adult life. Estimates from Africa suggest that 20–50% of school-aged children suffer from malaria in a given year and up to 20% of mortality in schoolchildren may be attributable to the disease. Studies have shown that up to 8% of school absenteeism and about 50% of preventable absenteeism is due to malaria.[140] Similar rates have been observed in other regions. For example, in Sri Lanka presumed malaria resulted in children being absent for up to 10% of school days.[141] Anecdotal evidence suggests that malaria may also account for high levels of teacher absenteeism, with further negative effects on children's educational outcomes. However, few studies of the effects of malaria on schooling have used parasitological diagnosis. In addition to the effects of absenteeism, a severe bout of malaria can have direct effects on cognition, behaviour and school performance.[142] . In SSA 900–19,000 children experience neurological complications that last for more than six months.[143] Some effects are lifelong, resulting in children and adults who require special support from family, community, health services and education services.

Direct costs

The direct costs associated with preventing and treating malaria represent a substantial burden on poor households. Households purchase a variety of preventive measures (mosquito coils, aerosol sprays, bed nets and mosquito repellents) and a review of evidence from SSA found that monthly per capita household expenditure on prevention ranged from $0.24 (in rural Malawi) to $15 (in urban Cameroon).[144] Care seeking costs include expenditure on travel, consultation fees, medicines, and food and accommodation at distant health facilities. The costs of care seeking weigh more heavily on the household budgets of the poorest people and they are also more likely to delay care seeking or use less effective services.[145,146] The ability to access treatment is an important determinant of health outcomes. With lower access to treatment, poorer households are more vulnerable to the consequences of malaria including progression to severe disease and death. Poorer households are more likely to self-treat and less likely to access private and public providers.[147] In SSA over 70% of patients with suspected malaria diagnose and manage their illness at home with traditional remedies or drugs bought from local shops.[148]

Most studies of the direct costs of malaria express these expenditures as a proportion of household income. One review found direct costs per episode ranging from 2.0% to 2.9% of household income, well below the 10% of total income applied as the threshold for

catastrophic household expenditure.[149] This does not account, however, for the frequency of malaria episodes affecting household members over the course of a year. A number of other studies compared cost burdens by socio-economic status, and found these to be highly regressive;[150,151,152] i.e. poor people spend a significantly higher proportion of their income on malaria than those who are more wealthy. In Malawi for example, total cost burdens averaged 7% of monthly household income but poor people incurred burdens of 32%. A study in northern Ghana found that while the cost of malaria care was just 1% of the income of rich households, it accounted for 34% of the income of poor households[153]. More recently, a survey of 2250 households in south-east Nigeria found the average cost of treatment to be $6.64 for adults and $6.58 for children,[154] and malaria expenditure accounted for 7.8% of monthly food expenditure of the poorest households compared with 3.9% for the least poor. This study also found a significant difference in monthly treatment expenditure burdens between households in rural and urban areas, at 7.1% and 5.0% respectively. In the absence of effective risk protection schemes, most of these expenditures were paid for out-of-pocket. Chuma et al found 40% of those who self-treated for malaria in Kenya used shop-bought drugs and 42% of health facility visitors reported not having enough money to pay for treatment.[155]

In rural Kenya for example, the direct costs (defined as all cash spending due to malaria for both the patient and caretakers, including spending on consultation, drugs, tests, gifts, transport and special foods) were 7.1% and 5.9% of total household expenditure in the wet and dry seasons respectively.[156] In Malawi, the annual cost per household of malaria was found to be $40.02 or 7.2% of household income. For very low income households the direct and indirect costs for malaria were $24.89, equivalent to 32% of income, compared to 4.2% in more wealthy households.[157] Total household costs amounted to 9–18% of annual income for small farmers in Kenya, and 7–13% in Nigeria.[158]

This conventional approach to measuring household burdens does not capture the consequences for households that spend less, or delay seeking care because they cannot afford to seek treatment. Filmer found the poorest groups in a society did not seek care as much as the non-poor, and did so at a lower level of public facilities.[159] Gollin and Zimmermann present a household based model showing an economy may inhabit a ‘malaria trap’ in which sickness begets poverty and poverty makes disease prevention unaffordable, which can reduce income per capita by about half.[160]

Economic benefits of good malaria control

Mills and Shillcut examined the relationship between the macroeconomic benefits of malaria control and the estimated costs of control.[161] Estimates of the benefit-cost ratio ranged from 1.9 to 4.7 (using a 3% discount rate), suggesting that in terms of its positive impact on economic growth alone, malaria control is an extremely attractive investment.

3. Determinants of infection

There is a wide range of evidence that shows that multiple and often inter-related risk factors affect an individual's vulnerability to malaria. These factors can act at three levels: individual; household and community; and meso/macro. [162] This section of the paper reviews the evidence around some of the key risk factors for malaria concentrating on those which have policy implications.

3.1 Individual level: biological and disease-related factors

Within the human host many biological, genetic, immunological, and pathophysiological mechanisms predispose people to disease. Human populations vary in their susceptibility to malaria, the severity of illness when they have an infection and their responses to treatment.[163,164]

3.1.1 Immunity and other biological factors

An individual's immune status plays a major role in the response to infection. Immunity to clinical malaria (ie malaria exhibiting symptoms) is acquired and maintained when exposure is frequent and maintained. In areas of high stable transmission, mortality is greatest amongst infants and children who have little or no acquired protective immunity. This is one reason why in SSA, more than 80% of the estimated malarial deaths currently occur in children under five years of age.[165] In areas with low or unstable transmission, all age groups are at risk.[166] Immunity is not complete, however; non-pregnant adults resident in high-transmission settings have an increased rate of malaria (evidenced by a high prevalence of asymptomatic parasite rates in surveys) although they do not generally get severe disease. In high transmission areas, non-pregnant adults rarely experience severe clinical attacks of malaria although they may continue to get infected. This difference between immunity to disease and immunity to infection has policy implications. In high-transmission settings many, and often the majority, of transmission of malaria is from adults who are infected but have no evidence of infection as they are themselves asymptomatic.[167] In these settings targeting only those with symptoms will reduce morbidity and mortality from disease, but will have a more limited impact on transmission if used in isolation from other control measures.[168] In areas where immunity is limited or absent virtually all patients with malaria will have symptoms and treatment of these subjects may have a significant impact on the overall level of transmission. It also has implications for malaria vaccines (see Section 5.7 New technologies).

Transmission rates are generally lower in regions with a high proportion of *P. vivax* incidence than in areas where both vivax and falciparum occur; or more accurately, vivax has an advantage over falciparum in areas of the world where transmission is lower and seasonal, as the hypnozoites which cause relapse can get vivax malaria through periods when transmission drops away (see Annex C Quantifying malaria transmission). Most of the affected populations in these regions do not achieve full immunity to vivax infection, although this can occur (e.g. in Papua New Guinea).[169] Although *P. vivax* is generally more benign than *P. falciparum*, it remains a cause of substantial morbidity and mortality, particularly in infants. [170,171] In areas where both infections occur, *P. vivax* infections tend to occur at an earlier age than *P. falciparum* infections and that immunity to this infection develops at an earlier age.

A number of genetic factors are known to make certain groups relatively less susceptible to malaria. These include sickle cell, trait, alpha and beta thalasaemia,[172] G6PD enzyme

deficiency,[173,174] and the Duffy-negative blood group which protects against vivax malaria (although a recent study in Madagascar has shown that under certain circumstances *P. vivax* is capable of causing blood-stage infection and disease in Duffy-negative people[175]).[176] Although important for understanding of malaria, pathogenesis and epidemiology study of genetic determinants of malaria risk has limited immediate policy relevance. Exceptions are the absence of the Duffy receptor in most Africans making it unlikely that vivax malaria will become a major problem in Africa even if falciparum rates fall (this would not apply to *P. ovale,* however, which is similar to vivax malaria), and the complex interaction with G6PD deficiency because this interacts with a number of antimalarial drugs, especially drugs to prevent relapse of vivax malaria.[177] (See Section 5 Interventions and delivery).

3.1.2 Age

There is a large amount of data on malaria related morbidity and mortality in children under five.[178] Recent modelling suggested that malaria accounted for 0.732 million or 8% (range 0.601–0.851 million) of the estimated 8.8 million global deaths in children under five years in 2008. The proportion increases to 16% when just looking at Africa.[179] Of note, the country-level estimates of deaths by cause were adjusted for estimated effects of recently scaled up interventions – notably for malaria this was ITNs. In higher-transmission settings, in addition to a heavy weighting for infants and young children, the pattern of severe malaria varies with age. Anaemia predominates in young children; as children get older, cerebral malaria becomes a much larger proportion of severe malaria, although absolute numbers fall[180] and the pattern varies in different settings.[181] The age effect with anaemia predominating in young children is seen at all levels of transmission. The difference in the pattern of severe malaria is even more marked – and in particular adults have a much higher likelihood of renal failure and acute lung injury than children, who in turn are more likely to have anaemia and acidosis. The reasons these differences have potential implications for public health is that if efforts to reduce malaria transmission are successful and the overall burden of malaria goes down, there will be a shift in the burden of disease to older children and young adults who will become symptomatic on infection and present for diagnosis and treatment.

Morbidity and mortality data alone will not capture all of the impact of malaria upon children, since malaria also is linked to stunted growth and reduced mental development, although quantifying this has been difficult. Survivors of cerebral malaria can experience long term neurological problems although the extent and pattern remains controversial.[182] Evidence that the long term negative impact of malaria on cognitive function and educational attainment in children subsequently has an impact on workforce productivity is plausible but currently not conclusive.

The risk of infection and its severity is lower in the first few months of life. Reasons for this are complex but probably include transmission of protective antibodies across the placenta, the presence of red cells containing Hbf – which are relatively resistant to malaria infection, breast feeding and lack of exposure.[183] The protective effect of maternal antibody is likely to be less when effective malaria control is achieved and the overall level of malaria infection declines.

In lower transmission settings clinical malaria is spread more widely across the age groups. In such settings, occupational issues may become more important than age; this is especially true where mosquitoes which transmit malaria bite outdoors away from dwellings. Forest workers in south-east Asia are one example of this phenomenon.[184] In these settings young adults, especially males, may be more at risk than children, because they are the group at most risk from being bitten by forest dwelling vectors.[185]

3.1.3 Gender

Evidence of biological differences between men and women in acquiring malaria is limited, although evidence of sex differences is accumulating. The literature on gender differences in malaria relates mainly to pregnancy, occupational risks (e.g.: forest workers) and care-seeking behaviours. There is no strong evidence of the biological impact of gender being a major factor for malaria acquisition and severity of disease in non-pregnant women and girls. The exception is pregnancy, when women are at considerably increased risk[186] (see Section 4.1 Pregnancy and malaria). Occupational and cultural differences related to undertaking activities likely to lead to malaria transmission; and when malaria is acquired, access to health services is more mixed and varies considerable across different cultural settings.

Reported gender differences with regard to increased risk of infection and impact of malaria on individuals largely focus on women; however, there is some evidence that suggests that in some countries men have increased exposure because they spend more time sitting outside in the evenings during peak mosquito biting times[187] and that some male-dominated types of work lead to increased exposure. For example, agricultural work extending to the evenings or sleeping away from settlements may raise risk, especially in forests, which can make men more vulnerable than women.[188,189] Forest clearance in the Peruvian Amazon, a male-predominant activity, was reported to have led to substantial increases in abundance of major local malaria vectors.[190]

A number of studies have investigated differences in knowledge and reported health seeking behaviour between men and women. Most found either no difference or that women had more limited decision-making and financial power to act. This was associated with failures and delays in seeking treatment, with differential understanding of malaria between men and women, and differential health-seeking behaviour. Women delayed seeking care until men were available, while men were less willing to spend on child health.[191,192] These differences are critical when considering the main child-caring role of women and children's increased vulnerability to malaria. There is also some limited evidence that girls in some settings are treated differently from boys in relation to care-seeking.[193] However gender discrimination should not always be assumed, even in societies with strongly defined gender roles. For example a study in Afghanistan found women to be equally knowledgeable about malaria.[194]

Studies examining gender differences in mortality rates have explored whether girls and non-pregnant women with malaria die more frequently than age-matched males either for biological reasons or because of reduced access to care leading to delayed presentation. These studies have generally found a negative result (no gender difference), especially in Africa, although there are very few community-based studies and most are hospital series[195] which have significant limitations. One study in Yemen found higher mortality rates in girls than in boys.[196]

3.1.4 Nutritional status

It is well established that undernutrition affects the immune system and increases the incidence, duration and severity of many infectious diseases. The evidence of which nutritional factors have most impact on malaria severity is still patchy. There is, however, now reasonable evidence for a link between some aspects of both acute and chronic malnutrition and severe malaria.[197] Undernutrition prolongs the severity of malaria episodes and increases the chance of death.[198] Children who have severe chronic undernutrition are twice as likely to die of malaria as children of normal height.[199] Children who are acutely undernourished (of which there are 55 million worldwide) are two to three times more likely to die of malaria.[200] Vitamin A and zinc deficiency appear to be particularly important in elevating the risk of morbidity and mortality from malaria, because of the role these nutrients play in supporting the immune system. Children with zinc deficiency may have increased risk

of getting ill from malaria and higher risk of death from malaria than children whose zinc status is adequate but evidence on the size of effect is contentious.[201]

There is a clear association between malnutrition and malaria mortality. For example, it was estimated in one study that 57% of malaria deaths among children under five are associated with undernutrition.[202] Since poverty is a risk factor for both malnutrition and malaria ascribing causality is, however, not easy without intervention trials as confounding makes observational studies difficult to interpret.

3.2 Household and community levels: social and economic factors

At a household and community level there are strong links between incidence and outcomes of malaria and poverty but there has also been debate about the extent and direction of causation and its magnitude. Gallup and Sachs argued that there is a correlation between malaria and poverty but that malaria produces poverty more than the other way round.[203] They highlighted, however, that this relationship could be spurious and noted the problems with data and its interpretation.

An analysis of demographic and health survey data from 22 malaria endemic countries found a weak but positive association between reported fever and poverty across regions. However this became insignificant after controlling for a mother's education; *e*qually, the relationship between fever and different income groups was found to be insignificant.[204]

More specific malaria studies have looked at the association between wealth and malaria incidence but again the findings are inconsistent. A study of 1,200 households in a holoendemic area of Nigeria found no significant difference in malaria morbidity patterns between different socioeconomic groups.[205] Coleman et al, however, found a significant inverse association between household wealth and malaria incidence in a household matched case–control study designed to explore associations between household characteristics and malaria risk in seven towns in the hypoendemic area of Mpumalanga Province in South Africa.[206]

Less controversy surrounds treatment seeking behaviour and access to healthcare and services by different wealth groups. Evidence shows poor people benefit less from most malaria control interventions than higher income groups.[207,208,209] (See Section 5.8.3 Reaching the poorest). Poor people are also less likely to seek prompt effective treatment when they fall sick.[210,211] The direct and indirect costs associated with malaria represent a substantial burden on poorer households (see Section 2.3.2 Burden on wider economy).

High costs of malaria treatment may lead to delays in treatment seeking behaviour. Filmer (2002) found the poorest groups in a society did not seek care as much as the non-poor, and did so at lower level public facilities.[212] The burden of malaria is greatest among poor people, imposing significant direct and indirect costs on individuals and households and pushing households into in a vicious circle of disease and poverty.[213] Gollin and Zimmermann present a household based model showing how economies may inhabit a 'malaria trap' in which sickness begets poverty and poverty makes disease prevention unaffordable, which can reduce income per capita by about half.[214]

Vulnerable households with little coping and adaptive capacities are particularly affected by malaria. Households can be forced to sell their food crops in order to cover the cost of treatment,[215] depleting household resources and leading to increased food shortages, debts, and poverty for the poorest households. The costs of malaria are highly regressive, with the poorer households spending a significantly higher proportion of their income on the

treatment of malaria than their least poor counterparts. Wealthier households are better able to cope, and spend more on malaria prevention.[216]

The ability to access treatment is an important determinant of health outcomes. With lower access to treatment, poorer households are more vulnerable to the consequences of malaria including progression to severe disease and death. Poorer households are more likely to self-treat and less likely to access private and public providers.[217] In SSA over 70% of patients with suspected malaria diagnose and manage their illness at home with traditional remedies or drugs bought from local shops.[218]

Households are particularly vulnerable to malaria in the rainy season, when malaria prevalence is highest but also liquidity is lower. Chuma et al found seasonality to be a major variable in cost burden and that the main coping strategy for poor people is borrowing.[219]

3.3 Environmental and institutional factors

3.3.1 Conflict affected and fragile states

Those living in conflict affected and fragile states are disproportionately affected by malaria compared to similar environments where conflict is not occurring– the mortality rate is estimated at up to 13 times greater in fragile states compared to other developing countries.[220] In 2000, it was estimated that up to 30% of malaria deaths in Africa occur in countries affected by war, local violence or natural disaster.[221] In 2005, RBM estimated that up to 80% of malaria incidence is in conflicted affected and fragile states (CAFs).[222] This should, however, be interpreted with caution in terms of definitions, as many of the countries with the highest malaria burdens (e.g. Nigeria, Uganda, India) have geographically limited conflict which is not associated with most malaria. Evidence that conflict is associated with elevated malaria mortality has, however, been reported in multiple settings. As one example mortality surveys undertaken by the International Rescue Committee in the DRC found that when violent deaths increased 5.5-fold, malarial deaths rose 3.5-fold.[223]

However, there is no uniformity in the evidence of the size and importance of the impact of conflict. Conflict preceded an increased incidence of malaria in Afghanistan[224] and in Burundi, where incidence rose to 50% in 1998.[225] But increases were not observed in Timor-Leste.[226] Post-conflict, there is some evidence to suggest that malaria mortality may relatively quickly return to previous levels, and to that of similar non-conflict countries as health systems improve, control interventions take effect and living conditions improve.[227] The evidence of the impact of conflict on infectious diseases is significant, but this subject is still insufficiently studied and it is not easy to generalise from one setting to those with very different epidemiological and conflict environments where fighting may be protracted or shift geographically over time.

Meek et al (1998) identified the key conflict-related drivers of malaria as: breakdown of health services (e.g. diagnosis, treatment) and of malaria control programmes (e.g. IRS); movements of non-immune people to, or concentration of people in, high risk areas for malaria; weakened nutritional state of the displaced population; environmental deterioration that encourages vector breeding; and problems of food and medicine supply and of access.[228]

Civil unrest has clearly led to malaria resurgences in the past. Following aggressive vector control programmes in the 1960s and 1970s malaria was almost eliminated in Afghanistan. Since then, malaria has returned with 12 of 21 million people at risk, and malaria reinvaded neighbouring Tajikistan where it had been eliminated.[229]. Traditionally caused by *P. vivax*, *P. falciparum* became an increasing problem.[230] This increase has now been reversed in areas of Afghanistan where there has been sufficient stability to allow basic health system

development and LLIN distribution.[231] Currently Helmand is one of the most malaria-affected areas of Afghanistan.[232]

Malaria flourishes in conditions of crisis and population displacement and refugee camps may be ideal malaria vector breeding areas, to which traditional prevention tools are poorly adapted, and where local health services may be denied.[233]. One influencing factor appears to be the speed of conflict development. Rapid onset of conflict, as in Rwanda, allows for less preparation than gradual escalation, like Sudan.[234] However, disruption of routine health services does not necessarily lead to an increase in malaria incidence – even in a rapid developing conflict, as found in East Timor.[235] Part of the explanation for the success of malaria control in Timor-Leste was rapid coordination between key stakeholders[236] and the expanded role of community health workers and personal protection from vectors.[237]

One reason for increased risk is that newly displaced populations are often settled in marginal areas, prone to vector breeding which becomes exacerbated by the digging of pits for building material which fill with rain water and lead to increased transmission rates in an exposed population still lacking adequate shelter.[238] To remedy this problem efforts have been made to develop more appropriate vector control tools such as polyethylene refugee shelters or tents impregnated with insecticide during manufacture or blankets impregnated with long lasting repellent insecticides.[239]

Vulnerability varies according to that stage of a conflict. Many displaced people are most at risk during the acute phase,[240] probably through factors of malnutrition or passage from low to or through high transmission areas, although there is relatively little documented evidence of this. Immunity levels may also affect malaria prevalence amongst refugees. For example, higher prevalence of malaria in Afghan refugees in Pakistan during the 1980s compared to the local population was most likely due to low immunity amongst the refugees rather than that they brought a high infection load with them from Afghanistan.[241]

Host populations often suffer increased poverty, and humanitarian assistance may not be offered to them. As a result there is a risk they experience higher levels of morbidity and mortality than the displaced – but this association has not been tested adequately. Where conflict has an ethnic or religious element to it, as in Burundi, some groups may be deliberately neglected, boosting malaria incidence.[242] Even without cross-border migration, high malaria prevalence in a conflict area can act as a reservoir to raise incidence across regional/international borders through economic and seasonal migration or as a result of further displacement from conflict across borders. In Burma, conflict areas where malaria prevalence is high probably serve as a reservoir causing higher infection rates over the border in Thailand.[243]

CAFS are also likely result in a worsening of the usual malaria drivers present in all lower income countries. Conflict exacerbates poverty, which is closely linked to malaria.[244] It also brings political instability and governance problems which link closely to failing health systems.[245] CAFS disproportionately occur in SSA, where the most effective vectors and most dangerous parasites are found.

A review of HIV and malaria National Strategic Plans and Global Fund approved proposals in African countries hosting populations with refugees and/or internally displaced persons (IDPs) found that conflict affected displaced persons needed to benefit more from non state providers (NSPs) and Global Fund Grants. Refugees were not mentioned in 47% of malaria NSPs and IDPs were not included in 44%.[246]

3.3.2 Environment

Climate and environmental conditions greatly affect the transmission and incidence of malaria, by influencing primarily the abundance and survival of vectors and parasites, and also exposure of humans and other hosts.[247] The most important environmental factors for malaria transmission have to do with conditions for *Anopheles* mosquito breeding and survival – water in which they can breed, and minimum temperatures and humidity to allow them to survive long enough for the vector stage of the parasite's life cycle to be completed – usually about ten days. These factors are influenced by climate, as well as by topography and soil conditions, drainage, vegetation cover, land use and water – all of which vary greatly depending on local conditions. As such, changes in climate and land use such as water management, agriculture, urbanisation, and deforestation can lead to significant increases or decreases in malaria transmission, depending on local contexts.[248] Malaria control strategies need to consider how changing environmental conditions – some of which may be linked to development initiatives – may increase or decrease malaria transmission. Opportunities exist for integrating environmental management interventions into vector control strategies in order to reduce malaria risk. This section examines how changes in climate, water and sanitation, agricultural practices, urbanisation and deforestation affect malaria.

3.3.3 Climate change

Combating the effects of climate change is a major development priority for many reasons. Because of its importance to the work of DFID and other development agencies, this section briefly reviews the evidence that climate change is having an impact on malaria. Climate factors – particularly rainfall, temperature and humidity – interact to greatly affect the development, behaviour and survival of mosquitoes transmitting malaria.[249,250] However, as the Intergovernmental Panel on Climate Change (IPCC) reports,[251] 'despite known causal links between climate, malaria and transmission dynamics, there is still much uncertainty about the potential impact of climate change on malaria at local and global scales' (p. 404). This is in part due to the complexity and local specificities of malaria transmission. Different mosquito vector species and parasites react differently to various climate conditions. For example, a change in temperature can affect the growth of the parasite within the mosquito and a change in local climate may make it less suitable for one vector but better for another.[252] This particularly applies to water habitats for mosquito breeding (see Section 3.3 Environmental and institutional factors**)**. However, while there is substantial knowledge on mosquito vectors, there is uncertainty about how climate change may change and influence malaria transmission.

Two impacts of climate change at least have to be considered as major factors: temperature and rainfall patterns. The less important, but easiest to model, is the direct effect of temperature. This has effects both on mosquito range and survival, and the period of time it takes for mosquitoes to become infectious following biting an infected individual; the shorter the period, the greater the vectoral capacity. For both reasons, higher temperatures are likely to lead to more malaria– but the effects of this should not be exaggerated, and changes in temperature are unlikely to occur with all other environmental factors remaining constant. Modelling suggests that the most likely consequence of an increase in global temperature is that malaria will move up mountains in countries such as Tanzania, Kenya and Uganda where malaria transmission ceases to occur above a certain altitude.[253,254] There is empirical data to suggest this is already happening, but the evidence is mixed. In the East African highlands for example, scientists have linked increases in temperature to transmission potential,[255] while others suggest malaria incidence has increased in the absence of climate trends,[256,257] although those conclusions are also disputed.[258] Research groups argue alternative explanations exist for these increases in disease such as drug resistance, decreases in vector control and changes in surveillance making it difficult to determine the contribution of climate variables to changes in malaria.[259,260,261] Key reasons for this diverse evidence are the lack of historical data on malaria and challenges in including

socio-demographic and drug resistance factors in the analyses. At a global level, a recent study provides evidence that despite observed global warming over the last century, the overall prevalence of malaria has decreased. They attribute this to disease and mosquito control programmes, suggesting that interventions will have much more impact on malaria than climate in the future.[262]

Increasing temperature will increase the theoretical range of malaria, a staple of alarmist reports on the effect of climate change on malaria, but due to the complex interaction with other factors such as rainfall and development this is probably of very limited importance for practical planning purposes. Experience from countries such as the USA suggests that if localised outbreaks do occur on the fringes of the areas of stable malaria transmission as a result of global warming these are likely to be contained rapidly.

The more important environmental factors are changes to rainfall patterns, and consequent changes to land use, humidity, salinity due to water stress and other factors. These variables are much more difficult to model reliably.[263] It is not just how much rain falls, but over what period, and in what pattern, which is important. The distribution of malaria across Africa, Asia and Latin America will almost certainly be affected by changes to rainfall. We already know for example that the El Niño oscillation has had a significant impact on malaria in both Africa and Asia,[264] so any change in rainfall will have consequences. Weather patterns associated with the El Niño southern oscillation (ENSO), and influenced by climate, have been strongly linked to increases in malaria in parts of southern Asia, South America and East Africa.[265] ENSO – a periodic warming and cooling of the Pacific Ocean coupled with changes in air pressure – leads to changes in precipitation, temperature and extreme rainfall events. ENSO related drought has historically led to increases in malaria in Sri Lanka, and three times more cases in Venezuela. A recent study in Colombia provides evidence that even weak ENSO events have led to approximately 20% increase in malaria cases even when other factors are accounted for such as changes in population and malaria prevention and control efforts.[266] In some cases, particularly related to ENSO, seasonal climate forecasts that predict the likelihood of weather patterns several months in advance have been proven to be useful in providing early indicators of malaria epidemic risk.[267] A malaria epidemic prediction model developed and used in Kenya[268] has been successful in forecasting outbreaks that will occur within three months based on observed temperature and rainfall parameters. Such models may facilitate early public health initiatives which can mitigate effects of epidemics and improve cost-effectiveness of malaria control activities– although whether the opportunity costs are justified compared to other priorities in malaria is not currently clear.[269]

Current modelling of changes to major weather systems is, however, too crude to make more than broad-brush predictions on what will happen to malaria. Realistically it is only possible to say with some certainty that malaria incidence is likely to rise in some areas and fall in others as a result of these changes. The net effect globally, and more importantly where these changes will be, is not known and for practical planning purposes should be considered unknowable over the next decade based on the limitations of current models. Even were we to know in greater detail the nature of the changes in rainfall patterns around the equator (itself a considerable scientific challenge[270] to which DFID is contributing by supporting work by the Hadley Centre), the impact of these changes on land use and on the relative success of different malaria vectors is difficult to predict. Details of some of these factors are laid out below.

Changes in rainfall have always affected malaria transmission in some sites. Transmission of malaria typically occurs within seasonal patterns of changing temperature, rainfall, humidity and day length, although the effects of this vary widely. As a generality, where malaria is highly seasonal and dependent on rainfall patterns, changes to climate are more likely to have an early impact than where transmission is high all year. Increases in rainfall enhance transmission by creating pools of water and breeding sites, although heavy rainfall

events may also have a flushing effect, cleansing sites of mosquitoes.[271] Drought can also both decrease and increase malaria transmission depending on local habitats and vectors. Long-term drought or decreases in annual rainfall may reduce mosquito habitats, resulting in decreases in malaria, such as has been observed in parts of the Sahel.[272] However, in areas with flowing water such as small rivers (unsuitable for local mosquito species) drought may create isolated pools suitable for breeding and stimulate people to store water in containers that could serve as breeding sites, although this is probably more of a problem for *Aedes*-transmitted diseases such as dengue. Furthermore, drought can also lead to decreases in immunity (due to decreased mosquito activity), that make people more vulnerable to infection when the drought breaks and malaria transmission increases.[273]

It is also important to factor in the obvious point that climate and environmental factors do not occur in isolation. Other factors including changing socioeconomic development, human behaviour, migration, public-health infrastructure, drug resistance and vector control measures are equally critical in affecting the transmission and incidence of disease.[274,275] In addition, indirect climate impacts related to migration and displacement, increasing urbanisation, decreased food and nutritional security, social disruption, economic decline could increase vulnerability to the disease.[276]

Future climate impacts on malaria- predictions and limitations

In its most recent report, the IPCC concluded that climate change will have mixed effects on malaria. It is expected that malaria will increase in some areas (both in terms of latitude and altitude), and decrease in others. The length and timing of seasonal transmission may also be changed.[277] Climate changes may cause transmission to become unsustainable in previously endemic areas, or sustainable in previously non-endemic areas.[278] However, such changes will not necessarily translate to a change in overall incidence of disease or global disease burden, as these also depend greatly on intervention and control measures.[279,280] These conclusions are broadly supported by most opinion, and nothing which has come out since the last IPCC report changes this.

Of particular concern to health workers, populations at the marginal areas of exposure may be most affected by changes in malaria due to less immunity, instability of transmission and limited public-health infrastructure to address malaria in these areas. Areas at the fringe of endemic zones such as desert and highland areas may be most vulnerable to climatic shifts.[281] Even small increases in disease distributions could expose non-immune populations.[282]

Most projections, which are largely speculative due to the complexities of modelling, laid out above, have been for Sub Saharan Africa which has the highest disease burden. For example, one of the more detailed studies,[283] while recognising limitations of their model, suggests that parts of the Sahel may become too hot and dry to sustain *P. falciparum* malaria, while there may be an increase in highland and upland areas. This study projects longer transmission seasons resulting in the overall person-months of exposure to malaria in Africa to increase by 16–28% by 2100. While a change in transmission season does not automatically increase the disease burden, it does have implications for vector control.[284]

The biological and empirical models used to arrive at these and other estimates of climate change impacts on malaria[285] have significant limitations, however, and need to be considered in this light. These are due to extensive uncertainties in climate projections, the lack of integration with non-climatic factors (e.g. population growth, public-health infrastructure, management of deforestation and surface water, mosquito control programmes; insecticide resistance), and uncertainties of how these may change in the future.[286,287]

In order to better assess impacts of climate change on malaria, improved models that better integrate environmental, biological, socio-economic, and behavioural factors are needed.[288] More robust surveillance and monitoring systems can provide needed empirical data. Opportunities exist to build on existing seasonal forecasting and malaria risk prediction models which can influence preparation and planning for public health interventions.[289]

3.3.4 Water management and sanitation

Poorly maintained water supply, sanitation and drainage systems contribute to the transmission of malaria by providing potential breeding areas for mosquitoes. The relative impact of this depends on the local mosquito vectors, but some impact is found in almost all countries, and in countries in Asia in particular changes to water management can have a substantial impact on malaria transmission. Even in Africa, where important vectors are broadly less selective with regard to breeding sites, this can play a role in both urban and rural settings. For instance the drain network can be an important larval habitat: one study in Dar-es-Salaam showed that more than 33% of all anopheline-positive habitats were drains.[290] Standing pools of water can result from a lack of operation and maintenance of drinking water supply systems – broken water pipes, leaking taps, spillage of water around stand-pipes and wells as well as broken manhole covers – and so are implicated in providing larval habitat for malaria vectors. With respect to sanitation, mosquitoes are associated with wastewater treatment systems (such as waste water treatment plants.[291] and waste stabilisation ponds.[292.293] Increased malaria vector abundance in some countries is associated with interventions for improved water resources management such as water-holding structures (mini dams and small-scale irrigation projects) but this is very vector dependent.[294]

Restoring, cleaning and maintaining the drainage network and introducing an effective system for solid waste management (to stop solid waste collecting in draining channels) may be important for vector control.[295] In Dar-es-Salaam, simple, low-cost interventions are projected to reduce the costs of the ongoing Urban Malaria Control Program by eliminating an average of 42% of all potential mosquito larval habitats (including *Anopheles* larvae), which are currently treated with larvicides at weekly intervals, although direct evidence of these projections being possible to realise is lacking. [296] Pools of stagnant water can be eliminated by repairs or improvements to the water supply system; soak pits can be built to remove water accumulating around stand pipes; and cisterns (water tanks) can be covered with mosquito nets or lids. With respect to wastewater treatment systems, again, simple low-cost interventions like clearing away vegetation and other matter from the sides of structures, repairing cracks in the structures and reducing the amount of floating matter in the ponds can act as vector control. And whilst sanitation structures, such as pit latrines, imperfectly sealed septic tanks, etc., do not tend to act as habitats for *Anopheles* mosquitoes.[297,298,299] in the context of Environmental Management programmes, they should nevertheless be targeted for control in order to reduce biting nuisance by other culicine mosquitoes[300,301,302] Such environmental management strategies may be effective measures to reduce malaria transmission if well delivered in the context of integrated vector control management strategies, but this is mainly based on evidence of reduction of vectors rather than reduction of malaria.[303] These measures however have potential benefits beyond the agenda of reducing malaria, with wider impacts of improved health, such as reducing diarrhoeal disease, malnutrition, and particularly child mortality, and evidence for this is stronger for that on malaria.[304]

3.3.5 Agricultural practices

Agricultural practices and associated land use changes (e.g. drainage, irrigation) can significantly increase or decrease malaria risk. Some practices, such as drainage and management of vegetation of marsh area, have historically been successful methods to

decrease malaria by creating less favourable conditions for mosquitoes to breed, particularly in Europe (e.g. draining the Fens in the U.K.) and in Asia.[305] Conversely, agriculture practices that are important for food security – such as irrigation for rice or other crops, the creation of small dams, and fish ponds – create standing bodies of water potentially leading to an increase in the number of mosquitoes, and increases in human exposure.[306] Whether or not this translates to an increase in disease burden, however, depends on local contexts and vectors. Furthermore, intensification of agriculture often leads to increases in pesticide use which may contribute to resistance of mosquitoes to insecticide control measures.[307]

Evidence of impacts of irrigated agriculture on malaria has received the most attention. In most cases in both rural and peri-urban areas[308], introduction or expansion of irrigated agriculture has led to increases in malaria incidence, such as a five-fold increase in Sri Lanka[309] and seven-fold increase in northern Ethiopia.[310] Fringe areas such as highland and desert areas are especially vulnerable where malaria is less stable and people have less immunity.[311] However, a growing body of evidence related to irrigated-rice cultivation in SSA suggests that in areas where malaria is stable, crop irrigation has no or little impact on, or even decreases incidence of, malaria.[312,313,314] This is in part due to the presence of different mosquito vectors with less transmission potential, but also improved incomes among farmers in irrigated areas enables them to have better access to bed nets and improved healthcare.[315] Shifts from rainfed to irrigated agriculture have also changed the timing of malaria from a few months a year during the rainy season to being constant all year round, with implications for intervention strategies.[316] While local contexts must be better understood, development agriculture and irrigation programmes – whether large or small scale – must consider opportunities to decrease malaria risk through provision of improved healthcare facilities and environmental management. Techniques such as clearage of irrigation canals, vegetation management, and intermittent irrigation have all proven effective (in some cases between 80–85%) in reducing malaria risk and can be useful strategies for vector control.[317]

3.3.6 Urbanisation

While malaria transmission rates are generally higher in rural than urban areas, rapid unplanned urbanisation is leading to an increase in malaria risk in cities. Unprecedented rates of urbanisation are occurring globally, and already 40% of the population in Africa and 42% of the population in Asia live in cities. Sub-Saharan Africa is the most rapidly urbanising region in the world, while in Asia urban growth rates are ten times that of rural areas.[318] When accompanied by adequate housing and sanitation, urbanisation will usually lead to a decrease in malaria due to fewer vector breeding sites, less human exposure, and better access to healthcare and education.[319,320] However, in developing countries, rapid, unregulated urbanisation is resulting in poor drainage, increases in water storage tanks, and construction areas which create fertile breeding grounds for mosquito vectors.[321] Poor housing conditions particularly in expanding slum areas, poverty, and a lack of diagnosis of malaria in urban settings can put vulnerable urban populations further at risk.[322,323] Irrigated agriculture in urban and peri-urban areas may also support *Anopheles* mosquito breeding in places with high human density.[324,325] Urban malaria risk may also increase if vectors adapt further to city environments and/or develop resistance to insecticides used for control. The latter has already occurred in Benin, where rapidly expanding urban agriculture to feed growing populations has led to improper use of insecticides resulting in the emergence of resistance in malaria vectors.[326] The movement of people is also of concern. Infected migrants can introduce malaria to areas where it is rare, and non-immune people may be at risk if they move into areas of transmission.[327]

The numbers of people at risk in urban areas warrant attention. In SSA, an estimated 200 million people living in urban areas (almost 25% of the total African population) are currently at risk of contracting malaria, with poorer peri-urban households having similar risks to rural

dwellers.[328] Given rapid expansion of urban populations with estimates of 750 million in SSA and 2.7 billion in Asia by 2030[329] attention needs to be paid to specific strategies for malaria control and treatment in urban areas. Integrated vector control management including environmental management strategies such as drainage control measures described earlier, together with public health interventions can be effective measures,[330,331] although what is meant by integrated vector control measures can vary widely. Disease risk mapping can also be useful to target those most vulnerable populations. Good potential exists to limit malaria in urban areas, which are generally less favourable to anopheline mosquitoes than surrounding rural areas. In Asia many cities are malaria-free because local vectors do not enter them. In Africa the major vectors can breed in urban environments (see below). However, as Keiser et al. note, given challenges that many urban authorities have in Sub Saharan Africa for supplying basic services, strategic investments and public-private partnerships to over-come operational constraints in supply and delivery are required.[332]

3.3.7 Deforestation

Deforestation can affect malaria transmission both directly through changes to the local environments of the disease vectors as well indirectly as a precursor to other intensive land-use changes, migration, and climate change. Deforestation, resulting from logging, settlements, expansion of agricultural and industrial use, and hydropower development, affects local climate conditions and micro-environments for mosquitoes and parasites.[333] Substantial evidence has demonstrated that deforestation has accompanied increases in malaria in Latin America, Asia and Africa,[334] although it may also lead to decreases. In the Amazon, forest clearing has reportedly increased the abundance of *A. darlingi* mosquitoes,[335] and its biting rate to 278 times greater than in forested areas.[336] A recent study in a county in the Brazilian Amazon provides evidence that a 4% change in forest cover was associated with a 48% increase in malaria incidence.[337] In south-east Asia, species have been differently affected by forest clearance with varied impacts on the incidence of malaria.[338]

Deforestation may also affect the transmission of malaria in more indirect ways. Large-scale clearing, such as has occurred in the Amazon, can affect climate at local, regional and even global scales, which may have potential impacts on malaria, although the extent of which remain unclear.[339] Deforestation is also a precursor to other land-use changes such as agricultural expansion, intensification, and hydropower development which affect local conditions for vectors and parasites.[340,341] Forest clearing for new settlements may also be linked to migration, exposing new populations to malaria. In Brazil, deforestation paved the way for rapid colonisation programmes in the Amazon that led to progressive increases of reported cases from 52 000 in 1970 to 578,000 in 1989.[342] In areas where forest cover may be linked to lower levels of malaria incidence, such as in rural Indonesia[343] and Brazil,[344] there may be opportunity for stronger links between forest management and public health sectors; research into interventions which might reduce malaria is likely to be helpful.

In some settings, including south-east Asia, where local vectors predominantly bite outdoors and in forested areas, forest workers are at particular risk of malaria, and may act as transmitters, bringing malaria into their communities or moving malaria (including drug-resistant malaria) around.[345]

4. High risk groups

Malaria affects a number of high-risk groups, but it is important to stress that in almost all settings in Africa the burden of disease falls on very young children.[346]

4.1 Pregnancy and malaria

4.1.1 Effects on mother and infant health

Malaria in pregnancy is dangerous for the mother and the unborn child in multiple ways (see Table 2).[347,348] There is clear evidence that the effect of infection on the mother varies depending on the level of exposure to, and therefore immunity to, malaria infection that the mother has acquired prior to pregnancy, although the basis for this is not completely understood.[349] Acquired antimalarial immunity depends on the intensity of malaria transmission, the number of previous pregnancies and the presence of other conditions such as HIV infection which may further impair the efficacy of immune responses during pregnancy.[350] Women in high-transmission areas who were semi-immune to malaria prior to pregnancy become vulnerable, especially to malarial anaemia, when pregnant, and this is often missed because they do not present with typical symptoms.[351] This is most marked in early pregnancies and, in the absence of HIV, malarial anaemia in pregnancy becomes less likely as the number of pregnancies increases.[352]

Women in the second and third trimester of pregnancy are more likely to develop severe malaria than other adults, and in low transmission settings, this is often complicated by pulmonary oedema and hypoglycaemia.[353] Maternal mortality from malaria is higher than in non-pregnant adults whatever stage of pre-existing immunity. Foetal death and premature labour are common. During the latter stages of pregnancy, malaria infection, in combination with maternal anaemia, can impair foetal weight gain and contribute to intrauterine growth retardation or prematurity and thus result in low birth weight. This has been demonstrated most convincingly by trials of malaria prevention strategies in which both drugs and bed nets were shown to reduce these adverse outcomes.[354]

4.1.2 Effects of intensity of transmission

The symptoms and complications of malaria during pregnancy differ according to the intensity of malaria transmission (Table 2). The burden of malaria in pregnancy is highest in areas of high or moderate (stable) transmission, which dominate much of SSA. Malaria may be present in the placenta but not be seen in the peripheral blood; for example one typical recent study showed 6% of women had malaria in the peripheral blood but 61% had infection in their placenta.[355] In areas of high transmission the ill health effects are especially apparent in the first and second malaria-exposed pregnancies.[356] Effects of malaria on the mother, who may have no fever or other classical symptoms of malaria, are dominated by anaemia, which may be profound and lead to foetal or occasionally maternal mortality either during pregnancy or if bleeding complications occur in pregnant women in childbirth.[357] The effects on the foetus/newborn include a small placenta and small-for-dates babies at increased risk of neonatal mortality. As stated previously, intervention trials demonstrate this relationship is causal rather than just an association.[358,359] In areas with stable malaria transmission, malaria during pregnancy contributes to between 2% and 15% of maternal anaemia and 8% and 14% of low birth weight.[360,361] The contribution of malaria to other adverse health events, for which there is good evidence, is shown in Table 3.

Table 2: Malaria's contribution to anaemia, low birth weight and infant death[362]

Adverse health events	% of total
Maternal anaemia	2–15
Low birth weight	8–14
Preterm	8–36
Intrauterine growth retardation	13–70
Infant death	3–8

Table 3: Number of pregnancies at risk of *P. falciparum* and/or *P. vivax* malaria by WHO regional office in 2007 (millions) (column %)[363]

WHO region	*P. falciparum* Transmission[a]			*P. vivax* transmission[a]	Any species
	Stable transmission	Unstable transmission	Overall	Overall	Overall
AFRO	29.6 (54.1)	0.4 (1.2)	30.0(35.1)	3.6 (3.9)	30.3(24.2)
EMRO/EURO	4.0(7.3)	4.2(13.7)	8.2 (9.6)	10.4 (11.2)	13.1(10.5)
AMRO	1.4 (2.5)	1.6 (5.2)	3.0 (3.5)	2.9 (3.1)	4.3 (3.4)
SEARO/WPRO	19.7 (36.1)	24.5 (79.9)	44.2 (51.8)	76.0 (81.8)	77.4 (61.8)
Global	**54.7**	**30.6**	**85.3**	**92.9**	**125.2**

[a] Includes countries where *P. falciparum* and *P. vivax* co-exist
[b] Stable transmission ≥ autochthonous *P. falciparum* cases per 10,000 people per annum; unstable transmission >1 autochthonous *falciparum* cases per 10,000 people per annum.[364]

The evidence of the potential adverse effects of antimalarial drugs on the foetus is broadly encouraging; this is reviewed in Section 5, Interventions and delivery.[365]

4.2 HIV and malaria

4.2.1 Impact of HIV on the population burden of malaria

Contemporary models of immunity to malaria in the 1980s led to an expectation by many that HIV infection would have a substantial impact on the incidence of malaria. When early evidence suggested that, in areas of intense transmission of both diseases this did not happen, many leading authorities moved to stating there was little or no impact of HIV on malaria.[366] More recent evidence has led to this being challenged and there is now a reasonable consensus that HIV has a significant impact on malaria incidence and severity.[367,368] Convincing empirical evidence of the size of the effect is still remarkably sparse, however, given the high incidence of both diseases in many areas. Regions with a high burden of malaria and HIV overlap in SSA and Asia, and especially in southern and eastern Africa. However, the burden of morbidity and mortality attributable to malaria in people with HIV infection is not well characterised at a population level due to lack of routine reporting and data collection.

Most of the evidence is based on models which rely on a limited range of data points. Two examples are given below.

Modelling the impact of HIV on the incidence of malaria across SSA by the WHO led to the conclusion that HIV is likely to have the greatest impact on malaria incidence (>50% increase in incidence) in regions of very high HIV burden, even where they are not high transmission settings, especially Botswana, Namibia, South Africa, Swaziland and Zimbabwe.[369]

Using previously published data to inform its parameters, the modelling exercise concluded that in these areas the incidence of clinical malaria was increased by up to 28% and deaths, as a consequence of malaria, increased by up to 114%. The model also concluded that for any given HIV prevalence, malaria incidence attributable to HIV would be higher in areas with unstable or low malaria transmission rates.

HIV had a very small effect on malaria incidence in areas of high transmission (West and Central Africa) because HIV prevalence is low in these regions.

HIV was estimated to have a medium impact (8–49% increase in incidence-wide confidence intervals) on malaria in Kenya, Tanzania, Rwanda, Burundi, Malawi, Zambia, Mozambique and the Central African Republic.

This study estimated that for SSA as a whole, HIV infection leads to an additional three million cases of malaria each year, assuming a baseline incidence of 228 million cases and 65,000 of 1.3 million estimated deaths due to malaria.

Another modelling exercise, designed to assess the impact of HIV on the malaria parasite biomass, and thus the influence of HIV prevalence on the emergence of antimalarial drug resistance, also concluded that HIV infection has the greatest impact on malaria mostly in southern Africa, notably in Zambia, Malawi, Mozambique and the Central African Republic.[370] This model led to the estimate that HIV infection increased the malaria parasite biomass by 17.4% across SSA as a whole.

Through modelling, it has been estimated in a widely-cited study that the interaction of malaria and HIV in one Kenyan district alone caused 980,000 excess malaria episodes due to impaired immunity resulting from HIV infection and 8,500 excess HIV infections due to increased infectivity as a result of malaria co-infection, since HIV's emergence in the 1980s.[371] These modelling exercises are useful, but should be interpreted with caution, as they extrapolate from relatively limited reliable data sources.

4.2.2 Impact of HIV on individual risk of malaria

There is some evidence to suggest that people with HIV are more likely to become infected with malaria,[372,373] to suffer higher parasite burden,[374] and to have a higher risk of clinical malaria and a higher risk of recurrence – especially at a CD4 count below 200 cells/mm^3.[375,376] However, larger longitudinal studies show an inconsistent relationship between HIV infection and an increased risk of morbidity and mortality as a consequence of malaria.

In malaria-endemic settings several observational cohort studies have shown a significantly greater risk of parasitaemia and clinical malaria among HIV-infected adults. An eight-year prospective study conducted in Uganda prior to the introduction of antiretroviral therapy found a significantly higher frequency of parasitaemia and malarial symptoms in HIV-positive people at routine quarterly clinic visits, with a trend towards greater frequency of symptoms in those with lower CD4 counts.[377] However, the same group did not find an association between parasitaemia or clinical malaria and mortality in the HIV-infected patients in this study.[378]

A separate cohort in Uganda, of 1371 HIV-infected adults, showed a strong relationship between immunosuppressant (CD4 <200) and symptomatic malaria during a median follow-up of 1.2 years.[379]

A longitudinal study in people with diagnosed HIV infection conducted in Malawi, using more intensive surveillance and case ascertainment and including a higher proportion of severely

immunosuppressed HIV-positive people at baseline, found a higher incidence rate of malaria in immunosuppressed patients; unsurprisingly malaria was a less significant cause of illness in the most immunosuppressed patients than tuberculosis, sepsis and pneumonia, and was not associated with severe malaria.[380] The authors concluded that HIV-related immunosuppression does not obliterate immunity to malaria in endemic areas, but does lead to a higher frequency of malaria in people with HIV.

Another observational cohort study in Malawi found that adults with HIV infection were at significantly greater risk of parasitaemia; density of parasitaemia was associated with immunosuppression.[381]

In regions of unstable transmission where early immunity is not established, HIV infection appears to increase the risk of severe malaria; it is in these regions that the interaction between HIV and malaria may result in the greatest additional burden of disease.

A study of consecutive adults with malaria in a non-endemic region of South Africa with high HIV prevalence found an elevated risk of severe clinical malaria in non-immune HIV-positive patients when compared to non-immune patients with no HIV infection (OR 4.15), but no significant difference in the risk of malaria according to HIV status among patients born in malaria-endemic areas.[382]

A second observational cohort study in South Africa, conducted in northern Kwazulu-Natal, found an elevated risk of microscopically-confirmed severe malaria (OR 2.3) and death (OR 7.5) in HIV-infected people.[383]

A systematic review of the burden of co-infection in pregnant women in SSA identified 11 studies and concluded that in settings with high HIV prevalence (10%), 5.5% of malaria incidence in pregnant women was attributable to HIV infection, but in settings with extremely high HIV prevalence (25% or 40%), 12.7% and 18.8% of malaria cases respectively were attributable to HIV infection.[384] For sub-Saharan Africa as a whole, HIV infection was estimated to lead to an additional 505,000 cases of malaria during pregnancy, out of an estimated 10.5 million malaria cases occurring in pregnant women. This review was not able to distinguish between risk elevations in endemic and unstable transmission settings.

The review found a consistently increased risk of parasitaemia in HIV-positive pregnant women during pregnancy, at delivery and in the placenta. Clinical malaria was more common in women with parasite-confirmed malaria; pregnant HIV-positive women were at significantly greater risk of developing any anaemia and moderate-to-severe anaemia. The effect of co-infection on birth outcomes was reported in 7 of 11 studies. A consistent trend towards lower birth weight was seen in infants born to co-infected mothers.

Although the evidence is consistent, there is a potential methodological problem with all observational studies done in areas with a reasonably high background prevalence of malaria. HIV infected subjects have more febrile illnesses than controls due to non-malarial illnesses (eg non-typhi salmonella and pneumococcal disease) and some of these will be associated with coincidental parsitaemia. Some studies have tried to allow for this but not all and doing so reliably where bacterial culture facilities is limited makes it difficult; the result is likely to lead to an overestimate of malaria associated severe febrile disease in HIV positive individuals.

Impact of HIV on malaria in pregnancy

The usual decline in complications associated with placental malaria over multiple pregnancies tends not to occur in HIV infection,[385] [386] but the mechanism by which HIV

infection causes this defect in immunity remains unclear, since it is not related to degree of immunosuppression.

Malaria, HIV and infants

Studies have reached varying conclusions about the impact of HIV on malaria in infants and children. While a large cohort study in Uganda[387] failed to find any association between HIV infection or perinatal exposure to HIV and incidence or severity of malaria in children, another study in Uganda in a cohort of children who received blood transfusions found that HIV infection was associated with increased morbidity and all-cause and malaria-related mortality in those children with malaria who developed severe anaemia.[388]

The latter study highlights perhaps the key area of risk for children: the risk of HIV acquisition as a consequence of a blood transfusion to treat anaemia associated with malaria in areas where screening for blood-borne viruses is limited.

Another study, in South Africa, found a higher incidence of severe malaria in children with HIV infection, although HIV status was a less strong predictor than age.[389] Other prospective studies have also found a higher incidence of malaria in children with HIV, but quality, definitions and populations vary. The extent to which children with HIV are affected by malaria as a consequence of their HIV infection and the extent to which this risk is modified by age or transfusion exposure is not known.

Malaria treatment is less likely to be successful in people with more advanced, untreated HIV infection, or treatment responses may be slower.[390] [391]

4.2.3 The impact of malaria on HIV infection

The current evidence suggests malaria has a number of significant effects on HIV disease and potentially transmission, especially mother-to-child (MTC).

Mother-to-child

Placental malaria causes a low grade inflammatory response in the placenta and there are theoretical reasons for thinking that this might lead to increased MTC transmission of HIV peri-partum, but this has not yet been confirmed epidemiologically.[392] Co-infection with malaria causes a transient but substantial increase in HIV viral load lasting for several months after malaria treatment is successfully concluded.[393] Malaria infections lead to significant increases in HIV viral loads in blood and breast milk; the theoretical reasons this might lead to increased MTC transmission of HIV are obvious, but again the link has not been proven to be causal to date.[394,395,396,397]

HIV viral loads

The increase in viral load as a consequence of malaria was observed in a prospective study in Malawi. Viral load elevations were greatest in patients with the highest parasite density (>2000/ul) or more preserved immune status (CD4 count > 300), and peaked at levels associated with a high risk of sexual HIV transmission,[398] before returning to baseline levels within eight to nine weeks of malaria diagnosis as a consequence of treatment.

Of particular note in this context is the observation in the Malawian study that viral load increases in malaria cases were associated with a higher CD4 count. Even though Malawi and other countries in the region plan to change HIV treatment guidelines to begin treating when the CD4 count falls below 350, expansion of antiretroviral therapy would be expected

to have little impact on viral load changes as a consequence of malaria, if this association is robust.

It is not entirely clear whether malaria, which in addition to increasing HIV viral loads, also activates the immune system including widespread CD4 cell activation and therefore increases HIV disease progression.[399] There are obvious theoretical reasons to think it might, but no convincing evidence to date and it is unlikely that for obvious ethical reasons definitive randomised intervention studies will be undertaken.

5. Interventions and delivery

5.1 Vector control

5.1.1 Insecticide-treated nets

The technology: insecticide-treated nets and long-lasting insecticide nets

ITNs, and the newer version, LLINs, are the most prominent malaria preventive measure for large-scale deployment in endemic areas; the evidence for their efficacy is strong. A systematic review of 22 randomised controlled trials (13 in SSA, five in Latin America, two in Thailand and one each in Pakistan and Iran) concluded that the use of ITNs reduced under-five mortality in malaria-endemic areas in SSA by about a fifth and halved clinical episodes of uncomplicated malaria in areas of stable malaria transmission in Africa. In Asia and Latin America, ITNs significantly reduced the number of clinical episodes due to *P. falciparum* and *P. vivax*, although the number of included trials was small.[400] Many of the component trials are of high quality and several show reductions in malaria in excess of these composite figures. Trials in pregnant women also show efficacy.[401] Individually randomised trials may actually underestimate the effect of ITNs; an ITN protects not only the person sleeping under it, but others in the vicinity (a mass effect). Once coverage reaches a high level in a village or region even those not sleeping under nets are partially protected against malaria (although the strength of any mass effect will depend on vector behaviour).[402,403]

There are limitations to the trials, however. There are several settings in which evidence of the effectiveness of ITNs should be extrapolated with caution:

1. Where there is pyrethroid insecticide resistance. This is likely to reduce the efficacy of ITNs to somewhere between the figures quoted above and the effectiveness of untreated bed nets.

2. Where the predominant *Anopheles* species bite outdoors or early in the evening. This is common in parts of south-east Asia and Latin America,[404] although nets have been shown to be effective in specific cases in these regions (e.g. against *A. darlingi* in the Yanomami indigenous ethnic group of southern Venezuela[405]). There is some evidence that outdoor biters are less efficient vectors and ITNs may therefore still be effective in these settings. In all parts of Africa the major mosquito malaria vectors such as *A. gambiae* and *A. arabiensis* bite indoors and at night, although if there is selection pressure from effective bednet campaigns there may be selection for earlier biters.

3. ITNs are only effective if people use them and maintain them; this is a major limitation on their use.[406] This can vary with season, cultural practice (e.g. in Sudan some groups prefer opaque nets) and the presence of other nuisance biters (which encourage bed net use).[407] Because these vary with setting, operational research may often be needed to ensure that ITNs are accepted and used properly.

4. Where older bed nets which have been dipped in insecticide have not been retreated, or have been washed. This has been a major limitation to use,[408] although the advent of LLINs which do not need regular retreatment has had an impact on this.

The introduction of LLINs is relatively recent. Their advantage is that they do not need to be retreated, previously a significant limitation. It is likely that data from recently treated ITNs

can be extrapolated to LLINs, at least where there is no insecticide resistance. There are currently only a handful of LLIN producers, who use different methods to produce the long-lasting insecticide-releasing material. The technology is evolving rapidly and we do not have many studies of currently deployed nets used for five years. Initial studies suggest long-term efficacy varies across products and is affected by particular handling practices and that LLINs may have a maximum lifespan of three years. Studies have shown a specific product (Olyset) retained appreciable insecticide activity for as many as seven years.[409] However, personal protection, as measured by a reduction in blood-feeding rate relative to that of untreated nets, was evident in laboratory tunnel tests but not under field conditions where nets had developed holes. Another net (PermaNet 2.0) has shown superior performance against conventionally treated nets after 20 washes.[410] However, other LLINs have not out performed conventional ITNs and have shown some reduction in performance with washing.[411] Continuous exposure to sun has also been shown to reduce efficacy, although brief exposure (less than three hours after each wash) is not harmful. [412,413] The limited range of LLINs currently available makes it more difficult to match the net to local cultural, colour and other preferences, whereas older ITNs had the advantage of a wide range of styles, sizes, colours and opacity.[414] Long-lasting dip technologies are being developed such as K-O Tab123 which may fill this gap, but currently are not equally effective on all materials.[415]

ITNs are effective in reducing the adverse effects of malaria in pregnancy. A systematic review of randomised controlled trials involving the use of ITNs by pregnant women found miscarriages in Africa were reduced by a third in those women who were in their first few pregnancies.[416] The proportion of babies who were low birth weight went down by nearly a quarter. In the one Asian study, in Thailand, that met the selection criteria for the review, women using ITNs were less anaemic (measured by packed cell volume) and miscarriage rates were again lower, although there was no change in the low-birth-weight figures. There is no evidence of adverse effects on the foetus, with the caveat that low-incidence high-impact effects cannot be excluded.

Studies in which children have been followed-up for extended periods of time have demonstrated a sustainable reduction in child mortality conferred by ITNs over a broad range of malaria transmission intensities.[417,418,419]

Insecticide-treated curtains (ITCs) have also proved effective in some settings especially in West Africa where a six-year study in Burkina Faso estimated the reduction in child mortality associated with ITCs ranged from 19% to 24%.[420,421] However, ITCs have not been as widely deployed at scale as ITNs.

Both ITNs and LLINs are considered highly cost-effective; in a study of five ITN distribution programmes in Africa for conventional ITNs the cost per treated net-year of protection ranged from USD 1.21 in Eritrea to USD 6.05 in Senegal. The cost per child death averted ranged from USD 438 to USD 2,199. For LLINs giving five years protection, the cost per treated-net year of protection ranged from USD 1.38 in Eritrea to USD 1.90 in Togo. The cost per child death averted ranged from USD 502 to USD 692.[422] As with all preventive measures, the cost per case averted is likely to rise as incidence drops, but LLINs are likely to remain cost-effective to quite low levels of transmission.

The greatest threat to current ITNs/LLINs is that they depend on a single insecticide class, pyrethroids, which is both effective and for which there is extensive safety data in humans. There is already evidence *Anopheline* mosquito resistance to some pyrethroids has arisen and this is likely to spread.

Delivery systems for insecticide-treated nets

Whilst evidence that ITNs and LLINs work, especially in Africa, is very strong, evidence on best delivery systems is less clear cut and is likely to be context-specific. Countries with the highest coverage are often the smallest countries where it is relatively easier to attain high coverage. ITN use in the late 1990s was estimated at 5% in children under five across 23 African countries.[423] Coverage rates in many malaria-endemic countries are still below 20%,[424] although improving rapidly in some places where concentrated efforts have been made,[425,426] and where this has happened at scale good studies show that the impact on malaria has been significant.[427] Research studies of nets – notably randomised controlled trials of sufficient rigour to be included in well-conducted systematic reviews – have often achieved levels of coverage, use and impact that may be unobtainable under large-scale programme conditions,[428] and modelling the probable effectiveness of strategies on malaria transmission is not simple.[429] This means there may be a gap between efficacy under trial conditions and 'real life' effectiveness. The challenge for national and regional ITN programmes is to devise delivery and distribution systems that approach rates of use and therefore impact found in research trials. There is also often a time-lag for scale-up of net manufacturing, availability of finance and distribution of ITNs.

The World Health Assembly and the RBM partnership both set a target of 80% coverage of children and pregnant women in endemic areas by 2010 and have now shifted to Universal Coverage as a target; universal coverage for the same groups would require an estimated 327 million LLINs between 2008 and 2012.[430] Coverage data show that most countries are well below this target.[431]

Views vary on the best delivery strategy or (more usually) mix of strategies for delivering such outputs.[432] In particular the debate in the literature has sometimes seemed a rather ideological debate on whether ITN/LLINs should be provided free to users or by other means; this debate has continued because robust evidence of which approach works best depends on the setting and a mix of strategies used to first to achieve high coverage ('Catch-up) and then maintain it (Keep-up) often has to be employed; this often requires the use of both public and private strategies.[433,434]

Delivery strategies can be categorised by:

- the source of logistical and human resources for moving ITNs from manufacturer to end user (public, private, mixed public-private, community-based)
- cost to the end user (free, partially subsidised, unsubsidised)
- delivery channels from manufacturer to user (e.g. routine health services, campaigns, voucher schemes, retail sector).[435]

These delivery strategies may be complemented by 'social marketing' campaigns, such as radio and television messages, poster exhibitions and community-based information, education and communication activities.[436]

Prior to recent scale up efforts, in addition to ITN coverage rates across Africa being generally low, there have been inequality gaps between rich and poor. [437] One of the greatest challenges in implementing bed net programmes by all methods is reducing rather than increasing this inequity; the burden of malaria tends to fall on the poorest people, but distribution methods run the risk of being less rather than more effective for this group.[438,439] Well-designed programmes can, however, improve equity whilst increasing coverage.[440]

Net usage is in principle a more useful measure than net distribution as it has a more meaningful direct link with impact, but is more difficult to measure. If there are fewer nets per household than people there is a theoretical risk that the most vulnerable groups (infants, young children and pregnant women) may remain unprotected. Data on household net

usage is generally encouraging, with little evidence from most settings that they are reserved for adults. For example, research in Tanzania showed that in households with a net: person ratio better than 1:4, nets were most likely to be used by infants, young children (1–4 years) and women of childbearing age and that the nets used by infants and women of childbearing age were in better-than-average physical condition.[441]

The reasons people do or do not use their nets are as important as their having them. Qualitative data on usage shows that nets are used in part to prevent malaria, but importantly mainly to reduce nuisance biting, most of which is by mosquitoes which do not transmit malaria; for this reason the efficacy of nets against Culex mosquitoes, whilst not relevant for transmission directly, may be relevant indirectly.[442] Other factors such as season (with lower use when it is hot) are also important.[443] Many folk beliefs about malaria transmission, e.g. that malaria transmission occurs through flies or via breast milk, can undermine the rationale for net usage.[444] Evidence therefore suggests that net distribution should not be offered in isolation but instead, linked to public information campaigns tailored to local conditions and beliefs.

Several types or mechanisms of ITN distribution system are described in the literature. These include mass distribution campaigns, vouchers, continuous distributions and public/private sector mix schemes. No single approach can be considered to have universal applicability. This summary is a brief version of a large literature.

Campaigns – free nets and voucher schemes

Net campaigns

Net campaigns involve free ITN distribution, either through a standalone programme or linked to mass vaccination campaigns. Net campaigns have been evaluated in several studies in Kenya, Zambia and parts of West Africa.[445] Campaign outcomes in terms of coverage rates have been mixed, with rapid scale up which is not maintained being a common finding. The most common positive finding is rapid *equitable* scale up.[446] One review found that overall, campaigns increased coverage by between 30% and 80% but this is highly dependent on the baseline coverage.[447] A Kenyan study showed that campaigns can remove wealth-related inequalities in ITN coverage.[448] However, very few campaigns have reached the 80% Abuja target for ITN coverage among women and children under five and evidence of coverage sustainability is not well documented. Following campaigns, coverage levels can drop between 5–13% points per year for the first two years, with sparse data on time points beyond that.[449] Four countries have conducted surveys more than 12 months after mass net distribution to children and pregnant women. In Sierra Leone, household ITN ownership declined 37% within two to three years after mass campaign. In Togo, ownership declined 13% and ITN use in children under five years old declined 20% within three years of the campaign. In contrast, household ITN ownership coverage was maintained for 15 months in Rwanda and for 30 months in Kenya.[450] Evidence suggests that decline in ownership can be avoided if campaigns are combined with continuous distributions.[451] No difference has been shown in the model of campaign. For example, no differences were found amongst stand-alone, integrated, house-to-house campaigns.[452]

It is likely that a variety of distribution strategies will be needed to achieve and sustain delivery targets.[453] However, only a few robust comparative studies of the effectiveness, impact and cost of different delivery systems for ITNs have been undertaken and it is difficult to draw general conclusions on their relative merits. Data are limited to small-scale research projects that are context-specific, for example:

- The free distribution of ITNs to pregnant women through governmental antenatal care services in addition to ITN social marketing substantially improved ITN household ownership in rural Burkina Faso.[454]
- In rural Burkina Faso, costs of distribution per ITN did not differ substantially between two alternative interventions – subsidised sales supported by social marketing and free distribution to pregnant women through antenatal care.[455]
- Public sector targeted campaigns and routine antenatal care services (ANC) increased LLIN retention and use in Uganda, although delivery through ANC facilities was is comparatively expensive (although this difference is likely to be at least partially due to higher start-up costs for ANC distribution in this case).[456]

Voucher schemes

Pilots or geographically limited voucher schemes have been conducted in Ghana and Uganda, but the Tanzania National Voucher Scheme is the only national level incentive-based ITN distribution scheme to date.[457] Since 2006, Tanzania has implemented a discount voucher system to deliver nets to pregnant women. The process involves a sequence of five steps: attending an antenatal clinic, obtaining a voucher there, using the voucher to buy a net packaged with insecticide, treating the net with the insecticide and using the net.

Studies show that the scheme has a positive overall effect on household possession and use of ITNs, with possession increasing from 18% to 36% over three years and use increasing from 12% to 26%. However, the delivery system was not efficient in reaching the poorest groups, particularly when compared to free mass distribution. Large differences in coverage by socio-economic status have been observed, from 7% among participants in the poorest households to 48% among those in the richest households.

Rates of possession and use are in part a consequence of the five-step process. Each step has a success rate of between 60%–98%, the cumulative effect of which diminished the overall rate of coverage, most markedly among the poorest participants. Delivery of nets treated with long-lasting insecticide rather than untreated nets packaged with an insecticide-treatment kit could result in an improvement in coverage of 22 percentage points.[458]

Findings from Tanzania cannot be assumed to be generalised to other settings. For example, antenatal clinics are well used in Tanzania, which also has well established systems for the manufacturer and retail of nets. These favourable conditions will not be found in all malaria endemic regions.

Aside from the delivery system itself, other factors that affect the uptake and sustained use of ITNs are also highly context specific and include household income, education, ethnicity, gender, awareness, beliefs regarding malaria causation and severity, and perceived inconvenience of using nets.[459,460,461]

Free versus subsidy

There has been a protracted debate between those who believe strongly ITNs should be distributed free and those who promote subsidy-based methods or vouchers linked to social marketing.[462,463] The current WHO position is that rapid scale-up of LLIN coverage can best be achieved through free or highly subsidized distribution through existing public health services (both routine and campaigns). A recent systematic review concluded that when continuous distribution involved the commercial sector alone, increases in coverage rates ranged from 3% to 5% per year, whereas combining the commercial market with the distribution of free or highly subsidized nets through routine services achieved increases in the range 6% to 25%.[464]

5.1.2 Indoor residual spraying

IRS refers to the application of long-acting insecticide formulations on the walls and roofs of all houses and domestic animal shelters in a given area.[465] IRS shortens the life of female vector mosquitoes that land and rest on treated surfaces, and some insecticides also repel mosquitoes reducing the numbers that enter buildings. It is this last which is generally the most important for malaria transmission (See Annex C Quantifying malaria transmission, for the mathematical demonstration of this).

There is clear evidence that IRS can reduce malaria incidence and improve health outcomes where mosquitoes bite and rest indoors (and insecticide resistance is not a problem). IRS made a major contribution to malaria elimination from the United States, the former Soviet Union, several counties in Asia and the Caribbean and European countries, as well as reducing malaria burden in Asia and Latin America.[466] IRS is widely used, although in most endemic areas of Africa IRS has not been taken to scale since the earlier malaria eradication campaign. In those African countries that have implemented large, well-organised, well-funded and sustained IRS control programmes, advances have been made in malaria control.[467] Where malaria incidence was moderate or low and IRS was combined with other methods including effective drugs this has, in some cases, reduced malaria to a minor public health problem; for example in South Africa.[468] On the other hand, in hyper or holoendemic areas IRS can reduce malaria incidence but is (or was) insufficient to interrupt transmission, even when used with other methods. The most famous experiment on this was the Gharki project in Nigeria.[469]

Despite these widely accepted observations, relatively few recent studies have sought to quantify the epidemiological effects of IRS either alone, or in comparison or in combination with other newer malaria control strategies such as ITNs. To date, evidence linking IRS with improved health outcomes is largely limited to long-term observational data documenting the decline in malaria following large-scale programmes.[470]

A systematic review published in 2010 aimed to quantify the impact of IRS and compare the relative merits of IRS and ITNs.[471] Of 134 potentially relevant studies, just six met the criteria for inclusion in the review. Not all exclusion criteria were linked to the quality of study methodology and so not all excluded studies were methodologically poor (for example, 12 studies were excluded because they were reviews or conference abstracts and did not provide enough information for analysis). Even so, the authors stated that ‘the present review confirms the paucity of high-quality evidence in the comparative assessment of health impact. There are too few high-quality randomised controlled studies on the health effects of IRS and not enough geographical coverage’ (p18). The issue of geographical coverage is key; variables including local vector species, insecticide resistance, human behaviour, housing materials and patterns of living can all have an effect on the likely impact of IRS, and have changed, sometimes markedly, since the global eradication effort of the 1950s and 1960s. Assuming IRS will work in settings where it has not been tested, and in particular that it will work for local vectors when no trial has tested IRS with those vectors, is not justified.

The few studies included in the review confirmed that IRS worked in reducing malaria in unstable malaria settings, and limited data suggested that ITNs may be more effective than IRS in unstable areas. But the authors stress that:

- The current evidence is insufficient to quantify the effect of IRS in high transmission settings.
- At present, a quantitative epidemiological comparison between IRS and ITNs is not possible.
- No recent trial has investigated the effect of IRS in reducing child mortality

- There is insufficient epidemiological evidence to assess the effect of other determinants of impact, such as the insecticide used for IRS, the type of transmission, the dominant vector species and socio-cultural determinants.

It is important to note that this is not a judgement on the efficacy of IRS; the authors accept the broad conclusion that the effectiveness of IRS in reducing, or, in some settings, interrupting malaria transmission is beyond doubt. Rather, the lack of positive evidence from formal trials compared to large scale programmes points to a need for more high-quality long-duration trials. Without these, the specific contribution of IRS within multi-pronged malaria control programmes will remain unknown. Most of the best data on IRS comes from the eradication campaign, but since then a great deal has changed, both in study methodology, housing, socioeconomic factors, and in the use of ITNs and ACTs. In contrast, the relative cost of IRS compared with ITNs is better known and summarised in the economics Section of this paper.[472]

Compared to ITNs, IRS may make use of a wider range of insecticides with concomitant benefits for management of insecticide resistance and long-term sustainability of vector control.[473] Dichloro-Diphenyl-Trichloroethane (DDT) and pyrethroids are the current mainstay of IRS with pyrethroids now the predominant insecticide, but a range of organophosphates and carbamate can be used and potentially novel products such as fungal biopesticides – could be as well (see Section 5.1.3 Other vector control measures). Since IRS is less dependent on a single insecticide class, it is at lower risk of being rendered obsolete by pyrethroid resistance than ITNs.

In common with other malaria control interventions, the efficacy of IRS depends on context and local conditions. For example, IRS is less effective where people are exposed to transmission well away from sprayed buildings, or in areas where mosquitoes bite and rest outdoors.[474] Seasonality, house construction, housing density and geographic setting all have a potential impact on efficacy of IRS in addition to local vector populations. The practical issues with IRS should also not be underestimate; moving people and their possessions out every 6 months, coordination of large spray teams and maintaining support all present challenges.

5.1.3 Other vector control measures

Novel methods of delivering insecticides

ITNs/LLINs and IRS are not the only effective method of delivering insecticides. Insecticide-impregnated curtains have had a significant impact on malaria transmission.[475,476] Insecticide-treated wall-hangings are also being investigated and should be seen as an alternative to IRS if they prove effective. In both cases they may be more acceptable to end-users in certain groups, or for particular environments of house constructions. Novel methods of designing ITNs are also needed for particular sleeping arrangements or populations. Examples include ITNs designed for hammocks in Latin America or for forest worker and migrant populations in south-east Asia.[477]

In areas where the major vector species are zoophilic and bite animals as well as humans, applying insecticide to the surface of domestic animals can be an effective method of malaria control. For example, trials in south Asia showed that insecticide sponging or spraying of cattle has been shown to be cost-effective and decrease the incidence of falciparum malaria in certain environments.[478],[479]

A method which is still experimental is using fungal biopesticides, which are sprayed on walls and kill the mosquitoes by infection. Currently there is limited evidence that this is superior to (or equivalent to) conventional pesticides, but if widespread resistance to

pyrethroids occurs this technology may become relatively more important.[480] To be viable, this technology will need to be able reach acceptable commercial criteria for production, including cost and stability of formulation. This may prove a significant barrier to their potential future use.

In areas of complex emergency and where people sleep outside, insecticide-treated tents and tarpaulins for refugee camps and insecticide-treated top sheets or blankets have been demonstrated to be effective at reducing malaria.[481,482,483]

Larval control

Particularly in areas where malaria transmission is relatively low and mosquitoes breed in predictable areas, there are data, much of it from over 50 years ago, showing that larva control can have a substantial impact on malaria transmission, although this is likely only to be as an adjunct to other control measures. This is generally more relevant where important vectors have more selective breeding sites and has historically been used more in Asia, but it is being re-examined in Africa, especially for use in urban and peri-urban settings. Broadly speaking, larva control can be divided into engineering solutions, larvicides and use of larva-eating fish. Substantial entomological expertise is needed to use these methods as they require an understanding of local vector breeding habits.

All mosquitoes have a favoured water environment in which to lay their eggs. Some are highly selective. Where this is the case, altering the aquatic landscape can lead to substantial falls in malaria transmission, provided that vectors which prefer the new environment do not spread. An example from the UK was the draining of the fens in East Anglia and subsequently the Pontine Marshes near Rome, which at the time were both major malaria mosquito breeding grounds. Draining of these led to dramatic falls in malaria. Work in south-east Asia over 50 years ago showed that speeding up flow in the klongs or canals in some cities in Malaysia (then Malaya) led to substantial falls in malaria as local vectors required slow-flowing water. Examples such as this show that eliminating malaria through engineering has clear advantages; in the right environment it can be a permanent solution (although this is the case in a minority of settings).

The second method of larva control is to prevent access to the breeding site by covering it. This is only likely to be effective where local vectors breed in relatively small water sources, such as water tanks or latrines. This is generally more important for vectors of other diseases such as dengue and filariasis, although urban malaria transmission especially in India by *A. stephensi* may be helped by this.

The third method is to put a relatively non-toxic larvicide chemical into water where mosquitoes breed, or use microbial methods. This is most relevant for still, semi-permanent breeding sites where water cannot be easily covered or drained. There have been recent successes with this in peri-urban areas, for example one study (which has been criticised for its methodology) found a positive impact in Dar-es-Salaam.[484] A range of other larvicidal methods, from neem oil through engine oil through to polystyrene beads can work in specific environments, with varying efficacy, cost-effectiveness and environmental impacts.[485]

Finally, in some water environments draining, covering and putting chemicals on water sources is not practical. Examples might be rice paddies, wells or some rivers which are an important environment for some malaria vectors. Here, larvivorous fish such as *Gambusia affinis* fish can be used, although the data supporting the impact on malaria are not strong.[486,487] The evidence that this actually reduces malaria transmission in most settings is, however, non-existent. A systematic review of larvivorous fish for malaria control is due in early 2011.[488]

Combining insecticides, engineering and other larvicidal methods into *integrated vector control management* is effectively a new label for an established methodology developed in the 1950s, although some of the methods are novel.[489]

Common to all these methods is that they have to be tailored to the local environment and local vectors; generalisation is thus challenging. Where the expertise exists this is clearly preferable to a campaign which relies on a single tool, but it does depend on field entomological expertise which is now in (often very) short supply globally. To date these selective larva control measures have been more widely used in Asia than in Africa under operational conditions, partly because the impact is more obvious where the transmission is lower, and partly because the predominant vectors in Africa are less selective in breeding sites (e.g. breeding in hoof-prints), making targeting those sites less easy.

Building out malaria

Although not designed to reduce malaria, it should be noted that the building environment can have a significant effect on malaria over and above the effect on the water environment. With the exception of urban malaria due to *A. stephensi* in the Indian subcontinent, urban environments are generally hostile to malaria vectors, combining limited breeding sites with pollution. In many countries in south-east Asia, urban malaria transmission effectively does not occur at all (depending on local vectors) and is almost invariably much lower than in the surrounding countryside. There is some evidence of vectors adapting to increased pollution.[490] Even in rural areas, however, building design will have an effect and improvements in housing stock will reduce malaria transmission. Corrugated iron rather than thatch, plastered walls rather than earthen walls, and screened windows and doors are all associated with less malaria; whether this is because they make houses more hostile to mosquito vectors, because of associated socioeconomic factors or both is not clear.[491,492]

A recent randomised controlled study showed that in a setting where insecticide-treated bednets were infrequently used, full screening of windows, doors and closed eaves and screened ceilings reduced indoor exposure to *A. gambiae* and reduced the frequency of anaemia in children living in the screened houses. However, frequency of parasitaemia did not differ between intervention and control groups.[493]

Space spraying and insecticide coils

Insecticide coils are widely used even in poorer households. They probably do have a modest effect on malaria transmission, but in most of Africa where transmission occurs late in the evening this is relatively modest compared to LLINs and is therefore not cost-effective.[494] Despite this, families who cannot raise the capital for LLINs often spend more than the cost of a LLIN over the year on coils and similar methods probably because they are non-capital items and require smaller outlays of cash at one particular time.[495] In areas such as parts of Latin America where peak biting is early in the evening the relative impact is much greater and they may have a place although there are relatively few studies.[496]

Novel methods – genetically modified mosquitoes and so on

A number of novel vector control methods have been developed over the years and some remain in use. It is likely that some will have a role in niche environments. Some of the currently discussed methods include:

Early experimental methods

Bed nets which kill mosquitoes because their surface design disrupts cuticles and dehydrates the mosquito which lands on them are being developed, so they will work even

with insecticide-resistant mosquitoes. Another approach is lasers which shoot down mosquitoes.[497] These are interesting technologies, a long way away from deployment; their place in malaria control is far from clear.

Mosquitoes selectively bred or genetically modified to be resistant to malaria[498]

These exist and have done for more than three decades,[499] although new ones are being developed. The science behind this is exciting and frequently appears in the media. The key practical question is: will any of them have a sufficient survival advantage that their genes will spread through the massive wild mosquito population and displace malaria-prone mosquitoes? The mosquitoes that could be released would have to be linked to drive mechanisms that should allow a selective sweep of the gene(s) of interest through the field population. Most people who have examined this think the evidence this is likely, at least not in a realistic timeframe is limited; the survival disadvantage to mosquitoes being infected with malaria is limited and in any case most wild-type mosquitoes do not get infected with malaria so they have no survival disadvantage.

Sterile male mosquitoes

This technology has worked for eliminating some insect pests such as screwworm and has been considered for malaria for over half a century.[500,501] The principle is relatively simple; if females predominantly mate with sterile males (generated by irradiation) mosquitoes will die out. The key to this technology working is releasing sufficient numbers of sterile males that they overwhelm the fertile ones. It is possible this has a role in, for example, urban malaria transmitted by a single species, or on small islands. The agricultural success stories with sterile male insects mostly come from islands, peninsulae and isthmuses. The aim is to eliminate the mosquitoes completely. Current evidence that it is practical on a larger scale is lacking although it can be deployed on a small scale,[502] and there is no current clear indication for the technology.

Giving adults oral, injectable or wearable insecticides

Drugs taken by humans which kill mosquitoes which bite them exist; ivermectin is widely used and effective against malaria vectors.[503] It may be relevant to investigate human-based insecticides in limited settings where specific groups acquire malaria outside (making IRS and LLINs irrelevant) such as forest workers in south-east Asia or gem miners in Latin America. A more conventional approach for these groups would be insecticide-treated clothes, which have been used for many years by military groups and travellers although their efficacy is probably not great.[504]

5.2 Case management: diagnosis and treatment

5.2.1 Treatment of malaria

One pillar of malaria control is prevention, largely through anti-mosquito measures. The other is treating people for malaria so that deaths do not occur. In low transmission settings, early diagnosis and treatment additionally has a significant impact on malaria transmission.[505] In high transmission settings, the impact of early diagnosis and treatment of symptomatic individuals on transmission is limited since much of the burden of infectiousness is in adults who are not symptomatic.[506]

In all settings, the early diagnosis and treatment of malaria saves lives. Diagnosed early, and treated with effective drugs, there is clear evidence that virtually all children and adults with malaria will recover, and in high-income countries where deaths rarely occur in otherwise well children with malaria because they are identified early.[507] We have effective tools for

diagnosing malaria, and currently drugs capable of treating non-severe malaria in all parts of the world. The technology for diagnosing malaria, already good at least for falciparum malaria, will stay the same or probably get better. This cannot be assumed with drugs for malaria since, over time, resistance to antimalarials always emerges, so a continuous pipeline of new antimalarial drugs is likely to be needed for as long as malaria is a significant problem. At present, however, we have a number of drugs which are currently effective. Lack of technologies which work is therefore not the reason those with malaria are dying at present.

In an idealised model, the child or adult is recognised as being ill early and well before malaria becomes severe, taken to healthcare, receives a reliable diagnostic test, a positive test in acted on by prescribing an effective antimalarial, which the patient is given or can afford, and which is taken at an effective dose for the correct period of time. This is however not the experience of many with malaria, and in those who die of malaria almost always one or more of these steps will not have occurred as it should.

5.2.2 Technologies for identifying cases of malaria

Diagnostic tests for malaria

The diagnosis of malaria depends on proving that a child or adult with fever or other symptoms of malaria carries malaria parasites. The WHO has recently moved over to advocating a proven (parasitological) diagnosis in all cases of suspected malaria prior to the administration of antimalarial treatment.[508] This approach is backed by strong evidence that diagnosing people with malaria purely on the basis of symptoms is ineffective since it both misses cases of true malaria and wrongly identifies people who have fevers due to other causes.[509,510,511] Diagnosing malaria accurately is as important for those who have malaria as it is for those who do not. Those of a syndrome suggestive of malaria will generally have other infections, many of which are potentially serious but treatable with antibiotics.[512,513,514] There are now technologies that can be used in almost any setting to diagnose clinical malaria in febrile patients: these are outlined below, along with evidence of their use in practise.

In summary, the technologies are available but their impact is limited by inappropriate use in the public sector, poor quality control in many settings and limited incentives for proper use in the private sector.

Microscopy

Light microscopy for the detection of malaria parasites remains the gold-standard for diagnosis of malaria and initiation of antimalarial treatment more than a century after it was first used. In expert hands, properly quality controlled, with a high-quality microscope, reliable supplies of slides and stains, good training and supervision of staff, uninterrupted electricity and sufficient time to examine slides, malaria microscopy is very sensitive (it identifies almost all cases of clinical malaria) and very specific (if it says it is malaria, it is malaria, rather than a false-positive). It is able to diagnose all the species of human malaria. At high through-puts (as found in hospitals) it is highly cost-effective compared with other mechanisms.[515]

Microscopy has a number of limitations when used in low-income countries where malaria is endemic. These include the fact that training and supervision of staff is often poor, electricity erratic, microscopes and supplies often of low quality or poorly maintained, and sufficient time to examine slides properly is seldom available; whilst improvements are possible they need constant work to be maintained.[516,517,518] For this reason, the operational sensitivity

and specificity of microscopy is far below that which is in theory possible and achieved in industrialised, low-endemic countries.[519]

Newer technologies based on Rapid Diagnostic Tests (RDT) (see below) are likely to supplant microscopy in some areas but supporting improvements in microscopy have a number of clear advantages where the through-put is high. The first is cost. The cost-effectiveness of microscopy is substantially higher when there is a high through-put compared with RDTs. Secondly, microscopy is not only used for malaria diagnosis but also for diagnosis of tuberculosis, other parasitic diseases such as schistosomiasis and worms and blood disorders. Improving microscopy, training, quality control and equipment in the right settings therefore has the potential to improve health services both for malaria and for other diseases.[520] It is seldom appropriate for low-volume settings or peripheral settings without electricity or trained staff at least in Africa, although it has been used successfully in these settings in some countries in Asia, for example Thailand.[521]

Rapid diagnostic tests

RDTs have matured rapidly over the last ten years. Like microscopy, they involve a finger-prick to obtain a blood sample. The results of single species RDTs look similar to a pregnancy test; a single line is a control line, a second line is positive for malaria, and in tests which are not falciparum specific there is a third line for vivax malaria and other species. There are three broad technological groups, of which two form the basis for the most commercially available RDTs: HRP and LDH.

RDTs have a number of advantages over microscopy. They are light and portable, making them ideal for use in peripheral settings. They can be used with very limited training.[522] If kept in good conditions, they are as sensitive and specific as light microscopy, at least for falciparum malaria.[523] Results are available rapidly and visible both to healthcare providers and patients. However, compared with microscopy, they also have limitations. For microscopy, the primary cost is the capital of getting the microscope, plus the costs of training and maintaining the skills of personnel- although in practice the ongoing training quality control is often not there making microscopy unreliable. For RDTs, each test costs between $0.60 and $2 (depending on test and market). Additionally, they have some technical limitations. Many commercially available tests are not stable in hot climates, although this is improving, and their sensitivity can decline rapidly if exposed to the kind of temperatures which are routine in transport in Africa and Asia.[524] Whilst all high quality tests are capable of detecting falciparum malaria only the more expensive tests are capable of detecting other species, making their use in Asia and Latin America, in particular, more expensive.[525] There is a wide variation in quality between different manufacturers, with the less good ones being very poor indeed and missing many cases of true malaria.[526] WHO has an on-going programme of quality assurance for tests and it is essential that if tests are bought it is from the WHO list of recommended tests.[527]

Diagnostic tests and elimination of malaria.

One important technical point is that they are designed to identify clinical malaria which may cause illness in the individual. Low rates of asymptomatic carriage are not always identified by existing clinical methods, and for elimination of malaria (where these people could be a reservoir) this may be a technical limitation that needs to be overcome.

5.2.3. Applying technology: evidence of what works

Impact of tests on operational practise: formal healthcare settings

There is good evidence that simply deploying tests without a significant training package and ongoing support has limited impact on prescribing practise. Several studies demonstrate that over 50% of those with a negative test will still be given an antimalarial in randomised trials, even where a training package has been provided.[528,529] In low-transmission settings, over 90% of those who have a diagnostic test, whether microscopy or RDT, have a negative test and yet frequently the doctor still prescribes an antimalarial.[530] Other studies, largely made in the context of countries where malaria incidence is decreasing, have succeeded in getting test results adhered to so that clinicians are guided by test results.[531,532,533] What is clear is that purchasing and deploying RDTs without also addressing major changes to clinical behaviour is unlikely to have more than limited impact and is not effective or cost-effective (and the cost-effectiveness of RDTs is a complex issue),[534,535] Therefore, if diagnosis is to be addressed, diagnostic practise (of which providing effective diagnostic tests is only a part) must be addressed as a whole rather than simply assuming that purchasing tests will solve the problem of mis-diagnosis and over-diagnosis of malaria. To date, there is only limited evidence that this can be achieved in East Africa although the evidence is now accumulating.[536] Evidence from West Africa is limited. There is virtually no evidence from south and central Asia, although what evidence that does exist, to date, suggests that, as in Africa, malaria is over-diagnosed as well as under-diagnosed, and that test results are often ignored.[537] In south East Asia, notably Thailand, there has been much more success in ensuring that all diagnosis is based on parasitological diagnosis.

Evidence of impact of tests: peripheral settings

Where microscopy has not routinely been available in peripheral settings, the tendency of clinicians to ignore tests will not be as deeply ingrained and it may be that in such areas RDTs have a greater chance of success.[538] To date there is only limited evidence outside the formal healthcare sector of the impact of RDTs as few studies have been conducted. There seems to be greater impact in the community where microscopy has not been used and this can be linked with improvements in other treatments; less senior staff may also be more amenable to changes in practice.[539,540] It does not lead to patients with malaria not being treated for malaria. In Asia, there is almost no data on the use of tests outside the formal healthcare sector. This is a significant evidence gap.

Use of rapid diagnostic tests in the private sector

In many parts of Africa and Asia, the private sector (shops) provides most care for non-severe malaria. The impact of using RDTs (microscopy is generally not practical in this setting) is unknown as very few studies have been undertaken. It is possible to get private shop-keepers to change prescribing practise – at least in some settings.[541] The difficulty with private sector settings is providing an incentive economically for either providers or customers to purchase a test in addition to the drug they wish to purchase. There is very little published evidence on this from anywhere in the world. There are potential risks to providing tests in the private sector, including the possibility that cheaper but poor quality tests are used (which will give an inaccurate result), and the dangers of untrained personnel taking blood from multiple people where blood-borne viruses such as Hepatitis and HIV are common. Given the uncertainty on the likely outcome of deploying RDTs in the private sector it would be sensible only to do this within the context of operational research.

Why aren't patients who have malaria diagnosed with malaria; would more RDTs help?

Evidence from throughout Africa shows that where patients present to the formal healthcare sector, the chances of their being identified as potentially having malaria are currently very high and where diagnostic tests are available anyone with a positive test will be treated as having malaria.[542,543] This does not necessarily translate into being treated with an effective antimalarial.[544,545] In Africa, therefore, the major barrier to patients with malaria not being

diagnosed is that they do not present to formal healthcare in the first place. The provision of diagnostic tests has the potential to have a major impact on reducing the amount of unnecessary prescription of antimalarials and in identifying patients who do not have malaria and need alternative treatment.[546] Diagnostic tests in the formal healthcare sector Africa should not therefore be deployed mainly as a means of increasing the number of people who have malaria who are identified, since there is no current evidence that this actually occurs. As malaria incidence falls however, the assumption by clinicians that everyone with a fever has malaria until proved otherwise may change, in which case diagnostic tests may become more important in identifying cases of malaria which otherwise would have been missed. This is difficult to predict, however; the decisions to test and treat for malaria are complex and not always based on clinical logic.[547,548,549] In Asia, where incidence of malaria is generally much lower, evidence remains sparse but it is likely that diagnostic tests help to identify people with malaria who otherwise would have been missed.

In addition to the need for diagnostic tests to identify and treat cases of malaria, they are needed for surveillance, and to test the impact of control measures on malaria incidence.

5.2.4 Drugs for malaria

There are many drugs which can cure falciparum malaria parasites where there is no drug resistance. There is, however, resistance to most of the older, cheaper drugs used to treat falciparum malaria which varies in prevalence by geographical location. This evidence paper, which is not designed to guide clinical practice, will only treat this important and rapidly changing topic briefly to outline principles, and readers wanting a more thorough review relevant to guide clinical practice should consult the *WHO Malaria Treatment Guidelines*.[550] There is *P. falciparum* resistance to some drug classes, for example the four-aminoquinolone chloroquine which used to be the mainstay of treatment, which are so widespread that the drugs is essentially useless against falciparum malaria. When its use is stopped for long periods prevalence of resistance to chloroquine falls, but would probably rebound if it were reintroduced.[551] Some older antimalarials remain moderately effective if used as monotherapy in parts of the world, particularly in West Africa, and may still have some use in combination with other drugs. Following WHO advice, national drug policies throughout the world, including all countries of interest to DFID, recommend combination treatment with at least two effective drugs.[552] Most of these combinations are currently in the Artemisinin-based Combination Therapy (ACT) class of drugs. There is strong evidence for this advice including that obtained from many large clinical trials over many years and well conducted systematic reviews.[553] Most non-falciparum malaria (especially vivax malaria) remains sensitive to most antimalarial drugs, including chloroquine for treatment but there are particular issues with drugs for vivax to prevent relapse of the disease (see below).

5.2.5 Patterns of drug resistance

Evidence of drug resistance comes primarily from clinical trials and has recently been summarised in a review by WHO's Global Malaria Programme.[554] Individual country policies should be guided by the most recent locally conducted trials since drug resistance can spread rapidly. There are also quite marked difference in drug resistance patterns occasionally within and often between countries with the same combination being effective in one and not another neighbouring country[555]. In broad terms, however, drug resistance patterns for falciparum malaria are similar within four geographical areas.

1. *South-east Asia*. There is clear trial evidence that monotherapy with any of the widely available drug classes has a high rate of failure.[556] This includes mefloquine, sulphadoxine-pyrimethamine (two drugs, but given similar mechanisms of action, they generally considered a monotherapy), chloroquine and amodiaquine, halofantrine, and quinine (evidence of slower cure suggesting some parasite

resistance). For oral treatment of non-severe malaria, some of the Artemisinin Combination Therapy (ACT) drugs, particularly dihydoartemisinin-piperaquine (artequine) are recommenced and still have evidence of good activity. There is however good early evidence of tolerance (essentially resistance) to the Artemisinin class of drugs in western Cambodia with delayed clearance of parasites when ACTs are used and with an increased proportion of failures when Artemisinin are used alone (reviewed more fully in Section 6, Artemisinin drug resistance).[557] Currently although there is early resistance to artemisinins used alone there is however a good clinical cure rate with locally recommended ACT combinations. If significant resistance artemisinins, and hence to ACTs, was to emerge and spread in south-east Asia, this would be a serious problem. Historically drug resistance, including resistance to chloroquine and sulphadoxine pyrimethamine, appears to have emerged in south-east Asia and then spread through Asia to Africa and Latin America[558]. It is currently uncertain (because of a lack of reliable studies, especially in Burma) how far artemisinin tolerance has spread, and this has operational significance. If it is confined to the area where it was first identified, Pailin in Cambodia, containment is realistic. If it has spread more widely, especially into Burma, different policies will need to be adopted. Currently getting good data from across Burma is not easy. A global plan on artemisinin resistance containment (GPARC) which is due out in January 2011. The only non-ACT co-formulated oral combination which currently works in south-east Asia, atovaquone-proguanil (Malarone), is currently too expensive for wide-scale use. It is anticipated that, if it were widely deployed, resistance to this drug will emerge relatively quickly as it takes only one mutation to confer significant resistance.[559]

2. East Africa/southern Africa. In East Africa there is now widespread resistance to all the widely used older mono-therapies, including sulphadoxine-pyrimethamine (Fansidar, SP), amodiaquine, and chloroquine.[560] There is currently no evidence of resistance to artemisinin drugs or to quinine. Various ACT combinations have been demonstrated to be clinically active and in particular artemether-lumefantrine (Coartem) and dihydorartemisinin-piperaquine (Artekin).[561,562] The problem in East Africa is not so much that there are no effective drugs, but rather that the effective drugs are substantially more expensive than relatively ineffective monotherapy. This issue of the cost of effective antimalarials is a significant problem operationally – see below.

3. West Africa/Central Africa. There was a slower rate of development of resistance to monotherapy with sulphadoxine pyrimethamine (Fansidar, SP) and amodiaquine than in East Africa but clinically relevant resistance is now present both to the drugs used alone and to their use in combination.[563] There is, however, still some evidence of activity for the combination of non-artemisinin drugs for certain uses such as intermittent preventive treatment in pregnancy[564]. There is no current evidence of resistance to Artemisinin, or to ACT combinations that do not use sulphadoxine pyrimethamine or amodiaquine, or to quinine.

4. Rest of the world, including south/central Asia, Middle East, Latin America. Information on resistance patterns is not easy to generalise. Except where there is clear evidence to the contrary, it should be assumed, however, that all falciparum malaria is resistant to monotherapy with older non-artemisinin drugs. It should also however be assumed, in the absence of evidence to the contrary, that quinine and the ACT class of drugs will be effective.

5.2.6 Drugs for vivax malaria and other non-falciparum malarias

Clinical vivax malaria (the ring forms in the blood causing clinical disease) remains sensitive to almost all antimalarial drug classes including chloroquine, which remains the drug of choice to treat clinical attacks of vivax malaria except in parts of Oceania and Indonesia.[565] Several other drugs, including ACTs, are also effective, but generally cost significantly more with no advantage in treatment or reduction in transmission.[566,567] The major problem for treating vivax malaria is preventing relapse, caused by the hypnozoite forms of malaria which are laid down in the liver in the initial infection and which are not killed by chloroquine or the ACTs. Currently the only licensed drug that can do this is primaquine which has to be used in increasingly high doses and for longer have effect, suggesting some degree of tolerance. This should be caveated with the fact that determining resistance in vivax malaria is more complex than for falciparum malaria.[568]

Of more widespread importance, primaquine and its probable successor tafenoquine (still under development), can cause significant haemolysis in subjects with the common genetic abnormality G6PD deficiency.[569] This is more common in countries where malaria is common (5-20% prevalence). Since rapid testing for G6PD deficiency is not currently available in most viva-endemic countries,[570,571] for practical purposes there is no drug to prevent relapses of recurrent malaria that can safely be deployed in the field. Getting a safer drug or a rapid test for G6PD deficiency are likely to be needed if vivax malaria is to be effectively controlled.

5.2.7 Drugs for use in pregnancy

Pregnancy and malaria are a dangerous combination for both the mother and her unborn child. Women who are symptomatic with malaria therefore need to be given an antimalarial which is rapidly effective. There is a small theoretical risks of teratogenicity (damage to the foetus) when ACTs are used in early pregnancy but this risk has to be set against the real and significant risks of under-treating women with malaria in pregnancy with an ineffective drug. There is no good trial evidence of tertatogenicity of any antimalarial drugs, although there are theoretical or animal-based data that raise concerns about antifolate and artemisinin drugs in the first trimester of pregnancy.[572,573,574,575,576] In practice both antifolates and artemisinin have been used widely in pregnancy, and have not raised concerns, although active surveillance for adverse effects has not been widely undertaken. In the second and third trimester, artemisinin-based drugs (ACTs and artesunate in severe malaria) are definitely preferred because of their rapid action.[577] The risk of Artemisinin in the first trimester of pregnancy is not a reason to not give them to women with malaria on current evidence. It does make it important that women who do *not* have malaria are not given artemisinin in early pregnancy, in line with current WHO recommendations; this is an additional reason for better test-based diagnosis of malaria in women of child-bearing age to minimise the risk that non-malarial febrile illness is treated with an artemisinin drug in early pregnancy, which will do her no good and has the potential to do the foetus harm.

5.2.8 Severe malaria

Only two drugs are recommended for use in severe malaria; artesunate and quinine. There is some evidence of partial resistance to quinine in south-east Asia. There is no evidence of resistance to artesunate except in a very limited area of south-east Asia. In both children and adults, artesunate should be used as it has been shown conclusively to be more effective than quinine[578]. A recent randomised trial in nine African countries compared artesunate with quinine in children with severe malaria[579]. The artesunate group had significantly less mortality, and fewer incidences of coma and convulsions. When combined with meta-analysis of all trials comparing artesunate and quinine, the study reasonably concluded that there is strong evidence that parenteral artesunate should replace quinine as the treatment of choice for severe falciparum malaria worldwide.

Currently artesunate is not widely available outside Asia, and whilst efforts to increase availability are underway where quinine remains the only alternative it is still an effective drug. There are rectal antimalarial formulations which work in clinical trials and in principle could be used in the periphery, potentially by community health workers.[580,581,582] The evidence around whether this can be safely deployed in the periphery without some carers not taking severely ill children (who may not have malaria) to hospital or delaying their care is still lacking however- see below.[583] In all cases there is good evidence that initial artemisinin therapy should be followed up with a complete course of ACTs.

5.2.9 Need for new drugs and drug classes

When drugs are widely used against malaria, resistance has often developed within a matter of years to two decades, and then spread within a decade. There exceptions to this however, quinine being the most important; the oldest antimalarial, it still has only limited resistance in southeast Asia and no good evidence of resistance elsewhere. In general however it should be assumed that resistance will both arise and spread to any new drug, and strategies such as combination therapy (proven) and rotating drugs (speculative) can slow this, but not stop it.[584] It should therefore be assumed based on past evidence that resistance to all new antimalarials will emerge over time and a continuous pipeline of new drugs against falciparum malaria will be needed. It takes upwards of ten years to get a promising drug entity to registration, and many promising drugs fail at late stages of development, either because they do work as well as initially expected or because new side effects are found in large scale phase three trials or during Phase 4 post-marketing studies. A recent example of this is chlorproguanil-dapsone (Lapdap), a cheap and effective antimalarial drug which got as far as registration and extensive field testing before safety problems emerged that led to its withdrawal from the market (always easier to spot with the benefit of hindsight)[585]. Because of this long lead-time and the relatively rapid spread of malaria drug resistance when it emerges there is therefore good indirect evidence that investment in antimalarial drugs for falciparum malaria is needed in advance of losing drug classes to drug resistance. Ideally, new drugs should be new classes of drugs using different mechanisms of action making cross resistance less likely.

For vivax malaria, the main challenge is finding better and safer drugs for preventing relapse of the disease which do not have the safety problems associated with G6PD deficiency which limit the use of current drugs (see Section 2.2.3 *Plasmodium vivax*: additional reasons to be cautious).[586,587,588]

Whilst it is tempting to hope that developing new drugs for malaria could be left to the private sector, the evidence from the period 1970–2000 is that almost no new drugs for treating malaria suitable for use in developing countries were developed by the private sector alone. Drugs for prevention of malaria were developed, probably because of the travel and military markets. Public-private collaborations have, however, proved very productive, whether through government-funded institutions (e.g. the artemisinin class in China), military medicine, or public-private consortia such as the Medicines for Malaria Venture (MMV), the Institute for OneWorld Health and the Drugs for Neglected Diseases initiative.[589,590] Almost all currently used antimalarials for treatment have been developed in part through private-public collaborations.

5.3 Applying technology: evidence of what works

5.3.1 Getting effective drugs to people who need them

Currently in many parts of the world a significant proportion, and probably most of those who have malaria, are not treated or are treated with ineffective drugs; at the same time, many people who are given antimalarial drugs do not have malaria. The solution to the over-

treatment of non-malarial illness with antimalarial drugs is better targeting, which generally will mean better diagnosis (see Section 5.2 Case management: diagnosis and treatment). The reason people who have malaria are not treated is complex, and research evidence demonstrates that there are many stages along the pathway between a patient becoming unwell with malaria, and receiving treatment with an effective antimalarial which can cause problems. One general point about all the interventions discussed below is that increasing access can bring its own problems of over-use of services and stock-out of drugs which neutralise the positive effects unless they are anticipated and planned for.[591]

Failure to seek care of any kind, or to seek it too late

In many settings, children and adults who have symptoms or signs of malaria seek no care of any kind[592,593,594,595,596] and do not receive antimalarials. Solutions to this largely revolve around awareness campaigns, including education in schools, posters and other systems. Relatively little recent research has investigated robustly which of these are most effective at reaching those who currently are not seeking care and changing behaviour, and those that have examined this issue do not consistently show an association between care seeing and knowledge of malaria.[597] Linked to this is a failure to seek care early enough to prevent adverse outcomes. Children and adults who do come to formal healthcare, but delay their visit until the patient has severe malaria have an appreciable mortality even when correctly treated; between three and ten% mortality is typically quoted.[598,599] This should be close to 0% if correct treatment was started when malaria is still mild, as shown by multiple trials of drugs in non-severe malaria.

Physical access to antimalarials: distance from healthcare

Patients or parents may wish to seek care but be unable to do so due to physical barriers to access. There is clear evidence that distance from healthcare is associated with less care seeing and poorer outlook from malaria in many settings.[600,601,602,603] The interactions between distance and healthcare seeking are complex, however, and it cannot simply be assumed that getting healthcare closer to people will increase utilisation.[604]

Solutions which have been tested vary and have to be tailored to local settings. They include:

1. Community health-workers trained to manage malaria and other diseases. These are widely used in countries in Africa and some parts of Asia. Evidence that they are effective is broadly encouraging, where adequate training, supply of drugs and supervision can be maintained, but this is not a light undertaking. The Integrated Management of Childhood Illness (IMCI) initiative contains a community-based component which, though not widely deployed, has been evaluated. In both Africa and Asia there is evidence that IMCI can improve prescribing practice in health facilities and the community component improved access to health workers in Asia. However, evidence that it reduces mortality is not strong.[605,606] Community-based systems of care have to be tailored to local situations; it cannot be assumed that a system which works in one setting will work in others (or vice versa). Evidence from many community-based health systems (not just malaria) demonstrates that maintaining support is as difficult as setting up the delivery system. Community workers need to be recruited, managed and supervised, supplied with commodities and report reliable information into the health systems.

2. Home based delivery of care. This term or the related one of Home Management of Malaria are used to describe the situation in which antimalarial drugs are deployed in the community and treatment for fevers is given by relatively inexperienced carers who are easily accessed by a patient. In some situations mothers have been used

but more usually the carer is a person living in the community chosen for this role and given some training, but less than community health workers, and generally they only provide antimalarials.[607] Home based management of fever/home based care has been shown to work in some settings, particularly rural settings where malaria is common.[608,609,610] In areas where malaria transmission is lower or in urban settings where physical access to care is less of a problem, evidence of their effect is much less strong and is unlikely to be cost-effective where incidence of malaria is low or access to treatment is relatively easy; on the other hand in high-transmission rural areas it is potentially both effective and scalable.[611,612,613]

3. Improving transport in rural areas. Improving transport links between centres with health facilities and peripheral areas makes logical sense, and distance from healthcare and time taken to travel are risk factors for progression of disease. There is, however, no convincing evidence either way about whether providing roads to existing health facilities improves outcome. Wherever road-building/improving programmes are occurring in malaria-endemic countries opportunities should be sought to test this. In a few settings (eg the Amazon) road building has actually facilitated the spread of malaria but this will generally be exceptional.

Patients or carers seek care but from the private or informal sector

The proportion of patients with symptoms suggestive of malaria who seek help from the informal private sector (generally meaning shops, drug-sellers or traditional healers) varies between countries and settings. In most countries in Africa it is the majority– typically 60%, but in some countries higher.[614,615] This is especially true in rural areas.[616] There are however exceptions to this including South Africa, The Gambia and Senegal where the majority of care is in the public sector. Evidence from Asia is even more mixed, but the informal private sector is often the major provider of healthcare to the poorest in countries where DFID works.[617,618] Here they may be given either no antimalarials or old antimalarials which are likely to fail due to drug resistance.

Possible reasons for this include:

1. Private or traditional clinicians do not consider a diagnosis of malaria.
2. They consider it and prescribe a treatment with no efficacy because they do not know that the drugs now have limited efficacy. There is relatively little research on training of private shops and traditional healers but the research that does exist is relatively encouraging suggesting that this can lead to better prescribing practises[619] and that it can be maintained.[620]
3. That private providers consider malaria and prescribe an antimalarial but patients cannot afford or are unwilling to pay for the more expensive but more effective combination treatments. There is relatively limited evidence on willingness to pay but what exists suggests that most patients are unwilling to pay the market price for ACT drugs.[621] The cost of drugs is frequently cited as a reason for delaying care, buying ineffective drugs or buying no drugs.[622] There are broadly two solutions to this problem which are not mutually exclusive:

   - Make it easier for patients to access the public health sector.
   - Subsidise effective antimalarials so that the private sector prescribes these rather than ineffective monotherapy.

There are currently no convincing studies, however, which compare these two approaches side-by-side.

Relatively few studies have investigated whether efforts to improve the public sector lead to an improvement in malaria outcomes through diverting patients from using private shops towards the public sector, although since reasons for treatment seeking patterns are complex the probability of any single intervention having a significant impact is low.[623] There is limited evidence that increasing the quality of public healthcare does lead to diversion of patients to that, but this is very limited. The limited evidence that exists that diverting patients to the public sector actually improves outcome overall is mixed. For example, the provision of free healthcare in one study led to a change in utilisation patterns but not to a change in malaria outcomes.[624] Improving healthcare in the formal sector and improving access to it are clearly highly desirable in their own right, there is no evidence currently that doing this will mean poorer patients do not access ineffective antimalarials through shops – but this is absence of evidence rather than evidence it does not work.

The evidence that the cost of drugs is a barrier to people buying effective drugs is clear cut (see Section 2.3.2 Burden on the wider economy and Section 3.2 Household and community levels). It is unlikely, even with open competition between several effective drugs, that purely through market mechanisms ACT drugs will fall in price to the extent that this problem disappears in Africa. This makes subsidy of some form currently the only realistic solution to ensuring that drugs sold through the private sector are the effective newer ones. The evidence for the need for this is summarised in the All Party Parliamentary Group report on the need for a subsidy, and the Institute of Medicine report on the same subject.[625,626] The Affordable Facilities for Medicines-malaria (AMFm) was set up in the light of this evidence. What is not known currently is:

1. The extent to which providing subsidised drugs into the private sector will lead to lower cost of drugs. Some initial studies, especially those conducted in Tanzania by the Clinton Foundation, are encouraging in that at least in some settings the subsidised cost of drugs can be made to 'stick' as the drugs move from central procurement into shops, and that this leads to better uptake of effective antimalarials, especially in rural areas.[627,628] Whether this will be true in other markets, which have very different structures, remains to be seen. The AMFm is potentially a major public health experiment which could be used to provide answers to this important question; it is important that evidence is collected rigorously as part of the AMFm.
2. What effect this will have on malaria mortality. For reasons outlined in Section 5.2 Case management, access to effective antimalarial drugs is necessary, but not sufficient to ensure that the right people to get them. Integrating cheap effective drugs with better targeting will be essential if AMFm and similar ventures are to reach their potential.
3. What the impact will be on the slowing of drug resistance. Part of the rationale for the AMFm is to reduce use of monotherapy and so slow spread of resistance, but evidence for this is weak. It will however not be easy to test.
4. Whether, and if so how, to deploy rapid diagnostic tests with AMFm.

Patients or their guardians seek care from the public sector, but are not diagnosed with malaria, or are given inferior or poor-quality drugs.

In Africa, evidence from across the continent suggests that the roughly 30% of patients with malaria who reach formal healthcare are very likely to be diagnosed as malaria and treated with antimalarials, often without testing. Evidence that there is substantial under-diagnosis of malaria in the formal healthcare setting is very limited; the problem is mainly the other way round. This may change as malaria decreases in some countries to levels where it becomes uncommon, but so far there is no evidence of this. Clinical behaviour is often slow to respond to changed circumstances, and studies suggest that currently clinicians pay relatively little notice to the epidemiology of malaria locally.[629] There is, however, evidence

from some countries where malaria incidence has dropped markedly that this has been followed by an improvement in targeting and many of the studies which have shown a positive impact of diagnostic tests on prescribing have been in areas where malaria incidence is low or falling; whether this is cause-and-effect, or due to the malaria control activities which led to the fall is not clear.

If malaria is diagnosed, evidence as to whether new, effective drugs or ineffective drugs will be prescribed is mixed. Certainly there is evidence that in most African countries where ACTs are the recommended first-line treatment for malaria, and available free or heavily subsidised in the private sector older, less effective drugs continue to be prescribed by some clinicians in the public sector. Evidence on reasons for this vary, and there is some evidence that clinicians are more likely to give effective antimalarials to those with test-positive malaria, although this is not universal.[630,631] Widespread availability of subsidised ACTs meaning clinicians do not feel they have to reserve ACTs for special cases seems to make this less of a problem- for example there seems to have been an improvement in Zambia where initially many patients with possible malaria were not given ACTs; now this is rare.

Patients with malaria or their guardians are correctly given or buy locally effective antimalarial drugs, but do not take the complete course.

There is usually a difference between the efficacy of a drug (the best it can achieve in trials) and its effectiveness (how it performs in real life, operational conditions); in some cases effectiveness can be substantially lower than efficacy.[632] In part this is because people do not take drugs as prescribed, either because they do not know how to, or because affordability problems lead to incomplete courses being bought or taken, or because they stop courses when they feel better, but before the parasites have gone.[633] Whilst there is undoubtedly some fall-off in effectiveness for ACTs, there is no good evidence this is a major problem. Probably packaging of drugs has a significant impact; the packaging for co-artem was for example very well tested prior to deployment.[634,635,636,637,638]

Patients with malaria (or their guardians) are correctly given antimalarial drugs or buy them locally, take the complete course only to find the drugs are fake or substandard.

Patients of guardians may buy a drug in good faith, and take it, but fail treatment because the drug is fake or substandard. The basis of these two is very different.

Fake drugs have become a major problem since more expensive drugs began to be used for malaria treatment; the margins on faking drugs such as chloroquine where a course costs $0.15, are so small they probably protected them. In contrast, in parts of south-east Asia up to 80% of some Artemisinin drugs have been found to be fakes.[639] These fakes are very sophisticated, with convincing packaging including fake holograms and their production involving major criminal conspiracy.[640] There is now clear evidence that fake drugs are penetrating the African market, although the extent of this is currently unknown.[641,642,643] Fake drugs have the capacity to undermine confidence in antimalarial drugs with significant implications at the community level, on top of the potentially catastrophic effects for individuals. Vigorous law enforcement led by Interpol has led to some arrests. In reality, however, given the difficulties of detecting fake drugs, the complexity of legal disputes where drugs often cross several boarders, and the relatively limited technical resources in most malaria-endemic countries it is unrealistic to expect law enforcement alone to solve this problem. Wherever there is a gap between people's willingness to pay and market value the potential for profits from fakes exists, so only reduction in the price of real drugs to end-users is likely to solve this problem.

Sub-standard drugs are generally perfectly legitimate, but made without sufficient regard to good manufacturing practice (GMP) and are common in Africa and Asia. Drugs may contain

too little or too much ingredients, or be too tightly compressed (thus failing to dissolve appropriately after taking, reducing appropriate absorption of the drug).[644] The solutions to this are tighter regulation of drug manufacture, and lower prices for high-quality drugs; unfortunately these are not easy to achieve simultaneously.

5.3.2 Complexities in delivering drugs to those with non-severe malaria

There are multiple reasons people in poorer parts of malaria-endemic countries do not get antimalarials. On the negative side, this means any single solution is unlikely to have more than a very modest impact; the problems need to be tackled at multiple levels. On the positive side, many of the solutions which are needed will improve not only the management of malaria, but of other diseases which present like malaria (currently often missed) and diagnostic and curative services more widely.

5.3.3 Managing severe malaria: the public health perspective

The key to preventing most individuals with malaria from dying is to ensure they receive rapid diagnosis and appropriate treatment with an effective antimalarial whilst their malaria is not severe. Where good prevention of malaria is combined with rapid treatment with effective drugs the incidence of severe malaria has declined rapidly.[645,646,647] Severe cases will continue, however, even where control is good. There is a large literature on how best to manage severe malaria; for clinical audiences treating cases in hospital this is essential reading. For public health purposes, however, only a few points in the evidence are worth highlighting as they have public health significance.

1. The importance of pre-referral care is clear, and there is good evidence that earlier treatment leads to better outcomes. How best to design the referral pathway is likely to depend on local settings. The best use of rectal artesunate in pre-referral care is not yet clear (see below).
2. Only two drug classes are relevant for severe malaria; artesunate and quinine, and artesunate is the drug of choice based on current evidence for both adult and paediatric malaria.[648] Based on this evidence, ensuring that injectable artesunate is available in all health centres has the potential to improve outcomes.
3. Proper diagnosis and making sure clinicians think both of malaria and other causes of severe febrile illness, especially bacterial causes, is important: this is a matter of training, mentoring, coaching, and supervision. Many bacterial diseases have similar symptoms and signs as malaria, and treating them with antimalarials will not have a useful impact.[649] Some patients have both malaria and bacterial disease, and reducing malaria may well reduce bacterial disease, especially salmonella infections.[650]
4. Access to a safe supply of blood is probably another priority; severe malaria is often associated with anaemia for which transfusion is required.[651] Whilst there remains legitimate doubt about exactly which patients need transfusion, there is reasonable evidence that blood saves lives. Countries with greater access to blood have lower mortality from malaria in children, and early transfusion is likely to be one reason for this.[652]
5. There is ongoing debate about the role of fluids in the management of severe malaria and this is being investigated currently in a large clinical trial[653].

To improve the outlook for those who reach hospital with severe malaria, better training of clinicians, better diagnosis and a secure supply of safe drugs and blood are the most obvious evidence-based targets.

In the pre-hospital setting, better spotting of potentially severe cases with rapid referral is crucial; unfortunately this does not always lead to patients attending hospital. Training with IMCI can, however, improve the management of severely ill children, including for malaria (see Section 5.8.2 Evidence on approaches to improve systems effectiveness). There is some debate about how and when to use rectal antimalarials for severe malaria in the periphery; current evidence is that in principle this will save lives,[654] but needs further work to operationalise it and test how to deliver it in different settings without delaying diagnosis and treatment of severe non-malaria illness. See Section 5.2 Case management: diagnosis and treatment.

5.4 Drugs to prevent malaria

In addition to being used to treat patients who are symptomatic with malaria, antimalarial drugs can be used to try to control transmission, or to prevent harm from malaria.

5.4.1 Chemoprophylaxis

Many drugs can be used to prevent malaria, and the use of chemoprophylaxis for malaria is standard practice when people such as travellers and military personnel from non-endemic countries make short trips to high-risk areas.[655] Chemoprophylaxis involves the use of sub-therapeutic (ie not curative) doses of antimalarials. There is clear evidence that has been known for some time that if children in endemic countries take effective chemoprophylaxis continuously the incidence of clinical disease, admission to hospital, severe disease and death would fall.[656] This has, however, been considered impractical for several reasons, including: cost; the cumulative risk of side effects; the likely pressure for drug resistance; the operational challenge of delivering prophylactic anti-malaria drugs to large numbers of individuals for prolonged periods of time; and impairment of the development of naturally acquired immunity. It is therefore likely to remain something used only for vulnerable individuals or groups exposed to malaria for defined periods of time.

5.4.2 IPTp, IPTi, ITPc: the concept

Whilst permanent prophylaxis has been considered impractical, the idea of giving people drug treatment *when they have no symptoms* at particularly vulnerable times in their lives has theoretical attractions. IPT is the administration of a treatment dose of antimalarial at pre-determined intervals, regardless of infection status, with the aim of ameliorating the worst effects of malaria infection at the population level. Whether this should be considered to be intermittent treatment of asymptomatic malaria or chemoprophylaxis is fairly academic; the reality is that prophylaxis is likely to be more important than treatment, given the low prevalence of infection in most of the groups receiving IPT, although long-acting drugs (which provide both treatment and prophylaxis and treatment) are likely to have a greater impact than shorter acting drugs.[657,658]

5.4.3 Intermittent preventive treatment in pregnancy (IPTp)

In high-transmission settings the question in pregnancy is not whether a woman will be exposed to malaria but when. Intermittent preventive treatment of malaria in pregnancy (IPTp) involves the administration of a full therapeutic course of antimalarial treatment, 2 or more times during pregnancy, of women who have no overt symptoms of malaria. This approach is based on clear evidence of effectiveness including randomised trials and systematic reviews in high-transmission settings.[659,660,661,662,663,664,665,666,667,668,669] The drug recommended by WHO for IPTp is SP. However, with the spread of drug-resistance to anti-foliate drugs it is not clear whether SP should remain the drug of choice, especially in East Africa.[670] At the current time, however, there is not sufficient evidence regarding safety and efficacy of any antimalarial drugs other than SP for use as IPTp. There is good evidence that

those with HIV should receive more frequent (monthly) IPTp than HIV-negative pregnant women.[671,672]

Whilst there is strong trial-based evidence for IPTp, and it is recommended by WHO for moderate-to high transmission settings in sub-Saharan Africa, some key questions remain unanswered.[673]

There is a consensus that IPTp is not an appropriate intervention where the chances of malaria in pregnancy are low (most of Asia, and some areas of Africa, such as large areas of Ethiopia[674]). There is a clear consensus IPTp is appropriate where incidence is very high. Where to draw the line between these two is a non-trivial point, for which evidence is currently lacking.

The risk of malaria in pregnancy decreases with the number of pregnancies (probably due to the acquisition of immunity). There is some data suggesting that IPTp therefore has less impact in non-HIV infected multiparous women, so the costs and small risks of providing IPTp may not be justified in these women.[675]

Because IPTp is given to women who do not have symptoms of malaria (and many of whom will not have malaria parasites) the risk of adverse effects from antimalarial drugs is more important than in the treatment of confirmed symptomatic malaria. Most published trials have used SP, generally administered during a time when SP was more efficacious than it is now. Alternative drugs are either more expensive, have less safety data, or both. There is some evidence that older drugs remain effective in semi-immune pregnant women even when they are failing in children.[676],[677] One practical question is whether long-acting drugs (which provide prophylaxis in addition to treatment are preferable to short-acting drugs (equally effective in treatment but not prophylaxis).[678]

5.4.4 Intermittent preventive treatment in infants (IPTi)

The concept of intermittent preventive treatment in infancy (IPTi) was launched by a trial which demonstrated significant improvement in malriometric measures in infants given the long-acting antimalarial SP at the same time as routine infant vaccinations.[679] A subsequent systematic programme of research, with a linked policy programme, means that this is an intervention for which there is now a very strong evidence base for IPTi showing that it reduces clinical episodes of malaria, anaemia and hospital admissions due to malaria, but it is not known if it reduces deaths.[680] It can be scaled up operationally.[681] A précis of some key points would include:

- IPTi works in most settings in malaria-endemic Africa, but the size of the effect varies considerably. As with IPTp, exactly what the transmission cut off below which IPTi is unlikely to be useful is unclear, but it is unlikely to be cost-effective in low transmission settings.682
- In areas of seasonal malaria most of the benefit is seen in the high transmission season.683,684
- There is sufficient evidence to state that there is generally no rebound effect, so children protected in the first year of life do not have more malaria in the second year.[685]

Based on this evidence, WHO now recommends IPTi with SP for the prevention of malaria during infancy in areas of moderate-to-high transmission in SSA. [686]

5.4.5 Intermittent preventive treatment in children (IPTc)

IPTc in young children

Studies conducted in several countries of the Sahel and sub-Sahel where malaria transmission is highly seasonal have shown that administration of antimalarials during the high transmission season to young children is highly effective in preventing attacks of uncomplicated and severe malaria, reducing attacks by 70-90%.[687] IPTc can be given effectively by community health workers and is cost effective (see Section 5.4.5).

IPTc in school-children

Studies have also been undertaken in which IPT has been administered to schoolchildren through their schools. Malaria and anaemia were reduced and in one study undertaken in Uganda educational performance was improved.[688,689]

Data are encouraging from both East and West Africa.[690,691,692] It is likely to be cost-effective[693,694] and can be operationalised.[695] Following a review of the evidence, WHO will be providing policy guidance regarding IPTc in 2011.

With all of IPTi, IPTp and IPTc there is now reasonable evidence of efficacy against clinical malaria. All of them will, where they work, lead to reductions in morbidity and possibly mortality from malaria.

5.4.6 Mass treatment with drugs which kill gametocytes

One of the attractions of ACTs is that they reduce gametocytes, and infectiousness of humans to mosquitoes. They are (or should be) generally only given to those with proven clinical malaria. There are theoretical reasons for trying to give mass treatment for malaria to the whole population, or screening and treating, especially with gametocytocidal drug such as primaquine just before the peak malaria transmission season, as a way of potentially reducing the subsequent malaria cases.[696,697] The aim of this is to interrupt, or reduce, transmission of malaria for the benefit if the population as a whole rather than to cure cases; the concept has been well reviewed.[698]

Mass treatment is not a new concept, and was used in the malaria eradication campaign. There are two settings it is being considered at present

1. In low transmissions settings where the aim is elimination of malaria or extreme control; the most important example is the attempt to reduce malaria in Cambodia to as close to zero as is possible in the area of Artemisinin resistance. Evidence on the effect of this is being collected but is not yet clear.[699]
2. In high transmission settings at the start of the rainy (malaria) season or when malaria is common. Initial attempts at this were not encouraging.[700] More effective gametocidal drugs such as primaquine might have a greater effect but there are risks to mass treatment of otherwise well people, including women in early pregnancy (see Section 5.4.3 IPTp) and those with conditions such as G6PD deficiency who are susceptible to haemolysis.[701]

These approaches should be considered experimental, in the sense that there is perfectly good logic behind them, and no evidence that they do not work, but also no clear evidence that they do. For that reason its use is not widespread, although where elimination of malaria is being considered it may be re-examined.

5.5 Interventions amongst high risk or specific populations

5.5.1 Nutrition Interventions

Malaria is associated with malnutrition; both malaria and malnutrition affect poor people. The extent to which this association is causal is uncertain, and the impact of intervention strategies with several minerals and vitamins remains controversial.

A small number of trials of Vitamin A and Zinc supplementation have been carried out to test their impact on malaria-related morbidity and mortality, with some limited positive data for both.

Supplementation with high dose Vitamin A capsules has been shown to reduce *P. falciparum* febrile episodes by a third.[702] Impacts were greatest among older children (aged 12–36 months) and on episodes which were less severe (no effect was seen on episodes with parasitaemia ≥100,000 μL).[703] The impact of Vitamin A on all-cause mortality is around 20%,[704] largely due to the effects on measles mortality, but there is no measurable impact (in a limited number of trials) on malaria-specific mortality.[705]

Daily zinc supplementation is estimated overall to reduce by a third the number of clinic visits for falciparum malaria (trials conducted in Gambia and Papua New Guinea)[706] though no impacts have been found on *P. vivax*.[707] zinc has also been shown to reduce severe *P. falciparum* febrile episodes (parasitaemia ≥100,000 μL) by 69% suggesting that zinc may preferentially protect against severe malaria episodes.[708] One trial in Burkina Faso showed no impact on childhood morbidity but diagnosis was through home rather than clinic visits.[709] A zinc supplementation trial in Zanzibar showed no significant impact on mortality but the study was not powered to pick up impacts less than 20% and the zinc dose was relatively low.[710]

A recent small trial in Burkina Faso has shown that periodic supplementation with Vitamin A combined with daily zinc supplementation reduced falciparum malaria episodes by 43% and also had significant impacts on malaria cases, duration to first episode and fever episodes.[711]

A study published in 2006 concluded that routine iron and folic acid supplementation in pre-school children can result in an increased risk of severe illness and death.[712] The authors suggested that in the presence of an active programme to detect and treat malaria and other infections, iron-deficient and anaemic children can benefit from supplementation but that supplementation of those who are not iron deficient might be harmful. This study led WHO to recommend that to avoid adverse events in iron-sufficient children universal iron supplementation should not be implemented without the screening of individuals for iron deficiency.[713] However, a recent systematic review of randomised controlled trials that compared iron with placebo or no treatment concluded that iron does not increase the risk of clinical malaria or death, when regular malaria surveillance and treatment services are provided.[714]

There is some evidence that combining zinc with iron supplementation may provide protection against *P. vivax*, but may also interfered with some of the diarrhoea protection associated with zinc supplementation.[715]

Overall the evidence for specific nutritional interventions to combat malaria is sparse or conflicting, but indirect evidence that reducing overall malnutrition will reduce the impact of malaria is moderately strong. Malarial anaemia and nutritional anaemia often coexist. HIV and malnutrition may be co-factors in increased risk of severe malaria.[716]

5.5.2 Control of malaria in pregnancy

See specific sections in ITN, Drugs, IPTp and vaccine sections

The current WHO recommendation consists of a three-pronged approach to the prevention and management of malaria during pregnancy: Insecticide treated nets; intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) and effective case management of malaria illness. Reducing transmission of malaria through vector control measures is uncontroversial, although questions around best delivery methods remain. IPTp and case management are more difficult because of spreading drug resistance, the difficulties of diagnosis of malaria in pregnancy in high-transmission settings, and balancing the absolute need to achieve rapid effective treatment of all pregnant women with malaria with risks of exposing the foetus to antimalarial drugs in a pregnant woman who does not have malaria.

Insecticide-treated nets

ITNs should be provided to pregnant women as early in pregnancy as possible as there is clear evidence from randomised trials for their use improving health outcomes.[717] There are no documented risks with this. Their use should be encouraged for women throughout pregnancy and during the post partum period. Various methods of achieving high coverage, including free distribution, subsidised nets and voucher schemes have been evaluated. Which combination is most appropriate is likely to depend on local circumstances, including existing net coverage (see Section 5.6.2 Interventions and their delivery).

Intermitted Preventive Treatment (IPTp)

See Section 5.4.3 IPTp.

Effective case management of malaria (also see Section 5.5.2 Control of malaria in pregnancy).

Case management of malaria illness is an essential component of malaria prevention and control during pregnancy in all areas where pregnant women are at risk of malaria. The aim is to eliminate quickly and completely the infection because any level of parasitaemia has serious consequences to the mother and the foetus. Using an effective drug is essential, and given the risks of malaria in pregnancy outweighs all other considerations. Where more than one drug is effective the safety of drugs for use in pregnancy has to be considered. The recommended antimalarial drugs of uncomplicated malaria are either ACTs (in the second and third trimester) if available or quinine plus clindamycin.[718]

Cost-effectiveness of MiP interventions

Malaria prevention during pregnancy using a package consisting of IPTp and ITNs is highly cost-effective. The incremental cost effectiveness ratio of IPTp with SP has been estimated to be in the range of US$9-21 per DALY prevented.[719] ITN use by children in several setting has been shown to be one of the most cost-effective public health interventions.

Future directions for control of malaria in pregnancy

The global focus on malaria transmission reduction is likely to have implications for the burden and control of malaria in pregnancy.[720] As countries move towards good control and possible eventual elimination the proportion of women with pre-existing immunity will decline. The clinical implications of malaria are more severe in women with low levels of protective immunity and the burden of disease could become more wide spread over all gravid groups rather than being concentrated in first and second pregnancies. Pregnant women are likely to remain a very important risk population for malaria.

There is a danger that with increased efforts to reduce malaria transmission, countries will reduce strategies which target interventions to specific high risk groups, such as pregnant women.[721] This could have serious consequences for maternal health where transmission is reduced but still present. The optimal mix of interventions for pregnant women is likely to change substantially as we move towards good control and elimination. In particular we need a much better understanding of the relevant interventions for lower transmission areas and of the changes in transmission which could trigger such changes in strategy. One important example is that it is not yet clear at what transmission intensity a change from IPTp for all to one of screening and treating just women with parasitaemia is appropriate.

5.5.3 HIV co-infection: intervention and preventive measures

There is now clear evidence of an interaction between HIV and malaria both biologically and operationally.[722,723] In particular, there is now reasonable evidence that HIV makes severe malaria more likely, and that HIV in pregnancy increases the risk of malaria-associated pregnancy complications.[724] HIV-positive individuals should therefore be considered an at-risk group for malaria. It likely, but not proven by trial evidence, that malaria-control interventions will reduce the impact of HIV. Since it is likely that reducing malaria will have a positive impact on HIV, and ITNs reduce malaria episodes they have been recommended for use in HIV positive individuals. Direct evidence for the impact of ITNs on health outcomes in HIV-positive individuals is lacking, but the logic that insecticide-treated bed nets (ITNs) should be distributed to all people living with HIV in areas with significant malaria transmission is reasonable, and there are no counter-arguments as ITNs are safe. The absence of trial evidence of size of effect makes a calculation of cost-effectiveness impossible. Evidence about how best to deliver this operationally is currently lacking, although concerns that there will be poor retention and use of ITNs where these are distributed free as part of comprehensive HIV control programmes are probably unfounded.[725]

Cotrimoxazole, recommended as prophylaxis against pneumonia and bacterial infections in people with HIV, also protects against malaria, and has been shown to reduce the incidence of malaria by around 70% and mortality by around 40% in HIV-positive adults in a Ugandan cohort study.[726] If cotrimoxazole is discontinued in people taking antiretroviral treatment the risk of malaria increases very substantially – a randomised study in Uganda found that after just 120 days after discontinuing cotrimoxazole, people with HIV had a 28-fold higher risk of developing malaria, indicating the need not only for continuous cotrimoxazole prophylaxis, but also the need for consistent drug supplies and healthcare worker and patient education on the need to use cotrimoxazole consistently in endemic areas.[727]

The use of both cotrimoxazole and ITNs combined reduced the risk of malaria in children with HIV by 97% in Uganda.[728]

Antiretroviral therapy is also probably associated with a reduced risk of malaria, due in part to improved immunity over time. A cohort study in Uganda found that the incidence of malaria was 70% lower in people who received ARVS and cotrimoxazole compared to cotrimoxazole alone. Use of both interventions together with ITNs was associated with a 95% reduction in malaria incidence compared to no intervention.[729] Some caution should, however, be used in interpreting some studies which investigate symptomatic malaria; in high incidence countries asymptomatic parasite prevalence is common (up to 20% of well adults is not atypical); in some of those with HIV and fever finding parasites leads to an assumption it is malaria, when in some cases malaria may be a bystander.

The interaction of malaria and HIV is complicated in pregnancy. In pregnant women intermittent preventive treatment with pyrimethamine plus sulphadoxine (*Fansidar*), consisting of two doses, is already recommended, but for HIV-positive women cotrimoxazole

may be the preferred preventive treatment, with at least three doses of IPT recommended where cotrimoxazole cannot be used, although direct evidence for this being effective is lacking.[730] [731]

As for non-HIV positive individuals, the treatment of falciparum malaria should be based on ACTs.[732] There is, however, evidence of significant adverse interactions between some antimalarials and some antivirals. Treatment of malaria using lumefantrine (the part of the most widely used ACT artemether-lumefantrine) is complicated where antiretroviral therapy includes nevirapine, since this drug changes both lumefantrine and artemisinin levels. Another commonly used drug combined with Artemisinin in Africa, amodiaquine, probably increases neutropaenia in the presence of zidovudine.[733] Other drug interactions require further research before interactions are clear.[734]

5.5.4 Conflict affected and fragile states

Malaria in conflict-affected and fragile states is a significant problem. In most countries where conflict occurs and malaria is endemic malaria incidence increases, and increases most in conflict areas, decreasing when conflict is over and public health services can be re-established.[735,736] In some areas where malaria had been almost eliminated it reinvades due to public health breakdown during conflict.[737] Many of the problems of delivery and health systems outlined elsewhere occur even more acutely in this setting.

Despite the challenges, there are many excellent examples of effective malaria control programmes, often NGO delivered, in conflict-affected, post-conflict and fragile states.[738] The attempt to eliminate malaria in Iraq led by the WHO continued through the Iraq conflict, and Iraq is likely to be certified as malaria-free in the foreseeable future.[739] Eritrea has had one of the most effective malaria control programmes in Africa.[740,741] There have been advances in control and excellent operational research on malaria in Pakistan, Afghanistan, Sudan (Darfur) and DRC.[742,743,744,745,746,747] Recovery from conflict provides real opportunities; Rwanda has one of the most impressive malaria-control successes in the last few years, for example.[748] Although the data collected in these settings is sometimes sparse, health-centre based, and should not be over-interpreted,[749] assumptions that malaria control is not possible in these settings are, therefore, not evidence-based. Indeed many of the most powerful malaria control interventions developed in recent years such as ACTs and ITNs in Asia were piloted or developed in populations undergoing or affected by emergencies.[750] Effective measures, however, do need to be tailored to the particular conditions which occur in fragile states. This section outlines some general issues and examples where these have been tackled with reasonable evidence of effectiveness. Every fragile state is, however, very different both epidemiologically and operationally, and country pages provide greater detail on specific situations.

Examples of problems common to most conflict-effected and fragile states include:

- Bottlenecks and constraints to scaling up interventions include poor health infrastructure, weak capacity, inadequate human and financial resources, poor logistics and management systems, poor coordination, and insecurity.
- In the acute phase, particularly in refugee camps, surveillance, outbreak preparedness and case management will all be important.[751]
- ITNs represent one of the few options for obtaining protection against malaria in unstable settings deficient in health infrastructure.[752] But scaling up ITN coverage can be more challenging in conflict-affected areas. Specific interventions such as insecticide-treated tents, tarpaulins and sheets may be appropriate for refugee camps.[753]

- Socio-economic factors influence access to ITNs and to ACTs and, as a result, health outcomes. However, in some instances, displaced populations may paradoxically be more advantaged than host populations through the provision of malaria prevention and treatment as humanitarian aid through NGOs.
- One risk of conflict is that non-immune populations are displaced to areas of high malaria endemicity.

Alternatively:

- Crises can provide an opportunity for positive policy change – in this case the introduction of ITNs, RDTs and ACTs; some NGOs such as Médecins sans Frontières, HealthNet and Merlin have been particularly active in this area. This can also provide the seed for much needed reform to control programmes after the emergency (e.g. in the case of East Timor[754] and Afghanistan[755]).

- Evidence from DRC and Ethiopia suggests that volunteer Community Health Workers (CHWs) represent a potentially valuable human resource for expanding accurate and practical malaria diagnostics to avoid unnecessary treatments and save lives to remote rural areas that have limited health facilities.[756],[757]

Bottlenecks and constraints to scaling up interventions

Bottlenecks and constraints to scaling up interventions include poor health infrastructure, weak capacity, inadequate human and financial resources, poor logistics and management systems, poor coordination, and insecurity. Apart from perhaps the last point, these are the same problems that plague healthcare delivery in virtually all lower income countries.

Early warning is vital for a rapid response to malaria epidemics (see Section 2.2.4 Epidemics) with indicators well identified. Response times greatly affect disease burdens with the epidemics common in CAFS.[758] In CAFS established information systems may have collapsed or never existed. But technological advances suggest potential future progress even where reliable on-the-ground data are difficult or slow to obtain, including remote sensing (of rainfall; surface water; temperature; number and type of mosquitoes); and relatively cheap micro-satellite systems (to collate remote data, e.g. Disaster Monitoring Constellation system).[759] Some trials in CAFS are ongoing.[760]

Prevention interventions in CAFS

No single malaria control method is superior because of the need to cater to local epidemiological conditions and the phase of the emergency.

Much of the literature addresses the trade-off between the rapid results of vertical programmes and the longer term benefits of working with governments, or other local partners.[761] In SSA, one of the most successful national integrated preventive campaign in a high burden country occurred substantially post-conflict, yet in a country still considered fragile – Eritrea.[762]

ITNs and LLINs represent one of the few options for obtaining protection against malaria in unstable settings deficient in health infrastructure.[763] But scaling up ITN coverage can be more challenging in conflict-affected areas. Mass distribution of insecticide-treated bed nets (ITN) to prevent malaria is often carried out in complex emergencies, but there are relatively few data on the outcome or operational effectiveness of such programmes.[764] There is limited evidence that LLINs can be used outdoors to good effect though the lifespan of LLINs might be truncated due to wear and tear in emergencies.[765,766] Other interventions may be more conducive to emergency conditions such as insecticide impregnated plastic shelters[767]

or tents.[768] Pyrethroid treated tents have been used to control an epidemic of malaria in tribal areas of Pakistan.[769]

In June 2001, Médecins Sans Frontières completed a mass distribution of ITNs (Permanet) to internally displaced persons in Bundibugyo, southwest Uganda, distributing one to four nets per household, and aiming to provide coverage for all residents. A cross-sectional survey in 2002 showed that an ITN was present in 75.6% of the households, but only 56.5% of individuals were sleeping under an ITN, and nets were often damaged. The prevalence of malarial parasitaemia was 11.2%, and was significantly lower in ITN users compared to non-users (9.2% vs. 13.8%); ITNs with severe damage were effective.[770]

An integrated malaria control programme operating since 2006 amongst Sudanese refugees and their host communities in the border region of Chad and southern Darfur, Sudan, reported a reduction in malaria incidence from health facility consultation data from 22% to 4% over two years. This suggests that integrated malaria preventative and treatment programmes, including differential and confirmatory (with RDTs) diagnostics, ACTs for uncomplicated malaria and artemether for severe malaria, supply monitoring, continuous health worker training – all of this is feasible in humanitarian crises and can result in significant reduction of malaria.[771]

In Burundi vector controls programmes resulted in high coverage but limited impact on prevalence, possibly because it occurred after the epidemic's peak.[772] This is a frequent problem with IRS in emergencies – the intervention is inherently effective but has greatest effect at the start of the transmission season and organising and mounting a timely campaign in such conditions is very difficult.[773] However, even when prevalence is barely affected there can be gains in future preparedness for epidemics (e.g. through improved surveillance and early warning systems).

Socio-economic factors influence access to ITNs whether they are subsidised or provided free of charge. In Afghanistan, social marketing of subsidised ITN by a consortium of non-governmental organisations has taken place since 1993. A study found that ITNs were 4.5 times more likely to be purchased by families from the richest quartile and 2.3 times more likely to be purchased from the upper-middle quartile than from the two lower quartiles. Even so, a significant minority from the lower quartiles did prioritise and buy an ITN. In conflict affected countries where livelihoods are compromised, many argue that it is necessary to target subsidies at the most impoverished to make ITNs affordable and to improve overall coverage.[774]

The nature of refugee camp accommodation may render traditional IRS and ITNs ineffective,[775] but innovative approaches can get around this.[776] Also, refugee camps allow efficient access to the population, relative to more dispersed populations. IRS with malathion in refugee camps in eastern Sudan in 1997 was associated with reduced mortality from, but not incidence of, malaria.[777]

Research from an Afghan refugee camp in Pakistan shows that insecticide-treated bedding materials (sheets and blankets) could be protective against vectors of malaria and leishmaniasis - especially in complex emergencies, epidemics and natural disasters where people are more likely to sleep in an exposed situation.[778] Another Afghan study showed that permethrin-treated chadors (Islamic scarves) used as top sheets reduced the odds of a malaria episode by 64% in children younger than ten years old, at a cost of US$0.17 per person protected.[779]

Spraying of canvas tents with residual pyrethroid insecticide is an established method of malaria vector control in tented refugee camps. In recent years, plastic sheeting (polythene tarpaulins) has replaced canvas as the utilitarian shelter material for displaced populations in

complex emergencies. Advances in technology enable polythene sheeting to be impregnated with pyrethroid during manufacture. But the efficacy of such material against mosquitoes when erected as shelters under typical refugee camp conditions is unknown. Tests in an Afghan refugee camp to compare the efficacy of different types of insecticide impregnated tarpaulin mass coverage with deltamethrin-sprayed or impregnated tarpaulins or tents suggest that this approach has strong potential for preventing malaria in displaced populations affected by conflict.[780]

Research from an Afghan refugee camp in Pakistan shows that insecticide-treated bedding materials (sheets and blankets) could be protective against vectors of malaria and leishmaniasis – especially in complex emergencies, epidemics and natural disasters – where people are more likely to sleep in exposed situations.[781] Another Afghan study showed that permethrin-treated chadors (Islamic scarves) used as top sheets and to sleep in reduced the odds of a malaria episode by 64% in children younger than ten years old, at a cost of US$0.17 per person protected.[782]

Meek et al (1998) list a number of preventive interventions inappropriate at any stage of a complex emergency: aerial spraying (too dangerous in acute phase, too expensive in post-emergency phase); scrub clearance (no evidence that this reduces man-vector contact); and outdoor spraying with residual insecticide (expensive, environmentally contaminating, usually fails to reach the targeted vector, limited impact).

Treatment in fragile states

Evidence from DRC suggests that volunteer CHWs represent a potentially valuable human resource for expanding accurate and practical malaria diagnostics to avoid unnecessary treatments and save lives to remote rural areas that have limited health facilities.[783] Although in a high transmission setting presumptive treatment may still be more cost effective. Syndromic diagnosis was mainly used in the acute stage of successful containment of malaria in Timor-Leste[784]. Martins (2009) describes how the crisis was an opportunity for positive policy change – in this case the introduction of RDTs.

Teaching people, particularly where health workers are scarce, as in chronic conflict areas, to self-treat can also succeed[785]. Under-five mortality was reduced in post-conflict Ethiopia by teaching mothers to give children antimalarial drugs. A major reduction in under-five mortality was achieved in Ethiopia through training mother coordinators to teach mothers to give under five year old children antimalarial drugs.[786]

These examples provide snapshots of the kinds of positive impact on malaria that can be obtained even in challenging settings, but what obviously they have in common is that they were tailored to local issues and opportunities.

5.6 Economic evaluation of malaria interventions and their delivery systems[787]

5.6.1 Introduction: interventions, delivery systems and interpreting cost-effectiveness

Most malaria control interventions can be delivered through more than one system, and therefore decisions are needed about which one to use, and whether multiple systems are necessary to achieve desired goals. Systems will differ according to the level of coverage, tempo of change, and even the level of equity that they can achieve. Their costs will also differ, leading to potentially different levels of cost and cost-effectiveness for the same intervention delivered to the end user in different ways. An intervention, therefore, is only as cost-effective as the system through which it is delivered.

Because of earlier debates about the best way to provide ITNs, a number of typologies for classifying delivery systems for this intervention have been developed, which can be expanded to accommodate the full range of malaria interventions[788,789.] Following both Webster and Killian, the first level of typology used here is the delivery *channel* (the route through which the end-user receives the intervention). Additional elements of the delivery *strategy* include duration (whether availability is time-limited or continuous), whether the intervention is targeted (at economic or biologically-determined vulnerable groups), and the cost to the end user. Further elements of the delivery strategy are intervention-specific, such as the shape and size of ITN or the communication channels used for behaviour change communication). Two types of 'mixed' systems are of interest.

- Some delivery systems provide an intervention through multiple channels, and the economic evaluation evidence does not distinguish the costs of the different channels. For example, the KINET ITN social marketing programme delivered nets through public, formal retail and informal retail channels.[790]
- Some delivery systems separate the provision of the entitlement and the commodity itself, with these reaching the user through different channels. This is the case, for example, with the Tanzania and Ghana ITN voucher schemes in which a woman receives a voucher from a public health facility, and redeems the voucher for a net in the formal retail sector.[791,792]

The matrix below (Table 4) presents the typology used for classifying the evidence on cost-effectiveness of malaria interventions. It should be noted that some of these channels have been used only in small-scale research studies, while others have operated on a large scale; nonetheless, they illustrate the point that decisions about which interventions to provide cannot be separated from the question of how to provide them.

Table 4: Delivery channels for malaria interventions

Channel	Malaria interventions that are delivered via this route
Community – continuous	IPTc ITNs RDTs and ACTs
Community – limited timeframe (=campaigns) Note: These can be further divided between 'standalone' and 'integrated with other interventions'	ITNs IRS School-based IPTc / IST
Routine – Fixed delivery point (usually health facility)	ITNs IPTp

	IPTc IPTi ACTs RDTs
Routine – regular mobile/outreach service	ITNs
'Enhanced' routine services	ITNs/net retreatment
Retail – formal (pharmacies, drug shops, general shops – with fixed premises and some kind of trading license)	ITNs ACTs RDTs
Retail – informal (markets, itinerant vendors and hawkers)	ITNs ACTs
Mixed	ITNs

A range of approaches to interpreting cost-effectiveness results have been adopted in the literature. One strand proposes that an intervention which costs less than $150 per DALY averted should be considered 'cost effective' and interventions costing less than $25 per DALY averted 'highly cost effective'.[793,794] Some analysts have opted to inflate these thresholds to current price levels.[795] A second approach is to use multiples of GDP or GNI per capita as the threshold[796], on the argument that a decision maker should be willing to pay at least the value of average annual output to save one year of healthy life. Even for the poorest countries this puts the threshold above the $150 / DALY averted proposed by the World Bank and WHO.

5.6.2 Interventions and their delivery

ITNs

In total, 23 studies on the cost or cost-effectiveness of ITNs published since 1999 were identified. Of these 21 are empirical studies and two model-based. The empirical studies describe 28 identifiable delivery channels (Table 5) covering high and low transmission areas. Two of the empirical studies are from south Asia, one from Latin America and the remaining studies from SSA. Comparability is limited by the large number of different outcome measures used, which include health outcomes where these were collected in the specific study (cost per death averted, translated into DALYs averted or life years gained) through to a range of process or output measures (cost per net delivered, delivery cost only per net, cost per treated net year, cost per person protected). Until recently, most ITN programmes targeted pregnant women and children under five, although universal coverage is now recommended. Effectiveness in economic evaluations has primarily been measured in terms of the benefits to children, as there is little evidence about the impact on severe anaemia on maternal mortality.[797]

Table 5: ITN cost effectiveness studies, classified by delivery channel

Channel	Number of sites
Public routine	8
Public campaign	4
Private (formal and informal)	2
Mixed	14

The first economic evaluations of ITNs were undertaken alongside clinical trials, and therefore the costs presented applied to the delivery system used to provide nets to the trial

population (typically some form of house-to-house distribution in the intervention clusters). At that time conventional polyester nets were used which needed regular re-treatment with insecticide - generally assured by trial staff to ensure adherence. Goodman et al used data from these trials to construct a cost-effectiveness model for SSA settings and estimated that provision of ITNs and their treatment/retreatment cost at $19-85 per DALY averted, well within the 'cost-effective' range.[798] A further trial in Kisumu, Kenya, included the positive externality arising from the mass effect of ITN use in the measurement of health outcomes, and estimated the net cost-effectiveness to be $34 per life year gained.[799] Health outcomes were also measured in a cluster randomised trial in India, which estimated a cost per case averted of $52.[800]

As interest in delivering ITNs on a large scale increased, studies of the costs and effectiveness of a broader range of delivery systems have been undertaken. Few of these second-phase studies measured health outcomes and instead report process outcomes such as cost per net delivered, or cost per treated net year, or they impute health impact from the Cochrane review estimate of ITN effectiveness.[801] One exception was the KINET study of the impact and cost-effectiveness of social marketing in an operational setting in two districts in Tanzania, which distributed subsidised nets through a mix of channels (public routine, retail formal (shops) and retail informal (hawkers and itinerant vendors), supported by a marketing strategy and a voucher scheme targeted at pregnant women and under fives. Health outcomes were measured through household demographic surveillance. The cost per death averted was estimated at $1,559 and the cost per DALY averted $56.8.[802] Many of the remaining studies examined a variety of different delivery systems (NGO, community-based organisations, and employers) at a relatively small scale, and are therefore not very informative for contemporary programme decisions.

The cost of achieving a more equitable distribution of ITNs was also explored in the context of the KINET project, where it was shown that while social marketing was more costly per net distributed than the unassisted private retail sector (both formal and informal), the social marketing programme achieved higher coverage of the lowest socioeconomic group and of those living in the periphery of their villages.[803]

In their study of the costs of subsidised ITN sales through ANC facilities (assisted by a non-governmental organisation) in Malawi, Stevens et al. demonstrated the importance of programme scale as an influence on costs. They found that the cost per net distributed fell from $5.04 in the first year of the programme, when 72,196 nets were distributed to $1.92 in year five, when annual output had increased to 1.3 million nets.[804]

As investment in malaria control measures expanded through the 2000s, evidence has accumulated from large scale (often national level) systems for delivering ITNs. These include studies of the cost of time-limited, free mass distribution 'campaigns', either standalone or integrated with delivery of other interventions such as immunisation;[805,806] national level combined strategies (public, time-limited campaigns + public routine);[807] national level 'mixed' strategies such as a voucher scheme;[808] and national level delivery through routine public sources.[809,810] The cost-effectiveness results of these national level programmes are summarised in Table 6 below.

Table 6: Cost effectiveness of large scale ITN delivery systems

Country	Delivery channel	Cost results
Togo[811]	Public, limited timeframe, integrated with measles vaccination	Cost per LLIN distributed $4.41 Cost per case averted $3.26 Cost per death averted $635 Cost per DALY averted $16.39
Togo[812]	Public, limited	Annual economic cost per net distributed $3.23

	timeframe, integrated with measles vaccination	Economic cost per death averted $1174 Economic cost / DALY averted $36
Eritrea[813]	Combined public routine and community groups	Annual economic cost per net distributed $3.98 Economic cost per death averted $438 Economic cost / DALY averted $13
Malawi[814]	Routine public, through ANC	Annual economic cost per net distributed: $3.36 Economic cost per death averted $1,105 Economic cost / DALY averted $33
Senegal[815]	Private retail	Annual economic cost per net distributed $8.05 Economic cost per death averted $2199 Economic cost / DALY averted $67
Tanzania[816]	Combined private retail plus mixed public routine/private retail voucher scheme	Annual economic cost per net distributed $4.80 Economic cost per death averted $788 Economic cost / DALY averted $24
Tanzania[817]	Mixed voucher scheme employing public routine and private retail channels	Cost per ITN delivered $7.57 Cost per death averted $873

The cost per DALY averted in this set of programmes varied from around $13 to $67, and therefore would all be designated as 'cost-effective' according to the threshold of less than $150 per DALY averted; many are 'highly cost effective' at less than $25 per DALY averted.

A number of studies have been able to compare directly the costs of continuous delivery channels with public, time limited (campaign-type) delivery in a single study setting. In Uganda, Kolaczinski et al.[818] found the financial cost per net distributed to be very similar between the two channels, and the economic cost per net delivered through ANC services to be about half that of delivery through a stand-alone campaign. In Burkina Faso, de Allegri et al.[819] estimated the economic cost of LLIN delivery through social marketing to be slightly more expensive than through routine, public ANC services ($8.08 vs. $7.21), but the financial cost of the two systems to be identical ($4.81 per net distributed).

Most recent thinking about how to sustain high levels of ITN coverage now recognises that continuous/routine and time limited, catch-up campaigns are not alternatives but rather that both strategies are needed to achieve and sustain rapid scale up to high levels of population coverage.[820]

This means that it is not particularly informative, nor does it fit with current programme recommendations, to put these delivery systems 'head-to-head' in a cost-effectiveness comparison. Rather, the important outstanding questions are:

1. How quickly is the coverage achieved through a campaign expected to fall off due to natural decay and loss of LLINs (estimated at 5-13 percentage points per year)?[821]
2. What are the most effective and cost effective continuous delivery systems and mixes of systems to maintain universal coverage?
3. At what frequency are campaigns needed to return to a high level of population coverage within the context of continuous routine systems, taking into account the resources and organisation required to do this?

There are simply not enough data on the longevity of ITNs, the patterns of net use within households, age specific patterns of risk, or the effectiveness and cost effectiveness of mixes of campaign and continuous routine systems to provide clear answers to these

questions, although some of their elements have been modelled.[822] Certainly these parameters will vary by setting, and therefore influence resource requirements.

A further recent development is a shift from targeting nets to those who are at the greatest individual biological risk (pregnant women and children under five, at least in high transmission settings) to 'universal coverage' of sleeping places with the aim of reducing malaria transmission. There are as yet no published data on the cost of national scale universal coverage campaigns (though see below for one estimate).

Most recent studies have examined the cost-effectiveness of long-lasting insecticidal nets. This would be expected to have two effects on cost effectiveness estimates compared with conventional ITNs: one the one hand, the commodity cost of LLINs is higher, making the intervention more expensive; on the other hand, LLINs have generally been assumed to have a longer useful life, reducing their cost per treated net year. Finally, because there is no need for retreatment, the delivery of a LLIN (given equal or superior lifespan of the net itself) would be expected to provide more treated net years than previous conventional ITNs, which would have needed to be retreated to continue to deliver full protection.

There is, nonetheless, controversy regarding the useful life of a LLIN. There is insufficient evidence to understand the influence of environmental and cultural context on different types of netting material and consequently their months of useful life. What is clear, however, is that there is no such thing as a 'five year net' and a 'three year net', but that the lifespan of the net is highly variable based upon the conditions of its use. This has important implications for the frequency of net distribution activities, and for cost-effectiveness since the commodity cost is a substantial share of the total cost of providing an ITN.

A further influence on the cost-effectiveness of ITNs is the impact of malaria transmission. Only Mueller et al.[823] have considered the effect of transmission level in their sensitivity analysis, finding that that the intervention becomes less cost-effective in lower transmission settings.

Indoor residual spraying

Despite the resurgence of interest in IRS as a means of vector control, in both high transmission settings and as part of an early response to epidemic malaria, there are very few recent studies of its cost and cost-effectiveness. In total, ten papers reporting the effects of nine projects/programmes were identified that had been published since 1999. Five of the nine programmes were in SSA, one in Latin America, two in south Asia and one in Afghan refugee camps in Pakistan. Four of the papers looked at the cost-effectiveness of IRS alone, three compared IRS with ITNs, one with sponging cattle with insecticide, one with ITNs, larviciding and water management, and two were modelling studies that compared IRS with a variety of different malaria control interventions.

Studies varied in the extent to which they included user costs, with the majority reporting provider costs only. The cost per person protected ranged from $0.34 in Pakistan[824] to $7.4–10.3 in Colombia[825], with the more recent studies reporting provider cost per person protected of $2–4.[826] Four studies present the cost per DALY averted, making the results more directly comparable with those of ITN studies. These range from $30 to $60 in the two modelling studies[827,828] and $119–132 in the most recent studies of large scale programmes.[829] Based on this limited evidence, it appears that IRS is a cost-effective intervention but possibly less so than ITNs; this is in any case likely to be context specific.

We did not identify any recent empirical studies on the cost-effectiveness of packages of vector control measures, such as ITNs and IRS, implemented as part of recent 'scale up for

impact' activities; nor is there much evidence about the cost-effectiveness of IRS in lower transmission settings.

Table 7: Cost-effectiveness of IRS, summary of evidence

Country	Costing perspective	Cost per person protected ($)	Cost per death averted ($)	Cost per DALY averted ($)
South Africa[830]	Provider	3.27	4,357	132
Mozambique[831]	Provider	3.90	3,933	119
India	Societal	*		
Kenya[832]	Provider	**		
Kenya[833]	Provider	0.88		
Colombia[834]	Provider	7.4-10.3		
Mozambique[835]	Provider	2.16-3.48		
Pakistan[836]	Provider	0.34		
Sri Lanka[837]	Provider	2.11-2.87		
High transmission SSA (model)[838]	Provider			30-40
Low income SSA (model)[839]	Societal			32 - 58

*Cost per malaria case averted $87
** Cost per malaria case averted $9

Intermittent preventive treatment

IPT in pregnant women (IPTp)
IPTp reduces severe anaemia among pregnant women and reduces the incidence of low-birth weight among their newborns. All the studies which have examined the cost-effectiveness of this intervention have found it to be highly cost-effective, with estimates ranging from $4–43 per DALY averted[840,841]. Most studies have assumed that IPTp is delivered through routine public services. One study in Uganda assessed the cost-effectiveness of community-based delivery of IPTp provided by traditional birth attendants, drug vendors, community health workers and adolescent peer mobilisers, and estimated an incremental cost per DALY averted (compared with facility-based services) of $1.10, with improved effectiveness due to improved access and adherence.[842]

IPT in children (IPTc)
Two studies of cost-effectiveness of intermittent preventive treatment in children (IPTc) were identified. Conteh et al.[843] present results of a randomised, placebo controlled trial of three different drug regimens, administered to children under five years through a network of community-based volunteers that was established and trained specifically for the trial. Artesunate-amodiaquine (AS-AQ) administered monthly had the highest cost per adherent child, but was most cost-effective because of its higher protective efficacy. The cost per malaria case averted of IPTc with monthly AS-AQ was $61 (including treatment cost savings to households as well as providers); and the cost per adherent child was $14.79. This cost per case averted is higher than other interventions to prevent childhood malaria (IRS, ITNs). However, these costs reflect in part the small scale of operation, and the vertical delivery system that was created specifically for the trial. When costs were modelled to reflect costs of delivering the intervention at district level, the cost per child adherent decreased by 71%, and the cost per malaria case averted by about two-thirds, reflecting the high level of fixed and semi fixed costs (e.g. training costs and volunteer allowances). A second study, in Kenya, explored the cost-effectiveness of IPTc in schools for children aged five to 18.[844] The estimated cost per case of anaemia averted was $29.84, and per case of parasitaemia

averted was $5.36. Because different outcomes are presented it is difficult to compare these results directly.

IPT in infants (IPTi)

In contrast to the IPTc study above, where new delivery channels had to be developed to reach children, infants are regularly in contact with the health system through visits for immunisations. Clinical trials have now been undertaken in a variety of African settings which differ in both their malaria and health system contexts. One multi-country trial found that in those locations where it was found to be efficacious, IPTi using SP was highly cost-effective with cost per malaria episode averted ranging from $1.36 to $4.03 using trial-specific efficacy data, and $0.68 to $2.27 using pooled data.[845] Where it was efficacious, the cost per DALY averted by IPTi ranged from $2.90 (with SP) to $39.63 (with mefloquine). In addition, significant treatment cost savings and household savings were observed, making this a highly cost-effective intervention. In two of the trial sites, with lower malaria transmission, the intervention had no significant impact on malaria outcomes, and was not cost effective. Very similar results were found in a second study which reported the cost-effectiveness of trials conducted in Mozambique and Tanzania.[846] In the latter, costs from a large scale effectiveness trial undertaken in southern Tanzania were applied to the trial-specific efficacy data, as these costs were felt to resemble more closely real life conditions. The cost per malaria episode averted was $1.6 in Tanzania and $4.7 in Mozambique; the costs per DALY averted were $3.7 and $11.2 in Tanzania and Mozambique, respectively. These estimates exclude treatment cost savings. All cost-effectiveness results fall clearly in the 'highly cost effective' range. Cost-effectiveness ratios were more favourable in the Tanzania trial, where efficacy was higher. These results indicate the clear advantages of linking the administration of a new intervention to an existing delivery system. At the same time this identifies the importance of considering the existing health system characteristics in interpreting cost-effectiveness results. For example, in both Ifakara, Tanzania and Manica, Mozambique there was high utilisation of EPI services. Both studies also note, however, the risk of over-burdening the immunisation services with an additional intervention.

Case management (ACTs, RDTs)

In face of high levels of resistance to chloroquine and sulphadoxine-pyrimethamine, WHO recommends Artemisinin-based combination therapy for treatment of uncomplicated *P. falciparum* malaria.[847] In addition to their superior clinical effectiveness, published studies of the cost-effectiveness of ACTs vs. monotherapy have shown they are also more cost-effective and generate substantial cost savings, primarily because their use leads to fewer treatment failures thereby averting additional costs of care.[848,849,850,851] For instance, Agnamey et al. in Senegal estimated that switching to treatment of confirmed malaria cases only would reduce costs by 36%, and combining this with a change in first line drug from chloroquine/quinine to artesunate-amodiaquine (AS-AQ) would lead to a 53% cost reduction.[852] Muheki et al., studying the costs and consequences of switching from SP to AL in South Africa, estimated a cost of $18 per life saved for AL compared with $158 for SP, and that the switch had led to substantial cost savings due to the reduction in total malaria cases and hospital admissions for malaria.[853] One study has examined the cost-effectiveness of switching from quinine to artesunate for the treatment of severe malaria in south East Asia, estimating the incremental cost per death averted to be $140, making this a cost-effective use of resources.[854]

ACTs are, however, considerably more expensive than chloroquine and SP. The ACT watch project estimates the price per full adult treatment course for a WHO-approved ACT to be $3.66 in the DRC, $7.56 in Benin and $7.65 in Nigeria, compared with $0.29 for chloroquine (the most popular antimalarial in Benin) and $0.54 for SP (the most popular antimalarial in Nigeria); and that the price of a course of treatment with ACT is 3-4 times the average adult daily minimum wage.[855] The current public procurement price for an adult treatment course

of the ACT artemether-lumefantrine is $1.36-1.52,[856] compared with around $0.20 for a treatment course with chloroquine or SP. A major challenge, therefore, is how to increase access to these more effective drugs and at the same time, protect Artemisinin from the development of resistance.[857] A study in Cambodia examined the cost of a variety of approaches to increasing access to, and appropriate use of, ACTs. The cost of two schemes for improving access to ACTs for remote, rural populations were compared (malaria outreach teams and village malaria workers). The fixed cost per capita (excluding the costs of ACTs and RDTs) was estimated to be $0.44 for the malaria outreach team scheme and $0.69 for the village malaria worker programme, though the cost per patient treated was lower in the village malaria worker scheme because of its higher population coverage.[858]

This higher cost of ACTs compared with chloroquine and sulphadoxine-pyrimethamine (SP), together with the impact of falling malaria transmission in some areas, has led to increased interest in the cost-effectiveness of routine parasitological diagnosis, using either microscopy or rapid diagnostic tests, compared with the previous WHO recommendation of presumptive treatment of fever with an antimalarial in children under five years of age in high transmission areas. The WHO has for some time recommended parasitological testing in all ages in low transmission settings, and children >5 years. The challenge is to improve the targeting of antimalarial drugs, so that they are given only to those who actually have malaria and to improve the management of non-malaria febrile illness and to provide the basis for timely and accurate malaria surveillance. Most studies have addressed the question of whether the introduction of RDTs has the potential to be cost-saving, compared with presumptive treatment. The issue of cost-effectiveness of RDTs is more difficult: some papers have calculated a cost per DALY or life year averted from RDTs but these results are difficult to interpret without better evidence of the health gains from improved management of non-malaria fevers.[859]

Studies of the economic benefits of RDTs include those that have compared RDTs to microscopy,[860] and those which compare microscopy and RDTs to presumptive diagnosis.[861,862,863] Some of these are empirical studies presenting data from a particular study setting, including epidemic areas of Ethiopia,[864] Senegal,[865] Tanzania,[866] Nigeria,[867] and Mozambique.[868] Other studies adopt a modelling approach[869,870,871] which can consider multiple parameters simultaneously, and which can be adapted to local circumstances by the inclusion of appropriate context-specific parameters.

A number of studies have found no cost savings from the introduction of RDTs compared with presumptive treatment.[872,873,874,875] For instance, a study of the introduction of RDTs in health facilities in Dar es Salaam found a slight reduction in patient costs due to time savings and reduced out-of-pocket expenditure on drugs; but for providers, the costs of the RDTs and their introduction outweighed the cost savings from reduced expenditure on antimalarial drugs.[876] Studies in Senegal[877] and Nigeria[878] also found that introducing RDTs involved a net increase in costs. A study from DRC concluded that in high malaria prevalence areas, RDTs were not cost-effective, although the study demonstrated the feasibility of their introduction even in a context of high human insecurity.[879]

In contrast, Zikusooka et al.[880] estimated that RDTs were likely to be net cost saving in Mozambique under conditions where up to 52% of tested patients are parasite positive, using a relatively more expensive antimalarial drug (artemether-lumefantrine). This malaria prevalence threshold was reduced to 29% or less in the case of a less expensive drug (artesunate + SP). Both prevalence thresholds increased when RDT use was restricted to those older than six years of age, and even with malaria prevalence among febrile cases of 75%, the incremental cost per malaria positive patient treated was less than $1. Across a range of studies in different epidemiological contexts, results have generally been found to be sensitive to the proportion of febrile cases that test positive for malaria (more likely to generate cost savings at lower levels of malaria prevalence), the cost of the RDT (more

likely to generate cost savings as RDT cost decreases) and the cost of ACTs (less likely to generate cost savings as the drug cost falls). However, many authors stress the importance of additional benefits, including reduced drug pressure from improved targeting of ACTs, and reduced treatment harm from inappropriate treatment and improved management of non-malaria febrile illness and improved quality of health information.[881]

Most studies have concluded that there is no simple answer to the question of whether RDTs are cost-effective and that this depends on local context, in particular the transmission setting. These characteristics have been identified through modelling studies which are able to look at a number of parameters simultaneously. These consistently identify the level of malaria transmission (and therefore the prevalence of malaria positive results among fevers) as a critical influence on cost-effectiveness. Shillcutt et al.[882] estimated the cost-effectiveness of RDTs compared with presumptive treatment and microscopy, evaluated at $150 or less per DALY averted. They found reasonable likelihood (50% confidence) that RDTs would be cost effective compared with presumptive treatment below 81% malaria prevalence, and that they would be cost-saving below 58% prevalence. Compared with microscopy, RDTs were likely to be cost-effective across all prevalence levels, because of their superior sensitivity and specificity under operational conditions. However, like most studies of this genre, the authors rely on simple assumptions about the costs and benefits of better management of non-malaria fevers.

A further factor considered in the most recent studies of the economics of RDTs is the effect of provider compliance with a negative test result. Lubell et al. present a model for choosing between alternative RDTs, which they apply to illustrative data from Uganda.[883] They find that the choice of test is sensitive to patient age, transmission setting, assumptions about provider adherence, and the analytical perspective adopted, with results changing depending on the inclusion of direct costs only, the health consequences of incorrect treatment, and the potential harm from treatment with ACTs. The effects of provider adherence are further explored in Lubell et al[884] in which a cost-benefit perspective is adopted and the effects of provider compliance with test result are explored directly. At moderate and low levels of malaria transmission, RDTs were found to be more cost-beneficial than microscopy, and both were more cost-beneficial than presumptive treatment.

However, this result was highly sensitive to assumptions about provider response to test results. Where the actual level of adherence to results was set to 'realistic' levels (consistent with existing evidence from observational studies and clinical trials),[885] neither test method was likely to be cost-beneficial, and costs would be 10-250% higher, depending on the level of transmission, than where providers' response to rest results is fully consistent. The significance of these studies is not to suggest that improved targeting of ACTs is not warranted on economic grounds, but rather to emphasise the critical importance of provider behaviour on the estimates of economic benefits of targeting and the need for much better evidence about how this can be influenced.

Most studies considered here have assumed that RDTs are provided free of charge to users through routine public sector delivery channels. However, between ten and 90% of malaria treatments are provided in the private sector by informal providers[886] where parasitological diagnosis is rarely used. With the introduction of the AMF-m as a mechanism for subsidising drugs distributed through the private and public sectors, the total cost of the subsidy will depend on the degree of targeting of ACTs to those who need them. In the private sector in particular, more evidence is needed about how to structure the incentives facing both providers and patients to use RDTs and to comply with the results of a negative test.

Reflections on comparisons across interventions

Great caution must be taken when comparing the costs of different malaria interventions, since the results are sensitive to local epidemiology (e.g. the intensity of malaria transmission, which is changing in some settings based on interventions being deployed), the characteristics of the health system (which will influence both intervention costs and effectiveness), the costing perspective adopted (whether household costs are included), whether cost-savings have been incorporated, and the interactions between different interventions.[887] There is a need for better evidence on the incremental cost-effectiveness of adding IPTi to ITNs; and of adding IRS to ITNs.

Quality of evidence

The literature on the economics of interventions contains many high quality studies. However, there are relatively few studies for each intervention, and many have been implemented on a small scale so that the costing results may not be generalisable. Studies do not always undertake sensitivity analysis or address parameter uncertainty, and they adopt a range of costing perspectives (provider/societal). Failure to standardise outcomes makes it difficult to compare results directly, even for the same intervention.

Impact of investment

The economic benefits of controlling malaria have been assessed, with estimates of the benefit-cost ratio ranging from 1.9 to 4.7.[888]

There has been some initial exploration of the economics of malaria elimination.[889] While in the long run it is likely that the total benefits of elimination will outweigh its costs, there is less certainty about the medium term costs and effects. Comparing the costs and benefits of elimination with an alternative of 'controlled low-endemic malaria', Sabot and colleagues estimated the probability that elimination would be cost saving over a 50 year time horizon to range from 0% to 42%, with only one of their five case studies achieving cost savings in the base case. This result is influenced by discounting and the high initial costs of elimination. These estimates suggest that elimination is unlikely to be warranted on financial grounds alone, and that much better evidence is needed on the potential benefits of elimination.[890]

Sustainability

Only the debates on ITN distribution systems have explicitly considered the notion of sustainability, in the narrow sense of relying on user payments to reduce financial dependence on external sources, and (in the context about debates about the role of the private sector in ITN distribution) of building up and supporting local institutions capable of sustaining programme benefits over time.[891]

A related concept is the 'affordability' of an intervention to a national government, recognising that a particular intervention can be highly cost-effective yet still involve a considerable total financial commitment compared with available resources cost if the target group for the intervention is large. A good illustration of this is provided by the cost of recent national ITN distribution campaigns in Tanzania. The total cost of the 2009/2010 Under Five Catch-Up Campaign was estimated to be $63.8 million[892], compared with total recurrent expenditure in 2009/2010 by the Ministry of Health and Social Welfare of $162 million[893], implying that almost 40% of the central government expenditure on health would be needed to undertake this activity if it were to be funded through local resources. The cost of the upcoming universal coverage campaign, including behaviour change communication, is projected to be $97,332,707[894], an astounding two-thirds of the value of the central government's health budget. It is clear that national governments cannot be expected to fund these activities from domestic resources alone, and that a steady stream of external funding

will be needed to ensure that the high levels of coverage achieved by the campaigns can be sustained.

5.7 Malaria vaccines

5.7.1 Malaria vaccines: types and approaches

An effective vaccine for malaria has been sought for more than three decades, with significant resources devoted to this research. Over that time, substantial progress has been made in understanding the basic biology and immunology of malaria which might underlie an effective malaria vaccine. However, to date only one vaccine has made it through to the late stages of clinical development (RTS,S/AS01 – see below). The difficulty in developing a malaria vaccine in part reflects the complexity of malaria and the immune response to it.

The malaria parasite develops through several phases in the human body and the mosquito vector (see Annex A Life cycle and biology of malaria) and employs mechanisms to evade the immune system. Immunity to severe disease is acquired relatively quickly but immunity to milder disease and asymptomatic infection requires much greater exposure. This means that designing a vaccine for the malaria parasites is a greater technical challenge than for some of the simpler viruses, such as smallpox and measles for which a single natural infection provides lifelong immunity. This complexity presents multiple pathways to interrupt transmission or prevent the development and severity of disease, and there is considerable debate which path or paths to pursue.

Presently, vaccines for all phases of parasite development are under investigation. Vaccines that target the pre-erythrocytic stages usually aim to prevent infection. Blood-stage vaccines aim to reduce or eliminate the parasite once a person has been infected and thus to prevent disease. Potential vaccines that prevent transmission, that target specific conditions such as malaria in pregnancy, and which target specific *Plasmodium* species, are also in development.

Pre-erythrocytic vaccines

Pre-erythrocytic vaccines target the parasite before it invades the red blood cells. The aim is to prevent or reduce the force of infection being established in the human host despite a bite and inoculation of parasites by an infected mosquito. Vaccines of this type include those targeting the initial parasites (sporozoites) injected by a mosquito into the blood and those targeting the parasites developing inside liver cells.

Blood stage vaccines

Blood stage (or erythrocytic) vaccines target the asexual (blood) phase of the parasite's life, when the parasites are in human red blood cells. Blood stage vaccines aim to prevent a person from going on to develop severe disease despite being infected with malaria.

Transmission-blocking vaccines

Transmission-blocking vaccines target the gametocyte stage or sexual stage, when the parasites emerge from red blood cells and fuse to form a zygote inside the mosquito vector. Transmission-blocking vaccines do not confer immunity to infection or prevent development of disease in the person vaccinated. Rather, they are designed to stop the development of the parasites in the mosquito. This can be achieved by targeting gametocytes – the parasites which lead to transmission of malaria – in the blood or by targeting interactions between male and female gametocytes in mosquito guts, host antibodies and immune cells being taken up with sexual stage parasites into the mosquito's stomach.

Vaccines for malaria in pregnancy

Women in highly malaria-endemic areas can become semi-immune to malaria after their first or second pregnancy. This happens because they develop antibodies to antigens on the surface of infected red blood cells which are concentrated (sequestered) in the placenta. Vaccines based on this antigen are under development.

Vaccines for particular Plasmodium species

The majority of vaccine research has targeted *P. falciparum,* and vaccines for *P. vivax* malaria have not been very far developed. In theory, they do provide an attractive target biologically because the repeated episodes of vivax malaria are caused by hypnozoites which are present in the liver at relatively low levels for prolonged periods. Therefore a vaccine to prevent not only the initial attack but subsequent relapse from malaria may have a role in Asia and Latin America.

5.7.2 Vaccines in pre-clinical development and clinical trial

This is a brief summary of a complex and rapidly moving scientific field.

A substantial number of malaria vaccine candidates are in clinical trials or the late stages of preclinical development. A review in 2008 identified more than 30 vaccines that had previously or were at that time in clinical trial, with more undergoing earlier stages of development.[895] A review published in 2009 of blood-stage and multi-stage vaccines identified more than 20 in clinical trial.[896] A sizeable number of vaccines have not returned early promise, do not enter clinical trial or are abandoned after phase I or II trials (e.g. SPf66, CS-NANP, CS102, ME-TRAP, FMP1/AS02).[897] This should not be seen as an indication that vaccines will not work, but rather that developing a malaria vaccine is especially difficult.

Presently RTS'S, a pre-erythrocytic candidate vaccine, is the most advanced in clinical development and is intended primarily to protect infants and children in SSA against clinical disease caused by *P. falciparum*.[898] It is worth noting that because it is based on Hepatitis B vaccine it is an effective Hepatitis B vaccine in its own right. Phase I and II trials have demonstrated the safety and immunogenicity of RTS,S and an efficacy rate of between 30% and 60%, although the way the duration of efficacy is calculated remains controversial and may overstate the actually effectiveness.[899],[900] The immunological mechanisms underlying protection against infection and disease also remain unclear.[901] The impact of RTS, S on clinical malaria and severe disease will be evaluated in a range of different transmission settings as part of an on-going Phase 3 trial involving 16,000 children in 11 clinical trial centres in seven African countries.[902] The RTS,S/AS01 formulated candidate vaccine has entered a multi-country phase III trial and could be submitted for regulatory review by 2012 and be registered by 2013 (at the earliest), if safety and efficacy are confirmed.[903]

However, the complete dataset for the trial as designed (with 30 months of follow up in the EPI cohort), will not be available until 2014. WHO has stated that it will not issue a policy recommendation until the complete trial data are available, and that this would likely occur in 2015.[904]

If early encouraging findings are confirmed in Phase III studies, whether this vaccine will be considered to be a cost effective intervention compared to (or in addition to) other malaria control measures is currently uncertain. It is likely to depend on Phase 3 results, a realistic pricing strategy compared to other efficacious malaria control measures, duration of protection (which will not be known until there has been prolonged follow up) and a clear indication of the epidemiological settings in which it will have impact for a sufficiently long period to compare with alternative control strategies. It is likely that it will be most cost-

effective in very high transmission settings, as even an incompletely effective vaccine may avert a significant number of cases; the lower the transmission setting the higher the cost per case averted.

Trials suggest the RTS,S formulation RTS,S/AS02 may feasibly be integrated into a standard EPI schedule for infants and does not interfere with the immunologic responses to co-administered EPI antigens, potentially reducing substantially the cost and logistic implications of deploying it.[905]

Other vaccines currently under development or evaluation in clinical trial include:

- PfCS102, a pre-erythrocytic vaccine, shown in a Phase 1 trial to be safe and highly immunogenic allowing the design of trials to test its potential for protection against infection and disease.[906]
- FMP2.1/AS02A, a blood stage vaccine, which in Phase 1 trials has been shown to have a good safety profile, well-tolerated and highly immunogenic in adults and children. Phase 2 efficacy trials are currently underway in children.[907]
- GMZ2, a blood stage vaccine, shown in a phase I trial to be safe and immunogenic and suitable for further clinical development.[908]
- MSP3, a blood stage vaccine, shown to be safe, well tolerated and immunogenic in adults and children, and suitable for Phase 2 efficacy trials.[909]

Various strategies for making malaria vaccines have strong proponents, including prime-boost strategies and whole cell vaccines. Strategies for determining which antigens to combine at which stage of development are being discussed. There will be considerable challenges in the design and conduct of trials to evaluate second generation vaccines as they may have to be compared head to head with the existing vaccines, suggesting that trials even larger than the on-going Phase 3 RTS, S trail will be required to demonstrate efficacy.

Currently, only two *P. vivax* vaccines are being tested in clinical trial with a few others that are being assessed in pre-clinical studies.[910] Increasing *P. vivax* drug resistance, wide geographical coexistence of *P. vivax* and *P. falciparum* malaria species and co-infections, and observations of severe and lethal *P. vivax* cases, suggests continued development of a *P. vivax* vaccine for single and multi-species vaccines is required.[911]

Pregnancy associated malaria is a severe clinical syndrome associated with sequestration of *P. falciparum*-infected erythrocytes in the placenta. Consequences of malaria in pregnancy include anaemia for the pregnant women, and reduced birth weight and increased morbidity and mortality for their child (see Section 4.1 Pregnancy and malaria).[912]

Pregnant women become more susceptible to severe *P. falciparum* during their first pregnancy because the parasite escapes immunity acquired in earlier life. Current evidence suggests a relatively specific process underlies this: chondroitin 4-sulfate (C4S) chains (CSPGs) in the placenta mediate the adherence of parasite-infected cells. The parasite achieves this in part by expressing a unique protein variant, VAR2CSA, not encountered during childhood disease.[913] Prevention of pregnancy-associated malaria in women otherwise semi-immune may therefore be possible by vaccinating women of childbearing age before their first pregnancy.[914] VAR2CSA is the main candidate vaccine but remains in pre-clinical development.[915] However, researchers recently expressed and synthesised the entire VAR2CSA protein, considered important steps toward vaccine production.[916]

Progress in the search for an effective **transmission blocking** malaria vaccine has been slow but has received a boost from renewed interest in malaria elimination.[917] Recent pre-

clinical and phase I studies, as well as advances in malaria parasite biology, have increased confidence that a transmission-blocking vaccine is feasible.[918] However, some antigen and adjuvant combinations have shown low immunogenic responses or adverse events in human volunteers; current efforts are focused on development of a well tolerated formulation capable of inducing a strong immune response.[919]

The role of a **multi-component**, multi-stage vaccine that may combine pre-erythrocytic, blood stage and/or transmission blocking components is under discussion.[920] For example, given that the most promising pre-erythrocytic vaccine RTS,S is only partially protective, there is strong rational for the inclusion of blood-stage antigens in combination with RTS,S.[921] Models based on known and simulated efficacy of individual components have begun to assess the added value of combination vaccines and are discussed in the following section.

5.7.3 Modelling vaccine effectiveness

Opinions vary widely about the need for a malaria vaccine, its technical feasibility and, if considered necessary and feasible, the best scientific approach to adopt. From a public health point of view whether the pursuit and introduction of a partially effective malaria vaccine generally or in a given country or region is worthwhile depends on a combination of factors that include:[922]

- malaria disease burden
- economic burden of malaria
- level of effectiveness
- duration of protection conferred post-vaccination
- transmission setting in which it will be deployed
- extent of heterogeneity of the host response
- extent to which parasites have the ability to evolve around selection pressure from a vaccine
- natural force of infection and its seasonal variation
- operational feasibility and the vaccination coverage that could be achieved, given current or potential health systems and delivery modalities
- efficacy and coverage of other malaria control interventions
- whether the vaccine is cost-effective and the availability of financing mechanisms
- vaccine safety profile
- cultural perspectives
- public health objectives (e.g. transmission reduction; reduce mortality; prevent clinical cases; protect a vulnerable group).

Two models a) simulate the effectiveness of malaria vaccines under different conditions and b) simulate their cost-effectiveness. These are intended to provide vaccine developers with information that will assist decisions on: the allocation of resources amongst different candidates; which candidates to consider combining; and deployment strategies. Neither incorporates all these elements. The ability of parasites to evolve around selection pressure in particular is difficult to model as it is essentially an unknown.

Vaccine effectiveness

Penny et al. make quantitative predictions of the population effects of a range of malaria vaccines and vaccine combinations on transmission, morbidity and mortality.[923] Key results are:

- Pre-erythrocytic vaccines (PEV) have greatest benefits in low endemic settings with 12%-14% of all deaths averted when initial efficacy is 50%.
- In some high transmission scenarios PEV may lead to increased incidence of severe disease in the long term, if efficacy is moderate to low (<70%).
- Blood stage vaccines (BSV) are most useful in high transmission settings.
- Combinations of PEV and BSV generally perform little better than the best of the contributing components.
- A minimum half-life of protection of two to three years appears to be a precondition for substantial epidemiological effects.
- Herd immunity effects can be achieved with even moderately effective (>20%) malaria vaccines (either PEV or BSV) when deployed through mass campaigns targeting all age-groups as well as EPI, and especially if combined with highly efficacious transmission-blocking components.

This simulation accounted for the dynamic effects of natural and vaccine induced immunity, treatment of clinical episodes, and births, deaths and ageing in the cohort. However, interactions of the vaccine with other malaria control interventions were not included. Further modelling and comparison with field research is required to test the validity and robustness of this simulation.

Vaccine cost-effectiveness

Tediosi et al predict the cost-effectiveness of potential vaccines (PEV, BSV, Multi Stage Transmission Blocking Vaccine (MSTBV) and combinations of these) and show that transmission setting and delivery modalities affect cost-effectiveness. The simulation suggests:

- PEV is more cost-effective in low transmission settings
- BSV is more cost-effective in high transmission settings
- Combinations of MSTBV and PEV or PEV and BSV improve cost-effectiveness compared to PEV and BSV alone only when applied with EPI and mass vaccinations
- Adding booster doses to the EPI is unlikely to be a cost-effective alternative to delivering vaccines via the EPI for any vaccine
- Mass vaccination improves effectiveness, especially in low transmission settings, and is often a more efficient alternative to the EPI but the costs of increasing the coverage of mass vaccination over 50% often exceed the benefits.

Tediosi et al conclude that most vaccines and delivery modalities are likely to present cost-effectiveness ratios that compare favourably with other malaria control interventions. However, this may be challenged if certain assumptions (some not explicit) are not borne out; for example that the EPI coverage rate obtained is 89% and that different vaccines and combinations of vaccines have the same price. In practice it is likely that EPI coverage and price will be variable. This suggests effectiveness and cost-effectiveness studies need to be tailored to the particular settings where vaccines are likely to be deployed.

An important limitation of these simulation studies is that they do not consider the effectiveness of vaccines in the context of other malaria control technologies and interventions. Widespread simple control measures are reducing the burden of malaria in some African and Asian countries (see Section 5 Interventions and delivery, for more details). This raises the question of whether a partially effective malaria vaccine directed at disease prevention is still required.[924] Such a vaccine may not be required and/or cost effective if the following assumptions are borne out:

- initial success achieved with scaling up malaria programmes is found to be generally applicable (vaccines become increasingly less cost effective as overall burden of malaria falls)
- the pipeline for new drugs and insecticides in the face of resistance is maintained
- long-lasting ITNs, which also provide protection against other vector borne diseases, remain available at an affordable cost,

except where the following conditions apply:

- current methods of vector control are not effective because of the feeding and resting habits of the major vector mosquitoes in a given area (notably some part of south Asia and South America)
- an area lacks adequate health services for vaccine deployment

However, highly effective (>90%) vaccines targeted at malaria elimination may have an important role for those countries where elimination is a realistic goal.

5.7.4 Barriers, challenges and ways forward

Challenges to the development, registration and deployment of malaria vaccines can broadly be grouped into technical challenges and health system challenges. Technical challenges include: improving efficacy rates, ideally significantly above 50%, for periods long enough to make public health sense; overcoming genetic diversity found in the surface proteins employed as vaccine antigens; improving understanding of mechanisms underlying naturally acquired immunity; improving and standardising in vitro assays and animal models; overcoming the difficulty of diagnosing clinical malaria and therefore vaccine efficacy; and improving understanding of transmission dynamics and disease causation in the field which would lead to more accurate predictions of efficacy and outcomes at a population level.[925]

These technical difficulties are accompanied by, and often entwined with, infrastructure and delivery challenges. For example, to date in most clinical trials, clinical immunity is has not been followed observed in a large proportion of subjects for a significant length of time, and this has obvious practical implications. Children from endemic areas would need therefore to be in a position to access frequent vaccination doses.[926] Although studies have shown that a malaria vaccine could be delivered through the EPI, they may be more expensive than currently available EPI vaccines and new financing mechanisms may be required for them to be established in developing countries.

It has been argued that vaccine development would be facilitated through strengthening capacity in malaria-endemic countries to conduct clinical trials.[927] The Malaria Clinical Trials Alliance (MCTA) was launched in 2006 to facilitate the development of a network of centres in Africa with the capacity to conduct clinical trials of malaria vaccines and drugs. MCTA strengthened 13 centres to perform Good Clinical Practice compliant vaccine trials, including 11 centres that form the backbone of a large phase III trial. However, the costs are substantial and further support of other centres is required to meet the growing demand for clinical trial capacity.[928] Also, it has been suggested that the currently weak regulatory

framework in endemic countries may need strengthening to enable them have oversight over clinical trials.[929] Standardised and validated methods used for defining clinical endpoints in vaccine trials would facilitate regulatory decision-making.[930]

The Advanced Market Commitment (AMC) mechanism, which aims to pre-purchase vaccines when they are being developed, has been discussed as a potential vehicle for funding the introduction and scale up of an appropriate malaria vaccine.[931] Cost benefit analysis needs to be undertaken to examine whether this approach to malaria is the best one. The World Bank and GAVI aim to finalise a lessons learned paper from the pilot pneumococcal vaccine AMC by the end of June 2010. This paper is essential before any decision is made on a malaria vaccine AMC process. A malaria vaccine AMC would look very different, however, and would have to be modelled on the basis of a realistic threshold for the effectiveness, longevity and cost of a malaria vaccine compared to other control measures.

5.8 Approaches to health systems[932]

Almost all malaria-endemic countries have now outlined National Malaria Control Strategies and malaria indicators are improving with respect to coverage of interventions and health impact[933]. However, it is generally recognised that the success of such programmes is hampered by resources constraints and absorptive capacities, in particular the ability of a health system to deliver interventions at the required levels of coverage and quality to be optimally effective[934]. Some progress has been made in understanding health systems strengthening; the peer-reviewed literature on health systems and malaria broadly encompasses private, public, and community systems. Much of the evidence though is context-specific, descriptive, qualitative and based on convenience samples. High quality evidence on the effectiveness of health systems and their impact on health outcomes remains limited.[935] [936]

One approach to considering health systems strengthening is the WHO conceptual framework for health systems [937]. This describes six 'building blocks' that constitute a complete system, including governance, information systems, financing and workforce, and forms a potential structure for considering interventions in support of malaria control.[938] The main pillars of the health system, listed below, must be present simultaneously and continuously across the entire network including hard-to-reach places for the health system to function optimally and efficiently:

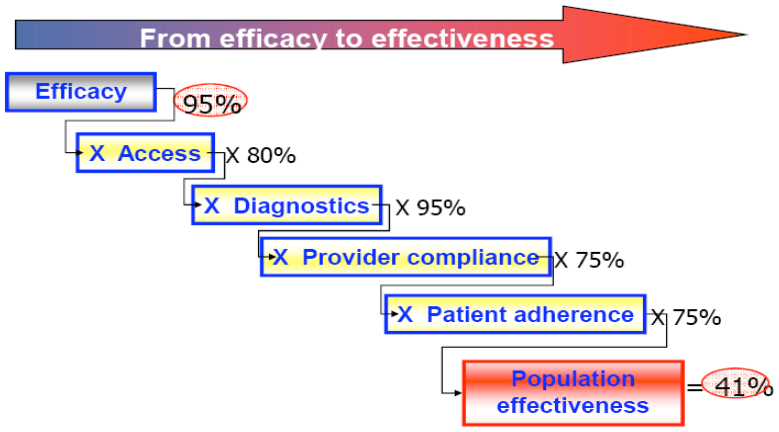
- *policy* – evidence-based policy that seeks to maximise health outcomes for the most vulnerable and to address the underlying causes of poor health;
- functioning health facilities with staffing – adequately trained and supported, available, accountable health workers;
- *medicines and health supplies* – affordable and appropriate preventative, curative and emergency commodities including essential medicines, diagnostic material and basic equipment consistently in stock, dispensed rationally by health workers and consumed correctly by patients;
- *financing* – a good health financing system raises adequate funds for health in ways that ensure people can use needed services, and are protected from financial catastrophe or impoverishment associated with having to pay for them;
- *information management* – essential for district health systems and necessary for budgeting, planning and decision-making: reliable information makes the difference to using scarce resources efficiently;

- *leadership and governance* – political will to prioritise prevention, the health of the poorest and to maximise health outcomes by allocating – and spending – resources in a way that reduces the greatest amount of preventable morbidity and mortality amongst the poorest.

Thus although the efficacy of interventions such as IRS, LLINs and Intermittent Preventative Treatment (IPT) is well documented in the literature (see Section 5.4 Drugs to prevent malaria), successful malaria control – considered here as sustaining effective delivery of prevention, diagnosis and treatment at sufficient coverage levels – requires combined investments in all the building blocks within a health system.

The 'systems effectiveness framework' outlined by Tanner et al[939] is a useful approach to understanding health systems' dynamics and their impact on coverage. It highlights how interventions diminish in efficacy through a cascade of interacting system barriers, such as poor access or provider-adherence (including inappropriate diagnosis and prescribing on the part of health workers) and is relevant in both public and private sectors. Figure 5 below shows a simplified framework, demonstrating the impact on treatment efficacy of various health systems factors to reduce overall population effectiveness when deployed.

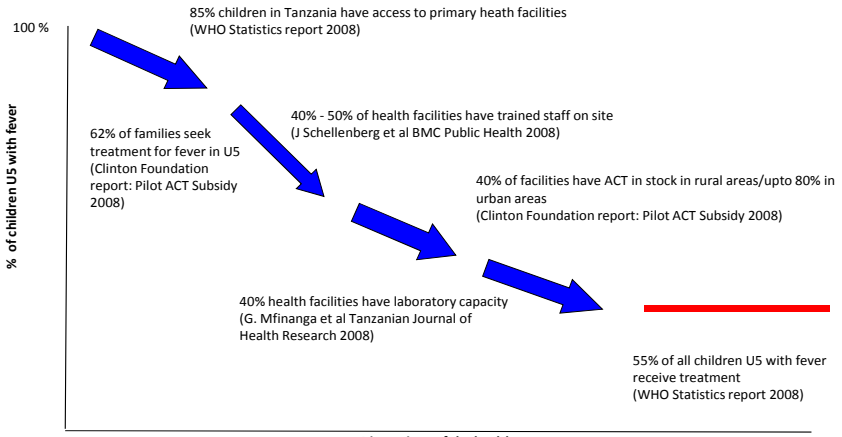
Figure 5: From efficacy to effectiveness: a systems effectiveness framework[940]



Treatment

Figure 6 below shows a schematic adapted from the systems effectiveness approach. This demonstrates the barriers to effectiveness for treating children under five for fever. Health systems, delivery approaches, prescriber and patient behaviours, and transmission settings all play an important part in determining the optimal delivery, scale up and use of current tools within malaria control.

Figure 6: Systems barriers to effectiveness for treatment of children under five with fever[941]



	Access to primary health care	Human resources: e.g. skilled provider availability	Diagnostic capacity: e.g. microscopy	Treatment capacity: e.g. ACT in stock			
	Utilisation	History Taking	Clinical examination	Drug dosage	Drug buying	Drug taking	Estimated end-Treatment efficacy
% effective procedures		x21	x7	x5	x4	x4	x3
% combined effectiveness (estimated)	21	7	5	4	4	3	3

Community effectiveness of healthcare: A study of malaria treatment in adults and children in Burkina Faso (Krause & Sauerborn Ann Trop Paed 2000)

Critically the framework demonstrates that the constraints to effective delivery of malaria control operate at multiple levels of the health system. The figure shows part of the story. It could continue with another reduction for those children who receive the wrong dose of medicine or who don't consume their medicine correctly. The indicative 55% efficacy could therefore decline further. Thus it follows that a series of solutions are required, both specific and inter-sectoral across these multiple levels.

5.8.1 Health delivery systems: public and private

With the advent of improved treatment and control technologies such as Artemisinin Combination therapies (ACTs), there is growing interest in harnessing the capacities both public and private delivery systems, including for example through innovative funding mechanisms such as the Affordable Medicine Facility – malaria (AMFm).

Government ministries of health (or equivalent) mostly oversee national malaria strategic plans and Control programmes, budget allocations, national guidelines, and drug and treatment policies.[942] Service delivery in the public sector is organised across government districts into dispensaries, health centres, district, and regional hospitals. Importantly the health facility is not only the main point of contact with the health system for many patients with fever, but it is also ideally the focal point for surveillance and data collection. However, although the formal public health system is the cornerstone of delivery in most endemic countries, utilisation is often poor.[943]

Many formal sector facilities are beset by drug and diagnostics stock outs, lack of human resources, poor health-worker prescribing behaviour, and a primary health system that is often distant and too costly for rural populations, poor people or those at highest risk. [944]

In practice, a large majority of poor people and those at highest risk do not use any formal health services for treatment of malaria. It is widely recognised that the first entry point to care is the informal sector, which typically consists of local drug shops, kiosks or drug sellers.[945,946] The majority of fevers are treated through this informal and unregulated private sector, often due to proximity, cost and perceptions of drug availability and perception of

quality[947,948,949], and thus needs to be a consideration when planning health systems strengthening.

Several descriptive studies highlight the barriers within formal public health delivery, as demonstrated by Figure 2 and the effectiveness framework. A Somalian study in 2009 showed distance to public health facilities is often further than private vendors, and 37% of the public health facilities charged for consultation, diagnosis or treatment thereby adding additional barriers to access. [950] It also demonstrated that public sector facilities had good compliance with national treatment guidelines for case management. However, despite the effective case-management practice, their services were hampered by widespread drugs and diagnostics shortages. In contrast, 53% of private sector facilities surveyed still prescribed chloroquine as a first-line treatment and 42% of whom maintained stocks of Artemisinin monotherapy.

A study in Kenya showed that two years after the adoption of ACTs as first line treatment, 26% of public sector facilities had no ACTs in stock. These stock outs were most severe in the places of greatest need, and especially more common in community outpatient dispensaries and for paediatric doses.[951]

There is limited evidence on the supply and demand of antimalarials in the informal private sector, and this makes developing strategies of effective interventions within this sector a challenge. However, systematic review of the literature highlights several issues with the informal private sector including:[952]

- *Lack of regulation*: the legal status of private retail outlets and use of licensed staff vary considerably. Most of the informal private sector is staffed by untrained shopkeeper rather than qualified dispensers. In most settings drug retailers are unlicensed, unskilled workers with limited knowledge of the drugs and dosages. Without microscopy or other diagnostics, drugs are prescribed, often incorrectly, or over prescribed presumptively based on fever. The accuracy, quality and consistency of information provided to patients can vary widely, if provided at all953.
- *Poor quality drugs:* There is substantial variation on a country and local level on the drugs administered through informal private sector. In most settings, a patient is more likely to receive anything other than a high quality ACT 954,955. There is good evidence of the extensive distribution of anti-pyretic OTC, counterfeit or substandard antimalarials, Artemisinin monotherapy or chloroquine as first line treatments. When high quality ACTs are provided, many high risk populations may find them unaffordable or unavailable 956.
- *Perverse incentives:* Private outlets are run as businesses with a financial stake involved. From a business perspective, the ‘buyer’ wants an affordable product, which is potentially less effective (e.g. antipyretic, substandard, etc). The ‘seller’ wants a satisfied customer, but also needs to sell a product, regardless of whether the product is actually needed (e.g. prescribing an antimalarial for a non-malarial fever)957. If appropriate diagnostics are deployed to confirm the diagnosis, sellers lose their profit margin from dispensing antimalarial. For this reason the idea of economically "bundling" a package of RDT plus treatment may be attractive (not physically bundling, which would encourage ignoring results). The idea is to pay one price, and then you get the diagnosis and if you need it the treatment. No data yet to support the idea however.

Quality assurance is also a systems barrier to effectiveness across the spectrum of providers and modes of delivery. A small retrospective study from Nigeria compared public and private facilities and found ACTs were available and were used significantly more in

public sector facilities, with private sector also using chloroquine and monotherapy as first line treatment.[958] However, there was low (32%) availability of rapid diagnostic tests (RDTs) across both public and private systems and worryingly only half (51%) of the facilities that stocked RDTs actually used them. Similarly, a Kenyan study in public clinics, found that even when ACTs are adequately stocked, drug dispensing and counselling varied by patient symptom, qualification of the health worker, drug formulations and availability.[959]

Qualified health workers are a vital requirement of any functioning health system and effective malaria control programmes. Yet, in most low and middle-income countries, this remains a critical weakness. Estimates from 2006 in the African region alone show a shortage of 1.5 million health workers[960]. Insufficient supply, inequitable distribution, poor motivation, lack of supervision and support of health workers are well documented in the literature.[961,962] The problem of the health workforce is not unique to malaria; however, lack of health workers is a significant bottleneck to implementing evidence-based case management of malaria.[963] Importantly, rural and poor areas where the malaria burden is disproportionately high, suffer the most critical gaps in trained health workers.[964]

5.8.2 Evidence on approaches to improve systems effectiveness

Access to local services and district health planning

It is commonly accepted from the time of Alma Ata that providing healthcare services at a primary care level is essential to reaching the widest section of the population, identify those at risk and reduce the burden of disease.

Public sector facilities have been at the heart of most National Malaria Control Programmes and are the main sources of regulated care in many communities serving poor people. They provide laboratory and diagnostic services, monitoring and evaluation functions, disease surveillance and treatment for severe malaria and complex cases. However the evidence outlined above demonstrates that in reality the first port of call for a fever is usually a private outlet, and therefore this sector does need to be included in strategic planning. To this effect, there is some evidence to suggest that interventions directed at private retail outlets can improve their capacity to provide safe and appropriate antimalarials.[965,966,967] However, these are mostly small scale, single-country studies, including training, regulation, voucher schemes, social marketing, banning monotherapies, and subsidising high quality ACTs, but there is little evidence of national scale up of such interventions.[968]

The causal relationship between improving delivery in public health systems and impact on health outcomes is unclear.[969] However country-based studies in Rwanda, Zanzibar, Kenya, Ethiopia, Uganda Zambia, and Sao Tome and Principe provide examples of how large scale distribution of LLINs and ACTs through formal public health channels is associated with reaching national targets on utilisation, access and coverage as well as reductions in malaria prevalence, admissions and deaths.[970,971,972,973,974]

Geographical access, or distance to a facility is a critical component of effective delivery at primary care level.[975,976] People living in close proximity to primary healthcare services have reduced odds of malaria progressing from mild to severe disease.[977,978] Noor et al.[979] found a reduction in the number of people using formal health facilities as distance to the facility increased. Importantly the distribution of public healthcare facilities in many parts of Africa is patchy, often with the most remote parts, which typically include the poorest populations with the highest rates of malaria morbidity, being underserved.[980]

Decentralising services, usually to local primary-level facilities or even providing community-based management or co-opting private outlets is one of the most significant approaches to reduce the physical access barrier to treatment and reach patients earlier in disease

progression.[981] However, patients will only attend these facilities if they can provide a quality service. Effective decentralisation requires adequate infrastructure, drug stocks, trained workers and affordable treatment. The issues of healthcare workforce, CCM, training, supply chain management and the cost of treatment are discussed later in the review.

Improving access to and the reach of primary care services requires investment and planning at the district and national level. Effective malaria control requires significant commitment at a national level as well as facility level, in order to develop a strategy based on technical feasibility, yet in line with economic and political considerations.

The district is the co-ordination hub for delivering service and for managing the health information and surveillance required to improve planning and forecasting. Some critical bottlenecks exist at the district level resulting in frequent stock outs, inefficient disease-control operations and poor quality services, which deter utilisation of public sector services.[982] Enhancing district-level system operations is vital to reducing the effectiveness losses for interventions, and increasing the cost-effectiveness of programmes. The district level functions of leadership, planning, resource allocation and surveillance are critical to the success of malaria control programmes being deployed successfully. Capacity building and investments at this level, however, need to be made in a context-specific manner for which robust evidence is difficult to obtain or generalise.

Availability of treatment and supply chain management

In order for public trust and utilisation of health service, the public need to be confident that the medicines required can be reliably obtained at the point of service delivery. Irrespective of whether patients have to pay for the ACTs, availability in peripheral public health facilities remains a challenge. In most instances, ACT movement from the central medical stores to the periphery is often irregular and inconsistent.[983]

The causes of stock-outs vary, but often reflect weak drug management planning systems in disease-endemic countries. Poorly resourced supply chains, erratic stock management practices, and inadequate lead-time planning can significantly affect the regular availability of drugs in the public health system.[984] In addition, unpredictable flow of funds in many countries, combined with inadequate distribution from central warehouses to peripheral points of care, undermine the ability to ensure that ACT and other essential drugs are always available as needed throughout a country. These are important limitations in the advent of the Affordable Medicine Facility for Malaria, which aims to increase consumer access to Artemisinin-based combination therapy (ACT), through a subsidy introduced at the top of the distribution chain.

Despite external organisations, such as the USAID Deliver project[985] often helping to support national programmes for supply chain management and forecasting, this remains an area where robust evidence of effective interventions and solutions is lacking.

Part of Rollback Malaria's Global Action Plan emphasises the need for rigorous procurement and supply chain management, identifying the challenge for national and district level services to improve forecasting, updating procurement guidelines, consideration of the varying shelf-life of malaria interventions (LLINs and ACTs) as well as international priorities such as the limitation of raw materials supply in the case of ACTs, and the different product eligibility amongst donors.

The plan acknowledges the paucity of best practice examples for countries that wish to leverage different distribution systems (such as private, public, and NGO systems) for malaria interventions. However, they suggest that innovative procurement mechanisms such as AMFm (see later in the review), considering pooling procurement, sharing of good

practices especially from the private sector as well as careful analysis of the delays in a country and district specific way. This would need considerable investment in capacity building at national and district levels to improve the surveillance, monitoring and evaluation and forecasting methods.

Drug quality and formulation

There is mixed evidence on improvements from pre-packaging, using fixed dose combinations and co-formulations of ACTs. A Cochrane review found insufficient evidence to conclude that unit-dose packaging reduces treatment failure.[986] However, other studies have shown that pre-packaging, along with prescriber training and patient information may improve treatment adherence.[987,988] Another benefit of pre-packing and co-formulations is it eliminates the problem of patients removing or only taking selected drugs from separate blister packs. Co-formulation also makes Artemisinin monotherapies less available and thereby decreasing the risk of resistance.[989]

Fraudulent and counterfeit drugs are also known to be a significant problem throughout endemic countries, and are a major impediment to malaria control[990]. Regulation through drug banning or interventions to improve drug quality has a very limited evidence base and is country-specific with respect to different regulatory processes that can be implemented and followed up. Enforcement and banning of anti-pyretic or malaria drugs in the private sector has worked in some settings[991] but may be detrimental when the alternative, formal public sector, provides an equally poor service.[992] A ban on Artemisinin monotherapy has appeared to work temporarily in Cambodia. This is, however, a large-scale concerted effort in specific zones to limit the spread of Artemisinin resistance. It is unknown how sustainable the ban will be and if it can be implemented at countrywide scale.[993] In reality this will require international coordination and legislation to enforce improved standards and deter such fraud.

Training in case management and rational treatment

Rational appropriate treatment of fever is essential to reducing morbidity and mortality from all causes. In addition, in order to preserve the effectiveness of medicines such as ACT over time and slow the development of resistance, it is important that they are used appropriately. Ensuring that medications are prescribed according to national guidelines with the provision of adequate dispensing and counselling is critical to maximise patients' adherence and treatment successes [994]. However non-adherence to malaria case management guidelines has been commonly reported in the past under ACT and non-ACT policies.[995,996] Healthcare worker training has thus been a main focus of donor and national programmes.

A Kenyan study[997] evaluated an initiative to improve malaria case-management through a package of enhanced in-service training and provision of job aids. The results found that no health facility or health worker was exposed to all components of the intervention but that approximately two-thirds did receive the enhanced in-service training. If the recommended first-line treatment for paediatric cases was in stock, correct prescription rose from 76.9% to 87.6% and there were some modest but non-significant improvements in dispensing and counselling practices. However this did not result in any significant improvements in reported case management tasks compared to baseline.

This study, one of the first to evaluate such training demonstrated that even enhanced, well funded in-service training and job aid development packages aimed at improving the way febrile patients are managed in health facilities does not produce more than modest improvements in quality of care. The authors acknowledge that improving intervention coverage must be a pre-requisite to any significant changes in the proportions of patients managed effectively with new ACT medicines. However, despite the limitations of the study,

the authors express reservations regarding future large-scale investments in in-service training and provision of job aids without other features of support, such as supervision, to enhance the value of training and printed materials.

In contrast, two systematic reviews showed that Integrated Management of Childhood Illness (IMCI) improves the performance of health workers in the public sector[998,999] and on malaria treatment, and clearly healthcare worker training is a component of quality assurance. However, there is significant country-to-country variation in success, for example IMCI effectiveness was twice as high in Tanzania as in Uganda.[1000] The impact may also depend upon the level of cadre of the healthcare worker and who actually writes the prescription.[1001]

Healthcare worker training requires adequate supervision (i.e. workforce planning), and importantly requires available drug stocks and sufficient health facility infrastructure for truly effective implementation.[1002,1003] Training of workers in private outlets shows similar results, although there no evidence at present which suggests any advantage over public sector training, or whether it results in more or less equitable access for patients.[1004]

Community case management / home malaria management

Recent and past experience indicates that fixed facilities are unable to provide care for all the population, and that in order to achieve improved access, further innovative extension of services may be required. There is good evidence to suggest that CCM (also known as home malaria management (HMM) using trained community health workers (CHWs) provides a valuable opportunity in reaching poor, rural and marginalised groups, as well as assisting both prevention and treatment intervention delivery. Bhutta et al's systematic review of the role of CHWs,[1005] published in 2010, highlights much of the evidence (see Box 1 below) and establishes a typology for CHWs in respect to malaria control (see Figure 7 below).

A number of countries have adopted this approach at varying levels, with several successful examples emerging from Indian, Sri Lanka, Cambodia Ethiopia and Uganda [1006], [1007], [1008].

A systematic review in 2007 showed that home and community based management can effectively reach all levels of a population, but is particularly useful for groups located far from formal facilities. The review indicated that such schemes could improve delivery, timing, adherence and dosing of treatment. However, the overall impact on morbidity and mortality outcomes were mixed, with limited evidence of a decreased risk of progression to severe malaria and only one study showing a decrease in prevalence and incidence. The review concluded that HMM evidence is mixed and that further evidence would be required, particularly on impact and outcomes, before widespread implementation should be supported.[1009]

Box 1: Global experience of community health workers

The role of malaria workers in the literature reviewed was to promote use of insecticide treated nets and provide treatment for uncomplicated malaria. While, from country case studies, their main role was found in counselling and referral for insecticide bed nets, IPTp treatment, and rapid diagnostic test. Only two programs, Ethiopia Health Extension Program and BRAC Bangladesh have trained their CHWs for rapid diagnostic tests and treatment. The CHWs working in this domain often faced shortage in supply of new malaria drugs and insecticide treated bed-nets preventing them from offering services in their true capacity. Since in many studies, CHWs were local farmers or drug distributors from the community, they were, in principle, always accessible to the villagers, who had been motivated through health education to consult the CHW for any fever episodes. Key problems in these interventions revolved around the limited scope of the CHWs' practice and their ambiguous role within the health care system. More specifically, Delacotte et al. observed that CHWs wanted to be more than symbolically remunerated for their services; they were eager to receive further training so as to expand their scope of practice, and they wanted to become a formal part of the health structure.

Source: Bhutta Z, Lassi Z, Pariyo G. and Huicho, L. (2010). Global Experience of Community Health Workers for Delivery of Health Related Millennium Development Goals

In the past, some CHW programmes have not been as successful as anticipated because they did not recognise the need to compensate or reward the workers for the time spent delivering services and because they were often not appropriately linked into or supported by more formal health systems upper levels.[1010] The literature suggests that given rapid changes in treatment and diagnostics as well the increase in private provision, the role of the CHW and home management is a potential avenue to be further explored, with more innovative approaches required to sustain performance and motivation, for example through supervision from health facilities and integration of the results into local health information systems or surveillance. A Cambodian study [1011] found that often the CHW role was focussed primarily on diagnosis and treatment, but that broadening their focus to cover other aspects of malaria control could further strengthen their role and impact, and potentially improve accountability between healthcare services and the populations they serve. The study noted that training and supervision of their actions and knowledge needed substantial improvement on a regular basis.

A cluster randomised trial in Zambia, investigated the CCM of fever due to malaria and pneumonia in children under five and found that such integrated management was both feasible and effective[1012]. The researchers randomly allocated 31 community health posts (fixed locations where CHWs provide medical services to several villages) to the study's intervention (CHWs who used RDTs, treated test-positive children with an ACT and those with non-severe pneumonia with amoxicillin) or control arms (CHWs who did not have access to RDTs, but treated all children with a fever with an ACT and referred those with signs of pneumonia to a health facility). The study outcomes showed a four-fold reduction in treatment with ACTs, and no presumptive malaria treatment in the intervention group (CHWs with access to RDTs). These findings indicate that CHWs in Zambia are capable of using RDTs and ACTs to manage malaria, and potentially could reduce the overuse of ACTs, which would also be relevant to coordinating with private sector outlets and practitioners.

Additionally, a Nigerian multicentre study, showed that the start-up costs of a CHW strategy was low, and would be both affordable and acceptable to malaria control programmes and communities. Using local data, they deemed the strategy a cost-effective source of timely and appropriate management of malaria in rural areas covered by few fixed facilities, and recommended that such a strategy rolled-out in other areas in a context-specific fashion. [1013]

Figure 7: Typology of CHWs for malaria control[1014]

Recommendations – Typology of Malaria Control CHW

Key competencies	CHW Contextual Factors								
	Recruitment	Educational criteria	Training content, duration & role (initial & ongoing)	Certification process	Monitoring supervision & evaluation	Volunteer / salaried	General or Performance incentives	Career pathway & development	Referral system
Malaria control CHW	Community Involvement in identification of potential community health workers -Advertisement in local newspaper or radio channel for interested candidates to join ***Applicant must be*** -18-40years of age -from the local community -permanent resident **Test:** on literacy and numeracy **Interview:** to judge on motivation and willingness **final selection by community and local health center**	primary level schooling	**Initial: 1 week** **On-the-job: 2-3 weeks** ***key Role*** **Promotive, preventive, and therapeutic interventions:** -prompt treatment with effective drugs for all people especially children suspected t have malaria -increased access to low cost insecticide treated bed nets, especially for children and women -protection for pregnant women (e.g. regular prophylaxis/ intermittent preventive treatment). -Community-based treatment of malaria (testing with Rapid Diagnostic Test or presumptive treatment for malaria per national guidelines.)	Exam after initial training → on passing exam and completion of initial training they should be awarded with title → on completion of on-job training they should be awarded with a certificate	Supervisors 1 supervisor: 20-25 CHWs Evalustion: annual internal evaluation external evalustion in every 5 year	**volunteers *** **OR** **Salaried** keeping in view that they are poor Full time employment	--identification of suspected case -sales of insecticide treated bed nets	Should be offered to advance their career as supervisor on completion of minimum education level and experience required to reach the next level.	linkages between TBAs and health system

*Volunteers (community members who volunteer few hours a week) Salaried (full time CHWs)

Health workers and workforce planning

A recent analysis of several systematic reviews on the human resources noted the following acute challenges: absolute shortage of trained staff, inequitable distribution largely within rural areas, staff absenteeism, and poor motivation.[1015] The causes are multi-factorial and the scale and impact on health outcomes varies from country to country. Overall, migration, low pay, lack of supervision and support, and sickness are all considered as contributors.[1016] Literature on health workers for malaria-specific interventions and the impact on treatment outcomes is limited.[1017,1018] A number of responses to address health worker shortages have been proposed, including the traditional approaches of training and supervision, performance-based compensation and bottom-up approaches through community accountability structures. Some potential approaches are more context-specific such as:

- Addressing health worker skill-mix and task-shifting from highly trained doctors to mid-level and community workers may deliver cost savings. Community and mid-level workers to work in rural and primary care settings can be trained more quickly and offer short-term solutions. Community and lay health workers for case management may assure better access to treatment as discussed previously.[1019,1020]
- Reducing competition for labour amongst private, public and NGO sectors through the use of guidelines such as the NGO Code of Conduct on Health Systems Strengthening may foster cooperation in areas where skilled health workers are limited.[1021]
- Developing innovative models and using workers from outside the traditional health services, such as school teachers, can improve case detection and manage acute episodes of malaria.[1022,1023]
- Human resource demands may be reduced through technology and simplified interventions. For example, using RDTs rather than microscopy can reduce human resource demands and mobile phones may be used to for case detection in rural areas.[1024,1025]

Health worker training and supervision is frequently cited as a solution to improving system performance and improved health outcomes in some areas,[1026,1027] However, training for malaria treatment has shown more mixed results as discussed earlier in this review,[1028] and there remains very limited evidence on 'what works' amongst providers, for example regardless of setting or method, treatment improvement from training can only be found in areas where there is an adequate supply of effective antimalarial drugs.[1029]

Despite the small scale and country specific nature of studies on health workers, there are several areas of consensus. This includes the following:

- Investment in health workers should be complemented by improvements to the overall health system.[1030,1031,1032] In Somalia, despite efforts to train and strengthen the health workforce for malaria, treatment outcomes were hampered by drug stock outs and lack of diagnostics.[1033]
- Human resources constitute the greatest expenditure of any health system or programme. Although there is strong country variation, trained health workers absorb a substantial proportion of health spending, sometimes taking up to three quarters of a government's spending on health.[1034]
- Health worker improvements such as introduction of guidelines, training and supervision may improve knowledge, behaviours and practice. Evidence is lacking, however, on how long this effect can be seen and whether it ultimately makes a substantial difference to malaria treatment outcomes.[1035]

It is important for any intervention aimed at improving health worker performance to recognise the interconnectedness of the systems approach, for example performance-based pay relies on health information systems as well as training, and the form and source of such payments. Some incentives may focus on certain targets and divert human resource away from services that are equally important yet not targeted. This requires parallel investments in Human Resource Management to ensure a coordinated approach.

Human resource management and information systems

Human Resource Management (HRM) is increasingly being identified as a critical input to health systems strengthening.[1036] Human resources, in the context of healthcare may be defined as the mix of different kinds and cadres of clinical and non-clinical staff responsible for delivering healthcare, both public and individual[1037].

The outcomes achievable by a health system rely to a large extent on these individuals responsible for intervention delivery, and thus it is important to achieve the necessary balance of cadres and roles[1038]. It therefore follows that as a result of the differences in roles and responsibilities, human capital also requires complex management to support skills and ensure the appropriate balance of workforce supply and the ability of those practitioners to practise effectively and efficiently[1039].

Effective HRM requires knowledge of population need in order to tailor services appropriately and training to deliver the services required. Development of health information system policies and procedures is necessary to generate consistent information to design and implement more effective and efficient prevention and control programmes, and other resource allocation.

In addition developing human resource capacity for utilising the health information systems will also allow for better analysis of data, leading to better decision-making for activities such as defining health information staffing needs, and recruiting staff.[1040,1041]

Health management information systems (HMIS) including routine surveillance systems at health facilities provide tangible evidence of the burden of malaria, which needs to be the basis for planning, including intervention costs, coverage and provider compliance[1042]. However, most malaria-related morbidity is treated at home or within the community utilising informal health services and networks. A study from rural Ghana illustrates the discrepancy between estimates of the burden of 'febrile illness presumed malaria' based on routine HMIS data, and that derived from community level data on morbidity and health seeking behaviour of households[1043]. The study suggests that community level health information and surveillance is also urgently needed in a timely manner to better plan and understand need, costs and logistics. Community health workers would be a possible key to such extension to information systems and may also empower community level decision making.[1044,1045,1046]

Cost and ACT subsidy (Affordable Medicine Facility-malaria)

As shown previously, the first point of contact with healthcare is through the informal private sector retail outlets. Most people who need medicines have to pay for them out of their own pockets, and even where the cost of drugs is covered by formal health services, spending on medicines is still a major part of the total healthcare budget. Unaffordable prices have been reported as the major barrier to accessing treatments such as ACTs in malaria-endemic countries.[1047,1048]

In 2009, the subsidy programme – Affordable Medicines Facility for malaria (AMF-m) – was launched, to address the price barrier by drastically reducing the price of ACT. The principle behind AMFm is to facilitate affordable access to ACTs in selected countries through the

public, private, and non-governmental organisations through a co-payment facility. AMFm negotiates a reduced price for high quality ACTs and then provides a co-payment toward the cost to lower the price to the end user.[1049] The aim is that, by creating competition and reducing the cost, access to ACTs would increase, monotherapies could be driven out, and emerging drug resistance could be curtailed.[1050] There is little evidence on the effectiveness of AMFm or a subsidy approach in practice and at scale, although a pilot study in Tanzania indicated that such a subsidy applied at the top of a private sector supply chain could significantly increase usage of ACTs and reduce their retail price to the level of more commonly sold monotherapies.[1051] Aside from the issue of cost, the AMFm aims to support interventions to address other barriers to effective access to ACTs, including socio-economic barriers, strengthening regulatory systems, improving supply chains and improving quality of services, although precise strategies have not been outlined.[1052]

5.8.3 Reaching the poorest

Malaria is a severely inequitably distributed infection, concentrated in the least developed countries in the world with 58% of malaria deaths occurring in the poorest 20% of the world's population. In many countries, malaria intervention coverage rates have increased as a result of scale up; but aggregate indicators mask limited coverage in these highest-risk populations.

The poorest people (lowest socio-economic status) within these countries have lower ITN coverage rates, a higher proportion of cases, and experience higher rates of severe disease and death.[1053,1054] (See Section 3.2 Household and community levels). Steketee and Eisele reviewed reports from nationally representative surveys in African malaria-endemic countries from 2006 through 2008 with data on household intervention coverage by urban or rural setting, wealth quintile, and sex. Household ownership of insecticide-treated mosquito nets (ITNs) varied from 5% to over 60%, and was equitable by urban/rural and wealth quintile status among 13 (52%) of 25 countries. Malaria treatment rates for febrile children under five years of age varied from less than 10% to greater than 70%, and while equitable coverage was achieved in eight (30%) of 27 countries, rates were generally higher in urban and richest quintile households. Across all countries, there were no significant male/female inequalities seen for children sleeping under ITNs or receiving antimalarial treatment for febrile illness. However, parasitaemia and anaemia rates from eight national surveys showed predominance in poor and rural populations. They concluded that recent efforts to scale up malaria intervention coverage have achieved equity in some countries (especially with ITNs), but delivery methods in other countries are not addressing the most at-risk populations.[1055]

This presents a difficult challenge regarding the most equitable and effective ways to deliver treatment and prevention services, contrasting a focus on universal scale up and improvements across all at-risk populations (including those of higher SES) with specially targeted programmes to reach the poorest and highest-risk groups in society. Some evidence suggests that pro-poor targeted programmes are not only effective and have beneficial effects on higher SE groups, but can also narrow disparities, depending upon the country, delivery mechanism and transmission setting.[1056,1057,1058] Inequitable service provision and treatment outcomes amongst poor people varies greatly from country to country, for example, studies from eastern and southern Africa showed the percentage not receiving any formal sector treatment between the poorest and least poorest quintiles to be 41% versus 21%, respectively. In western and central Africa this gap was 64% versus 23%.[1059]

Preventative measures are thought to be particularly less equitably distributed compared with access to treatment.[1060,1061,1062] This may, however, be inherent to the type of intervention or inequity by design, for example IRS is most effective in peri-urban and urban

areas where houses are spaced closely together and use particular construction materials.[1063]

Steketee and Eisele's review suggests that method of distribution and cost to the end user are critical considerations in achieving equity in intervention coverage such as ITNs.[1064] Evidence increasingly suggests that equitable household ITN possession is achievable through free wide-scale community distribution.[1065,1066,1067] As a result of such evidence coupled with the realisation that ITNs, like vaccines, are a public good,[1068] the policies and choices of delivery strategies for ITNs have increasingly evolved over the past few years to aiming for full household population coverage and acknowledge that impediments to coverage should be avoided.[1069]

Steketee and Eisele[1070] conclude that the full benefit of malaria control interventions will not be realised unless there is high coverage among the most at-risk groups, such as children and pregnant women, and that measuring equity is critical to the assessment of impact. For example they propose that countries with policies that prioritise high household coverage (e.g. an ITN for every sleeping space or one ITN for every two household members), in combination with free wide-scale distribution, are more likely to improve overall coverage and equity.[1071,1072,1073]

However a study from Kenya also showed that distribution does not equate to actual use. Their survey after a mass distribution campaign found that a substantial number of bed nets were not being hung or used. It is particularly notable that households in the poorest wealth quintile were 59% more likely to receive campaign bed nets, but that target populations in the wealthiest quintile were still 20% or more likely than those in the poorest quintile to actually have slept under an ITN during the previous evening. The authors suggest that targeted behavioural change and education programmes are vital to ensure the full and equitable impact of the intervention.[1074]

It is increasingly recognised that malaria control programmes need to overtly consider the issue of equity in their planning, and that this can be done through a range of channels including coordination with the private sector.[1075] As malaria in Africa is concentrated among children and pregnant women in poor rural areas, equitable access, with high levels of coverage and use is essential to control interventions achieving their full effectiveness and benefit.

5.8.4 Health systems financing

WHO estimates that malaria control programmes (in 2007) were financed with 34% through national government funds, 47% through donors and 19% through out-of-pocket spending[1076] These proportions underestimate the huge subsidies financed by national governments for health systems (health workers, infrastructure) and indirect spending by households. The large donor component raises concerns about sustainability. WHO's 2008 plan estimated that 'sustaining the build-up of control and elimination of malaria' would require $5-6.2 billion annually during 2009-2015, with IRS and ITNs being the two main items. Donor commitments to malaria are increasing, from $0.3 in 2003 to $1.7 billion in 2009 but it is unclear how these funds should be channelled for best impact on system strengthening, maximising all health outcome and improving coverage.

There is insufficient evidence on how donor funding affects national government allocations across sectors and, within health, across priorities. Donor funding per malaria case in Africa is still a small fraction of that in several other regions, though it does better per person at risk. There is also evidence that smaller countries, such as Rwanda, also receive more per capita than larger ones such as DRC and Nigeria.[1077]

The higher cost of ACT over previous antimalarials (10-15 times as much) represents a financing challenge and, in Malawi, if 65% to 85% of all malaria cases were detected and treated, it would consume almost a third of the national drug budget.[1078] International action has focused on reducing this upstream cost through the Affordable Medicines Facility for malaria (AMFm).[1079] Reducing upstream costs has not yet translated into reduced funding applications to the Global Fund. On the contrary, the rise in grant values may signal an increased number of vertical programmes. The cost-effectiveness of these programmes and impact on overall outcomes and wider health systems and infrastructure is not fully known. Drug costs are not the only cost implication of better case detection. In the same country, Malawian health workers would have to devote over 55% of their time to malaria.

More positively, RDTs may reduce the cost of diagnostics per case although the total cost will rise as the number of cases detected increases in the medium term. Suggestions for sustainable funding mechanisms include trust funds, ear-marked taxes and multi-year pledges from donors but there is little evidence about how to guarantee funding flows and what volume of funds are optimal in terms of country absorption capacity, budget management and sustainable aid flows across a range of health priorities in developing countries. There is substantial debate on the optimal level of spend on malaria. Many countries have seen good results from scaled up programmes using new resources. Getting those same returns with more limited resources will be a future challenge.[1080]

6. Artemisinin drug resistance

(See also Section 5.4 Drugs to prevent malaria**)**

Artemisinin combination therapies (ACTs) are the cornerstone of global malaria programmes and the most effective treatment against *P. falciparum*. ACTs provided a valuable replacement for the existing treatments of chloroquine and sulfadoxine-pyrimethamine; drugs which were rendered ineffective due to parasite resistance. ACTs are safe, fast acting, and well tolerated and are recommended by WHO as first line treatment for falciparum malaria in all endemic areas.[1081,1082] In lower transmission settings they have a major role in reducing transmission through their impact on gametocyte carriage.[1083,1084]

The Artemisinin class of drugs are the key component of ACTs. They are known for their powerful antimalarial qualities. What makes artemisinins such superior antimalarials is their rapid onset and broad spectrum range of killing *plasmodium* at multiple stages of the lifecycle. Artemisinins have the ability to act on parasites at the pre-erythrocytic stage, erythrocytic stage and the gametocyte stage (see Annex A Life cycle and biology of malaria). This means that Artemisinin can prevent further development of the parasite within the human body by targeting the merozoites, as well as preventing the onward spread by attacking the circulating gametocytes.[1085]

In 2007, Artemisinin tolerant (resistant) falciparum malaria was detected and subsequently confirmed in Pailin, Cambodia, based on prolonged time to clearance of parasites in patients treated with artesunate given alone.[1086] Surveillance studies which emerged in 2004 had shown a higher failure rate to the ACTs and increased parasites persisting in the blood after three days of treatment. However, the mechanism for this failure was unclear. A study published in the New England Journal of Medicine in 2009[1087] examining the Artemisinin component of ACTs, showed that parasites from patients in Pailin, Cambodia had significantly reduced susceptibility to Artemisinin. This provided the most conclusive evidence so far that parasites can develop resistance to Artemisinin, although there are other lines of evidence supporting this.[1088,1089]

Antimalarial drug resistance is not new. Chloroquine became available for treatment in 1946 and was expected to be one of the major cornerstones of the WHO Malaria Eradication Programme of 1955. By 1957, documented cases of chloroquine resistance (CQR) emerged in the Thailand-Cambodia border region near to the area where Artemisinin resistance has now emerged. By 1978, CQR was found in East Africa and it spread into Central and West Africa by 1986 and 1989. The pattern, route and time-span of this spread across Africa is not well known, due to limited surveillance; however, by 1990, chloroquine was seen as an ineffective drug throughout East Africa[1090], although chloroquine sensitivity has re-emerged in Malawi.[1091,1092]

Sulfadoxine-pyrimethamine (SP) was the antimalarial drug which replaced chloroquine in most of Africa. It was used to treat CQR in Africa during the 1980s. Resistance to this drug also occurred, and there is evidence of its spread to Africa from SE Asia, although drug-resistance has also arisen independently in various African sites,[1093,1094] Tanzania reported significant numbers of cases of clinical treatment failure in 1995 although limited resistance had been in place for some time;[1095] resistance again spread westward across Africa. After the loss of SP, ACTs then became the first-line agent. The importance of this for current policy decisions is that for SP and CQ at least there is clear evidence that spread of drugs resistance mutations through migration has been more important than mutations arising de novo.[1096]

Resistance to antimalarials seems to have occurred earlier in south-east Asia than elsewhere for almost all antimalarial classes.[1097] Parasites have developed relative or near

complete drug resistance in SE Asia to several antimalarial drug classes, including mefloquine, halofantrine and quinine.[1098] Artemisinins are the latest drug class to show resistance, emerging in the same geographical region as CQR and SP resistance. This threatens efforts in global malaria control.[1099] In the case of CQR and SP resistance, there was a drug replacement to offer as first line malaria treatment. With Artemisinin resistance, a new class of drugs to replace the Artemisinin class has not yet been developed and this will, even by the most optimistic predictions, take several years.[1100]

Several factors are thought to be the cause of the emergence of this resistance in south-east Asia, which are not mutually exclusive. The widespread use of monotherapy is likely to be the most important one for which there is clear experimental and clinical evidence, and the adoption of combination therapy (where two or more drugs are used together) has been a key advance, over 20 years after it was first advocated.[1101,1102] The most widely cited additional causes are a harmful combination of immense drug pressure and inappropriate drug courses.

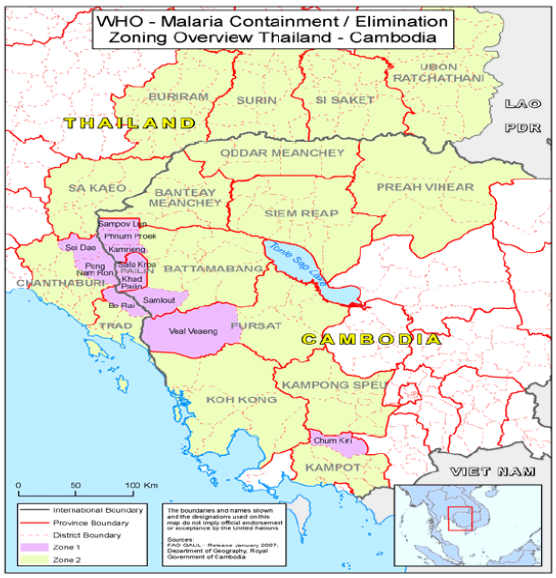
The establishment and spread of drug resistance may be influenced by several factors, including the transmission setting. It is striking that drug resistance has generally emerged in a relatively low-transmission setting rather than the areas of Africa where the highest numbers of cases are recorded.[1103,1104] Several population and drug factors are also suggested as contributors to the emergence of resistance. Given that resistance has emerged in the same geographic area with CQ and SP, studies also suggest that parasite genetics may contribute.[1105,1106] Drug factors that may be fuelling the establishment and spread of resistance include the use of monotherapy and substandard drugs or fake drugs with low amounts of active drug. Much antimalarial treatment in the area of south-east Asia where Artemisinin resistance has arisen is given in the private sector; for example in Cambodia, surveys showed that 70% of the population with fevers sought treatment from the unregulated private sector; mostly through local drug shops and sellers.[1107] Various types of monotherapies, including most recently oral Artemisinin monotherapies, have been widely available in the region for over 30 years.

The response

The primary response strategy to contain Artemisinin resistant malaria has been to: a) eliminate or delay the spread of resistance by controlling malaria; b) identify the molecular 'marker' or phenotype characterisation of resistance to facilitate identification and tracking of the resistant parasites; c) develop a safe, effective, drug alternative to replace Artemisinin. All of these responses are logical, although evidence for any but the third of them being effective are indirect.

Soon after resistance was confirmed, a large scale containment programme commenced. This Bill and Melinda Gates Foundation funded programme aimed to remove selection pressure and ultimately eliminate falciparum malaria from the area. It divided areas into 2 targeted zones for implementation (Figure 8)

Figure 8: Site of Artemisinin resistance and associated containment zones[1108]



Zone 1 (purple) covers areas of the Thai-Cambodian border where there has been evidence of artemisinin tolerant *P. falciparum*. **Zone 2** (green) covers areas that are considered at risk.

The zones were defined on the basis of antimalarial drug efficacy data from the sentinel sites and some research data.

Activities from this programme included the recruitment of 1300 village malaria workers to diagnose and treat malaria, increased surveillance, rapid and large scale distribution of LLINs, hammocks and insecticides and a ban on all monotherapies. Evidence of a reduction in malaria as a result of this programme is encouraging. Severe malaria and deaths have been reduced, and diagnosis and treatment has improved. Whether it can contain the spread of resistant malaria, is, however, not yet known.[1109] The question of which drug treatment to use, whether the containment approach is sufficient or if a more radical elimination programme is required, including mass drug administration (MDA) in Zone 1 is being discussed. Modelling frameworks suggest that elimination is possible using ACTs but it would require almost every case of *P. falciparum* malaria to be eliminated and only 60% of the target population was accessed in the Palin Intensive Control Phase 1. Failure to do so could result in the last remaining strains becoming the strongest and most resistant parasites, a significant risk if malaria incidence then rebounded.[1110,1111]

Currently there is no good evidence to suggest that resistance has already spread beyond Cambodia and possibly Thailand, although this is more a matter of absence of good evidence than clear evidence it has not. Increased attention is now focussed on detecting and preventing spread westward into Burma, where malaria transmission is high and health infrastructure is relatively weak in many of the malaria-endemic areas.

Finding the molecular marker for Artemisinin resistance is expected to take several years.[1112] In the meantime, clinical investigations are required to define parasite clearance rates and to confirm drug exposure.

Artemisinins are however not the only drugs in ACTs, and the partner drugs are also vulnerable. If they are used as monotherapy the changes of developing resistance and then that resistance spreading are considerable. Because they have longer half lives than the artemisinins they are also more vulnerable to drug resistance emerging and spreading even when used solely in fixed-dose combination ACTs because they have a tail period when they will be present in a treated individual of their own. Evidence that there is already selection pressure with lumefantrine, a drug which has not been used as monotherapy, is already present in genetic studies.[1113] Longer times to parasite clearance are likely to be the early warning of developing drug resistance, and occur in advance of actual clinical failures.

7. Insecticide resistance

7.1 Insecticide use in malaria control

One of the key ways to reduce the burden of malaria is to control the *Anopheles* mosquito vectors. Insecticides play a central role in vector control (see Section 5 Interventions and delivery, and Annex C Quantifying malaria transmission, for a discussion of the Macdonald-Ross model). Rising levels of insecticide resistance compromise the effectiveness of these measures.[1114,1115,1116]

The history of the systematic use of insecticide for malaria control in Africa and Asia dates back to the 1950s and 1960s. In the Global Eradication Programme, DDT, used as residual spray in houses was deployed worldwide and showed highly effective results, particularly in India, Sri Lanka and the former Soviet Union. Over time and with widespread agricultural use (which far exceeded the use of insecticides for malaria control), mosquito resistance to DDT emerged. This resistance reversed some of the previous gains made and, in some areas, rates of transmission actually increased. Between 1961 and 1966 disease rates in India climbed threefold, with DDT resistance a partial cause for this.[1117,1118]

Insecticide resistance is rarely insecticide specific and usually resistance selected by one insecticide confers resistance to one or more classes of insecticide. This phenomenon is not unique to malaria vectors. It is a serious threat to agriculture and crop failure as well as a problem of other vector-borne diseases such as dengue, leishmaniasis, and Chagas.[1119]

Four classes of mosquito insecticides are currently recommended for use in adult mosquito control (adulticides) for malaria. These are organochlorines, carbamates, organophosphates, and pyrethroids. These four classes of insecticide cover only two target sites, hence target site resistance, if at operational levels can compromise the effectiveness of two complete classes of insecticide. Common chemical backbones running through insecticide classes can also produce broad spectrum cross resistance from metabolic resistance mechanisms. Target site and metabolic resistance to all of these classes has been documented amongst *Anopheles* species.[1120] The cross-resistance pattern conferred depends upon the underlying resistance mechanism. For example, resistance to one pyrethroid compound often means that there is resistance across the whole pyrethroid class. This cross-resistance is also found between chemical classes such as between organophosthates and carbamates (multi-resistance).[1121] In some species of *A. gambiae,* managing resistance is extremely problematic as resistance has been documented across all four classes of adulticides.[1122]

This cross-resistance is also found between chemical classes such as organophosphates and carbamates when an underlying mutation in the acetylcholinesterase target site is selected.[1123] The bulk of resistance observed in *An gambiae ss* is a DDT-pyrethroid resistance due to one or more mutations in the target site, commonly referred to as kdr. This resistance was initially selected by extensive DDT use and in isolation does not produce sufficient levels of pyrethroid resistance to be operationally significant against pyrethroid impregnated LLINs or pyrethroid-based IRS. More recently increased use of pyrethroids has selected broad spectrum metabolic resistance in addition to kdr. This, alongside an altered acetylcholinesterase resistance mechanism, conferring organophosphate and carbamate resistance, may make mainstream vector control less effective in many parts of West Africa. In southern Africa metabolic resistance in *A. funestus* has resulted in the loss of effectiveness of pyrethroids in South Africa and Mozambique. In 2010 this resistance was first detected in the vector in Malawi and Zambia. Managing resistance is extremely problematic when resistance has been documented across all four classes of adulticides.[1124]

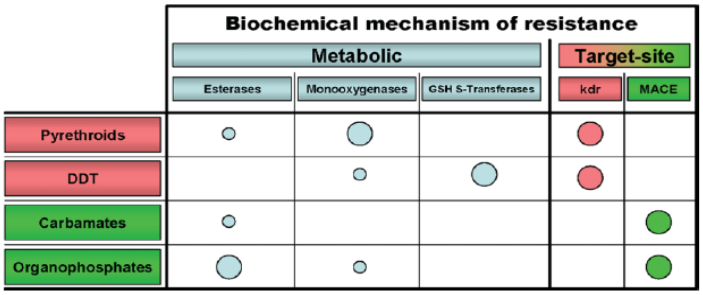
Pyrethroids have replaced DDT as the dominant insecticide of choice in malaria control except for IRS, where pyrethroids are now probably dominant but DDT is still used in places. They are the only class of insecticides currently used in treatment of LLINs because of their efficacy and low toxicity, and fast effect in low doses. Pyrethroids are used in 100% of bed nets and probably the majority of IRS. Thus our vector control efforts are highly dependent on this one class of insecticide. In many areas IRS is not cost-effective, not used, or is not practical. Because of this, many areas are completely dependent on LLINs for vector-based prevention. This means that operational levels of resistance to pyrethroids may potentially pose a great threat to malaria prevention and control. Resistance to pyrethroids is now widespread throughout West Africa among *A. gambiae* and *A. funestus* in southern Africa, and *A. arabiensis* in Cameroon. [1125] Evidence is more limited on the current epidemiological spread of pyrethroid resistance and resistance monitoring is very unevenly distributed and so the true extent of resistance globally is not well documented- but this is absence of evidence rather than good evidence of lack of spread.[1126,1127] It is however clear that significant spread of insecticide resistance in major vectors of malaria would be a very serous public health problem.

Two biochemical mechanisms are currently known to be predominantly responsible for causing resistance. Target-site resistance occurs when an insecticide fails to bind to its target. Several mutations can produce this type of resistance in the two target sites covered by current public health insecticides. Two types of target-site resistance are kdr (knock-down resistance) and MACE (modified acetylcholinesterase). Metabolic resistance occurs when the insecticide is degraded by enzymes including esterases, monooxygenases, and glutathione S-transferases.

Resistance management means deploying insecticide in such a way as to slow down further selection of resistance or to overcome mosquitoes carrying the resistance. One resistance strategy involves rotation of insecticides of different classes. Merely rotating within a class or rotating between one chemical class and another may address the same target-site or metabolic mechanism. Strategies to deal with resistance must take into account the mechanisms of resistance in order to provide a viable alternative. For example, in Figure 9, if the source of resistance is due to MACE, then rotational use of carboamates or organiophosphates will both select for the resistance. Better to alternate one of these classes with a pyrethroid.

Figure 9: Mechanisms of resistance[1128]

(The circle size indicates the importance of the resistance mechanism)



Apart from biochemical resistance mechanisms, cuticular and behavioural resistance (due to selection for these factors by insecticide use) may be overlooked as their presence is harder to demonstrate than molecular mechanisms. Their relevance is unclear.

Insecticide use in malaria is often delivered onto bed nets and walls. Insecticide absorption occurs through the insect's cuticle. Spreading agents in the insecticide formulations increase

the rate at which an insecticide spreads across the insect's cuticle once the mosquito comes into contact with a treated surface, increasing the dosage the insect receives. Cuticular resistance involves changes in the thickness of the mosquito cuticle, or a change in the waxy surface layer of the cuticle to reduce the rate of insecticide penetration.[1129,1130]

Behavioural resistance occurs when the dominant vector evolves to a changed behaviour as a result of intensive indoor use of insecticide providing selection pressure against indoor resting. The existence of this is more theoretical than actual but it could evolve now that IRS is being more widely applied. Much of our existing interventions are dependent on mosquito either resting on walls (IRS) or feeding patterns during hours when people sleep under nets. If genetic changes alter resting behaviour or the feeding cycle to early evening or early morning, this potentially could have a significant impact on our existing interventions.[1131]

7.2 Managing resistance

Resistance management, both biochemical and behavioural, is a challenge because the more a chemical control agent is deployed, the greater the selection pressure for resistance. This is as true for insecticide resistance as it is for drug resistance, and there are close parallels. Uncertainty about the underlying causes of resistance selection creates delays or impediments in applying effective solutions. Current solutions to insecticide resistance include:

- Development of new insecticide classes and larvicides.
- Slowing resistance selection or spread through rotations of insecticides, mosaics of insecticides, and mixtures.
- Introduction of new insecticide-based interventions that are less tied to the indoor environment.

Rotation is based on the idea that resistance in the absence of positive selection is disadvantageous to the insect and carries a fitness cost. Hence rotating insecticides with different modes of action (to disable cross-resistance) should prolong the life of the insecticides involved. The mosaic strategy constitutes a deployment of insecticide spatial in adjacent areas instead of temporally as with a rotation. The theoretical advantage is similar since selection pressure is reduces in space instead of time; either way a smaller proportion of insects are being exposed to a single agent. Mixtures involve using a combination of compounds such as two insecticides, or repellents and insecticides, on the basis it is less easy to develop resistance to two (ideally unrelated) insecticides simultaneously.

Evidence on the use of rotation in malaria control, at an operational level, is limited and is considered by some as less effective than use of mixtures.[1132] One large-scale trial conducted in Mexico, studied strategies to combat resistance in *An albimanus*. In this study, villages were sprayed over six years either with single insecticides, by using a mosaic application (spraying different households in the same village with different insecticides) or by rotating an organophosphate, a pyrethroid and a carbamate insecticide on a yearly basis. The study showed that resistance was kept at low levels by using rotation or mosaic schemes rather than compared with the use of single insecticides, although the study was limited by having no control arm.[1133]

Some speak of spatial deployment of insecticide on different parts of a net as being a mosaic, although this is a different usage of the term 'mosaic' to its original large scale spatial sense (as in the Mexico example above). For it to manage resistance on a net it requires any resistant insect to contact all sections of the net and will be killed by one or other of the insecticides. There is some evidence that *Anopheles* will contact both top and sides and are killed in the process.[1134] There are examples of small-sale experimental hut

trials to test the use of mosaic ITNs. The methodology involved treating the sides of the net with a pyrethroid and the top with either a combination of a pyrethroid and a synergist or a different class of insecticide such as a carbamate. Some trials show certain 'mosaics' can work to good effect.[1135] Other trials have not demonstrated this, not because the concept is wrong but because the active ingredients on the top of the net is not up to the task.[1136,1137] PermaNet 3, has undergone trials in this context but results are equivocal.[1138]

Studies suggest that using mixtures has potential as an alternative to pyrethroids. Trials of carbamate (insecticide) and DEET (repellent) combined with pyrethroid on nets have shown some efficacy against pyrethroid-resistant mosquitoes[1139]. Other field studies have examined the use of organophosphates and DEET and found them to be as lethal as pyrethroids against *A. gambiae* mosquitoes. However, the choice of active ingredients for mixtures needs to be made carefully and there is risk of enhanced mammalian toxicity.[1140,1141] LLINs containing mixtures of unrelated insecticides are likely to become available commercially in the next couple of years.[1142]

Another technique to combine products such carbamate-treated durable wall lining combined with pyrethroid-treated bed nets may be effective.[1143]

A combination approach may be required to address future challenges. For example, using rotation of non-pyrethroid insecticides for IRS may help to slow down the spread of resistance against pyrethroids allowing the continued use of this class of insecticides for ITNs. This may be particularly useful in areas where resistance is currently low. The reality is that LLINs are very widely used and IRS with carbamate is being increasingly used to reduce transmission. There is limited evidence on the durability, public acceptability and the costs of these strategies.[1144]

While it is clear that LLINs provide less protection to users in the face of certain types of pyrethroid resistant *A. Gambiae,*[1145] the operational impact of pyrethroid resistance on the effectiveness of integrated control using LLIN and other forms of vector control is not clear. The combination of the target site and metabolic resistance mechanisms would pose a problem in terms of operational impact, but the size of this could be anywhere from substantial to manageable, and is likely to depend on the mix of other strategies used for control. Studies from Cote d'Ivoire have shown that the target site insensitivity (or kdr resistance) on its own might not necessarily lead to control failure[1146] but once kdr is combined with metabolic mechanisms it appear to becomes more formidable.[1147]

7.3 New alternatives

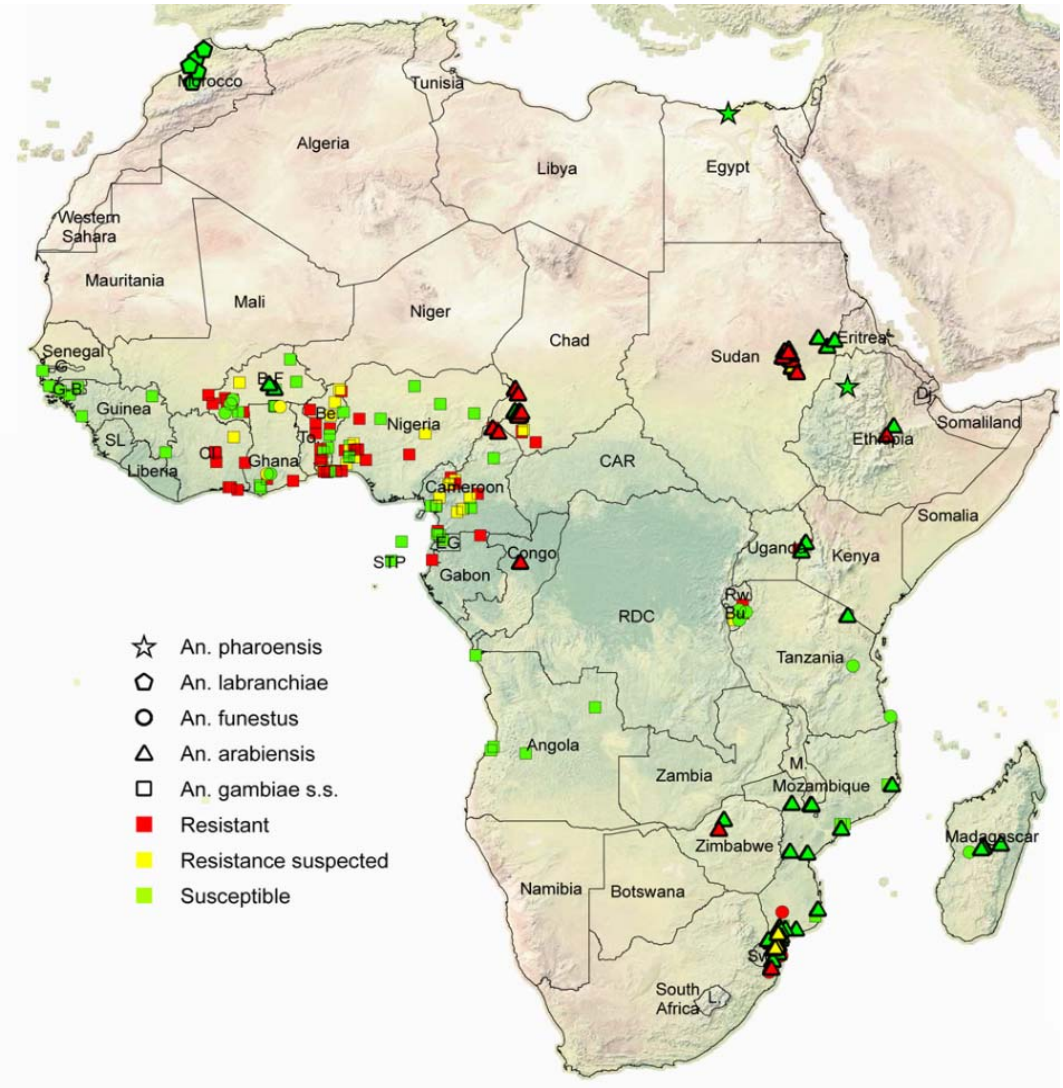
The need for new and alternative insecticides is based on present and future needs and historical evidence. For example the need to find good alternatives to DDT after DDT resistance evolved was a perceived as a major check on the eradication era programming.[1148]. Right now we are over dependent on pyrethroids as there is no alternative to put on LLINs. There are, however, currently very few new active ingredients and the timeframe from development to regulation and use may take as much as a decade after an active ingredient is discovered.[1149,1150]. This is not a trivial problem if the spread of pyrethroid resistance accelerates with increasing LLIN usage.[1151]

Historically most insecticides used in malaria control have come from the agricultural sector. This sector has consolidated substantially in recent years, with fewer and fewer firms working on developing new insecticides. Those companies that are still active are mostly focussed on the agricultural sector where different types of attribute are required in a model AI (e.g. short lasting and higher tolerable mammalian toxicities). Some novel types of insecticide from the agricultural sector may be suitable such as chemical groups known as the pyrrols (e.g. chlorfenapyr[1152]) and oxadiazines (e.g. indoxacarb[1153]). Several proof of

principle studies under field conditions are already completed.[1154,1155] The constraint with these existing formulations is their short residual activity – we take for granted that insecticides with long-lived activity such as DDT and pyrethroids are the norm – when they were exceptional. To increase residual activity the manufacturers are focussed on innovations in formulation such as microencapsulation or use of polymer resins.[1156] New products suitable for vector control are now under development and are likely to enter the market provided funding for the necessary field trials can be secured.

Various novel insecticidal methods have been proposed; see Section 5 Interventions and delivery.

Figure 10: Distribution of pyrethroid resistance amongst *Anopheles* species in Africa[1157]



The literature suggests that while insecticide resistance can be managed in the short term, it is unclear whether approaches to slow resistance or remove selection pressure are effective in the long term. As insecticidal methods are scaled up, resistance will continue to spread. As an interim measure, Insecticide resistance monitoring, molecular diagnostics and surveillance can be used to provide early detection but this tells us little or nothing about how to control resistance or provide solutions. For that we need more randomised controlled trials of alternative insecticides deployed as IRS or on LLINs against mosquito populations to provide the necessary evidence for an informed decision on future insecticide choices and management strategies.[1158]

8 Malaria eradication and elimination[1159]

8.1 Introduction

The first global malaria eradication programme formally ended in 1969 and collapsed in the 1970s, for reasons outlined below. This failure created such a deep sense of disillusion that eradication for some time seemed a taboo subject for malaria experts. In October 2007 Bill and Melinda Gates and the Director-General of the WHO said that eradication should be the only acceptable long-term solution. Both the Bill and Melinda Gates Foundation and the WHO were careful to stress that this was a long-term aim, and that they were not arguing that global eradication is possible with current tools. The debate this had triggered off has been followed by a number of major reviews of the potential ways forward,[1160,1161,1162] and research gaps that need to be plugged if we are to have a realistic chance of eradication.[1163] This section therefore briefly outlines some of the key issues, but for the wider evidence readers will want to consult the recent *Lancet* series on malaria elimination.[1164]

Global Eradication has a precise definition in international health: the complete and permanent worldwide extinction of the infectious organism. For malaria this means the parasite no longer exists, can never come back, and that all forms of control and treatment can be abandoned permanently.

Elimination means 'local eradication', interruption and maintained absence of transmission in a given country or region; there are a number of definitions in use, but all depend on no local transmission within a defined geographical area (generally a country). 'Elimination as a public health problem' is a looser concept which can be interpreted in different ways, but can be used to mean sustained malaria control leading to a reduction of malaria deaths to trivial levels. This second definition of elimination is generally not useful in malaria, and essentially means good control.

The 'once and for all' aim of eradication or elimination, of extra effort now to save greater effort in the long run, allows the promise of eradication justifiably to claim a much greater share of total health expenditure than would otherwise be regarded as cost-effective. For example, in India in the 1960s, expenditure on malaria control amounted to 35% of the total health budget.[1165] If viewed as control this was out of proportion to malaria's relative contribution to the burden of disease, and would not have been justified without the intention of eradication. If the aim of a permanent end to all expenditure on malaria control had been achieved, a few years of expenditure at this level might well, however, have been economically justified. If the risk of failure is ignored, initial economic analysis suggested elimination is normally highly attractive in economic terms,[1166] although once the potential for re-invasion is taken into account recent economic analyses are less encouraging and suggest the chance of recouping costs within 50 years is low in most countries, even where elimination is technically feasible.[1167] In part this is because of the ongoing costs after elimination is completed. On the other hand any analyses of the costs of malaria elimination in Europe in the 1940s would consider it an excellent investment.

Even if eradication cannot be achieved globally it may be worthwhile if elimination of malaria can be achieved in a country, landmass or island where reinvasion can realistically be prevented (as occurred in Europe and the USA). Malaria elimination does not eliminate the mosquito vector, but reduces the transmission of malaria to such a low level that the parasite dies out. However, this means that if the parasite should ever reinvade, the vectors will be there.[1168] This is to some extent the situation in Europe and the USA. Although environmental and socioeconomic changes have greatly reduced the potential for transmission in most areas, there are some locations where the vectors still exist in substantial numbers. For this reason, occasional cases of transmission within Europe and

the USA do occur, but these are rapidly detected and eliminated.[1169,1170] Without the health system that provides prompt detection and response, these isolated cases have the potential to initiate malaria outbreaks.

Elimination does not automatically claim absolute permanence or completeness, but it nevertheless promises that once elimination has been achieved, malaria will be relatively easy to maintain in a stable or semi-stable state. In many cases, natural geographic barriers (such as the ocean or deserts) combined with effective public health will make this possible. The first prevents mosquito movement and limits the number of infected human travellers to manageable numbers, the second ensures that outbreaks started by infected travellers are detected and eliminated when they are still manageably small. On the other hand, if *elimination* is intended to achieve a state of suppression short of local eradication, so that a local reservoir of infection (however small, and often in another country) still exists, then the question is whether this suppressed state is expected to be stable, and if so why? It may be if the control measures which achieve elimination are sustained with the same intensity indefinitely. If, however, relaxing the very costly intensity of control efforts once elimination has been achieved is anticipated, there must be some other reason to expect the situation to be stable. Like other infections, malaria is governed by the balance between its natural propensity to increase and the limitations imposed by finite resources and human immunity. This balance is a stable equilibrium: if it is disturbed, for example by a campaign that suppresses but fails to eradicate, the default expectation has to be that the disease will tend to return to its previous equilibrium as soon as these measures are relaxed, unless the underlying environment has changed substantially.

There are some vector-borne diseases for which there are good biological reasons to justify that elimination will be reasonably stable and sustainable in the medium term, for example lymphatic filariasis[1171]. In the case of malaria, however, there are no reasons to expect a state of suppression short of eradication to be stable once control measures are relaxed, except in cases where socio-economic and environmental development have occurred in the intervening period which make malaria transmission less likely.

Control is attempting to minimise the disease in a sustainable way. This is the current policy with malaria using a combination of anti-vector methods (e.g. ITNs and IRS with DDT and other insecticides), and early treatment with effective drugs such as Artemisinin combination therapy (ACT). In the African context, it is useful to distinguish between ‘transmission control’ and ‘disease control’.

For *transmission control* (the ‘sustained intensive suppression’ described above) the focus is on infection, and the aim to prevent people from becoming infected with malaria parasites by minimising transmission, mainly by means of vector control. This will always be a prerequisite of elimination or eradication.

For *disease control*, the main focus is on preventing, detecting, diagnosing and treating the illness when infection turns to disease without necessarily having any effect on transmission. Preventing the infection in the first place is given lower priority, although the realisation that ITNs can reduce childhood mortality has seen a resurgence of interest in preventive interventions in Africa.

It is theoretically possible to achieve complete control of mortality (in the sense that nobody dies from malaria) whilst significant transmission still occurs since malaria diagnosed early and treated with available effective drugs is a curable disease. This distinction between eliminating infection and eliminating clinical disease is therefore important.

A good example of the difficult choices on when to switch from excellent control to attempting elimination is that of two African island groups. In Zanzibar and Pemba malaria

was dropping prior to major control measures, and with combined vector control and ACT use clinical malaria incidence is now very low indeed.[1172,1173] Technically Zanzibar would probably be able to eliminate malaria, although it would be operationally difficult, but the risks of re-invasion from the mainland are so high that a well conducted technical analysis concluded it is unlikely to be economically sensible to do this with no scenario suggesting it would be cost-saving in the medium term.[1174] Historically Zanzibar also had excellent control during the first eradication attempt, which rebounded rapidly once the control measures were reduced.[1175] São Tomé and Principe is another island group where malaria is now potentially at levels where elimination would be possible, if reinvasion was unlikely[1176]. At the same time it demonstrates the potential hazards; a year after it appeared that malaria was at pre-elimination levels there was a malaria epidemic affecting all ages[1177]. What this demonstrates is that if elimination is to be considered in any country it should be after a thorough technical and economic evaluation, both of the feasibility of achieving it, and then of maintaining it.

8.2 History of malaria eradication

Much of our information on elimination comes from the Global Malaria Eradication Campaign, a massive and remarkable effort. It was prompted by successful campaigns using DDT in the 1940s, formally initiated as a time-limited campaign by the World Health Assembly in 1955 and eventually down-graded by the same body in 1969.[1178] It remains the single biggest global public health effort in history, employed substantial resources, and was well designed, well led and in most places well-executed. It occurred during the post-war pre-independence period when centralised planning was both easier to achieve and more widely accepted than currently is the case in some countries. It failed in its ultimate goal primarily for technical reasons. Donor fatigue was a factor, but it was secondary to the technical problems, which are as challenging now as they were then.

Outside Africa, the global eradication campaign made remarkable progress in its first decade, but by the end of the 1960s major problems had emerged. The most important technical problems were resistance to insecticides (which was widespread and a major obstacle), and to drugs (which had appeared and was starting to spread, although substantially less of a problem than it is now). There were also major operational problems: lack of access to remote and politically unstable areas, infrastructural weakness, and difficulty of maintaining technical standards in complex field operations. During the 'consolidation' phase of the local eradication process, it proved difficult and unexpectedly expensive to keep up the surveillance needed to detect persistent foci and local outbreaks of infection and stop them from spreading. This prolonged cost at the end of a period of elimination and immediately afterwards has been incorporated into more recent models[1179]. In addition, this surveillance phase turned out to be far more prolonged than had been expected. By the early 1970s, the struggle against malaria in many places outside Africa had reached, or at least seemed to be approaching, stalemate. In parts of Asia eradication came tantalisingly close -- Sri Lanka, for example, had only 18 cases of malaria in its final year of eradication compared to over 10,000 a year now. For reasons discussed below a sufficient amount has changed in Asia and the southern Americas to make it worth reconsidering eradication or elimination there again. The changes have not, however, been in our technical capacity, but rather that increasing wealth and industrialisation have had a dramatic impact on malaria transmission; we would now be attacking a much weaker target with similar tools.

In Africa the story was different, and even more discouraging. There were some pilot eradication operations around the edges of the continent: in South Africa (where house-spraying techniques were first developed) and on islands like Zanzibar and Cap Verde. There was also effective spraying in defined areas of high population density and economic importance, such as the Copper Belt in Zambia, and the Gezira irrigation scheme in Sudan. The most informative experience, however, came from a series of spraying trials, carried out

in order to measure (a) whether malaria transmission could be interrupted, i.e. brought to absolute zero at least locally, and (b) the health benefits of removing malaria as a public health problem. A series of trials were conducted in hyper-endemic areas in West and East Africa (Burkina Faso, Tanzania, Kenya, etc), culminating in an intensive and famous study by the WHO, in Garki, Nigeria. Despite the wide range of conditions and operational approaches, the conclusions from these trials were consistent.[1180] In all cases, a substantial degree of malaria control was achieved: in the longer trials, the prevalence of infection in the general population dropped to a few percent, and malaria was indeed more or less removed as a public health problem.

The health benefits of this were unexpectedly large: for example all-cause infant mortality was reduced by about half in all the trials where it was measured. But transmission was never reduced to zero, it persisted in at least parts of the sprayed area, and thus R_0 was never reduced low enough for long enough. Because of this, and because we were so fixed upon eradication, these trials were regarded as failures, despite the impressive health benefits.

In the early 1970s, in Garki, the experiment was repeated one last time, with no expense spared. The most powerful available insecticide was sprayed, with care to ensure the highest standards of operational quality and completeness of coverage, reinforced by mass drug administration giving an anti-malaria drug treatment to everyone. WHO experts concluded, in a very careful and influential report, that it was not feasible to interrupt malaria transmission in West Africa and sustainably achieve $R_0 < 1$, even using the best available control tools deployed in combination and in ideal circumstances because the force of transmission was simply too high and overwhelmed all current tools. Viewed in isolation the Garki project was excellently conducted but had some limitations and should not be over-interpreted. Coming on top of the previous series of trials, however, where the conclusions had been uniformly similar, the implications were considered inescapable: if eradication was not feasible in West Africa, then it was not feasible as a global goal. By that time, the global eradication campaign had already lost its ‘time-limited’ element, mainly because of the stalemate situations that had been reached in several other parts of the world. This new evidence from Africa was the final nail in its coffin.

In retrospect we must ask why, as the health benefits observed in these trials were so spectacular, did we not simply switch to a goal of sustained very intensive control? We had shown that malaria could indeed be reduced to a very low level as a public health problem in Africa, even though we couldn’t drive it to extinction. In part this is because the health impacts were not measured systematically or (as in Garki) they were given much less prominence than reduction in transmission.

A large part of the answer is that we now knew, through the experience of these trials, that the degree of suppression necessary in Africa could only be achieved with massive, intensive and unrelenting application of insecticides. Having now done this, we had good reason to doubt that efforts of this intensity could be scaled up to the necessary degree, and then maintained in the long run, throughout the vast, poor and remote parts of Africa. Doubts about operational sustainability were therefore important. Technical sustainability was, however, even more decisive. By that time, we knew from experience that our insecticides and drugs were vulnerable to the problem of resistance. We knew that the strength of selection for resistance depended on how intensively the drugs and insecticides were used, and we knew that elimination in Africa required highly intense application of insecticide without a break. We knew from large-scale experience in India, and from the more limited spraying in Africa, that in these circumstances, the capacity of vector populations to evolve resistance to successive classes of insecticide was greater and more rapid than our capacity to discover and develop new ones, and this has remained true to date.

In other words, although our tools were capable of suppressing malaria to a low level when they were new, parasite and vector populations could adapt to them quite quickly. A sustained attack using such tools would instigate an arms race, in which our industrial research capacity to invent new chemical tools would be matched against the biological capacity of mosquitoes and parasites to evolve resistance. We had no reason to be confident we could win such a race, in fact, we already had experience of running out of effective insecticides in trying to control several important vectors (*A. culicifacies* in India for example)[1181]. All this raised the serious risk that attempts to sustain a massive level of deployment of insecticides and drugs would render our best chemicals useless.

Financial and political sustainability was an additional factor, especially towards the end of the eradication effort in the late 1960s. This revolved around the nature of the decay curve of malaria eradication. If malaria reduces by a third in the first year, a third of that in the second year etc., early gains are spectacular, and political support is easy to maintain. 20 years later the same amount of money has to be spent, but by now malaria is a small problem, and the incremental improvements, whilst still 33% year on year, are hard to demonstrate. The end-game is actually even more expensive than the early gains, because in addition to maintaining excellent control (attack) measures (which still cost the same as in the heady first few years) a robust surveillance system (never cheap) has to be introduced to identify the pockets where malaria is still being transmitted. These often occur in marginalised areas of deprivation, where lack of funds to seek treatment, lowered immunity and poor housing combine, and these are difficult to access either for control or surveillance. The final tail of eradication of any disease is always therefore much longer (in decades for malaria) than enthusiasts expect. Measles, polio, filariasis and leprosy provide four recent examples of this. Maintaining political support for a massively expensive campaign which now affects only a small and marginalised proportion of the population has proved challenging. The first malaria eradication campaign encountered these problems in multiple sites, and this was one of the main problems that contributed to the decision to end the campaign. As one delegate to the World Health Assembly put it: 'It (malaria eradication) is rather like climbing a mountain: when it seems that the next crest ahead really *must* be the summit, but when you get to it you find a new prospect or continuing climb stretching away into the distance'.[1182]

8.3 What has changed since the global eradication attempt?

8.3.1 Changed epidemiology

In some areas of the world malaria has gone though a massive reduction in incidence since the eradication attempt. This does raise the possibility of elimination being considered in these areas. In some areas transmission is probably lower than assumed by current estimates, which are often based on historical data, or on modelling which has to be based on extrapolated data.

Malaria used to be the leading case of childhood mortality in much of south and south-east Asia. In many of these countries it is now only seen in fringe areas; for example in Thailand and Vietnam only border areas have any significant malaria risks. The same is true in much of Latin America, and a recent modelling exercise suggested that many of the countries where malaria elimination is both technically and operationally feasible are in Latin America[1183]. This has occurred only in part because of malaria control efforts; rather it is a welcome by-product of increasingly wealthy and industrialising societies. The reasons socio-economic development has this effect are complex, and vary by country. They include changes in mosquito habitat (such as deforestation), better housing which is less mosquito-friendly, changes in human behaviour (e.g. people not sleeping in forests at night), pollution, better health services, better resourced malaria control and the general propensity for healthy people not to die from infectious diseases of any sort. The combined effect of these can be substantial. In many areas malaria has essentially literally been built out of the

equation, because the places where humans and *Anopheles* mosquitoes come into contact are now very few. If the malaria eradication attempt of the 1947–1979 era had been made in these areas starting from the current base it might well have succeeded in elimination.

There is evidence that in certain parts of Africa malaria incidence is dropping (see Section 2 Epidemiology and disease burden). Transmission is, however, still many times above that seen in most parts of Asia when eradication was tried, and failed. It remains the case that more than 80% of the world's malaria deaths occur in Africa. Malaria in Africa could certainly be pushed down significantly further, with undoubted major health benefits, and all those involved in public health there would welcome a serious attempt to achieve this - but this is a long way short of saying elimination or eradication is feasible.

8.3.2 Where can we target elimination?

Elimination (meaning local eradication) is technically possible in many places near to the edge of malaria's current distribution, so 'shrinking the map' of malaria distribution. Exactly where are the best possibilities must be considered in geographical detail, since it depends both on the details of the local epidemiology and on the idiosyncrasies of local infrastructure. More comprehensive geographical detail is presented in Annex E, and in a recent modelling exercise.[1184] Some principles and initial ideas are nevertheless worth mentioning here.

First, it is important to re-state the points explained above: in hyper endemic areas of Africa, where more than 80% of malaria deaths occur, elimination is not possible using existing tools – or at least it cannot be sustained for technical (as opposed to financial) reasons. There is a wide consensus around this point. This does not mean it would not be possible with tools which have not been developed, but they would have to be a substantial advance on current tools. Malaria in these areas can be reduced to low levels, but only for as long as control efforts are maintained; as soon as they were relaxed, malaria would come back, probably at its previous rate[1185] (and morbidity and mortality might for a time be higher, due to reduced immunity).

Africa is a large and epidemiologically diverse continent, and there are parts of it where elimination is technically possible. Examples include South Africa and its borders, some countries in the Horn of Africa, and the central highlands of Madagascar. In all these areas, near the edge of malaria's distribution, transmission has always been relatively less intense and more unstable; in fact these areas would probably have achieved elimination long ago if they were not next door to much larger areas of hyper endemic transmission, which act as a massive reservoir of re-invading parasites and vectors. The problem would be preventing reinvasion, and the costs associated with that.

Asia. China is already reduced the incidence of infection to very low levels throughout the central lowlands, and is now discussing the possibility of nationwide elimination of *P. falciparum.* In south-east Asia, an elimination campaign could not succeed without finding a way to operate in Myanmar. However, elimination in south-east Asia could have substantial external benefits on a global scale. We have discovered in the last few years that south-east Asia has been a major global source of the genes which make the parasite resistant to drugs: in particular, much of the drug resistance in Africa is attributable to genes imported from the Mekong sub region. We don't know why these 'hotspots' are important in this way, but we do know that resistance to Artemisinin drugs, which is a global threat of frightening magnitude, has already been reported from the same area near to the Thai-Cambodia border. Eliminating malaria in these areas would therefore potentially provide substantial benefits for other areas.

The primary target of elimination campaigns would (or should) be *P. falciparum* malaria. The other common species in Asia and Latin America, *P. vivax*, is both a less important as a

cause of death and much more difficult as a target. It is also much harder to eradicate: it can remain dormant in the liver of the human host for years, eventually emerging to initiate a full-blown bloodstream infection up to 8 years later. Thus, the surveillance that is needed to detect and deal with such cases must be extended for a much longer period with this species. Eradication of vivax malaria is only likely to be possible when drugs or vaccines which kill the dormant liver phase, and are safe for mass deployment, are available.[1186]

Turning to individual countries, which are considered in greater detail in Annex E, they can broadly be grouped into four groups, although every country is clearly different, and a single country can have many epidemiological settings.

1. Countries which are hyper endemic for falciparum malaria, with R_0 well over 50, and often in the 100s. In these areas elimination is very unlikely to be achieved and sustained with current tools, but the health benefits of a major control effort would be greatest. Most of these countries are in tropical SSA.
2. Countries which have much lower rates of transmission of falciparum malaria, where elimination is a technically feasible option. Some counties in Asia (e.g. Thailand, Yemen) and Africa fall into this group -- the question about sustainability depends on whether reinvasion from neighbouring countries is likely.
3. Countries which have some falciparum malaria, but where vivax malaria is the predominant species. Eliminating falciparum malaria, but not vivax malaria, may be possible in these countries using current tools.
4. Countries which have levels of transmission which are not especially high, but where specific technical challenges greatly hinder the application or effectiveness of current tools. Examples include countries where much of the malaria transmission occurs outside or early in the evening (exophilic mosquitoes), with nomadic populations, with vectors already resistant to existing insecticides, or with difficult terrain and social structures for malaria control.

8.5 The three phases of malaria eradication and control

For endemic countries three distinct phases can be anticipated. The first two phases are the same for both substantial reduction in malaria transmission (which can be achieved with current tools, and would save many lives) and elimination/eradication. The third is specific to elimination; it is the longest and the most costly phase, and requires innovative thinking. A technical and operational plan for each of these phases needs to be thought through before elimination attempts are undertaken, as each has different technical challenges.

Phase 1. Attack. This aims rapidly to reduce malaria transmission. This requires proper mapping of risk, followed by highly effective application of a combination of all methods which have a substantial impact on transmission. It is likely to require some combination of IRS and other anti-vector methods with mass drug administration (see Section 5.7 New technologies). The technical lessons learned during the global eradication campaign will help to guide this. Maintaining political and financial support in this phase is generally relatively easy since early gains are often spectacular, and it can confidently be predicted that there will be a significant reduction in morbidity and, in settings where many children die from malaria, mortality. In some settings it may be possible to achieve an R_0 of less than 1 in this phase, in some settings with current control tools this is not likely to be possible; this depends mainly on the pre-existing R_0, as well as the technical challenges which vary by country. In some countries (for example those with mosquitoes which bite outside, or those with very difficult terrain or nomadic populations) new methods would be needed.

Phase 2. Initial consolidation. The anti-vector measures need to continue to be applied at the same intensity. Even if elimination is not the goal some form of surveillance needs to be instituted, both to identify hotspots where transmission has not been brought down, and because the high selection pressure due to massive anti-vector and anti-parasite measures will accelerate resistance, which must be identified early. In addition the health services of highly endemic countries need a massive change of emphasis, from a model where the default position is that all febrile illness in children is treated as malaria unless it obviously is not (the current situation) to one where only those with parasites are targeted with antimalarials. WHO now recommends parasitological confirmation of suspected malaria prior to treatment in all age groups in all settings.[1187] As time goes on an increase in the number of adults with severe malaria (currently a relatively small problem) can be anticipated. The scale of culture change this will require should not be underestimated, but if it is not achieved the attempt will be unsustainable. Maintaining political support is more difficult in this phase; the incremental gains are difficult to see.

Phase 3. End-game. This is the most difficult phase, and the one where the greatest degree of innovation is required. If elimination is the aim the planning for this phase is needed at the outset. It is only realistic to consider if R_0 has been brought below 1 in a country or region as a whole. Even then it will take a long time; the aim of an effective elimination attempt will be to accelerate this significantly. On the positive side at this stage adding interventions which have even a limited impact on transmission is helpful -- drugs with anti-gametocidal activity, vaccines and other interventions which have a relatively modest impact are all likely to be useful as any further reduction will speed the time to elimination.

On the negative side, experience from all the eradication campaigns (malaria, smallpox, polio, guinea worm, leprosy, filariasis) shows that this stage is always significantly longer, more technically challenging, more expensive and more difficult to sustain politically than those who embark on elimination or eradication anticipate. It places the greatest demands on the health system as it requires surveillance and response. All the anti-transmission measures and changes in health services need to be maintained. A robust surveillance system which covers the whole population, especially the hardest to reach areas where outbreaks are most likely is needed, along with a rapid response plan. In practice in this phase it is likely that transmission is very low (below R_0=1) in the general population, but that there are pockets of transmission which is well above this, and until all of these are identified and dealt with elimination cannot occur. Initially these may be large easily-identified areas, but as time goes on they become smaller and more fragmented, making detection more difficult. Maintaining support for this phase, which for malaria is likely to cost more than the other phases at a time when malaria is not seen as a major threat by the general population, proved challenging in the global eradication effort and is unlikely to be easier now. How long it would have to go on for depends partly on the technical excellence of the programme, but much more on the pre-existing force of transmission. It would be rash to plan for this phase to take less than decades in areas where the natural malaria transmission in the absence of enhanced control measures has an R_0 of greater than 50 (in practice many parts of Africa).

It is worth stressing that the first two phases of elimination are worth doing whether or not the last phase is attempted. Phase 1 and 2 of malaria elimination and maximising control look much the same. They would achieve a considerable degree of control, and save millions of lives, if well done, and they are certainly achievable with current tools. For practical purposes this would in many settings achieve elimination of malaria as a public health problem. Phase 3, which is the one over which most technical doubt hangs in high-transmission areas, should be seen as a separate challenge requiring a new approach. The difference between elimination (where it is technically possible) and control often comes often down to the question: given competing health priorities how much are we prepared to spend to achieve the final 10%?

8.6 Health system and delivery strengthening.

A prerequisite for any attempt at malaria elimination would have to be strengthening of health systems. At the same time, control of malaria in hyper endemic areas could have a very positive impact on the healthcare systems for all. The initial phase of attack can be delivered through vertical structures, although there are arguments for and against this. The second two phases would in many settings, especially in Africa, require substantial strengthening of medical and diagnostic services.

The primary reason for this is the need to detect and suppress outbreaks in order to prevent them from spreading. This involves far more than treating cases that turn up at the clinic (passive detection), but rather an elaborate and extended follow-up system: tracing the case to its origin, checking everyone in the house (and often neighbouring houses) for current infection, and then an extended period of active surveillance to detect further cases that may be already incubating in the rest of the community. Focal spraying is often included in this response. If these activities are not prompt and thorough, a small outbreak can become an incipient epidemic. All this is best done as an extension of the existing health system; the disadvantages (e.g. cost) of setting up parallel malaria-specific systems were amply illustrated in the first Global Eradication Campaign.

In addition, there are good practical reasons for considering a strong health service to be a pre-requisite, including:

- The further malaria elimination progresses, the smaller the proportion of people protected by immunity, so the greater the proportion likely to develop life-threatening disease when infected.
- The further malaria elimination progresses, the greater the proportional burden non-malarial causes of fever will represent: it will no longer be acceptable to treat all fevers as malaria because of the financial cost of over-treatment and the health cost of mis-management of other infections
- Stock-outs of drugs and other materials, currently a common occurrence, could have a substantial and dangerous impact on elimination efforts in areas of potential high transmission. Securing supply lines and substantial improvements in forecasting of drug needs is essential whether or not elimination is undertaken. This is more important with the ACT class of drugs, which have a relatively short shelf-life compared to other antimalarials.
- In Phase 3 of any eradication attempt the only realistic method of providing passive case detection of upswings in malaria is the formal healthcare system. This is because this phase has to be assumed to go on for many years in high-transmission settings (very possibly decades), at a point where malaria would by definition be a small problem, so maintaining a large parallel system would become politically hard to sustain against competing priorities. Currently few health systems in SSA except that in South Africa could realistically achieve this.

Phases 2 and 3 of elimination therefore require health systems which are able to provide appropriately trained and motivated staff and the drugs and other supplies needed to diagnose and treat this illness.

It might be tempting to achieve ‘quick wins’ by creating disease-specific delivery structures. The very weak state of health services in much of Africa is well recognised. There are, however, two good reasons to consider seriously how new resources for malaria control can be deployed in support of health system strengthening.

First, there is the opportunity to use new resources for malaria control to strengthen the systems, such as supply and logistics systems and health information systems, required to deliver a range of health interventions. For example, addressing supply chain problems to ensure regular availability of ACTs in health facilities could also improve the availability of essential commodities for other conditions, e.g. antibiotics for treatment of bacterial infections.

Second, the activities involved in the shift to Phase three (passive case detection and timely response) would necessarily require a health system response: it is simply not efficient to mount an independent and duplicative system for monitoring and rapid response to malaria outbreaks, particularly when the timeframe involved is considerable (decades) and when new malaria cases would be a declining, and eventually very small, share of total utilisation. Lessons from the previous eradication campaign point to the critical importance of ensuring that the surveillance phase receives adequate technical attention and funding over an extended time period. This must be put in place before moving to the next stage.

Effective malaria eradication would require addressing key weaknesses in all of the core health system elements: service delivery, information systems, systems for distributing commodities and supplies, health workforce, healthcare financing and governance. Challenges of service delivery were alluded to above: responding to these requires bringing together the elements of appropriately trained, remunerated, motivated and equipped health workers, a reliable system for distributing effective antimalarial drugs and other commodities to health facilities, and information systems which are able to provide timely information and feedback. In addition, there is a need to address concerns about resource availability and governance. In a world of expanded funding for malaria, narrow cash constraints are not expected to bind. However, the ability to spend this cash may be constrained by weaknesses in systems for planning and execution: these need to be addressed through strengthened planning and management systems. Furthermore, user fees in their various guises (formal fees or informal responses to insufficient health worker salaries) are known to create barriers to timely care seeking. Adopting health financing mechanisms which do not impede access, especially by the poorest, is a priority.

A final issue directly relevant to elimination relates to health system governance, particularly relating to the private sector which, in the case of malaria, is the source of treatment for around 50% (range 10 –80%) of patients with fever. This is mostly not in the formal private healthcare system, but rather shops, chemical sellers and other outlets for antimalarials which are the current source of most antimalarial drugs consumed, especially by the poorest. Ensuring that these providers are informed about correct treatment and have access to affordable and effective antimalarial drugs is critical. In addition, both control and eradication strategies rely on effective health sector governance. This might include regulation of the types of antimalarial drugs available (in particular, measures to reduce the use of Artemisinin monotherapy); and other complementary and voluntary measures such as training, accreditation, social marketing, etc. to ensure that the actions of private providers contribute to, rather than undermine, the public's health.

The health-service improvements may well be self-sustaining, and certainly would have a beneficial effect on healthcare for other diseases. A reduction of the burden on the health services, especially formal paediatric services, would accompany any serious reduction in incidence of malaria as malaria constitutes a substantial proportion of current outpatient and inpatient work. This has the opportunity to create a virtuous circle, where reducing incidence reduces strains on the service, which improves service levels overall, which in the later stages of elimination might lead to further reductions.

8.7 What might eradication cost?

Three main categories of cost can be identified which are relevant to the question of the resource requirements and cost-effectiveness of eradication: the costs of the attack phase (Phase 1); the costs of consolidation/maintenance (Phases 2 and 3); and the costs associated with the risk of development of resistance to existing malaria control tools when deployed for eradication.

Attack phase: It is possible to attach an indicative cost to the attack phase of an elimination/eradication effort. This requires identification of the following: a list of specific countries, the size of the population at risk, the scale and intensity of existing control efforts, specification of the eradication strategy (which interventions, how deployed (frequency, targeting approaches), delivery systems), and information about the intensity of malaria transmission. With these data it is possible to apply unit costs of interventions to estimate the incremental costs of new initiatives. More information is now available about the costs of vector control strategies in a variety of settings (IRS in Zanzibar, Angola, Uganda, Equatorial Guinea, South Africa and Mozambique;[1188] and ITNs distributed through a range of delivery mechanisms in five countries (Malawi, Tanzania, Togo, Senegal and Eritrea).[1189] Less information is available about the costs of vector control interventions outside of SSA, and almost nothing about the costs and cost-effectiveness of other measures such as environmental control methods. The costs of scaling up access to ACTs have been estimated for the IOM and adapted for the AMF-m, though little is known about the costs of delivering ACTs outside conventional channels. Non-linearities in marginal costs would also need to be considered, though available data do not permit this analysis.

Health system strengthening: It is also necessary to consider what is required to enable the delivery of interventions. Very few empirical data are available about these costs. In the case of the costs of the essential service package estimated for Commission for Macroeconomics and Health, intervention costs were inflated by 15% to reflect the costs of needed systems strengthening. The addition of these costs (increased salaries, higher levels of management, adequately funding existing services) had the effect of doubling the district-level costs.

Consolidation/maintenance phase: A robust surveillance and response system is a critical component of any elimination effort. As outlined above, this was found to be both expensive and difficult to sustain in the earlier eradication campaign. Estimating the cost of this component is even more difficult than costing the attack phase because it will also be highly dependent on the capacity of the health system and will also be required over a longer period. The interventions required and their associated costs will be highly context specific.

Costs of resistance: Alongside the costs of delivering interventions and sustaining a surveillance system there are the costs associated with the risk of development of resistance to existing and new tools. As noted above, there are reasons to be concerned that selection for resistance is more likely with the intense application of interventions that would be required under an eradication strategy. The potential costs are those related to the need to develop, test and apply new, potentially more expensive, tools (new insecticides, new drugs, etc), and the potential human costs associated with malaria rebound among a population that has lost its acquired immunity.

Cost and cost-effectiveness considerations: Any economic evaluation of eradication needs to take into account the benefits as well as the costs. These will include health benefits (cases averted, effects of prolonged use of effective drugs if elimination can be achieved in Asia where drug resistance is emerging) and broader economic benefits if elimination/eradication results in increased investment, tourism, etc. Changing the way that drugs are deployed (e.g. active case screening and detection, greater use of diagnostics) could also have the effect of reducing the speed of development of resistance compared with, e.g. widespread presumptive treatment. Dynamic transmission models are needed to examine the complex interactions between the ways that malaria control tools are applied

and the development of resistance. The inclusion of non-health outcomes will require a cost-benefit rather than a cost-effectiveness approach to economic evaluation. In addition, there will be important issues around what time horizon to use, since the main outcome is the (discounted) net social benefit over time.

Existing data on cost and cost-effectiveness of interventions have primarily been generated with an eye to personal protection, and estimates are largely derived from static rather than dynamic models, the latter including the effects of intervention on transmission. Using these static models, Disease Control Priorities Project (DCPP) estimates of the mean cost/DALY averted in a high-transmission, low income African setting are $11–17 for ITNs, $9–12 for IRS (one round a year) and $17–24 for IRS (2 rounds per year). A widely used threshold is that interventions costing less than $150 per DALY averted are considered to be 'cost-effective'. However, new analyses would be needed to model cost-effectiveness under an eradication scenario because of the need to consider a range of potential resistance trajectories, and to explicitly include effects on transmission among the outcomes. A number of transmission models are now in progress or available and could be adapted to model the cost-effectiveness of different eradication strategies.

Costs of expanding coverage of malaria control: The cost of expanded malaria control efforts has been estimated by BCG for the Gates Foundation and WHO has also produced a costing model for sustained malaria control in 81 most-affected malaria endemic countries[1190]. The WHO estimate includes the costs of scaling up vector control (LLINs), IPT in pregnant women, use of RDTs and ACTs for case management, management of severe and complicated malaria, and epidemic prevention and response. The incremental costs of these interventions (excluding the costs of running the health system) were included. Estimates of the cost of health infrastructure strengthening were made using the classification developed in the Commission for Macro-economics and Health costing. These measures included training for staff and CHWs, communication/health information, and monitoring and evaluation. The cost of scaling up to full coverage was estimated to be US$3.8 to 4.5 billion per year. The BCG estimate is around $7 billion per year. Both figures probably underestimate the costs of health system strengthening. This type of costing exercise is primarily useful for assessing global resource availability and benchmarking against needs, and more detailed country-level analyses would be needed to refine these estimates to be useful for country level programming.

There is one critical point that must be accepted at the outset of any eradication or elimination campaign: when eradication or elimination is the goal, the costs are likely to remain high throughout the course of campaign, even when the goal is near and the disease is rare. Generally costs actually increase at the end of an eradication campaign because of the cost of intensive surveillance. Eventually, the marginal cost per (observed) case will be exceptionally high. So it is important we do not embark on this course unless we are confident we have the determination to carry on to the end. A related point pertains to the issue of political commitment: the decision to continue eradication will have to be made by different people from those who make the decision to begin it; elimination even in Asia, would take many decades. This political problem was very apparent in the global eradication attempt.

The result of this is that a serious economic an political analysis of the costs and benefits of elimination should be undertaken, in addition to the technical feasibility, before any country or region decides to commit to moving from excellent control to elimination itself. Various models and decision tools now exist to help countries make this choice, and in some cases (for example recently in Zanzibar) the technical feasibility may be there but the economic case is currently not convincing. A fuller treatment of this can be found in a recent Lancet series.[1191]

Technical annex

Annex A Life cycle and biology of malaria

Annex B Measuring burden of disease and monitoring and evaluation

Annex C Quantifying malaria transmission: the Macdonald-Ross model and endemicity

Annex D Definitions in eradication and elimination

Annex E Malaria eradication and elimination by area

Annex A

Life cycle and biology of malaria

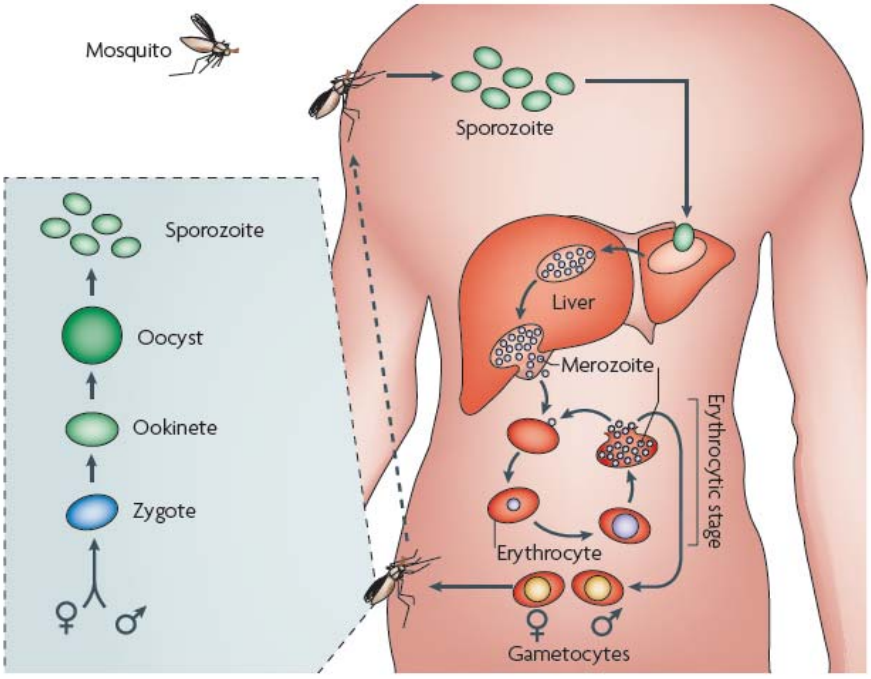
Understanding the malaria lifecycle is useful for a full appreciation of the complexities of treatment, prevention and surveillance. For example life cycle biology identifies several points where the malaria parasite can be damaged or destroyed. For example, Artemisinin drugs have the ability to target parasites in the erythrocytic stages which prevents the growth and spread of *plasmodium.*[1192]

Malaria infects both humans and mosquitoes spending its lifecycle partly in the mosquito and partly in the human host (Figure 11). The mosquito acts as the 'vector' to carry infection from one person to another. [1193]

Human stage: When a female *Anopheles* mosquito takes a blood meal on a human, it injects parasites from its salivary glands into the human blood stream. The parasites injected into the human are in their sporozoite form. Sporozoites then enter the liver cells and reproduce. These liver cells eventually rupture and release merozoites into the blood. The human blood stage is when these merozoites invade the red blood cells, reproduce and rupture red blood cells. This is often the stage when clinical features such as fever and chills begin. It is also the stage that is targeted by many antimalarial drugs. Some of the merozoites differentiate into becoming male or female gametocytes. *1194*

Mosquito stage: When another *Anopheles* mosquito takes a blood meal from an infected human it will then ingest these gametocytes; microgametocytes (male) and macrogametocytes (female). While in the mosquito gut, the fertilised gametocytes fuse into a zygote and become ookinetes. Ookinetes which traverses the mosquito gut wall develop into sporozoites-filled oocysts. These oocysts grow, rupture and release more sporozoites. The sporozoites travel up to the mosquito's salivary glands and are injected into the human during another blood meal. Thus, the process begins again. *1195*

Figure 11: Life cycle of the *P. falciparum* parasite[1196]



It is also important to understand that the life cycle of *P. vivax* is different to that of *P. falciparum*. Vivax parasites form a dormant liver stage known as hypnozoites which are resistant to drugs that target the erythrocytic stages. This makes eradication of vivax much more difficult using current tools because of the multiple relapses and lack of treatments for the hypnozoite stage. [1197]

Mosquito vectors

Malaria is transmitted through the bites of female *Anopheles* mosquitoes. There are over 400 species of *Anopheles* but only about 20 are important as vectors of malaria[1198]. All transmission occurs from female mosquitoes which bite between dusk and dawn. There are important differences between vector populations, and these have implications for malaria control.

- Peak biting times varies by species, which has implications for malaria control- later biting favours ITNs.
- Most important vectors bite indoors (endophilic). This favours ITNs and IRS. Where they bite outdoors (exophilic) these control measures are less effective. Most important African vectors are endophilic, but in south-east Asia and Latin America in particular substantial transmission occurs outdoors. It is, however, possible to use nets outdoors for protection from malaria.[1199,1200]
- Most indoor biting mosquitoes also rest indoors, but not all (endophagic). Where mosquitoes fly in to bite but then fly out IRS is less effective.
- Mosquitoes vary considerably in how selective their breeding habits are. Where they only breed in well-defined habitats (e.g. slow-flowing water), they are much more easy to target for larval control. Many African vectors are relatively unselective, making larval control more difficult.
- Mosquitoes vary significantly in the probability they will survive a full day- and this has major implications for their efficiency as a vector.
- Some anopheline mosquitoes take almost all their blood meals from humans; others take some from humans and some from animals. The higher the proportion from humans the greater their chance of transmitting malaria- see transmission below. Mosquitoes who feed on animals as well as humans may be susceptible to interventions (such as cattle sponging with insecticide) which target the animals.

For malaria transmission to occur there must be sufficient contact between the host and the vector, and the survival of the vector must be long enough for the parasite to complete a life cycle and the vector to become infective.

The greater difficulties in controlling malaria in parts of Africa than most of Asia relate to the local vectors, especially *A. gambiae*, *A. aribiensis* and *A. funestus*. They are hardy (so long-lived) and take almost all their blood meals from humans, making them efficient vectors of malaria. They are relatively non-selective in breeding sites, making larval control more difficult.

Transmission is most intense when the mosquito prefers to bite humans and in areas where the mosquito is long-lived which allows the parasite to complete its development inside the mosquito. Along with host immunity, the most important factors in malaria transmission are the number (or density) of the mosquito, the life-span of the mosquito and its human biting habits.

The *Plasmodium* parasite causes malaria. Of the five species of *plasmodia* affecting humans, *P. falciparum* and *P. vivax* are the most common causes of human malaria. *P falciparum* is by far the most the most common cause of severe illness and death and is the predominant form in Africa. *P vivax* is widespread through Central and South America and Asia but rare in Africa outside Ethiopia. It is less severe and causes fewer complications than *P. falciparum*, however, it often causes relapses months after the initial infection because it lays down dormant forms (hypnozoites) in the liver which then enter the blood stream months or occasionally years later.[1201] This has implications both for case management and control. The other forms are *P. malariae*, *P. ovale* (similar in many ways to vivax and does occur in Africa), and *P. knowlsei*, a monkey malaria which can infect humans in Oceania. All of these are relatively rare and of limited public health importance compared to *falciparum* (the cause of most mortality) and vivax (the cause of much morbidity outside Africa).

Annex B

Measuring burden of disease and monitoring and evaluation

An introduction to monitoring and evaluation (M and E)

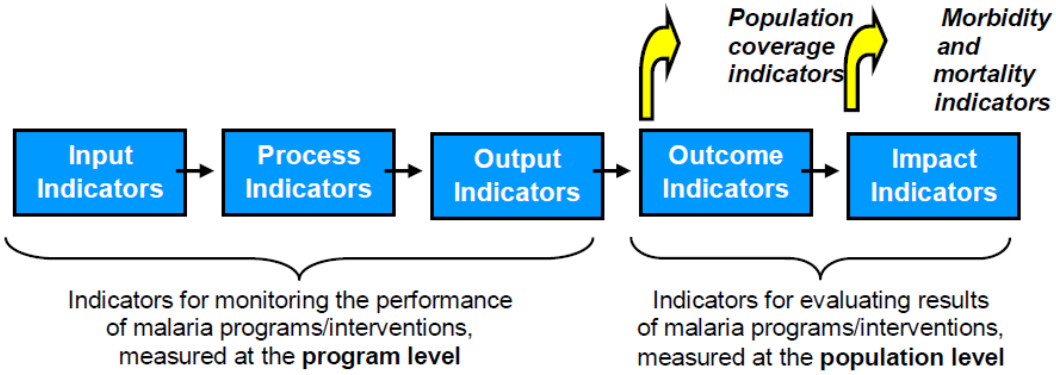
To be able to talk about 'measuring results' it is important to be clear about the different kinds of things (indicators) which can be measured and the ways in which those indicators are measured, the different methodologies.

First of all, it is important to understand the difference between monitoring and evaluation:

Monitoring is the ongoing tracking of progress towards an objective, often using routinely collected data. With respect to malaria control programmes, this is the step-by-step process of checking the progress of control programmes at different levels to check that activities are being implemented as planned and be able to detect and respond to problems quickly. Monitoring takes place at the programme level and tends to focus on input, process and output indicators. Input indicators are typically used to measure the resources available to a programme or intervention (such as financial and human resources). An example would be the financial resources available to purchase ACTs. Process indicators are used to check that a programme/intervention has been implemented as planned, e.g. that the ACTs had been purchased and were ready for distribution. Output indicators are used to measure programme-level performance e.g. the number of ACTs that have been distributed to health facilities. (Figure a below provides a schematic example of the different levels of indicators typically used for M and E).

Evaluation is the periodic assessment of whether objectives are being achieved, often requiring special surveys or studies. So, whilst monitoring is an ongoing process – which continues throughout the lifespan of a malaria control programme – the evaluation may only take place at the end of (or mid way through) the control programme. Evaluation is used to determine and document the extent to which results are attributable to a particular malaria control programme, as measured through outcome and impact indicators. Outcome indicators are typically used to measure medium-term population level results that can be attributed to the malaria control programme or interventions. Examples include population coverage indicators such as the percentage of children under five who received ACTs within 24hrs of onset of fever or the percentage of households with at least one insecticide treated mosquito net. The ultimate goal is measuring impact. Impact indicators refer to the overall, long-term goals of a malaria control programme or intervention, such as reducing malaria-related morbidity and mortality. It is assumed that the desired changes in outcome indicators (based on the changes in input, process and output indicators) will result in the desired impact. (See Figure 12 below for the different levels of indicators).

Figure 12: Level and function of M and E indicators[1202]



Measuring impact

As already mentioned, measuring impact is the ultimate goal; however, it is also the hardest thing to measure. This is particularly the case with malaria.

'True impact evaluation involves measuring changes in impact level indicators, such as morbidity and mortality, and empirically linking the observed change with a specific programme or intervention. This type of evaluation requires rigorous experimental design to make a causal association. However, in reality, public health interventions operate in the real world in existing communities and regions.'[1203]

trolled trial environment and so evaluators rarely have this luxury. On top of that, malaria-specific morbidity and mortality are very difficult to measure (due to non-specificity of symptoms, lack of parasitological diagnosis and the fact that most malaria deaths occur in the home and therefore do not register in health facility data).

As a result, the RBM Monitoring and Evaluation Reference Group (MERG) – one of the RBM working groups – recommends that malaria control interventions focus on measuring changes in the outcome indicators – i.e. the population-level coverage of core indicators. The different indicators are explored in more detail below.

Indicators

This section focuses on outcome and impact indicators as these are the ones of most interest (and hardest to measure). Input, process and output indicators have already been briefly described above. As they are more linked to programme management and less about measuring results in terms of impact, they will not be discussed in any further detail in this paper.

Impact indicators

Internationally, there is an increasing consensus around using a common set of impact indicators for malaria control programmes/interventions. These are largely those put forwards by the RBM/MERG group[1204]:

Figure 13: RBM/MERG impact indicators[1205]

RBM Impact Measures	Indicator Description
Mortality Indicator	9. All-cause under 5 mortality rate (5q0).
Morbidity Indicators	10. Parasitemia Prevalence: proportion of children aged 6-59 months with malaria infection.
	11. Anemia Prevalence: proportion of children aged 6-59 months with a hemoglobin measurement of <8 g/dL

For countries with high-intensity malaria transmission, RBM recommends that all-cause under five mortality is monitored regularly through DHS or MICS (detail on survey methods below). This is the minimum requirement. On top of this, RBM also recommends collecting data on anaemia and parasite prevalence, which are useful malaria morbidity measurements in children under five. Parasite prevalence is specific to malaria and gives an indication of levels of transmission. Anaemia (although not exclusively caused by malaria) can reflect the impact of malaria interventions.

The indicators MERG recommends are those which can practically be used by malaria control programmes. However, they also recommend that to really measure impact countries need to look at a range of information together over the same clearly defined time interval, such as: all-cause childhood mortality trends; changes in malaria intervention coverage (the outcome indicators); the prevalence of other factors which affect malaria and non-related childhood mortality (e.g. malnutrition, access to safe drinking water, immunisation rates etc); and malaria morbidity indicators (anaemia and malaria parasite prevalence).

'If statistically significant reductions in mortality and morbidity are found *and* malaria intervention coverage has increased to high levels *and* other factors influencing all-cause childhood mortality have not changed substantially, then it is a plausible conclusion that malaria control activities caused or contributed to reductions in malaria-associated mortality.'[1206]

A more detailed description of this way of evaluating impact and the incorporation of a plausibility argument can be found in Rowe et al's seminal 2007 paper: 'Evaluating the impact of malaria control efforts on mortality in SSA'[1207]

The main methods/tools for collecting data on these impact indicators are nationally representative, population-based surveys such as the DHS, MICS and MIS.

Demographic health surveys (DHS)

DHS surveys are nationally representative, population-based sample household surveys that are routinely undertaken in most SSA countries every four to five years. They collect data on a variety of health and demographic indicators and can include a malaria module to collect data on the RBM core indicators. All-cause under-five mortality can be ascertained from DHS, but the malaria-specific morbidity indicators are usually collected in MIS, see below. Importantly, the DHS surveys produce data which is comparable over time and across countries. Published reports and material related to DHS surveys can be found online at: www.measuredhs.com.

Multiple Indicator Cluster Surveys (MICS)

MICS surveys are also nationally representative, population-based sample surveys developed by UNICEF to help countries collect key data re the situation for women and children. MICS surveys take place roughly every three years and are also designed so that data is comparable over time and across countries. They are also harmonised with data collected from other major household surveys such as DHS and MIS. There is also an

optional module for malaria which includes most of (but not all e.g. not ITN use amongst pregnant women) the RBM key indicators. (Malaria-morbidity data is not usually available from MICS; this needs an MIS, see below.) Published reports and materials relating to the MICS surveys can be found online at: www.childinfo.org.

Both DHS and MICS collect data to generate all-cause under five mortality estimates, as well as collecting data on most/all of the major outcome indicators (population coverage rates for key intervention e.g. ITNs, access to ACTs). However, typically, neither household surveys collect data on the RBM malaria morbidity indicators, unless specifically included as this requires measuring biomarkers (i.e. taking blood samples).

Malaria Indicator Surveys (MIS)

RBM partners developed the MIS standard package for assessing key household coverage indicators and malaria-morbidity indicators. MIS surveys can be stand alone surveys covering all key malaria indicators or can be used in addition to DHS and MICS to complement the data collected through the large household surveys. The stand alone survey is implemented much like a DHS in the sense it generates nationally representative, population-based data. However, MIS surveys also include bio-markers such as malaria parasite prevalence rates and anaemia prevalence rates which require the collection of blood samples and analysis with diagnostic equipment. Published reports and material relating to the MIS surveys can be found online at: www.rbm.who.int/merg.html

RBM's overall advice is to rely on DHS and MICS surveys where possible, because of the rigour of their methodology (sampling frameworks) and the comparability of results over time and across countries. However, since these surveys are only undertaken every three to five years, if immediate data collection is needed (e.g. as a baseline) and the timing does not fit with the cycle of DHS or MICS surveys, then it is recommended to undertake a stand-alone MIS survey.

One important point to note relates to the timings of these different surveys. MIS surveys need to be conducted during (or within six weeks after the end of) the rainy season – to get realistic parasite prevalence rates. (This is particularly important where transmission is seasonal). In contrast, MICS and DHS are typically carried out in the dry season for logistical purposes. This has implications for the feasibility of adding on a malaria module (with biomarkers) to a standard DHS or MICS.

As is discussed below, USAID/PMI are also referring to and using the MERG recommended indicators. However, one criticism of the RBM impact indicators is that they do not include malaria-specific mortality. The reasons why this is hard to measure are also discussed below. However, the impact indicators used by the WHO are more malaria-specific, but as a result involve a lot more modelling and adjustment, to take into account the problems with malaria specific data gained from routine data collection.

The WHO, in its most recent World Malaria Report, has a slightly different set of impact indicators:

Figure 14: WHO impact indicators for measuring trends in malaria cases and deaths[1208]

IMPACT MEASURE	INDICATOR	NUMERATOR	DENOMINATOR	DATA TYPE/SOURCE	TARGET
Malaria cases					
	1.1 Confirmed malaria cases (microscopy or RDT, per 1000 persons per year) [a]	Confirmed malaria cases per year (< 5 years or total)	Population (< 5 years or total)	Routine surveillance	Reduction in cases per capita: ≥ 50% by 2010, and ≥ 75% by 2015 in comparison with 2000
	1.2 Inpatient malaria cases (per 1000 persons per year) [b]	No. of inpatient malaria cases per year (< 5 years or total)	Population (< 5 years or total)	Routine surveillance	Reduction in cases per capita: ≥ 50% by 2010, and ≥ 75% by 2015 in comparison with 2000
Malaria transmission					
	1.3 Malaria test positivity rate (both microscopy and RDT)[a]	No. of laboratory-confirmed malaria cases	No. of suspected malaria cases with parasite-based laboratory examination	Routine surveillance	No target set, indicates level of control [c]
Malaria deaths					
	1.4 Inpatient malaria deaths (per 1000 persons per year)	No. of inpatient malaria deaths per year (< 5 years or total)	Population (< 5 years or total)	Routine surveillance	Reduction in deaths per capita: 50% by 2010 and ≥ 75% by 2015 in comparison with 2000 [d]
	1.5 Malaria-specific deaths (per 1000 persons per year)	No. of malaria deaths per year (< 5 years or total)	Population (< 5 years or total)	Verbal autopsy (surveys), complete or sample vital registration systems	
	For high-transmission countries 1.6 Deaths of children < 5 years old from all causes (per 1000 children < 5 years old per year)	No. of deaths in children < 5 years old from all causes	Population (< 5 years)	Household surveys, complete or sample vital registration systems	No target set

Apart from the last indicator – 1.6 in the table above – where the data comes from household surveys e.g. DHS (as discussed above), these indicators all rely on routine surveillance data. There are two problems with this: 1) if the data is to be nationally representative it has to come from a large number of health facilities across the country, which means the data is generated through the health management information systems (HMIS) – the shortcomings of which are discussed further in Section 5.8.2. In brief, the main problems are lack of parasitological diagnosis in most health facilities and incomplete reporting. 2) The second problem is that if this data is collected from sentinel surveillance sites (where supervised and 'correct' diagnosis should be taking place and all diagnosis, treatment and data collection will be much better than the national average) the results won't be nationally representative. As discussed in the aforementioned 'current knowledge gaps/problems with data section' WHO have to do some serious adjustment to the figures they receive from HMIS/national data sources to generate national estimated figures.

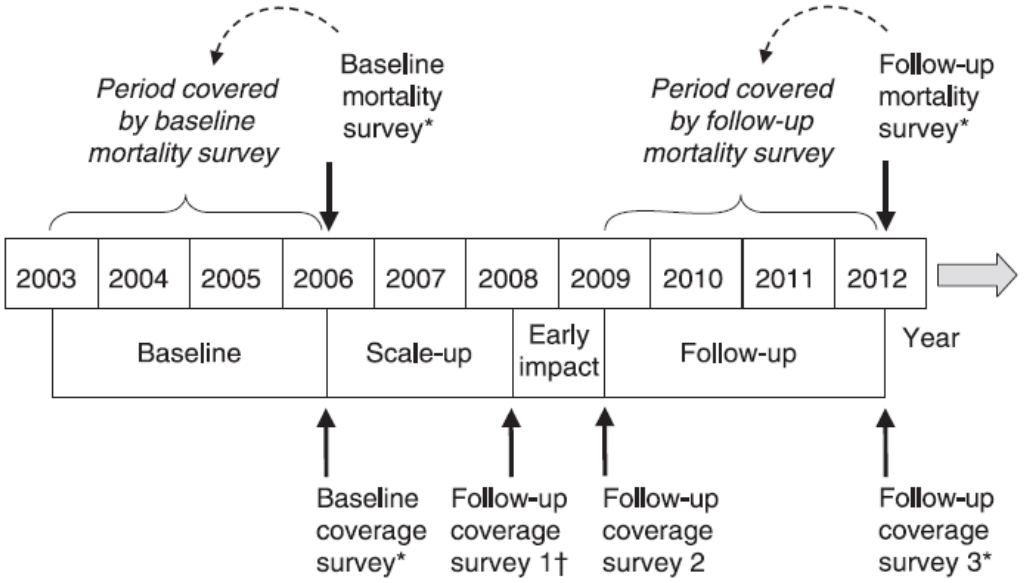
For example, the major limiting factor –with most national malaria control programmes in SSA – when it comes to measuring the first five indicators above is the lack of parasitological diagnosis in most public health facilities and the private sector.

Another key issue to take into account with respect to impact indicators is that impact is not something which can be measured frequently. Remembering that:

'To evaluate the impact of malaria control efforts on mortality, one must first measure a change in malaria burden, and then attribute the change to malaria control efforts.'[1209]

Being able to measure and correlate such changes, takes time, as the diagram below highlights:

Figure 15: An example of the timing of mortality surveys and intervention coverage surveys[1210]



Outcome/coverage indicators

Outcome indicators are generally fairly straightforward in comparison with the impact indicators. There is still, however, slight variation in the indicators used/recommended by different bodies.

The core outcome indicators, as recommended by MERG are in Table 8.

Table 8: Indicators of population coverage for evaluating RBM technical strategies[1211]:

RBM intervention	Indicator description
ITNs and IRS	1. Proportion of households with at least one ITN.
	2. Proportion of children under five years old who slept under an ITN the previous night.
	3. Proportion of Households with at least one ITN and/or sprayed by IRS in the last 12 months.
Prompt and effective treatment and use of diagnostics	4. Proportion of children under five years old with fever in last 2 weeks who received any antimalarial treatment.
	5. Proportion of children under five years old with fever in last 2 weeks who received antimalarial treatment according to national policy within 24 hours from onset of fever.
	6. Proportion of children under five years old with fever in the last 2 weeks who had a finger or heel stick.
Prevention and control of malaria in pregnant women	7. Proportion of pregnant women who slept under an ITN the previous night.
	8. Proportion of women who received intermittent preventive treatment for malaria during ANC visits

	during their last pregnancy.

For all of the above RBM outcome indicators[1212] data can be collected from DHS and MICS (or MIS) surveys.

WHO (in the World Malaria Report 2009) use largely the same indicators, but there is some slight variation:

Figure 16: WHO coverage with intervention (outcome) indicators[1213]

CONTROL STRATEGY	INDICATOR	NUMERATOR	DENOMINATOR	DATA TYPE/SOURCE	TARGET
Prompt access to effective treatment					
	2.1 Appropriate antimalarial treatment of children < 5 years within 24 hours of onset of fever[e–g] (MDG indicator 6.8)	No. of children < 5 years receiving appropriate antimalarial treatment (according to national policy) within 24 hours of onset of fever	No. of children < 5 years with fever in the past 2 weeks in surveyed households[e]	Household surveys	≥ 80%
Mosquito control with ITNs					
	2.2 ITN use by all persons or children < 5 years or pregnant women (MDG indicator 6.7)[h]	No. of persons (all ages) or children < 5 years or pregnant women who reported sleeping under an ITN during previous night	No. of persons (all ages) or children < 5 years old or pregnant women in surveyed households	Household surveys	≥ 80%
	2.3. "Administrative" ITN coverage[i]	No. of persons with ITN from numbers of ITN distributed[i]	No. of persons at risk for malaria	Routine NMCP data	≥ 80%
Mosquito control by IRS					
	2.4. Percentage of population at risk that is targeted for indoor-residual spraying (IRS)	No. of persons that are targeted for IRS	No. of persons at risk for malaria	Routine NMCP data	No target set. Indicates contribution of IRS to overall malaria control
	2.5. Households sprayed with insecticide among those targeted	No. of households sprayed at least once in one year according to national guidelines	No. of households targeted according to national guidelines	Routine NMCP data	100%
Prevention of malaria in pregnancy					
	For high-transmission countries 2.6. Pregnant women who received two doses of intermittent preventive therapy	No. of pregnant women who received two doses of intermittent preventive therapy	No. of pregnant women who made at least one ANC visit in one year	Routine antenatal clinic data	≥ 80%

Indicators 2.1 and 2.2 in the table above are the same as the RBM indicators. However, 2.3 to 2.6 differ slightly (2.6 only in its data source). All of the RBM coverage indicators can be determined from DHS / household surveys, whereas the WHO indicators 2.3 – 2.6 are using routine/HMIS data (the limitations of which have been described earlier).

Note that diagnosis coverage does not yet feature prominently in these coverage indicators as WHO only started to talk about parasitological diagnosis before treatment in 2010 (with the 2nd edition of WHO's malaria treatment guidelines). Including outcome/coverage indicators on diagnosis is something DFID should encourage MERG to consider adding now.

Why measuring malaria mortality is difficult/why all-cause under five mortality is the main impact indicator RBM recommends.

As is described earlier it is very difficult to get nationally representative malaria-specific mortality figures. This is because – particularly in the high-burden countries in SSA where the burden of malaria deaths occur in under fives – most deaths occur at home i.e. outside of the health system and so are not reported in national data. On top of this is the issue of lack of parasitological diagnosis in most cases of malaria treatment.

Rowe et al's influential paper in 2007: 'Evaluating the impact of malaria control efforts on mortality in sub-Saharan Africa' discusses the five main sources of information for measuring mortality.

1. All-cause under five mortality is the most practical measure, but it is not specific to malaria. The advantages of this mortality measure are: 1) in highly endemic areas most

malaria mortality is concentrated in U5s (the exception being pregnant women); 2) all-cause under fives mortality rate is sensitive to changes in malaria-specific mortality; 3) the data can be collected through household surveys such as DHS which results in figures which are nationally representative and reliable; 4) these mortality figures also include both direct and indirect malaria mortality (i.e. deaths where malaria was a co-infection); and 5) that the survey costs don't have to be covered by NMCPs (who traditionally have not been well funded). The disadvantages of this measure of mortality are: 1) it is not specific to malaria; and 2) as a result people will be less convinced by the results.

2. Demographic surveillance systems (DSS) and sentinel sites – In DSS information on births, deaths, migration and other population characteristics are collected via surveys, census updates and/or household surveys. Causes of death are determined by verbal autopsy – which is where detailed information on symptoms associated with deaths is collected and later analysed by doctors to ascertain the cause of death. However, verbal autopsies are neither sensitive nor specific for identifying malaria deaths and suffer from recall bias. This is a major limiting factor in the ability of this measure to generate malaria-specific mortality as the data generated is not reliable. DSS are often research sites for large scale intervention trials. 'Sentinel sites' – although definitions vary – are generally taken to mean one or more health facilities, usually including a hospital, from which morbidity and mortality data are collected. Causes of death are based on clinical and laboratory data and malaria cases and deaths are confirmed by laboratory testing. Sentinel sites also need a well defined catchment area so that death counts can be converted to death rates. The advantages of these methods are that you can get both malaria-specific (which is questionable for the figures based on verbal autopsies) and all=-cause mortality rates. The disadvantages of these methods are that you do not usually get nationally representative figures and there are serious limitations with the verbal autopsy method.

3. Mortality surveys with verbal autopsy – this is where verbal autopsies are added to large household surveys e.g. DHS. This has been trialled in a few countries through DHS or world health surveys. The advantage of this method is mainly that it can generate nationally representative figures. However, the major limitation/disadvantage here is that the results suffer from both recall bias (as it involves people recalling symptoms associated with the death of family members in the preceding 12 months) as well as the non-specificity of malaria symptoms and so limitations associated with the verbal autopsy method more generally.

4. Routine data from non-sentinel site health facilities – this is where data on malaria cases and deaths are collected from the routine data sources i.e. national health information systems (HIS) or directly from health facilities. The advantages with this method is that you can get both malaria-specific and all-cause mortality figures, data is available and can be nationally representative. The main disadvantages have already been described: doesn't capture deaths outside the health system; for those that reach the health system there is a lack of parasitological diagnosis; there is incomplete reporting and poor data quality.

5. Modelling – this is not so much a data source as an information source – where mathematical models and malaria control intervention coverage rates are used to calculate/predict impacts on malaria-specific mortality rates. Models include the Lives saved tool (LiST) and Spectrum (as developed by RBM and the WHO's Child Health Epidemiology Reference Group. However, these models generate predictions, not real figures and have not been validated.

Attribution

As already discussed, measuring impact – in terms of malaria-specific mortality – is already very difficult to do. Attributing this to different donors/individual programmes or interventions

is extremely difficult. As a result, the approach put forward by both Rowe and the MERG group is as follows:

- rather than trying to attribute changes in mortality to one donor or malaria control intervention, any impact on malaria mortality should be shared attribution between national governments and other supporting partners/donors working in country

- instead of focusing on individual attribution, donors/partners should focus on telling the impact story/narrative, through collecting as much information as possible and then triangulating i.e. al cause under five mortality, parasite prevalence rates, anaemia prevalence rates, changes in intervention coverage, other potential confounders and changes in other factors which could affect all-cause under five mortality rate (immunisation, malnutrition etc) and then tell the story, using the plausibility argument

The USG malaria strategy echoes this RBM philosophy (see below) and talks about the three 1s for malaria instead, where all partners support government and one national malaria strategy and costed M and E plan:

'Progress to date: As agreed upon when PMI was launched in 2005, and as a member of the RBM Partnership, PMI does not try to attribute increases in coverage of malaria interventions or reductions in malaria morbidity and mortality to PMI-supported efforts alone. Instead, PMI measures progress toward achieving national and international goals and targets that result from the combined efforts of host country governments and other partners involved in malaria control in that country.[1214]'

What others are doing

PMI
The indicators which will be used for M and E by the President's Malaria Initiative (PMI) are attached in annex 1: 'Monitoring and evaluation indicators to be used within the President's Malaria Initiative', from April 2009.

In summary, they are largely based on the RBM MERG indicators – which the new USG malaria strategy frequently refers to – but with additional detail.

The **impact** indicators include the three outlined above by RBM, plus two indicators to get at the proportion of deaths attributed to malaria in children under five from a) verbal autopsies attached to a national survey (which would be nationally representative) and b) from a DSS site.

The **outcome** indicators are largely based on the RBM MERG indicators, but with several variations of the basic indicators.

There are also detailed process and output indicators and sentinel site indicators described in this document.

MDG
The MDG indicators specific to malaria are as follows:

6.6 Incidence and death rates associated with malaria

6.7 Proportion of children under five sleeping under insecticide-treated bed nets

6.8 Proportion of children under five with fever who are treated with appropriate antimalarial drugs[1215]

As already described at length in this section, real figures for nationally representative incidence and death rates for malaria are impossible to collect at present and so the first indicator is meaningless.

As a result, there is no data on the MDG indicators website for indicator #6.6, whereas there is data for 6.7 and 6.8 which are the outcome/intervention coverage indicators.

The complete absence of data on the MDG indicator data site for malaria incidence and death rates is in stark contrast to the indicators for HIV/AIDS and TB which are populated with incidence and prevalence data.[1216] (This might change if WMR BoD data for malaria is added, but these would be modelled/theoretical figures in contrast with the 'real figures for HIV/AIDS and TB.)

Global Fund to Fight AIDS, Tuberculosis and Malaria
GFATM does not its own sets of indicators as country proposals and M and E plans should reflect national programme indicators. However, it does give guidance on indicators for malaria, e.g. in the M and E manual, it refers the reader to the RBM core population indicators guidelines which have been described at length above[1217].

There is also a more detailed list of possible indicators listed in the GFATM's Monitoring and Evaluation Toolkit (see annex 2)[1218].

In summary, although there is no one simple way of evaluating the impact of malaria control efforts in most of SSA, it is both possible and necessary, given the high levels of financial resources and efforts going in to global malaria control at present.

Overall, there seems to be a consensus that there are two approaches –depending on the level of assistance to national malaria control programmes. These can be described as the 'high-tech' and 'low-tech' options.

The high-tech option

Where resources are available, it is possible to link data from different sources through meta analysis and statistical modelling. I.e. a final estimate of malaria mortality trends can be made from the triangulation of several data sources e.g. all-cause under five mortality rate (from surveys) with malaria-specific mortality (from DSS/sentinel sites/HIS), combined with coverage rates of malaria control interventions, malaria morbidity data, data re coverage of other factors which could affect all-cause under-five mortality (immunisation rates etc) and some clever modelling.

The low-tech option

As described by Rowe et al:

'Our recommendations strongly support the notion that although it is worthwhile employing sophisticated methods to estimate impact in terms of malaria-specific mortality, practically speaking, donors and policymakers should be pleased with increasing coverage of malaria interventions, decreasing anaemia, and decreasing ACCM [all-cause child mortality].[1219]'

Regardless of how impact is calculated and how many different data sources are used, the other key point is that since countries will be supported by multiple malaria initiatives, it will be most efficient for all initiatives to use the same evaluation plan. This is in-line with the

'Three Ones' principle initially adopted by AIDS programmes and now espoused for malaria –one national disease control framework, one coordinating authority and one national system for monitoring and evaluation.

Challenges in measuring malaria burden of disease

Measuring accurately the burden of malaria in different areas is surprisingly difficult. This is important, both because it makes it complicates targeting of interventions, and because if our measures of malaria are inaccurate it will be difficult to track progress. Counter-intuitively, it becomes both more important and more challenging to measure malaria accurately as incidence drops to low levels.

Using all-cause mortality and malaria-specific mortality

About ten years ago, it was suggested that malaria-specific mortality should be the main indicator for assessing malaria's burden of disease, since it is the most important contributing factor to this burden, in terms of DALYs[1220]. However, there are major challenges to monitoring (changes in) malaria-specific mortality in the areas of high-intensity malaria transmission in SSA, where the greatest burden of malaria-specific mortality occurs, mainly in young children. These countries where transmission is greatest are often also those where vital statistics registration and health information systems (HIS) are weakest. On top of this, most malaria-related deaths occur outside the public/formal health system and are not confirmed parasitologically i.e. cause of death is not necessarily malaria.

'… measuring malaria-associated mortality directly (i.e. counting all malaria deaths annually) is not possible in most of SSA. Death registration systems miss many deaths, and the accuracy of reported causes of deaths is difficult to assess. As most deaths occur at home, it is not even feasible to obtain a representative sample of deaths with sufficient clinical and laboratory information to identify the true cause with certainty.'[1221]

In most high-transmission countries in SSA there is no one source of information that provides robust and timely information for mortality impact assessments.

We will now look at some of these challenges in more detail, including the impact this has on the global burden of disease estimates for malaria (and how WHO therefore calculates them).

Fever, and routinely reported malaria rates.

Some estimates of malaria use fever as a proxy for malaria, others use malaria as reported in routine hospital reporting. Both have limitations based on the same fundamental problems; malaria and other infections present very similarly[1222] (making it non-specific as non-malaria cases are recorded as malaria), and many of those with malaria do not present to health centres where their fever is recorded (making it insensitive). In endemic areas, malaria is commonly over-diagnosed in people presenting with febrile illness, especially in adults and in those living in areas with low to moderate transmission.[1223.1224] The symptoms of (non-severe) malaria are non-specific and are similar to the symptoms of a variety of other causes of febrile illness, both viral and bacterial. As a result, malaria is, therefore, often over-diagnosed on the basis of symptoms alone, particularly in areas endemic for malaria, because of this non-specificity of symptoms.[1225] Even amongst those presenting with severe febrile illness in hospitals, over diagnosis of malaria is a very real problem (see Section 5.2 Case management). The problem of over diagnosis is not limited to primary healthcare facilities - evidence demonstrates that this is a significant issue even in secondary and tertiary facilities,[1226] and in Asia as well as Africa.[1227] A recent randomised trial of 2,416 outpatients at public sector health facilities in low-moderate transmission settings in Tanzania revealed that

more than 90% of prescriptions for antimalarial drugs were for patients for whom a test requested by a clinician was *negative* for malaria.[1228]

Only as of 2010 – with the 2nd edition of the malaria treatment guidelines – have WHO recommended that all patients suspected of having malaria receive parasitological confirmation (by RDT or microscopy) before malaria treatment is started.[1229] The only exception to this in the guidelines is that treatment solely on the basis of clinical suspicion should only be considered when a parasitological test is not accessible. In the past, treating most febrile cases as malaria on clinical diagnosis alone (in the absence of parasitological diagnosis) was routine practice. This should improve estimates of malaria from routine data if implemented, but are unlikely to fix the problem.

One of the main problems with this misclassification/over diagnosis of malaria cases and deaths is that it means the data in health information systems (HIS) is unreliable, as is discussed below.

The challenges of collecting HIS data for malaria
Essentially, all countries in SSA have some degree of a HIS. Routine data from health facilities is aggregated together to produce national (and regional) figures of e.g. annual total number of malaria cases and deaths. In most SSA countries malaria accounts for a large proportion of reported cases and deaths, however, few if any of these will have been confirmed parasitologically. Combined with this is the fact that most HIS data include only the cases and deaths from within the formal/public health sector, thereby missing most deaths which occur at home and never even reach the health facility level. It is estimated that fewer than 20% of children with malaria in endemic areas are treated in formal health-care settings.[1230]

The combination of lack of specificity of diagnosis (due to lack of parasitological diagnoses to date) and the limited 'reach' of the formal/public health sector results in HIS data on malaria morbidity and mortality being fairly unreliable. Rowe et al (2007) quote examples where the sensitivity of national HIS systems for malaria deaths in under fives was as low as 5%.[1231]

Implications for global burden of disease estimates for malaria
WHO produces annual world malaria reports (at least currently) which estimate the global burden of disease for malaria. These include figures for numbers of malaria cases and deaths by country. As a result of the challenges identified above, with respect to measuring malaria-related mortality, WHO has a very challenging job in producing these annual malaria burden of disease figures.

The methodology used to produce these figures is described in detail in the annex of the World Malaria Report 2008.[1232] In summary, the methods are different for a) the Africa region and b) countries outside the Africa region. This division is because the countries in Africa region do not generate routine data (from reported cases) from which a 'convincing estimate' can be made. This reflects the weaknesses of routine data highlighted above.

To summarise:
For countries outside the African region (and a few selected Africa countries) malaria **cases** were calculated as follows:

- Reported malaria cases (from national routine data) were adjusted for: reporting
- Completeness; the extent of health service utilisation and the likelihood that cases are parasite-positive; where data permit, this is generally the preferred method.

*And malaria **deaths** were calculated as follows:*

- The estimated number of *P. falciparum* malaria cases was multiplied by a fixed case fatality rate for each country. (This method was used for countries where malaria accounts for a relatively small proportion of all deaths and where reasonable robust estimates of case incidence could be made.)
- Due to the lack of robust routine data in most SSA countries, the malaria case and death figures for SSA countries were based more on models than routine data.

For countries of the African region malaria **cases** were calculated from an empirical relationship between measures of malaria transmission risk and case incidence.

And malaria **deaths** were calculated from an empirical relationship between measures of malaria transmission risk and malaria-specific mortality.

As a result, none of the WHO burden of disease figures for malaria are actual numbers of malaria cases. However, for non-African countries (with a few exceptions) the figures were at least based on initial Health management information systems (HMIS) data which was then adjusted. For African countries, the figures are not even based on the routine HMIS data as it is not convincing enough.

This shows a real need to strengthen HMIS and routine data collection systems in SSA to enable real estimates of burden of disease to be calculated.

Annex C

Quantifying malaria transmission: the Macdonald-Ross model and endemicity

For malaria eradication or elimination, the goal is to interrupt the transmission of infection from one person to another. Transmission is influenced by many factors and we need to understand which interventions will have the most powerful effects on transmission. The essential concept is the *basic case reproduction rate*, R_o.[1233] This is defined as the number of secondary cases arising from a single primary case in one round of transmission, if the human population has no immunity. This is explained in the main document- in brief from a single primary case if $R_o = 2$, then there will be two new cases in the first round of transmission, 4 in the second, 8 in the third, etc. If $R_o = 10$, there will be ten cases in the first round, 100 in the second, and 1000 in the third. If $R_o > 1$, then the number of cases will grow exponentially until growth of the parasite is constrained by human immunity, or the entire human population is infected. If $R_o = 1$, the situation will remain stable. If each case causes less than one new case $R_o < 1$; if this is consistently sustained then the number of cases will decline until the infection disappears which is essential for elimination or eradication. For malaria in parts of equatorial Africa, R_o is in the range 100 to 1000, so many times greater than other eradicated diseases. In these areas in the absence of immunity malaria has an epidemic potential that is explosive.

Sir Ronald Ross, and later George Macdonald, analysed the elements of R_o by identifying all the events that have to occur for the parasite to be transferred from one person to another. The result was a model (formula), for R_o , which in its simplest form is:

$$\mathbf{R_o} = \frac{\mathbf{m}.\mathbf{a}^2.\mathbf{p}^{\mathbf{n}}}{-\mathbf{r}.\log_e \mathbf{p}}$$

m = the number of female mosquitoes per person

a = the frequency with which each mosquito bites man (so **ma** = bites per person per day)

p = survival rate in mosquitoes (proportion of females surviving one day to the next)

n = the maturation period of the parasite in the mosquito, in days

r = the recovery rate in man (proportion of infected people recovering daily)

If human malaria cases have an average recovery rate of **r** per day, the average case will last for 1/**r** days. During this period, the parasite must be taken up by a mosquito, which it does at the rate **ma** (bites per human per day). Once infected, the mosquito must then survive for **n** days before it becomes infective: a proportion $\mathbf{p}^{\mathbf{n}}$ of infected mosquitoes will do so. Each infective mosquito will then go on biting people (with frequency **a** per day) for the rest of its expected lifespan of $1/(-\log_e \mathbf{p})$ days. R_o is then the product of these elements. The rate at which mosquitoes feed on humans, a, appears as a square term because two such meals needed in a transmission cycle: one to infect the mosquito and one to pass the infection back to a human. To allow for the fact that the transfer from host to host is imperfect, some versions of the formula also include the terms **h** (the probability that a mosquito will become infected by a bite on an infected person) and **b** (the probability that a bite from an infective mosquito will result in human infection).

The model implies that R_o should be most sensitive to changes in **p**, the daily rate of survival (because this is raised to the **n**th power) and also relatively sensitive to changes in **a** (because it is squared). This explains why the African vector *A. gambiae* is the most efficient malaria vector in the world: compared to other *Anopheles* species, *A. gambiae* is not usually found in great abundance but it is relatively long-lived and it prefers to bite humans, which is why 80% of the world's malaria is in Africa.

This mathematical model demonstrated that the most obvious factor (the number of mosquitoes) was far less important than the length of time they live. Reducing the number of mosquitoes **m** by (say) 80%, is less effective than reducing the rate of daily survival **p** by half. The effect of the former is linear (an 80% reduction in transmission) while the effects of the latter are raised to the power of nine or ten(transmission reduced by 99.9%)[1234]. The effects of reducing mosquito numbers are linear: half the number of mosquitoes, half the malaria. In the 1950s, this model helped to inspire the first eradication era. At the time, campaigns of spraying houses with residual insecticides (IRS, which affects **p** as well as **m**) were proving to be much more powerful than any previous method of control: far more so than attacks on the breeding sites and insecticidal fogging (which affect **m** only), and efforts to improve the promptness and effectiveness of treatment (which increase the recovery rate **r**). By offering a persuasive technical explanation, Macdonald's theory accurately encouraged the belief that these successes could be generalised, and helped to inspire hope in the goal of global eradication. The reason the eradication failed was not that the model was proved wrong (data from eradication supported it), but rather that the extremely high starting R0 in many parts of Africa was not taken properly into account.

The model has proved very robust in predicting the effects of different control measures in many settings. It offers a way to assess the degree to which new technical developments will help to make eradication feasible. For example, vaccines will presumably act on transmission by reducing **h** and/or **b.** This will indeed reduce R_o, but unlike IRS, it will do so only in direct proportion to vaccine efficacy and coverage. The model can incorporate new tools as they emerge.

Other measures of transmission of malaria

R_0 is not the only measure of transmission, and cannot easily be measured directly in malaria. Its importance is mainly that it is the measure which predicts how difficult elimination/eradication is likely to be. Other important measures in malaria control include:

1. The entomological inoculation rate (EIR). This is the number of infectious bites a human will receive in a year. It is calculated by the proportion of mosquitoes which are infected (measured by catching and dissecting them) multiplied by the number of bites from *Anopheles* mosquitoes a human will get in a year. In Africa, typical EIRs vary from around 1 infective bite per person per year (very low by African standards) to several hundred per year (more than one infective bite per person per night). Outside Africa, EIRs of more than 1 per year are considered exceptionally high, and often the EIR is too low to be measureable.
2. The parasite prevalence rate. This is the proportion of people who at a given point in time are carrying malaria parasites in their blood. Not all of these will exhibit symptoms- in many parts of Africa it would not be untypical for a quarter of the adult population to have malaria at any given time, but be asymptomatic as they are protected by immunity to disease.
3. The clinical attack rate. This is the average number of clinical attacks (i.e. with symptoms) a person will have in a year. This is limited by immunity.

All of these measures are useful where transmission is high, and the impact of control measures can be measured by reductions in EIR or parasite prevalence. The EIR can,

however, be immeasurably small where R_0 is well above 1. Falls of EIR to zero therefore are excellent news for control, but do not necessarily indicate elimination. In 2007 Bill and Melinda Gates and DG Margaret Chan led the call for the long term goal of the global eradication of malaria[1235]. This is a medium-term goal as there is wide consensus on the biological and scientific basis as well as the cost and practical feasibility; that at this point in time global eradication is not possible using existing tools.[1236] There is, however, a range of steps which could be taken towards that goal, and some geographical areas where local elimination of malaria is technically feasible. There have recently been a range of reviews on the possible steps to elimination (see for example the recent Lancet series[1237]), and the scientific steps needed if eradication is to be achieved[1238,1239]. These reviews, and the processes behind them, suggest there is a fair degree of consensus on the scientific and technical side of elimination and eradication, with differences largely being around ordering of priorities and sequencing of control activities.

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Endemicity and levels of transmission

Endemicity is an epidemiological classification using infectious disease prevalence estimates obtained by surveys and surveillance systems. Figure 17 summarises the schema currently used by the Malaria Atlas Project which is now widely used.

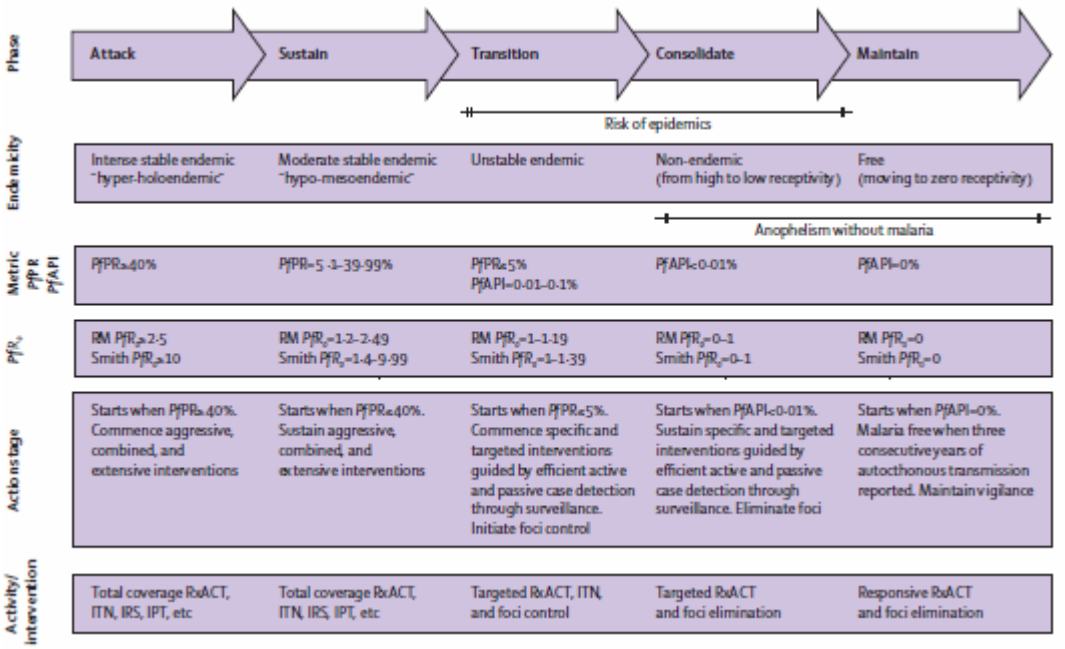

Figure 17:[1240] Malaria endemicity and classification, and the mapping criteria of the Malaria Atlas Project[1241]. The PfR0 (*P. falciparum* basic reproductive number) values are calculated using the RM (Ross-Macdonald) and Smith transmission models. IPT=intermittent preventive therapy. PfAPI=P *falciparum* annual parasite incidence. PfPR=P *falciparum* parasite rate. RxACT=radical treatment with ACT.

Older, and newer, ways of estimating malaria burden and transmission.

Two conventional ways for determining malaria transmission intensity were systematically to sample the population using 'spleen rates'- the proportion of children with enlarged spleens,

and blood film surveys to determine the prevalence of malaria parasites. Both lent themselves to the highly organised, vertical programmes of the first malaria eradication campaign. Both have strengths and weaknesses.

The strength of spleen rates are that with minimal training teams can be trained to sample very large numbers. They are non-invasive, not particularly uncomfortable, and since they do not involve blood are safe, improving compliance. They are also quick, cheap and require no specialist equipment, electricity or training. Their limitations are that the spleen can increase in size due to non-malarial reasons, especially Schistosoma mansoni a common cause of bilharzia, and that they are therefore only really useful in high transmission settings where the great majority of enlarged spleens are due to malaria.

Blood parasite surveys are still used, where the population is sampled with finger prick for blood. They are specific for malaria parasites, and sensitive. Their major limitation has been that they required microscopy, which is relatively complex and expensive to undertake in the field. This technical limitation is now much less relevant with the advent of rapid diagnostic tests for malaria (see Section 5.2 Case management). They are appropriate to determining the burden in malaria, and therefore the change in the burden with control, in areas where malaria is relatively common; in low transmission-settings (Zanzibar or Sri Lanka for example) they pick up so few people with malaria, most of whom will have fever and have treatment, they usefulness is reduced.

A newer variant of these is to measure transmission by serological methods. They require blood to be taken and shipped to areas with relatively specialist equipment and skills. Their usefulness is still being determined, but they will probably have a role in identifying islands of malaria transmission where malaria is at or have been controlled to low transmission levels.

Common to all these survey methods are the challenges of getting an accurate representative sample of the population, willing to cooperate. In general the areas most prone to malaria are those which are least easy to access, whether through geographical remoteness, conflict, extreme poverty, and often all three. DRC, Sudan or Yemen all provide obvious examples malaria-endemic areas where the challenges are likely to be around access and sampling rather than technology.

Annex D

Definitions in eradication and elimination[1242]

With an increasing number of global elimination initiatives in the 1990s, and on the background of the experiences with malaria and smallpox, came the need for more precise definitions. The following[1243] are one definition widely accepted as the basis for conceptualising such initiatives:

Control: Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction.

Elimination of disease: Reduction to zero of the incidence of a specified disease in a defined geographic area as a result of deliberate efforts; continued intervention measures are required.

Elimination of infection: Reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent re-establishment are required.

Eradication: Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed.

Extinction: The specific infectious agent no longer exists in nature or the laboratory.

For malaria, a recent WHO consultation defined malaria elimination for national certification purposes as 'the interruption of local transmission by mosquitoes'.[1244]

In some countries like China, the term 'Basic elimination' has been used for malaria to designate a situation, where elimination of infection appears to have been achieved, but small controllable outbreaks, mainly as a result of importation of cases may occur.[1245]

'Elimination as a (major) public health problem' is a term that has frequently been applied as the goal of control programmes. It is then implicitly accepted that there is no clear fully generalisable definition of what constitutes a public health problem, so that this depends on the context, and an elastic notion of 'locally acceptable level'. When this term has been used in international initiatives and campaigns, it has generally proved more useful when it has been pre-defined rather than being defined post-hoc when the elimination attempt had not succeeded as well as was initially anticipated. It can very useful as a concept in particular geographical regions or countries. It can be very useful as a concept in particular geographical regions or countries, when it is clearly defined what it means. For malaria for example this could mean preventing all deaths from malaria- a very important goal, but very different from elimination.

Annex E

Malaria eradication and elimination by area[1246]

Opportunities, obstacles and risks for elimination of *P. falciparum* malaria in different countries and regions of the world with currently existing tools - a summary.[1247]

Contents

Introduction

The following text is meant to present an overview of the kinds of problems faced by efforts to eliminate falciparum malaria in today's world. It is recognised that in rapidly industrialising countries overall risks of malaria may in certain circumstances drop rapidly due to changes in habitat and human behaviour which make human-anopheles interactions less likely. The political environment, which has to be sufficiently stable to maintain control efforts in all parts of a country over many years obviously may also change, for better or worse, unpredictably. Some remarks made about individual countries may not in all cases reflect the current situation when considering the dynamics of this disease, and additionally the progress that has certainly been made in recent years in many places thanks to support from GFATM and other sources. Given this unpredictability this annexe is therefore meant to be neither prescriptive nor predictive, but illustrative of the factors that need to be taken into consideration. The opinion of the authors is that a realistic view of the difficulties likely to be encountered in any setting is essential at the outset if political commitment is to be sustained in any elimination attempt. Optimistic claims have historically been instrumental in mobilising political support for elimination attempts of malaria and other diseases, but subsequently it

has sometimes been so much more difficult to maintain the commitment due to this over-optimism, when the true difficulties and costs were encountered.

When considering possibilities for elimination, it is worth recalling two concepts, which were established during the global eradication campaign:
Receptivity: which corresponds to vectorial capacity (or R_0) in the absence of continued insecticide-based vector control measures, and

Vulnerability: which corresponds to the risk of importation of parasite carriers and the spread of parasites from these, related to migrations from endemic areas and the performance of health services at border crossings and/or in receptive areas.

Clearly, in areas, where both vulnerability and receptivity are high, elimination is extremely difficult and is likely to demand high long-term investments. When both are low, the opposite is the case.

In the below, certain areas and countries, where malaria elimination is deemed to be *technically feasible*, have been identified. The main issue then becomes *operational feasibility*. In some of these areas, where transmission is of low intensity and health services well developed, implementation may not pose huge problems. It should, however, be considered that for most such areas, it will be necessary

1) to apply either IRS or LLINs or both with high coverage possibly supplemented with locally appropriate larval control, over a period of several years

2) that the determination of the best mix of vector control methods and the best insecticide and timing of operations would require a local assessment, district- or at least province-wise

3) that DDT resistance is widespread in many of these areas, making it necessary to use insecticides with shorter duration that would need to be applied 3-4 times a year or more, depending on seasonality and

4) that it is necessary to obtain full, sincere and durable political commitment and local community participation in areas, where malaria may no longer be a major public health problem and IRS may be perceived as a nuisance more than an activity to improve health.

5) There must also be sufficient political stability *over the time needed* to complete elimination, and the higher the initial transmission rate the longer this will, generally, take.

As long as it is not possible to set a time limit for eradication, any local or national elimination must be accompanied and followed by rigorous surveillance, which would be more difficult than in the past in areas which previously had centralised health services where private health services are now dominant. On the other hand, it should be said that health services in rural areas are often much better developed than they were 50 years ago, and that, in general, knowledge on the requirements for strengthening them is also better.

This report concentrates particularly on those countries where elimination is technically feasible, or might be technically feasible. Less emphasis is given to those countries where almost all technical opinion would be that elimination is not feasible with current tools, although clearly those countries are also those with the greatest malaria burden.

For more details on the experience of the past, reference is made to Gramiccia and Beales, 1988.

1. Oceania

Malaria occurs in New Guinea (island), Vanuatu and Solomon Islands. Malaria vectors are absent in other Pacific Islands. It is not known whether the ecology interdicts their establishment there, but these islands are obviously well justified in maintaining strict controls on air- and sea-craft.

Papua New Guinea, West Papua (Indonesia) and Torres Strait Islands (Australia)

Transmission is intense in lowland areas with gradual decreases in higher altitudes. In the midlands, economic development has been associated with increased mosquito breeding sites. The health services are better than in many other countries; technically a combination of intensive vector control and case management could, despite intense transmission, probably interrupt transmission in most of the country. However, a significant proportion of the population lives in areas where the development and maintenance of basic health services as well as provision of vector control is constrained by extremely difficult geographical access. This has historically been compounded by chronic, low level civil unrest.

Epidemiologically, the situation is similar in West Papua (the Western part of New Guinea Island); the health services there are somewhat better developed, the political situation is more controlled and the current malaria burden somewhat lower, but malaria elimination is currently unlikely to be possible because of the access problems.

It is worth noting that although Australia officially achieved ‘malaria eradication’ in 1981, the disease still occurs in the Torres Strait Islands.

Vanuatu
The country presents an epidemiological gradient from north to south, with unstable malaria in the southernmost islands. Malaria was eliminated from Aneityum, one of the southernmost islands, in the 1990s. Elimination should be easy in Tafea Province, which is comprised of several small islands. From there it would probably be possible to advance northwards, but in the larger northern islands, the costs of establishing and maintaining curative and preventive services in remote communities would be high. Vanuatu would have the advantage of low vulnerability: The islands are probably rarely reached by parasite carriers from other countries, but this would need to be examined more closely.

Solomon Islands
This country has a history of repeated elimination attempts followed by resurgences. The fact that it is comprised of isolated islands, that malaria is a major public health problem and perhaps that it played a significant role in WWII has attracted both well-designed and more capricious elimination schemes. The geographical isolation is a factor in favour of elimination, but it needs to be recalled that in the past, when malaria had reached a low level it was reintroduced from Papua New Guinea. From a technical viewpoint is possible that a multi-pronged attack could lead to elimination. It would have to be well synchronised over many of the islands because of the high internal population mobility. It should be noted that one of the reasons previous attempts have failed is that major civil strife has erupted repeatedly leading to destruction of health facilities including those of the malaria control programme.

2. East and south-east Asia

In many areas including irrigated rice cultivation plains with huge populations, elimination has been achieved or could be achieved. The core problem, which threatens sustainability in adjacent areas is forest and forest fringe malaria. Forest malaria refers to the situation of

communities living permanently in forests, often migrating from place to place. The vectors are often partially exophilic and exophagic; despite this, IRS and ITNs usually have some effect, the former of course only if there are sprayable walls, which is not always the case due to the very hot and humid climate. This effect is relative: there are no examples of lasting malaria elimination in south-east Asian forest village areas. Forest fringe malaria occurs in populations usually living in areas at some distance from forests, where the vectorial capacity is very low. For various reasons, mainly agriculture, these people enter forests, get infected and bring the parasites to their home villages, where they may cause outbreaks or maintain low level transmission – which can usually be controlled well with IRS or ITNs. Some people entering forests for gem-mining, smuggling, guerrilla warfare etc. come from far away, have low immunity, frequently use antimalarial drugs and are liable to carry the disease (sometimes with highly resistant parasites) to other countries. The great difficulty is in protecting people staying at temporary habitats in the forest. IRS is of course not feasible. Hammock nets have been tried, but the results have been variable. Improved control of forest and forest-fringe malaria would be possible by tailoring strategies and not least communication to each individual group, trying out and applying different vector control measures including repellents, and innovative methods for case-finding and management. In this, it should be considered that malaria is usually not the only problem affecting these communities. Curative services addressing only malaria tend over time to be supplanted by private services, often combining poor quality with high cost, on a background of poor education of both consumers and in many cases suppliers.

China

Falciparum malaria persists in China in Yunnan Province, which borders on Laos and Myanmar and in Hainan Island. It disappeared (at least as far as reported cases are concerned) from Guangxi Province, which borders on Vietnam, in the 1990s. The disappearance occurred as Vietnam succeeded in bringing its malaria problem under control, especially in the north. Interruption of transmission in Yunnan would be possible with appropriate investments, but would be under continued threat from importation across the long southern and western border. In this, it should be considered that from an international perspective, malaria in Laos and Myanmar is a problem for Yunnan, not vice versa. In contrast, elimination in Hainan Island is overdue. It would mean getting rid of a relatively small local health problem, with some benefit for tourism, but with no bearing on global malaria. China has over the years eliminated falciparum malaria from a number of provinces, with little fanfare.

Philippines

Thanks in large part to deforestation, malaria has been eliminated from or disappeared from most of the Philippine Islands. Subject to a proper analysis of population migration patterns, an effort at elimination, island by island would be rational. However, in the areas that are still endemic, the population is scattered in small communities and investments in basic healthcare have been declining. This has been compounded by chronic civil unrest in Mindanao and the Sulu Islands in the far south. Forest malaria persists in Palawan with scattered communities with rudimentary healthcare. It is impossible to say, whether elimination would be technically possible in this environment.

Vietnam and Thailand

Like in China, falciparum malaria has to a large extent become a border problem, meaning not that transmission has been interrupted, but that transmission probably could be interrupted in most areas, if importation of cases would cease. This is not likely to occur soon, and it has never been possible to control migration across the long borders. One technical issues is that Viet Nam and surrounding countries still have small isolated deep-forest communities who are migrants and/or live in houses without sprayable walls.

Laos

In most of the country, the intensity of transmission is moderate and elimination would be technically feasible. This would benefit also the China and Viet Nam (there is no malaria on the border to Thailand, which is largely the Mekong River, and the malaria situation on the other sides of the Cambodian and Myanmar borders is not better than in Laos). With increasing social stability in recent years, the main obstacle has become infrastructure. The populations in malaria endemic areas are extremely dispersed and extremely poor. Provision of both preventive and curative care to these remote communities is costly and labour-intensive.

Cambodia
Malaria in Cambodia has the characteristics of forest and forest fringe malaria. In the 1950s and 1960s, as it was realised that transmission could not be controlled with IRS, chloroquinised salt was introduced in western Cambodia and in all probability this is what led to chloroquine resistance, which later spread to the rest of the world. Today, western Cambodia is the epifocus of resistance to certain ACTs (and possibly Artemisinin per se), which has spread across the Thai border,[1248] and, it is feared, to the Myanmar-Thai border. This problem constitutes an international health emergency, which should be addressed vigorously. In comparison with the situation half a century ago, the forest cover has greatly diminished and there are more options for vector control and personal protection. The strategy needs to be creative and multi-pronged and include measures to engage both the affected communities and political authorities across the countries. It should aim at elimination in a defined area. Even if elimination is not achieved, such a strategy could still have huge benefits for the world in delaying and reducing the spread of multi-drug resistant parasites.

Myanmar/Burma
Myanmar is the weakest link in the south-east Asian malaria epic. The forest malaria of the other countries is present on a much larger scale both in terms of areas and population size. All of this is compounded by well known political problems, which in 2005 led to the interruption of support from GFATM. Even if favourable political change should come about this will not necessarily translate into improvements in operational feasibility as the inter-ethnic conflicts which occur in many of the most affected areas may well take many years to be resolved.

Bangladesh and North-east India (from Assam and eastwards)
Most of the malaria is similar to that of Myanmar and Cambodia. Particularly in India, the technical problems have historically been compounded by governance problems and intermittent insurgency.

Malaysia, Indonesia west of West Papua and Timor-Leste
Malaysia has built up good basic health services over decades. The ‘domestic’ malaria problem is now almost restricted to Sabah and the Orang Asli peoples living in forests in central peninsular Malaysia. It is possible that these two areas, having all the technical difficulties of forest malaria and none of the often accompanying political ones, would be useful testing grounds for innovative strategies. In other parts of Malaysia, transmission is now almost interrupted, but tends to flare up in small outbreaks due to importation, mainly from Indonesia. Most of the immigrants are poor clandestine labourers, and it has so far not been possible to control them. Thus, elimination in Malaysia, as much as it seems ‘around the corner’ would be an uphill struggle as long as malaria is regularly imported from Indonesia.

In eastern Indonesia, malaria occurs as coastal malaria, which is technically controllable, but remains a major problem, because of difficult access. More cases are forest and forest fringe malaria with the same technical difficulties as elsewhere. After many years of absence, malaria returned to central Java in the 1990s and has still not been eliminated from there. As

in the Philippines, it is rational to consider elimination island by island, but again based on a thorough analysis of migratory patterns. In contrast to the Philippines, however, Indonesia has huge populations, for example in Kalimantan, Sulawesi, Flores, West Timor and other eastern islands, where malaria is a major public health problem, and where civil unrest is not currently a generalised constraint on the development of curative and basic health services. A detailed analysis of vulnerability would probably show that the risk of reintroduction in the 'unstable malaria' foci in the central and western islands could be greatly reduced by reduction of the malaria burden and parasite reservoir in the east. Focusing first on elimination in the central islands (Java, Lombok and Bali) and the west may be politically popular, but not necessarily rational from an epidemiological or equity angle.

3. South Asia

India west of Assam, Bhutan, Nepal and Sri Lanka

Eastern India (Orissa, Jharkhand,West Bengal, Bihar and Madhya Pradesh) has the world's largest internationally neglected malaria problem. It is estimated that close to 50% of India's falciparum malaria cases and deaths occur in these areas in districts with a total population of 100 million. Data presented at a meeting arranged by WHO 21-23 November 2007 suggest that the number of deaths from malaria in India may be between 70,000 and 200,000 per year. In these states, most malaria is forest-related, but it seems that in general, the vectors and the human ecology makes the transmission more amenable to control, despite the fact that the entomological inoculation rate may reach 150 per year. After 50 years, IRS has grown unpopular and the quality of spraying is poor and sometimes associated with environmental and health hazards. It is now planned to introduce LLINs on a large scale and to establish basic curative services in villages to include RDTs and ACTs. These efforts, which constitute a major reform of the malaria control programme, are also in line with the government's high-profile *National Rural Health Mission*, which foresees increased investment in rural healthcare, which has been neglected for years (except family planning). Considerable health gains can be expected, but some of the areas are affected by long-standing insurgency and governance problems, which have historically acted as barriers to effective malaria control. In western India, malaria is generally unstable in rural areas and associated with irrigation and development activities, in the arid northwest also with rainfall. In many of these areas, malaria could technically be eliminated (though the negative impact of insecticide resistance should not be underestimated), but this would be much easier once the parasite reservoir in the east has been reduced, and is not an obvious national priority until other areas are controlled. India has an almost unique problem of urban malaria, transmitted by *A.stephensi* and to some extent *A.culicifacies*, being more serious than in adjacent rural areas and affecting most cities from Ahmedabad in the west to Kolkata in the east and from Delhi in the north to Chennai in the south. The vectors are mainly found in artificial containers, the parasites are often imported with a poor, unregulated work-force from the east and the transmission has been found to be extremely difficult to control. The problem will diminish, once malaria is better controlled in rural areas in the east, but it may well prove to be a technical obstacle to elimination in the Sub-continent. The possible spread of urban sub-species of *A.stephensi* to other countries is also a threat that should be taken seriously.

In Nepal and Bhutan there should be no major technical obstacles to elimination. The problems to be addressed are in access to health services and coverage of prevention. In Nepal, civil unrest is currently an obstacle. For both countries, the risk of importation from India needs to be considered.

In Sri Lanka, on the basis of past experience, elimination should be possible, if the civil war would come to an end. Some of the transmission occurs in areas of civil unrest. Sri Lanka may be among the few major nation-states, where malaria is currently an important public health problem, and where elimination of *P.falciparum* would be a rational objective in the

context of national public health planning. Elimination would have to be bolstered with a very good surveillance system and special measures to prevent introduction from across the sea.

4. Central Asia

Falciparum malaria is widespread in Afghanistan, but unstable, and should be eliminable from a technical viewpoint, although nomadism and terrain are important constraints. Planning for it is unlikely to be useful unless the security situation improves significantly. In Tajikistan, falciparum malaria has returned because of Afghanistan and an internal deterioration of health services including malaria control. Despite the persistent transmission in Afghanistan, it is reasonable for Tajikistan to aim at elimination, and progress is actually being made.

5. West Asia and the Middle East

Pakistan

Elimination in Pakistan should not meet any insuperable technical problem, though insecticide resistance needs attention. The political situation, both in Pakistan and is neighbours has historically not been ideal for an elimination campaign, and that remains the case in many areas. The problems of the decentralised health sector would provide a major challenge to the later stages of elimination. Urban malaria occurs in Karachi, but seems not to be of the same magnitude as in India, though it is difficult to know, given the state of surveillance.

Iran

Iran would probably be able to eliminate falciparum malaria were it not for the current high risk of importation from Pakistan and Afghanistan.

Saudi Arabia and Yemen

The two countries have committed to a joint programme for elimination of malaria supported financially by other Gulf states. If border collaboration can be further developed and health services with good surveillance developed, this could well prove to be technically feasible, although Yemen provides some unique technical challenges. Although malaria in the Arabian peninsula is a rather isolated phenomenon, such an achievement would be of international interest, because the main vector is *A. gambiae s.l*.

Other countries in the Middle East

These are already almost free from falciparum malaria. United Arab Emirates is the most recent country to have eliminated malaria (also vivax), and its experiences will be of great interest to its neighbours. Parasite importation, especially with labourers, will be a continued threat necessitating strong surveillance.

6. Islands in the Indian Ocean and around Africa

Mauritius

The long history of malaria control and elimination in Mauritius is highly instructive. Falciparum malaria has been eliminated from this island.

Comoros

This country has a situation, which could be considered somewhat comparable to that of the Solomon Islands, with the important difference that the political situation has historically been more stable. The possibility of elimination merits careful consideration, but given that the transmission is by Afro-tropical vectors, it should be anticipated that such an attempt would be both costly and long drawn out. It would therefore be important only to embark on

elimination of there is true national political commitment as opposed to receiving a kind offer from a foreign agency.

Madagascar
Transmission can be interrupted in most of the highland areas with unstable malaria. However, it is debateable whether it is a better investment (for population health and economy) to further reduce the now quite low transmission in the highlands or to reduce the still high morbidity and mortality burden in the lowlands. An equity perspective would prioritise the latter. Given the large population and the intense transmission in the lowlands, it seems highly unlikely that nationwide elimination is currently technically feasible.

Zanzibar (U.R: Tanzania)
Surveillance data indicates that transmission has been greatly reduced in recent years. However, because of the proximity to the mainland, this receptive island is highly vulnerable, so it is unlikely currently to more cost-effective to aim for elimination with the ensuing high demands on surveillance when compared with continued progress in reducing the burden.

Sao Tome and Principe, Bioko (Equatorial Guinea) and Cape Verde
A study has indicated that from a receptivity viewpoint, malaria could be eliminated from Principe, but the vulnerability of this island, and that of the nation as a whole, has not been properly assessed. Malaria control has made excellent progress in recent years and will hopefully be allowed to continue doing so. In Bioko island, elimination is currently being attempted, and the outcomes will be of great interest to others. In Cape Verde, malaria persists only in one small focus, and at least from a receptivity viewpoint, it should be relatively easy to eliminate it.

7. North Africa

By and large, falciparum malaria has been eliminated (and the elimination of vivax malaria is making progress).

8. Southern Africa

South Africa, with little or no transmission in much of the country and a very well organised control programme, has neither interrupted transmission nor been able to control the influx of parasite carriers. Attempting to push the boundary of malaria transmission further north, for example to the north of Zimbabwe, Botswana and Namibia is being considered but would be costly and would have to be associated with systematic screening of migrants and almost constant fire-fighting to put down outbreaks. Malaria in these areas can be reduced to low levels, but not sustainably, and at the potential cost of losing the usefulness of the current best drugs and insecticides.

In the 1960s and early 1970s in colonial times, malaria was largely eliminated from the southernmost part of Mozambique, but when the line was pushed towards the agriculturally important Limpopo valley, progress became increasingly difficult, slow and costly. Migrant labour and excito-repellency to DDT made it increasingly difficult to sustain the gains. After independence in 1975, the government decided to give higher priority to the development of rural healthcare and universal access to immunisation than to freeing the south of malaria.

In the Copper Belt of Zambia, a relatively arid area with moderate vectorial capacity, it was possible in the past and is now again in process, to establish a cycle of wealth and health, by using a mix of methods to suppress malaria to low levels. So far, the aim has been high-level control to minimise the public health impact of malaria but not elimination. That would imply very high investments in surveillance, which could arguably be better spent on malaria

control elsewhere, in areas of the country, where strengthened health services and malaria control could be part of social and agricultural development.

9. Horn of Africa

In Ethiopia, malaria control is making good progress again after serious setbacks in the 1990s culminating in an epidemic in 2003-4, which may have claimed around 70,000 – 200,000 malaria deaths in Ethiopia over a six month period in 2003-4 (Guintran: Technical support to malaria epidemics surveillance in Ethiopia December 2003 – April 2004, mission report. WHO, unpublished, 2004). Ethiopia includes large populations living in lowlands with hyper-endemic malaria, so national elimination is in no way technically feasible. Experience has shown that continued annual investments are necessary to prevent the potentially very dangerous epidemics. In contrast, elimination could be technically feasible in Djibouti, Eritrea and Somalia.

10. East Africa

The situation could be considered similar to that of Ethiopia. There is every reason to invest heavily in aggressive malaria control in the unstable highland malaria areas, as this is the only way to avoid major epidemics. Pre-eradication projects achieved interruption of malaria in some areas of East Africa, but these were on a small scale and with an operational perfection in the application of IRS, which could hardly be replicated anywhere in the world. Elimination can therefore not be considered technically feasible in lowlands with stable malaria and intense transmission. Very good progress, which is being made in a city like Dar es Salaam through a combination of vector control methods deserves to be emulated in any other places across Africa. In highly urbanised city centres, it is perfectly feasible to reduce transmission to extremely low levels, but setting elimination as an objective in such areas would currently not be rational.

11. Central Africa

Central Africa may be the region of the world with the most severe healthcare deficiencies and consequently highest malaria mortality. There is every reason to invest more in malaria control to save lives. For technical reasons outlined elsewhere in the report, elimination could not currently be envisaged.

12. West Africa

In relation to elimination, the situation is similar to that of Central Africa, although greater seasonality provides both greater challenges and some opportunities for control. There are serious constraints to malaria control, which now need to be better addressed, such as the risk of epidemics in the Sahel, the difficulties of providing basic health services for nomads, and the need to find alternative methods in areas, where the summer heat precludes the use of bed nets.

13. North and Central America

Falciparum malaria is slowly disappearing from most of the countries concerned, but it still seems to linger in Nicaragua and Honduras, especially in sparsely populated areas on the Atlantic coast of Nicaragua, where remote localities, extreme poverty, variety of ethnic groups and inadequate health services have for long been major obstacles. In other countries the main identified problems are labour migration, precarious dwellings and, in some areas, socio-political problems. Achieving elimination would require a more concerted effort, including revitalisation of properly conducted IRS campaigns and basic health services in the problem areas. The effort would be costly and necessitate inter-country

coordination, and deciding to prioritise this would require political commitment specifically to malaria elimination.

14. Haiti and Dominican Republic

Almost all cases in these two countries are *P.falciparum.* Those of Dominican Republic occur almost exclusively among Haitian workers, which led to strengthening of vigilance at roads and mountain paths with little success. The finding that transmission occurred in the labour camps of sugar cane plantations, led to some improvement. The obstacle to elimination of malaria in Hispaniola is political, not technical.

15. South America

Forest and forest fringe malaria with similar characteristics to south-east Asia are found in the interior of Brazil, French Guiana, Guyana, Suriname, Venezuela, Colombia, Ecuador, Peru and Paraguay. Based on the experience of the past, intense surveillance of drug resistance is of international importance. Gold mining in, the Amazon is mainly on the plain, and presents one of challenges. Mining is carried out by sizable groups of people. This would facilitate control among those particular groups, although they are often illegal and do not use public health services. Elimination of falciparum malaria in South America depends on the feasibility in the Amazon. Despite vigorous efforts in the days of the global eradication campaign, this has not been demonstrated, although the challenge may now be somewhat reduced by economic development and deforestation. Outside forest and forest-fringe areas, endemic falciparum malaria is now sporadic and could probably be eliminated, if the problem were first effectively addressed in forested areas. In Colombia and Peru the operational context is complicated by armed conflict and the drug trade.

References

[1] WHO. World Malaria Report 2009. Geneva: WHO.

[2] Greenwood BM, Bojang K, Whitty CJM, Targett GA. Malaria. Lancet. 2005 Apr 23–29; 365 (9469): 1487–98.

[3] Hay SI, Guerra CA, Tatem A, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. Lancet. 2004 Infect Dis 4: 327–336.

[4] WHO. World Malaria Report 2010. Geneva: WHO.

[5] WHO. World Malaria Report 2009. Geneva: WHO.

[6] Hay S, Okiro EA, Gething PW et al. Estimating the global clinical burden of malaria in 2007. PLoS Med 7(6): e1000290.

[7] Drakeley CJ, Carneiro I, Reyburn H, Malima R, Lusingu JP, Cox J, et al. Altitude-dependent and –independent variations in Plasmodium falciparum prevalence in northeastern Tanzania. J Infect Dis. 2005 May 15; 191(10): 1589–98.

[8] Keiser J, Utzinger J, Caldas de Castro M, Smith TA, Tanner M, Singer BH. Urbanisation in sub-saharan Africa and implication for malaria control. Am J Trop Med Hyg. 2004 Aug; 71(2 Suppl): 118–27.

[9] Roca-Feltrer A, Schellenberg JR, Smith L, Carneiro I. A simple method for defining malaria seasonality. Malar J. 2009 Dec 3; 8: 276.

[10] Al-Taiar A, Jaffar S, Assabri A, Al-Habori M, Azazy A, Al-Mahdi N, et al. Severe malaria in children in Yemen: two site observational study. BMJ. 2006 Oct 21; 333(7573): 827.

[11] Okiro EA, Al-Taiar A, Reyburn H, Idro R, Berkley JA, Snow RW. Age patterns of severe paediatric malaria and their relationship to Plasmodium falciparum transmission intensity. Malar J. 2009 Jan 7; 8: 4.

[12] Reyburn H, Mbatia R, Drakeley C, Bruce J, Carneiro I, Olomi R, et al. Association of transmission intensity and age with clinical manifestations and case fatality of severe Plasmodium falciparum malaria. JAMA. 2005 Mar 23; 293(12): 1461–70.

[13]Kobbe R, Adjei S, Kreuzberg C, Kreuels B, Thompson B, Thompson PA, et al. Malaria incidence and efficacy of intermittent preventive treatment in infants (IPTi). Malar J. 2007 Dec 9; 6: 163.

[14]Lubell Y, Mills AJ, Whitty CJM, Staedke SG. An economic evaluation of home management of malaria in Uganda: an interactive Markov model. PLoS One. 2010 Aug 27; 5(8): e12439.

[15] Lubell Y, Reyburn H, Mbakilwa H, Mwangi R, Chonya S, Whitty CJM, et al. The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. BMJ. 2008 Jan 26; 336(7637): 202–5.

[16]Okell LC, Drakeley CJ, Bousema T, Whitty CJM, Ghani AC. Modelling the impact of artemisinin combination therapy and long-acting treatments on malaria transmission intensity. PLoS Med. 2008 Nov 25; 5(11): e226;

[17] www.mara.org.za

[18] www.map.ox.ac.uk

[19] Guerra CA, Gikandi PW, Tatem AJ, et al. The limits and intensity of Plasmodium falciparum transmission: implications for malaria control and elimination worldwide. PLoS Med. 2008; 5: e38. doi: 10.1371/journal.pmed.0050038.

[20] WHO: World Malaria Report 2009. Geneva: WHO.

[21] Ibid.

[22] Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, et al. The International Limits and Population at Risk of Plasmodium vivax Transmission in 2009. PLoS Negl Trop Dis. 2010; 4(8): e774. doi: 10.1371/journal.pntd.0000774

[23] Welch SG, McGregor IA, Williams K. The Duffy blood group and malaria prevalence in Gambian West Africans. Trans R Soc Trop Med Hyg. 1977; 71(4): 295–6.

[24] Culleton R, Ndounga M, Zeyrek FY, Coban C, Casimiro PN, Takeo S, et al. Evidence for the transmission of Plasmodium vivax in the Republic of the Congo, West Central Africa. J Infect Dis. 2009 Nov1; 200(9): 1465–9.

[25] Abraha MW, Nigatu TH. Modeling trends of health and health related indicators in Ethiopia (1995–2008): a time-series study. Health Res Policy Syst. 2009 Dec 13; 7: 29.

[26] Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, et al. The international limits and population at risk of Plasmodium vivax transmission in 2009. PLoS Negl Trop Dis. 2010; 4(8): e774. doi: 10.1371/journal.pntd.0000774.

[27] Amexo M, Tolhurst R, Barnish G, Bates I. Malaria misdiagnosis: effects on the poor and vulnerable. Lancet. 2004 Nov 20–26; 364(9448): 1896–8.

[28] Hay S, Okiro E, Gething P, Patil A, Tatem A, Guerra C, et al. Estimating the global clinical burden of Plasmodium falciparum Malaria in 2007. PLoS Medicine 2010 (7): 6.

[29] WHO: World Malaria Report 2008. WHO: Geneva.

[30] Hay S, Okiro E, Gething P, Patil A, Tatem A, Guerra C, Snow, RW. Estimating the global clinical burden of Plasmodium falciparum Malaria in 2007. PLoS Medicine. 2010; (7): 6.

[31] Evans T, Stansfield S. Health information in the new millennium: a gathering storm? Bull World Health Organ. 2003; 81(12): 856.

[32] WHO. Global burden of disease: 2004 Update. 2008. WHO: Geneva.

[33] Ibid.

[34] Hay S, Okiro E, Gething P, Patil A, Tatem A, Guerra C. et al. Estimating the global clinical burden of Plasmodium falciparum malaria in 2007. PLoS Medicine. 2010; (7): 6.

[35] Dhingra N, Prahbat J, Sharma VP, Cohen AA, Jotkar RM, Rodriguez PE at al. Adult and child malaria mortality in India: a nationally representative mortality survey. Lancet. 2010 Oct 21; DOI: 10.1016/S0140-6736(10)60831–8.

[36] Owusu-Agyei S, Asante KP, Adjuik M, Adjei G, Awini E, Adams M, et al. Epidemiology of malaria in the forest-savanna transitional zone of Ghana. Malar J. 2009 Sep 28; 8: 220.

[37] Hill K. Making deaths count. Bull World Health Organ. 2006; 84(3): 162.

[38] Evans T, Stansfield S. Health information in the new millennium: a gathering storm? Bull World Health Organ. 2003; 81(12): 856.

[39] Hay S, Okiro E, Gething P, Patil A, Tatem A, Guerra C, Snow, RW. Estimating the global clinical burden of Plasmodium falciparum Malaria in 2007. PLoS Medicine. 2010; (7): 6.

[40] Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010 Jun 5; 375(9730): 1969–87.

[41] WHO. Global burden of disease: 2004 Update. 2008. Geneva: WHO.

[42] Ibid.

[43] Ibid.

[44] Mills A, Shillcutt S. Copenhagen consensus: challenge paper on communicable diseases. Health Economics and Financing Programme. London School of Hygiene and Tropical Medicine. 2004.

[45] Snow RW, Korenromp EL, Gouws E. Pediatric mortality in Africa: plasmodium falciparum malaria as a cause or risk? Am J Trop Med Hyg. 2004 Aug; 71(2Suppl): 16–24.

[46] Mackenzie G, Ceesay SJ, Hill PC, Walther M, Bojang KA, Satoguina J, et al. A decline in the incidence of invasive non-typhoidal Salmonella infection in The Gambia temporally associated with a decline in malaria infection. PLoS One. 2010 May 11; 5(5): e10568.

[47] Gray RH. The decline of mortality in Ceylon and the demographic effects of malaria control. Popul Stud (Camb). 1974 Jul; 28(2): 205–29.

[48] Cohen JE. Estimating the effects of successful malarial control programmes on mortality. Popul Bull UN. 1988; (25): 6–26.

[49] Prudhomme O'Meara W, Nekesa Mangeni J, Steketee R, Greenwood B. Changes in the burden of malaria in sub-Sahara Africa. Lancet Infectious Diseases. 2010 Aug; 10/8: 545–555

[50]Okiro EA, Hay SI, Gikandi PW, Sharif SK, Noor AM, Peshu N, et al. The decline in paediatric malaria admissions on the coast of Kenya. Malar J. 2007 Nov 15; 6: 151.

[51] Okiro EA, Alegana VA, Noor AM, Mutheu JJ, Juma E, Snow RW. Malaria paediatric hospitalisation between 1999 and 2008 across Kenya. BMC Med. 2009 Dec 9; 7: 75.

[52]Ceesay SJ, Casals-Pascual C, Erskine J, Anya SE, Duah NO, Fulford AJ, et al. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. Lancet. 2008 Nov 1; 372(9649): 1545–54.

[53] Ceesay SJ, Casals-Pascual C, Nwakanma DC, et al. Continued decline of malaria in The Gambia with implications for elimination. PLoS ONE. 2010; 5(8): e12242.

[54] Bhattarai A, Ali AS, Kachur SP, Mårtensson A, Abbas AK, Khatib R, et al. Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. PLoS Med. 2007 Nov 6; 4(11): e309.

[55] Mmbando BP, Vestergaard LS, Kitua AY, Lemnge MM, Theander TG, Lusingu JP. A progressive declining in the burden of malaria in north-eastern Tanzania. Malar J. 2010 Jul 23; 9: 216.

[56] Barnes KI, Chanda P, Ab Barnabas G. Impact of the large-scale deployment of artemether/lumefantrine on the malaria disease burden in Africa: case studies of South Africa, Zambia and Ethiopia. Malar J. 2009 Oct 12; 8 Suppl 1: S8.

[57] Otten M, Aregawi M, Were W, Karema C, Medin A, Bekele W, et al. Initial evidence of reduction of malaria cases and deaths in Rwanda and Ethiopia due to rapid scale-up of malaria prevention and treatment. Malar J. 2009 Jan 14; 8: 14.

[58] Rowe AK, Kachur SP, Yoon SS, Lynch M, Slutsker L, Steketee RW. Caution is required when using health facility-based data to evaluate the health impact of malaria control efforts in Africa. Malar J. 2009 Sep 3; 8: 209.

[59] Guerra CA, Howes RE, Patil AP, Gething PW, van Boeckel TP, Temperley, et al. The international limits and population at risk of plasmodium vivax transmission in 2009. Plos Negl Trop Dis. 2010; 4, e774.

[60] WHO. World Malaria Report 2010. Geneva: WHO.

[61] WHO. Global Malaria control and elimination: report of a technical review. 2008. Geneva: WHO.

[62] WHO. World Malaria Report 2009. Geneva: WHO.

[63] Tipmontree R, Fungladda W, Kaewkungwal J, Tempongko MA, Schelp FP. Migrants and malaria risk factors: a study of the Thai-Myanmar border. Southeast Asian J Trop Med Public Health. 2009 Nov; 40(6): 1148–57.

[64] Phetsouvanh R, Vythilingam I, Sivadong B, Hakim SL, Chan ST, Phompida S. Endemic malaria in four villages in Attapeu Province, Lao PDR. Southeast Asian J Trop Med Public Health. 2004 Sep; 35(3): 547–51.

[65] Azazy AA, Raja'a YA. Malaria and intestinal parasitosis among children presenting to the paediatric centre in Sana'a, Yemen. East Mediterr Health J. 2003 Sep–Nov; 9(5–6): 1048–53.

[66] Joshi H, Prajapati SK, Verma A, Kang'a S, Carlton JM. Plasmodium vivax in India. Trends Parasitol. 2008 May; 24(5): 228–35.

[67] Baird JK. Severe and fatal vivax malaria challenges 'benign tertian malaria' dogma. Ann Trop Paediatr. 2009 Dec; 29(4): 251–2.

[68] Dhingra N, Prahbat J, Sharma VP, Cohen AA, Jotkar RM, Rodriguez PE at al. Adult and child malaria mortality in India: a nationally representative mortality survey. Lancet. Online October 21, 2010; DOI: 10.1016/S0140– 6736(10)60831–8.

[69] Hay SI, Okiro EA, Gething PW, Patil AP, Tatem AJ, Guerra CA, Snow RW. Estimating the global clinical burden of Plasmodium falciparum Malaria in 2007. PLoS Med. 2010 Jun 15; 7(6): e1000290.

[70] Müller I, Bockarie M, Alpers M, Smith T. The epidemiology of malaria in Papua New Guinea. Trends Parasitol. 2003 Jun; 19(6): 253–9.

[71] Phetsouvanh R, Vythilingam I, Sivadong B, Hakim SL, Chan ST, Phompida S. Endemic malaria in four villages in Attapeu Province, Lao PDR. Southeast Asian J Trop Med Public Health. 2004 Sep; 35(3):547-51.

[72] Kolaczinski J, Graham K, Fahim A, Brooker S, Rowland M. Malaria control in Afghanistan: progress and challenges. Lancet. 2005 Apr 23 29; 365(9469): 1506–12.

[73] Al-Taiar A, Jaffar S, Assabri A, Al-Habori M, Azazy A, Al-Mahdi N, et al. Severe malaria in children in Yemen: two site observational study. BMJ. 2006 Oct 21; 333(7573): 827.

[74] Dysoley L, Kaneko A, Eto H, Mita T, Socheat D, Börkman A, et al. Changing patterns of forest malaria among the mobile adult male population in Chumkiri District, Cambodia. Acta Trop. 2008 Jun; 106(3): 207-12.

[75] WHO Regional Office for South-East Asia. Malaria: Disease burden in SEA region. 2005. New Delhi: WHO.

[76] Yiengprugsawan V, Lim LL, Carmichael GA, Seubsman SA, Sleigh AC. Tracking and decomposing health and disease inequality in Thailand. Ann Epidemiol. 2009 Nov; 19(11): 800–7; Epub. 2009 Jun 26.

[77] Manh BH, Clements AC, Thieu NQ, Hung NM, Hung LX, Hay SI, et al. Social and environmental determinants of malaria in space and time in Viet Nam. Int J Parasitol. 2010 Sep 15.

[78] Al-Taiar A, Assabri A, Al-Habori M, Azazy A, Algabri A, Alganadi M, et al. Socioeconomic and environmental factors important for acquiring non-severe malaria in children in Yemen: a case-control study. Trans R Soc Trop Med Hyg. 2009 Jan; 103(1): 72–8.

[79] Delacollette C, D'Souza C, Christophel E, Thimasarn K, Abdur R, Bell D, et al. Malaria trends and challenges in the Greater Mekong Subregion. Southeast Asian J Trop Med Public Health. 2009 Jul; 40(4): 674–91.

[80] Dhingra N, Prahbat J, Sharma VP et al. Adult and child malaria mortality in India: a nationally representative mortality survey. Lancet. Online October 21, 2010 DOI: 10.1016/S0140– 6736(10)60831–8.

[81] Hay SI, Okiro EA, Gething PW, Patil AP, Tatem AJ, Guerra CA, Snow RW. Estimating the global clinical burden of Plasmodium falciparum Malaria in 2007. PLoS Med. 2010 Jun 15; 7(6): e1000290.

[82] Baird JK. Neglect of Plasmodium vivax malaria. Trends Parasitol. 2007; 23: 533–9.

[83] Galinski MR, Barnwell JW. Plasmodium vivax: who cares? Malar J. 2008; 7 Suppl 1, S9.

[84] Mueller I, Galinski MR, Baird JK, Carlton JM., Kochar DK, Alonso PL, et al. Key gaps in the knowledge of Plasmodium vivax, a neglected human malaria parasite. Lancet Infect Dis. 2009; 9: 555–66.

[85] Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. Am J Trop Med Hyg. 2007; 77: 79–87.

[86] Rosenberg R. Plasmodium vivax in Africa: hidden in plain sight? Trends Parasitol. 2007; 23: 193–6.

[87] Guerra CA, Howes RE, Patil AP, Gething PW, van Boeckel, Temperley WH, et al. The international limits and population at risk of Plasmodium vivax transmission in 2009. PLoS Negl Trop Dis. 2010; 4, e774.

[88] Price RN, Douglas NM, Anstey NM. New developments in Plasmodium vivax malaria: severe disease and the rise of chloroquine resistance. Curr Opin Infect Dis. 2009; 22, 430–5.

[89] Kochar DK, Das A, Kochar SK, Saxena V, Sirohi P, Garg S. Severe Plasmodium vivax malaria: a report on serial cases from Bikaner in northwestern India. Am J Trop Med Hyg. 2009; 80: 194–8.

[90] Choi HJ, Lee SY, Yang H, Bang JK. Retinal haemorrhage in vivax malaria. Trans R Soc Trop Med Hyg. 2004; 98: 387–9.

[91] Kim A, Park YK, Lee JS, Chung MH, Kim ES. A case of symptomatic splenic infarction in vivax malaria. Korean J Parasitol. 2007; 45: 55–8.

[92] Mcqueen PG. Population dynamics of a pathogen: the conundrum of vivax malaria. Biophys Rev, 2 2010: 111–120.

[93] WHO. World Malaria Report 2009. Geneva: WHO.

[94] Rafael ME, Taylor T, Magill A, Lim YW, Girosi F, Allan R. Reducing the burden of childhood malaria in Africa: the role of improved. Nature. 2006; 444 Suppl 1: 39–48.

[95] Sullivan D. Uncertainty in mapping malaria epidemiology: implications for control. Epidemiol Rev. 2010; 32: 175–87

[96] Hay SI, Smith DL, Snow RW. Measuring malaria endemicity from intense to interrupted transmission. Lancet Infect Dis. 2008; 8: 369–78.

[97] Rosenberg, R. Plasmodium vivax in Africa: hidden in plain sight? Trends Parasitol. 2007; 23: 193–6.

[98] Rafael ME, Taylor T, Magill A, Lim YW, Girosi F, Allan R. Reducing the burden of childhood malaria in Africa: the role of improved diagnostics. Nature. 2006; 444 Suppl 1: 39–48.

[99] Mueller I, Galinski MR, Baird JK, Carlton JM, Kochar DK, Alonso PL. Key gaps in the knowledge of Plasmodium vivax, a neglected human malaria parasite. Lancet Infect Dis. 2009; 9: 555–66.

[100] Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, Temperley WH. The International Limits and Population at Risk of Plasmodium vivax Transmission in 2009. PLoS Negl Trop Dis. 2010; 4, e774: p. 8.

[101] Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. Lancet Infect Dis. 2004; 4: 327–336.

[102] Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. Am J Trop Med Hyg. 2007; 77, 79–87, p.2.

[103] Guerra CA, Snow RW, Hay SI. Mapping the global extent of malaria in 2005. Trends Parasitol. 2006; 22: 353–8

[104] Mueller I, Galinski MR, Baird JK, Carlton JM, Kochar DK, Alonso PL. Key gaps in the knowledge of Plasmodium vivax, a neglected human malaria parasite. Lancet Infect Dis. 2009; 9: 555–66

[105] Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. Lancet Infect Dis. 2004;4: 327–36

[106] Kiszewski AE, Teklehaimanot A. A review of the clinical and epidemiologic burdens of epidemic malaria. Am. J. Trop. Med. Hyg. 2004; 71: 128–135

[107] Zhou G, Minakawa N, Githeko AK, Yan G. Climate variability and malaria epidemics in the highlands of East Africa. Trends Parasitol. 2005 Feb; 21(2): 54-6.

[108] Worrall E, Rietveld A, Delacollette C. The burden of malaria epidemics and cost-effectiveness of interventions in epidemic situations in Africa. Am J Trop Med Hyg. 2004 Aug; 71(2 Suppl): 136–40.

[109] Abeku TA. Response to malaria epidemics in Africa. Emerg Infect Dis. 2007 May; 13(5): 681–6.

[110] Kiszewski AE, Teklehaimanot A. A Review of the Clinical and Epidemiologic Burdens of Epidemic Malaria. Am J Trop Med Hyg. 2004; 71/ 2: 128–135.

[111] Hashizume M, Terao T, Minakawa N. The Indian Ocean Dipole and malaria risk in the highlands of western Kenya. Proc Natl Acad Sci U S A. 2009 Feb 10; 106(6): 1857–62.

[112] Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Niño and health. Lancet. 2003 Nov 1; 362(9394): 1481–9.

[113] Jones AE, Wort UU, Morse AP, Hastings IM, Gagnon AS. Climate prediction of El Niño malaria epidemics in north-west Tanzania. Malar J. 2007 Dec 6; 6: 162.

[114] Cox J, Hay SL, Taekegn AA, Checchi F and Snow RW. The uncertain burden of plasmodium falciparum epidemics in Africa. Trends Paras. 2007 Feb; 23/4: 142148.

[115] Ibid.

[116] Worral E, Rietveld A and Delacollette C. The burden of malaria epidemics and the cost effectiveness of interventions in epidemic situations in Africa. Am J Trop Med Hyg. 2004. Aug; 71 (2 Suppl): 136–140.

[117] Cox J, Hay SL, Taekegn AA, Checchi F and Snow RW. The uncertain burden of plasmodium falciparum epidemics in Africa. Trends Paras. 2007 Feb; 23/4: 142148.

[118] WHO: World Malaria Report 2005. Geneva: WHO.

[119] www.alma2015.org/

[120] See: www.who.int/vaccine_research/diseases/soa_parasitic/en/index4.html

[121] Muula AS, Rudatsikira E, Siziya S, Mataya RH. Estimated financial and human resources requirements for the treatment of malaria in Malawi. Malaria Journal. 2007; 6: 168.

[122] Mills A, Shillcutt S. Copenhagen Consensus: Challenge Paper on Communicable Diseases. Health Economics and Financing Programme, London School of Hygiene and Tropical Medicine. 2004.

[123] Jowett M, Miller NJ. The financial burden of malaria in Tanzania: implications for future government policy, Int J Health Planning Man. 2005; 20: 67–84.

[124] See: allafrica.com/stories/201004141111.html

[125] See: allafrica.com/stories/200904260015.html

[126] Chima R, Goodman C, Mills A. The economic impact of malaria in Africa: A critical review of the evidence. Health Policy. 2003; 63(1): 17–36.

[127] Barat LM, Palmer N, Basu S, Worrall E, Hanson K, Mills A. Do malaria control interventions reach the poor? A view through the equity lens. Am J Trop Med Hyg. 2004 Aug; 71(2 Suppl): 174–8.

[128] www.rbm.who.int/cmc_upload/0/000/015/363/RBMInfosheet_10.htm

[129] Gallup JL, Sachs JD. The economic burden of malaria. 2000. CID Working paper 52.

[130] World Economic Forum. Business and malaria: A neglected threat?, WEF Global Health Initiative 2006.

[131] Gallup JL and Sachs JD. The economic burden of malaria. American Journal of Tropical Medicine and Hygiene. 2001. 64 (suppl1): 85–96.

[132] McCarthy FD, Wolf H, Wu Y. The Growth Costs of Malaria. 2001. NBER Working Paper 7541, National Bureau of Economic Research, Cambridge MA.

[133] Cole MA, Neumayer E. The impact of poor health on total factor productivity. Journal of Development Studies. 2006; 42(6).

[134] Hempel J, Najera JA. 1996. The burden of malaria. Available at: www.rollbackmalaria.org/cmc_upload/0/000/009/511/burden_najera.pdf

[135] Breman JG, Mills A, Snow RW, Mulligan J, Lengeler C, Mendis K, et al. Conquering malaria. In. Jamison DT et al. eds. Disease control priorities in developing countries, 2nd edition 2006. Washington DC: The World Bank and Oxford University Press.

[136] Ettling MB, McFarland DA, Schultz LJ, Chitsulo L. Economic impact of malaria in Malawian households. Tropical Medicine and Parasitology 2004; 45: 74–79.

[137] Leighton C, Foster R. 2003. Economic impacts of malaria in Kenya and Nigeria. Abt Associates, Health Financing and Sustainability Project, Bethesda, Maryland.

[138] Breman et al. Op cit.

[139] Audibert M, Matthonat J, Henry MC. Malaria and property accumulation in rice production systems in the Savannah Zone of Cote d'Ivoire. Tropical Medicine and International Health 2003; 8(5): 471–83.

[140] World Bank. Rolling Back Malaria: The World Bank Global Strategy and Booster Program. Washington DC: The World Bank 2005.

[141] Konradsen F, van der Hoek W, Amerasinghe PH, Amerasinghe FP. Measuring the economic cost of malaria to households in Sri Lanka. American Journal of Tropical Medicine and Hygiene 1997; 56: 656–660.

[142] Holding PA, Snow RW. Impact of Plasmodium falciparum malaria on performance and learning: review of the evience. American Journal of Tropical Medicine and Hygiene 2001; 64(1–2): 68–75.

[143] World Bank 2005. Rolling Back Malaria: The World Bank Global Strategy and Booster Program. Washington DC: The World Bank.

[144] Chima R, Goodman C, Mills A. The economic impact of malaria in Africa: A critical review of the evidence. Health Policy 2003; 63(1): 17–36.

[145] Worrall E, Basu S, Hanson K. Is malaria a disease of poverty? A review of the literature. Trop Med Int Health 2005; 10(10): 1047–59.

[146] Armstrong Schellenberg J, Victora CG, Mushi A. Inequities among the very poor: health care for children in rural Tanzania. Lancet 2003; 361: 561–6

[147] Worrall E, Basu S, Hanson K. Is malaria a disease of poverty? A review of the literature, Tropical Medicine and International Health 2005; 10: 10.

[148] Amexo M, Tolhurst R, Barnish G, Bates I. Malaria misdiagnosis: effects on the poor and vulnerable, Lancet 2004; 364: 1896–1898.

[149] Russell: The economic burden of illness for households in developing Countries: a review of studies focusing on malaria, tuberculosis, AIDS Am. J. Trop. Med. Hyg. 2004; 71(Suppl 2).

[150] Ettling et al Economic impact of malaria in Malawian households. Trop Med Parasitol. 1994; 45

[151] Attanayake et al Household costs of 'malaria' morbidity: a study in Matale district, Sri Lanka.Trop Med Int Hlth. 2000; 5

[152] Somi et al. Economic burden of malaria in rural Tanzania: variations by socioeconomic status and season. Trop Med Int Health 2007, 12

[153] Akazili J, Aikins M, Binka F. Malaria treatment in Northern Ghana: What is the treatment cost per case to households? African Journal of Health Sciences 2007;14: 70–79.

[154] Onwujekwe O, Hanson K, Uzochukwu B, Ichoku H, Ike E and Onwughalu B. Are malaria treatment expenditures catastrophic to diefferent socio-economic and geographic groups and how do they cope with payments? A study in southeast Nigeria.Trop Med Int health. 2010 Jan; 15 (1): 18–25.

[155] Chuma J, Okungu V, Molyneux C. Barriers to prompt and effective malaria treatment among the poorest population in Kenya. Malaria Journal 2010; 9: 144.

[156] Chuma JM, Thiede M, Molyneux CS. Rethinking the economic case of malaria at the household level: Evidence from applying a new analytical framework in rural Kenya, Malaria Journal, 2006; 5: 76.

[157] Ettling MB, Shepard DS. Economic cost of malaria in Rwanda, Tropical Medicine and Parasitology 1991; 42.

[158] Leighton C, Foster R. 1993. Economic Impacts of Malaria in Kenya and Nigeria. Abt Associates, Health Financing and Sustainability Project, Bethesda, MD.

[159] Filmer D. Op cit.

[160] Gollin and Zimmermann. 2007. Malaria: Disease Impacts and Long-Run Income Differences. IZA DP No. 2997

[161] Mills A, Shillcutt S. 2004. The Challenge of Communicable Disease. In Global Crises, Global Solutions. Ed. Lomborg B. Cambridge UK: Cambridge University Press.

[162] Bates I, Fenton C, Gruber J, Lalloo D, Lara AM, Squire SB, Theobald S, Thomson R, Tolhurst R. Vulnerability to malaria, tuberculosis, and HIV/AIDS infection and disease. Part 1: determinants operating at individual and household level. Lancet Infectious Diseases. 2004 May; 4: 267–277

[163] Breman J. The ears of the hippopotamus: manifestations, determinants and estimates of the malaria burden. 2001. Am. J. Trop. Med. Hyg., 64 (1.2)S, pp1–11

[164] Rogerson SJ, Wijesinghe RS, Meshnick SR. Host immunity as a determinant of treatment outcome in *Plasmodium falciparum* malaria. The Lancet Infectious Diseases 2010; 10(1): 51-59.

[165] Crawley J, Chu C, Mtove G, Nosten F. Malaria in children. Lancet Apr 2010; 375: 1468–81.

[166] Snow R, Marsh K. The consequences of reducing transmission of Plasmodium falciparum in Africa; Advances in parasitology. 2002; 52: 235–64.

[167] Drakeley CJ, Akim NI, Sauerwein RW, Greenwood BM, Targett GA. Estimates of the infectious reservoir of Plasmodium falciparum malaria in The Gambia and in Tanzania. Trans R Soc Trop Med Hyg. 2000 Sep–Oct; 94(5): 472–6.

[168] Okell LC, Drakeley CJ, Bousema T, Whitty CJM, Ghani AC. Modelling the impact of artemisinin combination therapy and long–acting treatments on malaria transmission intensity. PLoS Med. 2008 Nov 25; 5(11): e226;

[169] Cole-Tobian JL, Michon P, Biasor M, Richards JS, Beeson JG, Mueller I, King CL. Strain-specific duffy binding protein antibodies correlate with protection against infection with homologous compared to heterologous plasmodium vivax strains in Papua New Guinean children. Infect Immun. 2009 Sep; 77(9): 4009–17.

[170] Poespoprodjo J, Fobia W, Kenangalem E, Lampah DA, Hasanuddin A, Warikar N, Sugiarto P, Tijitra E, Anstey NM, Price RN. Vivax malaria: a major cause of morbidity in early infancy. Clin Infect Dis 2009: 48: 1794–12.

[171] Crawley J, Chu C, Mtove G, Nosten F. Malaria in children. Lancet Apr 2010; 375: 1468–81.

[172] Williams TN. Human red blood cell polymorphisms and malaria. Curr Opin Microbiol. 2006 Aug; 9(4): 388–94.

[173]Ruwende C, Khoo SC, Snow RW, Yates SN, Kwiatkowski D, Gupta S, Warn P, Allsopp CE, Gilbert SC, Peschu N, et al. Natural selection of hemi- and heterozygotes for G6PD deficiency in Africa by resistance to severe malaria. Nature. 1995 Jul 20; 376(6537): 246–9.

[174]Leslie T, Briceño M, Mayan I, Mohammed N, Klinkenberg E, Sibley CH, Whitty CJ, Rowland M. The impact of phenotypic and genotypic G6PD deficiency on risk of plasmodium vivax infection: a case-control study amongst Afghan refugees in Pakistan. PLoS Med. 2010 May 25; 7(5): e1000283.

[175] Menard D, Barnadas C, Bouchier C et al. *Plasmodium vivax* clinical malaria is commonly observed in Duffy-negative Malagasy people**.** PNAS March 30, 2010 vol. 107 no. 13 5967-5971

[176]Rowe JA, Opi DH, Williams TN. Blood groups and malaria: fresh insights into pathogenesis and identification of targets for intervention. Curr Opin Hematol. 2009 Nov; 16(6): 480–7.

[177] Beutler E, Duparc S, G6PD deficiency Working Group. Glucose-6-phosphate dehydrogenase deficiency and antimalarial drug development. Am J Trop Med Hyg 2007; 77: 779–789.

[178] Carneiro I, Roca-Feltrer A, Griffin JT, Smith L, Tanner M, Schellenberg JA, Greenwood B, Schellenberg D. Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. PLoS One. 2010 Feb 1; 5(2): e8988.

[179] Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010; 375: 1969–87

[180] Okiro EA, Al-Taiar A, Reyburn H, Idro R, Berkley JA, Snow RW. Age patterns of severe paediatric malaria and their relationship to Plasmodium falciparum transmission intensity. Malar J. 2009 Jan 7; 8: 4.

[181] Taylor T, Olola C, Valim C, Agbenyega T, Kremsner P, Krishna S, et al. Standardised data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network. Trans R Soc Trop Med Hyg. 2006 Jul; 100(7): 615–22.

[182] Kihara M, Carter JA, Newton CR. The effect of Plasmodium falciparum on cognition: a systematic review. Trop Med Int Health. 2006 Apr; 11(4): 386–97.

[183] Hviid L, Staalsoe T. Malaria immunity in infants: a special case of a general phenomenon? Trends Parasitol. 2004 Feb; 20(2): 66–72.

[184] Erhart A, Thang ND, Hung NQ, Toi le V, Hung le X, Tuy TQ, Cong le D, Speybroeck N, Coosemans M, D'Alessandro U. Forest malaria in Vietnam: a challenge for control. Am J Trop Med Hyg. 2004 Feb; 70(2): 110–8.

[185] Dysoley L, Kaneko A, Eto H, Mita T, Socheat D, Börkman A, Kobayakawa T. Changing patterns of forest malaria among the mobile adult male population in Chumkiri District, Cambodia. Acta Trop. 2008 Jun; 106(3): 207–12.

[186] Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb; 7(2): 93–104.

[187] Vlassoff C, Bonilla A. ender-related difference in the impact of tropical diseases on women: what do we know? J Biosoc Sci. 1994 Jan; 26 (1): 37–53

[188] Incardona S, Vong S, Chiv L, Lim P, Nhem S, Sem R, Khim N, Doung S, Mercereau-Puijalon O, Frandeur T. Large-scale malaria survey in Cambodia: Novel insights on species distribution and risk factors. Malar J 2007, 6(1): 37

[189] Erhart A, Thang ND, Hung NQ, Toi le V, Hung le X, Tuy TQ, Conge le D, Speybroeck N, Coosemans M, D'Alessandro U. Forest Malaria In Vietnam: A Challenge For Control Am. J. Trop. Med. Hyg., 70(2), 2004

[190] Coker R, Atun R, McKee M (Eds). Health Systems and the Challenge of Communicable Diseases: Experience from Europe and Latin America. McGraw Hill, Open University Press, 2008

[191] Al-Taiar A, Chandler C, Al Eryani S, Whitty CJ.Knowledge and practices for preventing severe malaria in Yemen: the importance of gender in planning policy. Health Policy Plan. 2009 Nov; 24(6): 428–37.

[192] Oberlander and Elverdan) Malaria in the United Republic of Tanzania: cultural considerations and health-seeking behaviour. Bulletin of the World Health Organization 2000.78:

[193] Nonvignon J, Aikins MK, Chinbuah MA, Abbey M, Gyapong M, Garshong BN, Fia S, Gyapong JO. Treatment choices for fevers in children under-five years in a rural Ghanaian district. Malar J. 2010 Jun 28; 9: 188

[194] Howard N, Shafi A, Jones C, Rowland M. Malaria control under the Taliban regime: insecticide-treated net purchasing, coverage, and usage among men and women in eastern Afghanistan. Malar J. 2010 Jan 6; 9: 7

[195] Accorsi S, Fabiani M, Nattabi B, Ferrarese N, Corrado B, Iriso R, Ayella EO, Pido B, Yoti Z, Corti D, Ogwang M, Declich S. Differences in hospital admissions for males and females in northern Uganda in the period 1992–2004: a consideration of gender and sex differences in health care use. Trans R Soc Trop Med Hyg. 2007 Sep; 101(9): 929–38.

[196]Al-Taiar A, Jaffar S, Assabri A, Al-Habori M, Azazy A, Al-Mahdi N, Ameen K, Greenwood BM, Whitty CJM. Severe malaria in children in Yemen: two site observational study. BMJ. 2006 Oct 21; 333(7573): 827.

[197] Bejon P, Mohammed S, Mwangi I, Atkinson SH, Osier F, Peshu N, Newton CR, Maitland K, Berkley JA. Fraction of all hospital admissions and deaths attributable to malnutrition among children in rural Kenya. Am J Clin Nutr. 2008 Dec; 08(6): 1626–31.

[198] Caulfield LE, Richard SA, Black RE: Undernutrition as an underlying cause of malaria morbidity and mortality in children under five years old. Am J Trop Med Hyg 2004, 71: 55–6

[199] Black R, Lindsay H Allen, Zulfiqar A Bhutta, Laura E Caulfield, Mercedes de Onis, Majid Ezzati, Colin Mathers, Juan Rivera, for the Maternal and Child Undernutrition Study Group. Lancet 2008, 371: 243–260

[200] Black RE. Zinc deficiency, infectious disease and mortality in the developing world. J Nutr 2003, 133: 1485S–1489S.

[201] Black RE. Zinc deficiency, infectious disease and mortality in the developing world. J Nutr 2003, 133: 1485S–1489S.

[202] Caulfield LE, de Onis M, Blossner M, Black RE: Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. Am J Clin Nutr 2004, 80: 193–198

[203] Gallup JL and Sachs JD. 2001. The economic burden of malaria. American Journal of Tropical Medicine and Hygiene. 64 (suppl1): 85–96.

[204] Filmer D. Fever and its treatment among the more and less poor in sub-Saharan Africa. Health Policy Plan. Nov 2005; 20(6): 337–46

[205] Somi et al. Is there evidence for dual causation between malaria and socioeconomic status? Findings from rural Tanzania. Am J Trop Med Hyg. 2007; 77.

[206] Coleman et al. Household and microeconomic factors associated with malaria in Mpumalanga, South Africa. Trans R Soc Trop Med Hyg. 2010 Feb; 104(2)

[207] Barat L, Palmer N, Basu S, Worrall E, Hanson K, Mills A. Do malaria control interventions reach the poor? A view through the equity lens. Am J Trop Med Hyg 2004, 71.

[208] Goesch et al. Socio-economic status is inversely related to bed net use in Gabon Mal J 2008, 7: 60

[209] Onwujekwe O, Uzochukwu B, Dike N, Okoli C, Eze S and Chukwuogo O. Are there geographic and socioeconomic differences in the incidence, burden and prevention of malaria? A study in southeast Nigeria. Int J Equity Health. 2009 Dec 23; 8: 45

[210] Chuma JM, Thiede M, Molyneux CS, Rethinking the economic costs of malaria at the household level: evidence from applying a new analytical framework in rural Kenya. Malar J 2006, 5: 76

[211] Schellenberg et al. Inequities among the very poor: health care for children in rural southern Tanzania. Lancet 2003, 361.

[212] Filmer D. Fever and its treatment among the more and less poor in sub-Saharan Africa. WashingtonDC: World Bank Development Research Group, 2001.

[213] Makundi EA, Mboera LEG, Malebo HM, Kitua AY. Priority Setting on Malaria Interventions in Tanzania: Strategies and Challenges to Mitigate against the Intolerable Burden, American Journal of Tropical Medicine and Hygiene 2007; 77(Supplement 6).

[214] Gollin and Zimmermann. 2007: Malaria: Disease Impacts and Long-Run Income Differences. IZA DP No. 2997.

[215] Wandiga SO, et al. 2006. Vulnerability to climate induced highland malaria in East Africa, AIACC Working Paper No. 25.

[216] Chuma JM, Thiede M, Molyneux CS. Rethinking the economic case of malaria at the household level: Evidence from applying a new analytical framework in rural Kenya, Malaria Journal. 2006; 5: 76.

[217] Worrall E, Basu S, Hanson K. Is malaria a disease of poverty? A review of the literature, Tropical Medicine and International Health 2005; 10: 10.

[218] Amexo M, Tolhurst R, Barnish G, Bates I. Malaria misdiagnosis: effects on the poor and vulnerable, Lancet 2004; 364: 1896–1898.

[219] Chuma JM, Thiede M, Molyneux CS. Rethinking the economic costs of malaria at the household level: evidence from applying a new analytical framework in rural Kenya. Mal J. 2006; 5: 76.

[220] Newbrander, William. Providing Health Services in Fragile States. Arlington, Va., USA: Basic Support for Institutionalising Child Survival (BASICS) for the United States Agency for International Development (USAID). 2006. P. 3. *It is unclear what data, and what definition of state fragility this figure is based on.

[221] Whyte B, Up to one third of malaria deaths in Africa occur in countries affected by complex emergencies. Bull World Health Organ. Aug 2000; 78(8): 1062.

[222] WHO. Malaria control in complex emergencies: An inter-agency support handbook. Geneva: WHO.

[223] Roberts L. Mortality in Eastern DRC: results from five mortality surveys by the International Rescue Committee. Bukavu, DR Congo; International rescue Committee; 2000.

[224] Kolaczinski J. Roll Back Malaria in the aftermath of complex emergencies: the example of Afghanistan. Trop Med and Int Hlth, 2005: 10(9): 888–893.

[225] ESPD, Poverty and Social Policy Team. Enhancing health Systems: Malaria's Negative Impact in Africa. 2005. Geneva.

[226] Martins JS, Zwi AB, Martins N, Kelly PM. Malaria control in Timor-Leste during a period of political instability: what lessons can be learned? Conflict and Hlth 2009; 3: 11.

[227] Huerga H. Adult and paediatric mortality patterns in a referral hospital in Liberia 1 year after the end of the war. Trans R Soc Trop Med Hyg 2009; 103(5): 476–84; Rowland M, Rab MA, Freeman T. Afghan refugees and the temporal and spatial distribution of malaria in Pakistan. Soc Sci Med. 2002 Dec; 55(11): 2061–72.

[228] Meek S, Rowland M, Connoly M. Outline strategy for malaria control in complex emergencies. 2000. Geneva: WHO.

[229] Roberts DR, Manguin S, Mouchet J. DDT house spraying and re-emerging malaria. Lancet. 2000 Jul 22; 356(9226): 330–2.

[230] Connolly MA, Gayer M, Ryan MJ, Salama P, Spiegel P, Heymann DL. Communicable diseases in complex emergencies: impact and Challenges. Lancet 2004; 364: 1974–83.

[231] Faulde MK, Hoffmann R, Fazilat KM, Hoerauf A. Epidemiology of Plasmodium falciparum and P. vivax malaria endemic in northern Afghanistan. J Egypt Soc Parasitol. 2008 Dec; 38(3): 679–92.

[232] Dr. Toby Leslie personal communication 2010

[233] Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Annals of Tropical Medicine & Parasitology 2001; 95, 741-754.

[234] WHO. Malaria control in complex emergencies: an inter-agency support handbook. 2005. Geneva: WHO.

[235] Martins JS, Zwi AB, Martins N, Kelly PM. Malaria control in Timor-Leste during a period of political instability: what lessons can be learned? Conflict and Hlth 2009; 3: 11.

[236] Zwi AB, Martins J, Grove NJ, Wayte K, Martins N, Kelly P. Timor-Leste Health Sector Resilience and Performance in a Time of Instability. Sydney: The University of New South Wales; 2007.

[237] Martins JS, Zwi AB, Martins N, Kelly PM. Malaria control in Timor-Leste during a period of political instability: what lessons can be learned? Conflict and Hlth 2009; 3: 11.

[238] Leslie, H. Kaur, Nasir Mohammed, K. Kolaczinski, R. Ord, M. Rowland. An epidemic of Plasmodium falciparum malaria in Afghan refugees in Pakistan involving substandard antimalarial drugs. Emerging Infectious Diseases 2009; 15, 1753–1759; Rowland M, Rab MA, Freeman T. Afghan refugees and the temporal and spatial distribution of malaria in Pakistan. Soc Sci Med. 2002 Dec; 55(11): 2061–72.

[239] K. Graham, N. Mohammad, H. Rehman, et al. Insecticide treated plastic tarpaulins for control of malaria vectors in refugee camps. Medical and Veterinary Entomology 2002; 16, 404–408; Rowland, M., Durrani, N., Hewitt, S. 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.

[240] Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Annals of Tropical Medicine & Parasitology 2001; Vol. 95, No. 8, 741-754.

[241] Suleman M. Malaria in Afghan refugees in Pakistan.Transactions of the Royal Society of Tropical Medicine and Hygiene 1988; 82 (1): 44–47.

[242] WHO. Malaria control in complex emergencies: an inter-agency support handbook. 2005. Geneva: WHO.

[243] E.g. Richards AK, Smith L, Mullany LC, et al. Prevalence of p. falciparum in active conflict areas of eastern Burma: a summary of cross-sectional data. Conflict and Hlth, 2007; 1: 9.

[244] Gallup JL, Sachs JD (2000). The economic burden of malaria. CID Working paper No. 52.

[245] Hanson K, Ranson MK, Oliveira-Cruz V, Mills A. Expanding access to priority health interventions: understanding the constraints to scaling-up. J Int Dev 2003; 15 (1): 1–14.

[246] Spiegel PB, Hering H, Paik E, Schilperoord M. Conflict-affected displaced persons need to benefit more from HIV and malaria national strategic plans and Global Fund Grants. Conflict and Health 2010, 4: 2

[247] Lafferty K. The ecology of climate change and infectious diseases. Ecology 2009; 90(4): 888–900.

[248] Reiter P. Climate change and mosquito-borne disease. Environ Health Perspect 2001; 109(supp 1): 141–161.

[249] Chaves LF, Koenraadt CJM. Climate change and highland malaria: fresh air for a hot debate. The Quarterly Review of Biology 2010 March; 85: 1.

[250] Lafferty K. The ecology of climate change and infectious diseases. Ecology 2009; 90(4): 888–900.

[251] Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue RS, Kovats BR, Woodward A. Human health. In: Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, editors. Climate Change 2007: Impacts, Adapation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press; 2007. p. 391–431.

[252] Lafferty K. The ecology of climate change and infectious diseases. Ecology 2009; 90(4): 888–900.

[253] Ebi K, Hartman J, Chan N, McConnell J, Schlesinger M, Weyant J. Climate suitability for stable malaria transmission in Zimbabwe under different climate change scenarios. Climatic Change 2005; 73: 375–393.

[254] Lindsay, SW and Martens, WJM. Malaria in the African highlands: past, present and future. Bull. World Health Organ. 1998; 76: 33–45.

[255] Pascual M, Ahumada JA, Chavez LF, Rodo Z, Bouma M. Malaria resurgence in the east African highlands: temperature trends revisited. Proc Natl Acad Sci 2006; 103: 582–5834

[256] Hay SI, Cox J, Rogers DJ, Randolph SE, Stern DI, Shanks, GD, Myers MF, Snow RW. Climate change and the resurgence of malaria in the East African highlands. Nature 2002; 415 (6874): 905–909.

[257] Shanks GD, Hay SI, Omumbo JA, Snow RW. Malaria in Kenya's western highlands. Emerging Infectious Diseases 2005; 11 (9): 1425–1432.

[258] Patz, JA. A human disease indicator for the effects of recent global climate change. P. Nat. Acad. Sci. 2002; 99: 12506–12508.

[259] Hay SI, Cox J, Rogers DJ, Randolph SE, Stern DI, Shanks, GD, Myers MF, Snow RW. Climate change and the resurgence of malaria in the East African highlands. Nature 2002; 415 (6874): 905–909.

[260] Shanks GD, Hay SI, Omumbo JA, Snow RW 2005. Malaria in Kenya's western highlands. Emerging Infectious Diseases 11 (9): 1425–1432.

[261] Lafferty K. The ecology of climate change and infectious diseases. Ecology 2009; 90(4): 888–900.

[262] Gething P, Smith L, Patil A, Tatem A, Snow R, Hay S. Climate change and the global malaria recession. Nature 2010; 465: 342–345.

[263] Reiter P. Global warming and malaria: knowing the horse before hitching the cart. Malaria Journal 2008; 7(Suppl 1): S3.

[264] Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Nino and health. Lancet 2003; 362: 1481–1489.

[265] Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Nino and health. Lancet 2003; 362: 1481–1489.

[266] Mantilla G, Oliveros H, Barnston AG. The role of ENSO in understanding changes in Colombia's annual malaria burden by region, 1960–2006. Malaria Journal 2009 January 8; 8: 6.

[267] Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Nino and health. Lancet 2003; 362: 1481–1489.

[268] Githeko AK, Ndgewa W. Predicting malaria epidemics in the Kenyan highlands using climate data: a tool for decision makers. Global Change and Human Health 2001; 2: 54–63.

[269] Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Nino and health. Lancet 2003; 362: 1481–1489.

[270] Christensen JH, Hewitson B, Busuioc A, Chen A, Gao X, Held I, Jones R, Kolli RK, Kwon WT, Laprise R, Magaña Rueda V, Mearns, L, Menéndez CG, Räisänen J, Rinke A, Sarr A, Whetton P. Regional Climate Projections. In Solomon S, Qin D, Manning M, Chen Z, Marquis M, Averyt KB, Tignor M, Miller, H.L., editors. Climate Change 2007: The Physical Science Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate. Cambridge and New York, Cambridge University Press; 2007.

[271] Reiter P. Climate change and mosquito-borne disease. Environ Health Perspect 2001; 109(supp 1): 141–161.

[272] Mouchet J, Faye O, Juivez J, Manguin. Drought and malaria retreat in the Sahel, West Africa. Lancet 1996; 348: 1735–1736.

[273] Bouma M, Dye C. Cycles of malaria associated with El Nino in Venezuela. J.Am.Med.Assoc. 1997; 278: 1772–1774.

[274] Chaves LF, Koenraadt CJM. Climate change and highland malaria: fresh air for a hot debate. The Quarterly Review of Biology 2010 March; 85: 1

[275] Gething P, Smith L, Patil A, Tatem A, Snow R, Hay S. Climate change and the global malaria recession. Nature 465: 342–345.

[276] Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue RS, Kovats BR, Woodward A. Human health. In: Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, editors. Climate Change 2007: Impacts, Adapation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press; 2007. p. 391–431.

[277] Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue RS, Kovats BR, Woodward A. Human health. In: Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, editors. Climate Change 2007: Impacts, Adapation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press; 2007. p. 391–431.

[278] Haines A, Kovats RS, Campbell-Lendrum D, Corvalan C. Climate change and human health: impacts, vulnerability, and mitigation. Lancet 2006; 367: 2101–2109.

[279] Reiter P. Global warming and malaria: knowing the horse before hitching the cart. Malaria Journal 2008; 7(Suppl I): S3.

[280] Gething P, Smith L, Patil A, Tatem A, Snow R, Hay S. Climate change and the global malaria recession. Nature 2010; 465: 342–345.

[281] McMichael A, Woodruff R, Hales S. Climate change and human health: present and future risks. Lancet 2006; 367: 859–69.

[282] Reiter P. Climate change and mosquito-borne disease. Environ Health Perspect 2001; 109(supp 1): 141–161.

[283] Tanser F, Sharp BL, Le Sueur D. Potential effect of climate change on malaria transmission in Africa. Lancet 2003; 362: 1792–98.

[284] Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue RS, Kovats BR, Woodward A. Human health. In: Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, editors. Climate Change 2007: Impacts, Adapation and Vulnerability. Contribution of Working Group II to the Fourth

Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press; 2007. p. 391–431.

[285] See for example, Tanser F, Sharp BL, Le Sueur D. Potential effect of climate change on malaria transmission in Africa. Lancet 2003; 362: 1792–98 and Thomas CJ, Davies G, Dunn CD. Mixed picture for changes in stable malaria distribution with future climate in Africa. Trends Parisitol 2004; 20: 216–20.

[286] Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue RS, Kovats BR, Woodward A. Human health. In: Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, editors. Climate Change 2007: Impacts, Adapation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press; 2007. p. 391–431.

[287] Reiter P. Global warming and malaria: knowing the horse before hitching the cart. Malaria Journal 2008; 7(Suppl 1): S3.

[288] Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue RS, Kovats BR, Woodward A. Human health. In: Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, editors. Climate Change 2007: Impacts, Adapation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press; 2007. p. 391–431.

[289] Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Nino and health. Lancet 2003; 362: 1481–1489

[290] de Castro MC, Kanamori S, Kannady K, Mkude S, Killeen GF, et al. The Importance of Drains for the Larval Development of Lymphatic Filariasis and Malaria Vectors in Dar es Salaam, United Republic of Tanzania. PLoS Negl Trop Dis 4(5): e693.

[291] Kengne N IM, Akoa, A, Atangana, ER, Nya, J, Ngniado, P, Fonkou, T and Brissaud, F. Mosquito development and biological control in a macrophyte–based wastewater treatment plant. Water Sci Technology 2005.

[292] Ensink JH, Mukhtar M, van der Hoek W, Konradsen F. Simple intervention to reduce mosquito breeding in waste stabilisation ponds. Trans R Soc Trop Med Hyg 2007; 101(11): 1143–6.

[293] Mukhtar M, Ensink J, Van der Hoek W, Amerasinghe FP, Konradsen F. Importance of waste stabilization ponds and wastewater irrigation in the generation of vector mosquitoes in Pakistan. J Med Entomol 2006 Sep; 43(5): 996–1003.

[294] Walker KR. A Review of Control Methods for African Malaria Vectors. Environmental Health Project, Activity Report 108. U.S. Agency for International Development; 2002.

[295] Amoatey PK, Winter J, Kaempf C. Solid Waste Disposal and the Incidences of Malaria: Any Correlation? Proceeding (604) Water Resource Management 2008.

[296] Caldas de Castro M, Yamagata Y, Mtasiwa DE, Tanner M, Utzinger J, Keiser J, Singer Integrated Urban Malaria Control: A Case Study in Dar Es Salaam, Tanzania. Am J Trop Med Hyg, 2004; 71(2 suppl): 103–117.

[297] Fillinger U et al. A tool box for operational mosquito larval control: preliminary results and early lessons from the Urban Malaria Control Programme in Dar es Salaam, Tanzania. alaria Journal 2008, 7: 20

[298] Chavasse DC, Lines JD, Ichimori K, Majala AR, Minjas JN, et al. Mosquito control in Dar es Salaam. II. Impact of expanded polystyrene beads and pyriproxyfen treatment of breeding sites on Culex quinquefasciatus densities. Med Vet Entomol 1995; 9: 117–154.

[299] Chavasse DC, Lines JD, Ichimori K, Marijani J. Mosquito control in Dar es Salaam. I. Assessment of Culex quinquefasciatus breeding sites prior to intervention. Med Vet Entomol 1995; 9: 141–146.

[300] The rationale is that if some people don't know that only some types of mosquitoes transmit malaria, and they continue to be bitten by mosquitoes, they will consider that the EM controls failed.

[301] Curtis CF. Alternatives to conventional insecticides for urban vector and pest control Proceedings of the First International Conference on Urban Pests. 1993.

[302] Curtis C, Malecela-Lazaro M, Reuben R, Maxwell C. Use of floating layers of polystyrene beads to control populations of the filaria vector Culex quinquefasciatus. Ann Trop Med Parasitol 2002; 96: S97–S104.

[303] Keiser J, Singer BH, Utzinger J. Reducing the burden of malaria in different eco-epidemiological settings with environmental management: a systematic review. Lancet Infect Dis 2005; 5: 695–708.

[304] World Bank. Environmental Health and Child Survival: Epidemiology, Economics, Experiences. Washington, DC: World Bank; 2008.

[305] Keiser J, Singer BH, Utzinger J. Reducing the burden of malaria in different eco-epidemiological settings with environmental management: a systematic review. Lancet Infect Dis 2005; 5: 695–708.

[306] Lindsay SW, Armstrong Schellenberg JR, Zeiler HA, Daly RJ, Salum FM, Wilkins HA. Exposure of Gambian children to Anopheles gambiae malaria vectors in an irrigated rice production area. Med Vet Entomol 1995 Jan; 9(1): 50–8.

[307] Yadouleton AWM, Asidi A, Djouaka RF, Braima J, Agossou C, Akogbeto M. Development of vegetable farming: a cause of the emergence of insecticide resistance in populations of Anopheles gambiae in urban areas of Benin. Malaria Journal 2009; 8: 103.

[308] Matthys B, N'Goran EK, Kone M, Koudou BG, Vounatsou P, Cisse G, Tschannen AB, Tanner M, Utzinger J. Urban agricultural land use and characterisation of mosquito larval habitats in a medium-sized town of Cote D'Ivoire. J Vector Ecol. 2006 Dec; 31(2): 319–33.

[309] International Irrigation Management Institute. Proceedings of the workshop on irrigation and vector-borne disease transmission. Colombo: International Irrigation Management Institute; 1986.

[310] Ghebreyesus TA, Haile M, Witten KH, Getachew A, Yohannes AM, Yohannes M, Teklehaimanot D, Lindsay SW, Byass P. Incidence of malaria among children living near dams in northern Ethiopia: community based incidence survey. BMJ 1999; 319: 663–666.

[311] Ijumba JN, Lindsay SW. Impact of irrigation on malaria in Africa: paddies paradox. Med Vet Entomol. 2001 Mar; 15(1): 1–11.

[312] Sissoko MS, Dicko A, Briet OJT, Sissoko M, Sagara I, Keita HD, Sogoba M, Rogier C, Toure YT, Doumbo OK. Malaria incidence in relation to rice cultivation in the irrigated Sahel of Mali. Acta Tropica 2004; 89: 171–170.

[313] Mutero Cm, Kabutha C, Kimani V, Kabuage L, Gitau G, Ssennyong J, Githure J, Muthamie L, Kaida A, Musyokac L, Kiarie E, Oganda M. A transdisciplinary perspective on the links between malaria and agroecosystems in Kenya. Acta Tropica 2004; 89: 171–186.

[314] Ijumba JN, Lindsay SW. Impact of irrigation on malaria in Africa: paddies paradox. Med Vet Entomol. 2001 Mar; 15(1): 1–11.

[315] Ijumba JN, Lindsay SW. Impact of irrigation on malaria in Africa: paddies paradox. Med Vet Entomol. 2001 Mar; 15(1): 1–11.

[316] Sissoko MS, Dicko A, Briet OJT, Sissoko M, Sagara I, Keita HD, Sogoba M, Rogier C, Toure YT, Doumbo OK. Malaria incidence in relation to rice cultivation in the irrigated Sahel of Mali. Acta Tropica 2004; 89: 171–170.

[317] Keiser J, Singer BH, Utzinger J. Reducing the burden of malaria in different eco-epidemiological settings with environmental management: a systematic review. Lancet Infect Dis 2005; 5: 695–708.

[318] Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. World population prospects: the 2006 world urbanisation prospects: the 2007 revision. 2007. Available at: esa.un.org/unup

[319] Donnelly MJ, McCall PJ, Lengeler C, Bates M, D'Alessandro U, Barnish G, Konradsen F, Klinkenberg E, Townson H, Trape JF, Hastings I, Mutero C. Malaria and urbanisation in sub-Saharan Africa. Malaria Journal 2005; 4: 12.

[320] Martens P, Hall L. Malaria on the move: human population movement and malaria transmission. Emerg Infect Dis 2000; 6(2): 103–109.

[321] Kolsky P. Engineers and urban malaria: part o the solution, or part of the problem? Environment and Urbanisation 1999; 11(1): 159–164.

[322] Donnelly MJ, McCall PJ, Lengeler C, Bates M, D'Alessandro U, Barnish G, Konradsen F, Klinkenberg E, Townson H, Trape JF, Hastings I, Mutero C. Malaria and urbanisation in sub-Saharan Africa. Malaria Journal 2005; 4: 12.

[323] Knudsen AB, Sloof R. Vector-borne disease problems in rapid urbanisation: new approaches to vector control. Bull World Health Organ 1992; 70: 1–6.

[324] Yadouleton AWM, Asidi A, Djouaka RF, Braima J, Agossou C, Akogbeto M. Development of vegetable farming: a cause of the emergence of insecticide resistance in populations of Anopheles gambiae in urban areas of Benin. Malaria Journal 2009; 8: 103.

[325] Afrane, A.A., Klinkenberg, E. Drechsel, P., Owusu-Daaku, K., Garms, R. and Kruppa, T. Does irrigated urban agriculture influence the transmission of malaria in the city of Kumasi, Ghana? Acta Tropica 2004; 89(2): 125–134.

[326] Yadouleton AWM, Asidi A, Djouaka RF, Braima J, Agossou C, Akogbeto M. Development of vegetable farming: a cause of the emergence of insecticide resistance in populations of Anopheles gambiae in urban areas of Benin. Malaria Journal 2009; 8: 103.

[327] Martens P, Hall L. Malaria on the move: human population movement and malaria transmission. Emerg Infect Dis 2000; 6(2): 103–109.

[328] Keiser J, Utzinger J, Caldas de Castro M, Smith TA, Tanner M, Singer B. Urbanisation in sub-Saharan Africa and implications for malaria control. Am J Trop med Hyg 2004; 71(Supp 2): 118–127.

[329] Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. World population prospects: the 2006 world urbanisation prospects: the 2007 revision. 2007. Available at: esa.un.org/unup

[330] Donnelly MJ, McCall PJ, Lengeler C, Bates M, D'Alessandro U, Barnish G, Konradsen F, Klinkenberg E, Townson H, Trape JF, Hastings I, Mutero C. Malaria and urbanisation in sub-Saharan Africa. Malaria Journal 2005; 4: 12.

[331] Caldas de Castro M, Yamagata Y, Mtasiwa DE, Tanner M, Utzinger J, Keiser J, Singer Integrated Urban Malaria Control: A Case Study in Dar Es Salaam, Tanzania. Am J Trop Med Hyg, 2004; 71(2 suppl): 103–117.

[332] Keiser J, Utzinger J, Caldas de Castro M, Smith TA, Tanner M, Singer B. Urbanisation in sub-Saharan Africa and implications for malaria control. Am J Trop med Hyg 2004; 71(Supp 2): 118–127.

[333] Pattanayak S, Dickinson K, Corey C, Murray B, Sills E, Kramer R. Deforestation, malaria and poverty: a call for transdisciplinary research to support the design of cross-sectoral policies. Sustainability: Science, Practice, and Policy 2006; 2(2): 45–56.

[334] Patz JA, Daszak P, Tabor GM, Aguirre AA, Pearl M, Epstein J, Wolfe ND, Kilpatrick AM Foufopoulos J, Molyneux D, Bradley DJ, Working Group on Land Use Change and Disease Emergence. Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence. Environ Health Perspect 2004; 112(10): 1092–8.

[335] Walsh JF, Molyneux DH, Birley MH. Deforestation: effects on vector-borne disease. Parasitology 1993; 106(Supp): S55–75.

[336] Vittor AY, Gilman RH, Tielsch J, Glass G, Shields T, Lozano, WS Pinedo-Cancino V, Patz JA. The effect of deforestation on the human-biting rate of anopheles darlingi, the primary vector of falciparum malaria in the Peruvian Amazon. Am J Trop Med Hyg 2006; 74(1): 3–11.

[337] Olson SH, Gangnon R, Silveira GA, Patz JA. Deforestation and malaria in Mancino Lima County, Brazil. Emerg Infect Dis. 2010 Jul; [Epub ahead of print].

[338] Walsh JF, Molyneux DH, Birley MH. Deforestation: effects on vector-borne disease. Parasitology 1993; 106(Supp): S55–75.

[339] Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue RS, Kovats BR, Woodward A. Human health. In: Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, editors. Climate

Change 2007: Impacts, Adapation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate.

[340] Patz JA, Daszak P, Tabor GM, Aguirre AA, Pearl M, Epstein J,et al. Working Group on Land Use Change and Disease Emergence. Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence. Environ Health Perspect 2004; 112(10): 1092-8.

[341] Pattanayak S, Dickinson K, Corey C, Murray B, Sills E, Kramer R. Deforestation, malaria and poverty: a call for transdisciplinary research to support the design of cross-sectoral policies. Sustainability: Science, Practice, and Policy 2006; 2(2): 45–56.

[342] Oliveira-Ferreira J, Lacerda M, Brasil P, Ladislau JLB, Tuail P, Daniel-Ribeiro CT. Malaria in Brazil: an overview. Malaria Journal. 2010; 9: 115.

[343] Pattanayak S, Dickinson K, Corey C, Murray B, Sill E, Kramer R. Deforestation, malaria and poverty: a call for transdisciplinary research to support the design of cross-sectoral policies. Sustainability: Science, Practice, and Policy [serial on the Internet]. 2006 [cited 2010 June 13]; 2(2): 45–56. Available at: http: //ejournal.nbii.org/archives/vol2iss2/0512-022.pattanayak.html

[344] Olson SH, Gangnon R, Silveira GA, Patz JA. Deforestation and malaria in Mancino Lima County, Brazil. Emerg Infect Dis. 2010 Jul; [Epub ahead of print].

[345] Dysoley L, Kaneko A, Eto H, Mita T, Socheat D, Börkman A, et al. Changing patterns of forest malaria among the mobile adult male population in Chumkiri District, Cambodia. Acta Trop. 2008 Jun; 106(3): 207–12.

[346] Carneiro I, Roca-Feltrer A, Griffin JT, et al. Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. PLoS One. 2010 Feb 1;5(2):e8988.

[347] Duffy PE. Plasmodium in the placenta: parasites, parity, protection, prevention and possibly preeclampsia. Parasitology. 2007; 134(Pt 13): 1877–81.

[348] Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb; 7(2): 93–104.

[349] Rogerson SJ, Hviid L, Duffy PE, Leke RF, Taylor DW. Malaria in pregnancy: pathogenesis and immunity. Lancet Infect Dis. 2007 Feb; 7 (2): 105–17.

[350] Briand V, Badaut C, Cot M. Placental malaria, maternal HIV infection and infant morbidity. Ann Trop Paediatr. 2009 Jun; 29(2): 71–83.

[351] Whitty CJM, Edmonds S, Mutabingwa TK. Malaria in pregnancy. BJOG. 2005 Sep; 112(9): 1189–95.

[352] Duffy PE. Plasmodium in the placenta: parasites, parity, protection, prevention and possibly preeclampsia. Parasitology. 2007; 134(Pt 13): 1877–81.

[353] Nosten F, McGready R, Mutabingwa T. Case management of malaria in pregnancy. Lancet Infect Dis. 2007 Feb; 7(2): 118–25.

[354] Menéndez C, D'Alessandro U, ter Kuile FO. Reducing the burden of malaria in pregnancy by preventive strategies. Lancet Infect Dis. 2007 Feb; 7(2): 126–35.

[355] Anchang-Kimbi JK, Achidi EA, Nkegoum B, Sverremark-Ekström E, Troye-Blomberg M. Diagnostic comparison of malaria infection in peripheral blood, placental blood and placental biopsies in Cameroonian parturient women. Malar J. 2009 Jun 8; 8: 126.

[356] Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb; 7(2): 93–104.

[357]Tako EA, Zhou A, Lohoue J, Leke R, Taylor DW, Leke RF. Risk factors for placental malaria and its effect on pregnancy outcome in Yaounde, Cameroon. Am J Trop Med Hyg. 2005 Mar; 72(3): 236–42.

[358] Garner P, Gülmezoglu AM. Drugs for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2006 Oct 18; (4): CD000169.

[359] Gamble C, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. Cochrane Database Syst Rev. 2006 Apr 19; (2): CD003755.

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

[361] Steketee RW, Wirima JJ and Campbell CC. Developing effective strategies for malaria prevention programmes for pregnant African women. American Journal of Tropical Medicine and Hygiene, 2996, 55 (1 Suppl): 95–100.

[362] WHO. A Strategic Framework for Malaria Prevention and Control during pregnancy in the African Region. Brazzaville: WHO 2004.

[363] Dellicour, S. et al. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. Plos Med 7(1): p.e1000221. Vol 7 (1). 2010.

[364] Guerra et al. The limits and intensity of Plasmodium falciparum transmission: implications for malaria control and elimination worldwide. PLos Med: e38. doi: 10.1371/journal.pmed.0050038.

[365] Orton LC, Omari AA. Drugs for treating uncomplicated malaria in pregnant women. Cochrane Database Syst Rev. 2008 Oct 8; (4): CD004912.

[366] Lucas SB. Missing infections in AIDS. Trans R Soc Trop Med Hyg. 1990; 84 Suppl 1: 34–8.

[367] Chalwe V, Van Geertruyden JP, Mukwamataba D, Menten J, Kamalamba J, Mulenga M, D'Alessandro U. Increased risk for severe malaria in HIV-1-infected adults, Zambia. Emerg Infect Dis. 2009 May; 15(5): 749; quiz 858

[368] Reithinger R, Kamya MR, Whitty CJM, Dorsey G, Vermund SH. Interaction of malaria and HIV in Africa. BMJ. 2009 Jun 3; 338: b2141

[369] Korenromp EL, Williams BG, d Vlas SJ, et al. Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. Emerg Inf Dis 2005; 11(9): 1410-1419.

[370] Van geertruyden JP, Menten J, Colebunders R, Korenromp E, D'Alessandro U. The impact of HIV-1 on the malaria parasite biomass in adults in sub-Saharan Africa contributes to the emergence of antimalarial drug resistance. Malaria Journal 2008, 7; 134; doi: 10.1186/1475-2875-7-134

[371] Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 2006; 314: 1603–6

[372] Kamya MR, Gasasira AF, Yeka A, et al. Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: a population-based study. J Infect Dis. 2006 193(1): 9–15.

[373] Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. J Infect Dis. 2005; 192(6): 984–91.

[374] Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. Lancet. 2000 356(9235): 1051–6.

[375] Ibid.

[376] Laufer MK, van Oosterhout JJ, Thesing PC, et al. Impact of HIV-associated immunosuppression on malaria infection and disease in Malawi. J Infect Dis. 2006; 193(6): 872–8.

[377] Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppresison on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. Lancet 2000; 356: 1051–56.

[378] Quigley M, Hewitt K, Mayanja B, et al. The effect of malaria on mortality in a cohort of HIV-infected Ugandan adults. Trop Med Int Health. 2005; 10: 894–900.

[379] French N, Nakiyingi J, Lugada E, et al. Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. AIDS 2001; 15: 899–906.

[380] Laufer MK, van Oosterhout JJG, Thesing PC, et al. Impact of HIV-associated immunosuppression on malaria infection on malaria infection and disease in Malawi. J Infect Dis. 2006; 193: 872–8.

[381] Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. J Infect Dis. 2005; 192(6): 984–91.

[382] Cohen C, Karstaedt A, Frean J, et al. Increased prevalence of severe malaria in HIV-infected adults in South Africa. Clin Infect Dis. 2005; 41: 1631–7.

[383] Grimwade K, French N, Mbatha DD. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. AIDS 2004 Feb 20; 18(3): 547–54.

[384] Ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-Saharan Africa. Am J Trop Med Hyg. 2004; 71 (suppl 2) 41–54.

[385] Bloland PB, Wirima JJ, Steketee RW, et al. Maternal HIV infection and infant mortality in Malawi: evidence for increased mortality due to placental malaria infection. AIDS. 1995; 9(7): 721–6.

[386] Van Eijk AM, Ayisi JG, ter Kuile, et al. HIV increases the risk of malaria in women of all gravidities in Kisumu, Kenta. AIDS. 2003; 17: 595–603.

[387] Kalyesubula I, Musoke-Mudido P, Marum L, et al. Effect of malaria infection in human immunodeficiency virus type-1-infected Ugandan children. Pediatr Infect Dis J 1997; 16: 876–881.

[388] Malamba S, Hladik W, Reingold A, et al. The effect of HIV on morbidity and mortality in children with severe malarial anaemia. Malaria Journal. 2007; 6: 143. doi: 10.1186/1475-2875–6–143

[389] Grimwade K, French N, Mbatha NN, et al. Childhood malaria in a region of unstable transmission and high human immunodefiency virus prevalence. Pediatr Infect Dis J. 2003; 22: 1057–63.

[390] Kamya MR et al. Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: a population-based study. J Infect Dis. 2005, 193: 9-1.

[391] Shah SN, Smith EE, Obonyo CO, et al. HIV immunosuppression and antimalarial efficacy: sulfadoxine-pyrimethamine for the treatment of uncomplicated malaria in HIV-infected adults in Siaya, Kenya. J Infect Dis. 2006; 194(11): 1519-28.

[392] Ordi J, Menendez C, Ismail MR, Ventura PJ, Palacín A, Kahigwa E, et al. Placental malaria is associated with cell-mediated inflammatory responses with selective absence of natural killer cells. J Infect Dis. 2001 Apr 1; 183(7): 1100–7.

[393] Kublin JG, Patnaik P, Jere CS, et al. Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. Lancet 2005. 365(9455): 233–40.

[394] Semrau K, Kuhn L, Kasonde P, Sinkala M, Kankasa C, Shutes E, Vwalika C, Ghosh M, Aldrovandi G, Thea DM. Impact of chloroquine on viral load in breast milk. Trop Med Int Health. 2006 Jun; 11(6): 800–3.

[395] Mwapasa V, Rogerson SJ, Molyneux ME, Abrams ET, Kamwendo DD, Lema VM, et al. The effect of Plasmodium falciparum malaria on peripheral and placental HIV–1 RNA concentrations in pregnant Malawian women. AIDS. 2004 Apr 30; 18(7): 1051–9

[396] Brahmbhatt H, Sullivan D, Kigozi G, et al. Association of HIV and malaria with mother-to-child transmission, birth outcomes, and child mortality. J Acquir Immune Defic Syndr. 2008 Apr 1; 47(4): 472–6.

[397] Msamanga GI, Taha TE, Young AM, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1. Am J Trop Med Hyg. 2009; 80(4): 508–15.

[398] Quinn TC, Wawer MH, Swankambo N et al. Viral load and heterosexual transmission of the human immunodeficiency virus type 1 infection. N Engl J Med. 2000; 342: 921.

[399] Lawn SD. AIDS in Africa: the impact of coinfections on the pathogenesis of HIV-1 infection. J Infect. 2004 Jan; 48(1): 1–12.

[400] Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews 2004, Issue 2.

[401] Gamble C, Ekwaru PJ, Garner P, ter Kuile FO. Insecticide-treated nets for the prevention of malaria in pregnancy: a systematic review of randomised controlled trials. PLoS Med. 2007 Mar 27; 4(3): e107.

[402] Maxwell CA, Msuya E, Sudi M, Njunwa KJ, Carneiro IA, Curtis CF. Effect of community-wide use of insecticide-treated nets for 3–4 years on malarial morbidity in Tanzania. Trop Med Int Health. 2002 Dec; 7(12): 1003–8.

[403] D'Alessandro U, Olaleye BO, McGuire W, Langerock P, Bennett S, Aikins MK, et al. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. Lancet. 1995 Feb 25; 345 (8948): 479–83.

[404] Pates H, Curtis C. Mosquito behavior and vector control. Annu Rev Entomol. 2005; 50: 53–70.

[405] Magris M, Rubio-Palis Y, Alexander N, Ruiz B, Galván N, Frias D, Blanco M, Lines J. Community-randomised trial of lambdacyhalothrin-treated hammock nets for malaria control in Yanomami communities in the Amazon region of Venezuela. Trop Med Int Health. 2007 Mar; 12(3): 392–403.

[406] Panter-Brick C, Clarke SE, Lomas H, Pinder M, Lindsay SW. Culturally compelling strategies for behaviour change: a social ecology model and case study in malaria prevention. Soc Sci Med. 2006 Jun; 62(11): 2810–25

[407] Ng'ang'a PN, Jayasinghe G, Kimani V, Shililu J, Kabutha C, Kabuage L, Githure J, Mutero C. Bed net use and associated factors in a rice farming community in Central Kenya. Malar J. 2009 Apr 16; 8: 64.

[408] Winch PJ, Makemba AM, Makame VR, Mfaume MS, Lynch MC, Premji Z, et al. Social and cultural factors affecting rates of regular retreatment of mosquito nets with insecticide in Bagamoyo District, Tanzania. Trop Med Int Health. 1997 Aug; 2(8): 760–70.

[409] Malima RC, Magesa SM, Tunga PK, Mwingira V, Magogo FS, Sudi W et al. An experimental hut evaluation of Olyset® nets against anopheline mosquitoes after seven years use in Tanzanian villages. Malaria Journal. 2008; 7: 38.

[410] Maxwell CA, Myamba J, Magoma J, Rwegoshora RT, Magesa SM, Curtis CF: Tests of Olyset ® nets by bioassay and in experimental huts. J Vect Borne Dis. 2006; 43: 1–6; Graham K, Kayedi MH, Maxwell C, Kaur H, Rehman H, Malima R, et al. Multi-country field trials comparing wash-resistance of PermaNet™ and conventional insecticide-treated nets against anopheline and culicine mosquitoes. Medical and Veterinary Entomology. 2005; 19: 72–83.

[411] Graham K, Kayedi MH, Maxwell C, Kaur H, Rehman H, Malima R, et al. Multi-country field trials comparing wash-resistance of PermaNet™ and conventional insecticide-treated nets against anopheline and culicine mosquitoes. Medical and Veterinary Entomology. 2005; 19: 72–83.

[412] Kayedi MH, Lines JD, Haghdoost AA, Vatandoost MH, Rassi Y, Khamisabady K. Evaluation of the effects of repeated hand washing, sunlight, smoke and dirt on the persistence of deltamethrin on insecticide-treated nets. Trans R Soc Trop Med Hyg. 2008 Aug; 102(8): 811–6.

[413] Atieli FK, Munga SO, Ofulla AV, Vulule JM. Wash durability and optimal drying regimen of four brands of long-lasting insecticide-treated nets after repeated washing under tropical conditions. Malar J. 2010 Aug 30; 9: 248.

[414] E.g. Tami A, Mubyazi G, Talbert A. Evaluation of Olyset™ insecticide-treated nets distributed seven years previously in Tanzania. Malaria Journal 2004; 3:19; Fernando SD, Abeyasinghe RR, Galappathy GN et al. Community factors affecting long-lasting impregnated mosquito net use for malaria control in Sri Lanka. Trans R Soc Trop Med Hyg. 2008 Nov: 102(11):1081-8; Harvey SA, Olórtegui MP, Leontsini E. et al. The Whole World Will Be Able to See Us: Determining the Characteristics of a Culturally Appropriate Bed Net Among Mestizo Communities of the Peruvian Amazon. Am. J. Trop. Med. Hyg. 2008; 79(6): 834-838.

[415] Oxborough RM, Weir V, Irish S et al. Is K-O Tab 1-2-3((R)) long lasting on non-polyester mosquito nets? Acta Trop. 2009 Oct; 112(1): 49–53.

[416] Gamble C, Ekwaru PJ, Garner P, et al. Insecticide-treated nets for the prevention of malaria in pregnancy: a systematic review of randomised controlled trials. PLoS Med. 2007 Mar 27; 4(3): e107.

[417] Curtis CF. Insecticide-treated bednets and child survival in rural Kenya. Lancet. 2008 Jan; 371/9607: 115–116.

[418] Phillips-Howard PA, Nahlen BL, Kolczak MS, Hightower AW, ter Kuile FO, et al. Efficacy of permethrin-treated bed nets in the prevention of mortality in young children in an area of high perennial malaria. Am J Trop Med Hy. 2005; 68, supplement: 23–29.

[419] Binka FN, Hodgson A, Adjuik M, Smith T. Mortality in a seven-and-a-half-year follow-up of a trial of insecticide-treated mosquito nets in Ghana. Trans R Soc Trop Med Hyg. 2002; 96: 597–599.

[420] Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews 2004, Issue 2.

[421] Diallo DA, Cousens SN, Cuzin-Ouattara N, Nebié I, Ilboudo-Sanogo E, Esposito F. Child mortality in a West African population protected with insecticide-treated curtains for a period of up to 6 years. Bull World Health Organ. 2004 Feb; 82(2): 85–91.

[422] Yukich JO, Lengeler C, Tediosi F, Brown N, Mulligan JA, Chavasse D et al. Costs and consequences of large-scale vector control for malaria. Malar J. 2008 Dec 17; 7: 258.

[423] Monasch R, Reinnisch A, Steketee RW, Korenromp E, Alnwick D, Bergevin Y. Child coverage with mosquito nets and malaria treatment from population-based surveys in African countries: a baseline for monitoring progress in roll back malaria. American Journal of Tropical Medicine and Hygiene. 2004: 71(2 Suppl): 232–238.

[424] Flaxman A, Fullman N, Otten M, Menon M, Cibulskis R et al. Rapid scaling up of insecticide-treated bed net coverage in Africa and its relationship with development assistance for health: a systematic synthesis of supply, distribution and household survey data. PloS Med, 7(8), Aug 2010.

[425] Grabowsky M, Nobiya T, Selanikio J. Sustained high coverage of insecticide-treated bednets through combined Catch-up and Keep-up strategies. Trop Med Int Health. 2007 Jul; 12(7): 815–22.

[426] Killeen GF, Tami A, Kihonda J, Okumu FO, Kotas ME, Grundmann H, Kasigudi N, Ngonyani H, Mayagaya V, Nathan R, Abdulla S, Charlwood JD, Smith TA, Lengeler C. Cost-sharing strategies combining targeted public subsidies with private-sector delivery achieve high bednet coverage and reduced malaria transmission in Kilombero Valley, southern Tanzania. BMC Infect Dis. 2007 Oct 25; 7: 121.

[427] Fegan GW, Noor AM, Akhwale WS, Cousens S, Snow RW. Effect of expanded insecticide-treated bednet coverage on child survival in rural Kenya: a longitudinal study. Lancet. 2007 Sep 22; 370(9592): 1035–9.

[428] Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. The

Cochrane Database of Systematic Reviews 2004, Issue 2.

[429] Gu W, Novak RJ. Predicting the impact of insecticide-treated bed nets on malaria transmission: the devil is in the detail. Malar J. 2009 Nov 16; 8: 256.

[430] Webster J Smith L and Lines J. Scaling-up ITN access and use in sub-Saharan Africa: estimated LLIN requirements and coverage outcomes based on the global delivery strategy mix. Available at: www.dfidhealthrc.org/what_new/Scaling%20up%20ITN%20in%20SSA.pdf

[431] Flaxman A, Fullman N, Otten M, Menon M, Cibulskis R et al. Rapid scaling up of insecticide-treated bed net coverage in Africa and its relationship with development assistance for health: a systematic synthesis of supply, distribution and household survey data. PloS Med, 7(8), Aug 2010.

[432] Eisele T, Steketee R. Distribution of insecticide treated nets in rural Africa. BMJ, 2009, 339: 60–61.

[433] Killeen GF, Tami A, Kihonda J, Okumu FO, Kotas ME, Grundmann H, Kasigudi N, Ngonyani H, Mayagaya V, Nathan R, Abdulla S, Charlwood JD, Smith TA, Lengeler C. Cost-sharing strategies combining targeted public subsidies with private-sector delivery achieve high bednet coverage and reduced malaria transmission in Kilombero Valley, southern Tanzania. BMC Infect Dis. 2007 Oct 25; 7: 121.

[434] Grabowsky M, Nobiya T, Selanikio J. Sustained high coverage of insecticide-treated bednets through combined Catch-up and Keep-up strategies. Trop Med Int Health. 2007 Jul; 12(7): 815–22.

[435] Jayne Webster, Jenny Hill, Jo Lines and Kara Hanson. Delivery systems for insecticide treated and untreated mosquito nets in Africa: categorisation and outcomes achieved. Health Policy and Planning 2007; 22: 277–293

[436] Müller O et al. Distribution Systems of Insecticide-Treated Bed Nets for Malaria Control in Rural Burkina Faso: Cluster-Randomised Controlled Trial. 2008 PLoS ONE 3(9): e3182.

[437] Chuma J. Okunga V, Molyneux C. Barriers to prompt and effective malaria treatment among the poorest population in Kenya. Malaria Journal 2010, 9: 144.

[438] Bernard J, Mtove G, Mandike R, Mtei F, Maxwell C, Reyburn H. Equity and coverage of insecticide-treated bed nets in an area of intense transmission of Plasmodium falciparum in Tanzania. Malar J. 2009 Apr 16; 8: 65.

[439] Ahmed SM, Zerihun A. Possession and usage of insecticidal bed nets among the people of Uganda: is BRAC Uganda Health Programme pursuing a pro-poor path? PLoS One. 2010 Sep 10; 5(9). pii: e12660.

[440] Noor AM, Amin AA, Akhwale WS, Snow RW. Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children. PLoS Med. 2007 Aug; 4(8): e255.

[441] Tsuang A, Lines J, Hanson K. Which family members use the best nets? An analysis of the condition of mosquito nets and their distribution within households in Tanzania.Malar J. 2010 Jul 22; 9: 211.

[442] Kulkarni MA, Malima R, Mosha FW, Msangi S, Mrema E, Kabula B, Lawrence B, Kinung'hi S, Swilla J, Kisinza W, Rau ME, Miller JE, Schellenberg JA, Maxwell C, Rowland M, Magesa S, Drakeley C. Efficacy of pyrethroid-treated nets against malaria vectors and nuisance-biting mosquitoes in Tanzania in areas with long-term insecticide-treated net use. Trop Med Int Health. 2007l Sep; 12(9): 1061–73.

[443] Korenromp EL, Miller J, Cibulskis RE, Kabir Cham M, Alnwick D, Dye C. Monitoring mosquito net coverage for malaria control in Africa: possession vs. use by children under 5 years. Trop Med Int Health. 2003 Aug; 8(8): 693–703.

[444] Al-Taiar A, Chandler C, Al Eryani S, Whitty CJ. Knowledge and practices for preventing severe malaria in Yemen: the importance of gender in planning policy. Health Policy Plan. 2009 Nov; 24(6): 428–37.

[445] Chuma J. Okunga V, Molyneux C. Barriers to prompt and effective malaria treatment among the poorest population in Kenya. Malaria Journal 2010, 9: 144.

[446] Kilian A, Wijayanandana N, Ssekitoleeko J. Review of delivery strategies for insecticide treated mosquito nets-are we ready for the next phase of malaria control efforts? TropIKA.net Journal; 1(1).

[447] Kilian A, Wijayanandana N, Ssekitoleeko J. Review of delivery strategies for insecticide treated mosquito nets-are we ready for the next phase of malaria control efforts? TropIKA.net Journal; 1(1).

[448] Noor AM, Amin AA, Akhwale WS, Snow RW, Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children. PLoS Med 2007, 4(8): 255.

[449] Kilian A, Wijayanandana N, Ssekitoleeko J. Review of delivery strategies for insecticide treated mosquito nets-are we ready for the next phase of malaria control efforts? TropIKA.net Journal; 1(1).

[450] WHO. World Malaria Report 2009. Geneva: WHO.

[451] Kilian A, Wijayanandana N, Ssekitoleeko J. Review of delivery strategies for insecticide treated mosquito nets-are we ready for the next phase of malaria control efforts? TropIKA.net Journal; 1(1).

[452] Kilian A, Wijayanandana N, Ssekitoleeko J. Review of delivery strategies for insecticide treated mosquito nets-are we ready for the next phase of malaria control efforts? TropIKA.net Journal; 1(1).

[453] Lengeler C, deSavigny D. Programme diversity is key to the success of insecticide-treated bednets. Lancet. 22 September 2007; 370/9592: 1009–1010.

[454] Müller O et al. Distribution Systems of Insecticide-Treated Bed Nets for Malaria Control in Rural Burkina Faso: Cluster-Randomised Controlled Trial. 2008 PLoS ONE 3(9): e3182.

[455] De Allegri et al. Comparative cost analysis of insecticide-treated net delivery strategies: sales supported by social marketing and free distribution through antenatal care. Health Policy and Planning 2010 25(1): 28-38.

[456] Kolaczinski JH. Costs and effects of two public sector delivery channels for long-lasting insecticidal nets in Uganda. Malaria Journal 2010, 9: 102.

[457] Kilian A, Wijayanandana N, Ssekitoleeko J. Review of delivery strategies for insecticide treated mosquito nets-are we ready for the next phase of malaria control efforts? TropIKA.net Journal; 1(1); Marchant T, Schellenberg D, Natan R et al. Assessment of a national voucher scheme to deliver insecticide-treated mosquito nets to pregnant women. CMAJ. 2010 February 9; 182(2): 152–156; DOI: 10.1503/cmaj.090268; Hanson K, Marchant T, Nathan R et al. Household ownership and use of insecticide treated nets among target groups after implementation of a national voucher programme in the United Republic of Tanzania: plausibility study using three annual cross sectional household surveys. BMJ 2009; 338: b2434.

[458] Marchant T, Schellenberg D, Natan R et al. Assessment of a national voucher scheme to deliver insecticide-treated mosquito nets to pregnant women. CMAJ. 2010 February 9; 182(2): 152–156.

[459] Toé LP et al. Decreased motivation in the use of insecticide-treated nets in a malaria endemic area in Burkina Faso. Malar J. 2009 Jul 29; 8: 175

[460] Biswas AK, Hutin YJ, Ramakrishnan R et al. Increased financial accessibility and targeted education messages could increase ownership and use of mosquito nets in Purulia District, West Bengal, India. Transactions of the Royal Society of Tropical Medicine and Hygiene. June 2010; 104/6: 423–428.

[461] Deribew A, Alemsegad F, Birhanu Z et al. Effect of training on the use of long-lasting insecticide-treated bed nets on the burden of malaria among vulnerable groups, south-west Ethiopia: baseline results of a cluster randomised trial. Malar J. 2010 May 10; 9(1): 121.

[462] E.g. Roberts L. Battling Over Bed Nets. Science 2007; 318:559.

[463] E.g. Teklehaimanot A, Sachs JD, Curtis C. Malaria control needs mass distribution of insecticidal bednets. The Lancet 2007: 369:2143-6.

[464] Kilian A, Wijayanandana N, Ssekitoleeko J. 2009. Review of delivery strategies for insecticide treated mosquito nets – are we ready for the next phase of malaria control efforts? TropIKA.net, March, 1(1).

[465] WHO. 2006. Indoor residual spraying: Use of indoor residual spraying for scaling up global malaria control and elimination.

[466] E.g. Lengeler C and Sharp B. Indoor residual spraying and insecticide treated nets. In: Murphy C, Ringheim K, Woldehanna S, Volmink J editor(s). Reducing malaria's burden: evidence of effectiveness for decision makers. Washington: Global Health Council, 2003: 17–24; WHO. 2006. Indoor residual spraying: Use of indoor residual spraying for scaling up global malaria control and elimination; Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD006657. DOI: 10.1002/14651858.CD006657.pub2.

[467] Mabaso M, Sharp B, and Lengeler C. Historical review of malarial control in southern African with emphasis on the use of indoor residual house-spraying. Tropical Medicine and International Health. 2004 Aug; 9 (8): 846–856.

[468] Barnes KI, Durrheim DN, Little F, Jackson A, Mehta U, Allen E, Dlamini SS, Tsoka J, Bredenkamp B, Mthembu DJ, White NJ, Sharp BL. Effect of artemether-lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal, South Africa. PLoS Med. 2005 Nov; 2(11): e330.

[469] Molineaux L, Gramiccia G. The Gharki Project: Research on the Epidemiology and Control of Malaria in the Sudan Savanna of West Africa. 1980. Geneva, Switzerland: WHO.

[470] Lengeler C and Sharp B. Indoor residual spraying and insecticide treated nets. In: Murphy C, Ringheim K, Woldehanna S, Volmink J editor(s). Reducing malaria's burden: evidence of effectiveness for decision makers. Washington: Global Health Council, 2003: 17–24.

[471] Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD006657. DOI: 10.1002/14651858.CD006657.pub2.

[472] Yukich J, Lengeler C, Tediosi F, Brown N, Mulligan J. Costs and consequences of large-scale vector control for malaria. Malaria Journal 2008; 7: 258.

[473] Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD006657. DOI: 10.1002/14651858.CD006657.pub2.

[474] Najera JA, Zaim M. Malaria vector control: insecticides for indoor residual spraying. 2001. Geneva: WHO.

[475] Diallo DA, Sutherland C, Nebié I, Konaté AT, Ord R, Pota H, Roper C, Ilboudo-Sanogo E, Greenwood BM, Cousens SN. Sustained use of insecticide-treated curtains is not associated with greater circulation of drug-resistant malaria parasites, or with higher risk of treatment failure among children with uncomplicated malaria in Burkina Faso. Am J Trop Med Hyg. 2007 Feb; 76(2): 237–44.

[476] Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004; (2): CD000363.

[477] Magris M, Rubio-Palis Y, Alexander N, Ruiz B, Galván N, Frias D, Blanco M, Lines J.Community-randomised trial of lambdacyhalothrin-treated hammock nets for malaria control in Yanomami communities in the Amazon region of Venezuela. Trop Med Int Health. 2007 Mar; 12(3): 392–403;

Thang N, Erhart A, Speybroeck N, Xuan Xa N, Thanh N, Ky P. Long-Lasting Insecticidal Hammocks for Controlling Forest Malaria: A Community Based Trial in a Rural Area of Central Vietnam. PloS One 4(10).

[478] Rowland M, Durrani N, Kenward M, Mohammed N, Urahman H, and Hewitt S. Control of malaria in Pakistan by applying deltamethrin insecticide to cattle: a community-randomised trial. Lancet 2001. 357(9271). Pg 1837–41.

[479] Mahande AM, Mosha FW, Mahande JM, Kweka EJ. Role of cattle treated with deltamethrine in areas with a high population of Anopheles arabiensis in Moshi, Northern Tanzania. Malar J. 2007 Aug 8; 6: 109.

[480] Mnyone LL, Kirby MJ, Lwetoijera DW, Mpingwa MW, Simfukwe ET, Knols BG, Takken W, Russell TL. Tools for delivering entomopathogenic fungi to malaria mosquitoes: effects of delivery surfaces on fungal efficacy and persistence. Malar J. 2010 Aug 27; 9: 246.

[481] Graham K, Mohammad N, Rehman H, Nazari A, Ahmad M, Kamal M, Skovmand O, Guillet P, Allan R, Zaim M, Yates A, Lines J, Rowland M. Insecticide-treated plastic tarpaulins for control of malaria vectors in refugee camps. Med Vet Entomol. 2002 Dec; 16(4): 404–8.

[482] Graham K, Mohammad N, Rehman H, Farhan M, Kamal M, Rowland M. Comparison of three pyrethroid treatments of top–sheets for malaria control in emergencies: entomological and user acceptance studies in an Afghan refugee camp in Pakistan. Med Vet Entomol. 2002 Jun; 16(2): 199–206.

[483] Graham K, Rehman H, Ahmad M, Kamal M, Khan I, Rowland M. Tents pre-treated with insecticide for malaria control in refugee camps: an entomological evaluation. Malar J. 2004 Jul 15; 3: 25.

[484] Geissbühler Y, Kannady K, Chaki PP, Emidi B, Govella NJ, Mayagaya V, Kiama M, Mtasiwa D, Mshinda H, Lindsay SW, Tanner M, Fillinger U, de Castro MC, Killeen GF. Microbial larvicide application by a large-scale, community-based program reduces malaria infection prevalence in urban Dar es Salaam, Tanzania. PLoS One. 2009; 4(3): e5107.

[485] Yapabandara AM, Curtis CF. Laboratory and field comparisons of pyriproxyfen, polystyrene beads and other larvicidal methods against malaria vectors in Sri Lanka. Acta Trop. 2002 Mar; 81(3): 211–23.

[486] Kusumawathie PH, Wickremasinghe AR, Karunaweera ND, Wijeyaratne MJ. Costs and effectiveness of application of Poecilia reticulata (guppy) and temephos in anopheline mosquito control in river basins below the major dams of Sri Lanka. Trans R Soc Trop Med Hyg. 2008 Jul; 102(7): 705–11

[487] Ghosh SK, Dash AP. Larvivorous fish against malaria vectors: a new outlook. Trans R Soc Trop Med Hyg. 2007 Nov; 101(11): 1063–4.

[488] Burkot T, Abdel-Hameed Adeel AA, Pyke GH, Beach R, Wirtz RA, Garner P. Larvivorous fish for malaria prevention (Protocol). *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD008090. DOI: 10.1002/14651858.CD008090.

[489] Beier JC, Keating J, Githure JI, Macdonald MB, Impoinvil DE, Novak RJ. Integrated vector management for malaria control. Malar J. 2008 Dec 11; 7 Suppl 1: S4.

[490] Awolola TS, Oduola AO, Obansa JB, Chukwurar NJ, Unyimadu JP. Anopheles gambiae s.s. breeding in polluted water bodies in urban Lagos, southwestern Nigeria. J Vector Borne Dis. 2007 Dec; 44(4): 241–4.

[491] Al-Taiar A, Assabri A, Al-Habori M, Azazy A, Algabri A, Alganadi M, et al. Socioeconomic and environmental factors important for acquiring non-severe malaria in children in Yemen: a case-control study. Trans R Soc Trop Med Hyg. 2009 Jan; 103(1): 72–8.

[492] Coleman M, Coleman M, Mabaso ML, Mabuza AM, Kok G, Coetzee M, Durrheim DN. Household and microeconomic factors associated with malaria in Mpumalanga, South Africa. Trans R Soc Trop Med Hyg. 2010 Feb; 104(2): 143–7.

[493] Kirby MJ, Ameh D, Bottomley C. et al. Effect of two different house screening interventions on exposure to malaria vectors and on anaemia in children in The Gambia: a randomised controlled trial. The Lancet 2009; 374 (9694):998-1009.

[494] Lawrance CE, Croft AM. Do mosquito coils prevent malaria? A systematic review of trials. J Travel Med. 2004 Mar–Apr; 11(2): 92–6.

[495] McElroy B, Wiseman V, Matovu F, Mwengee W. Malaria prevention in north-eastern Tanzania: patterns of expenditure and determinants of demand at the household level. Malar J. 2009 May 7; 8: 95.

[496] Hill N, Lenglet A, Arnéz AM, Carneiro I. Plant based insect repellent and insecticide treated bed nets to protect against malaria in areas of early evening biting vectors: double blind randomised placebo controlled clinical trial in the Bolivian Amazon. BMJ. 2007 Nov 17; 335(7628): 1023.

[497] See: en.wikipedia.org/wiki/Mosquito_laser

[498] Marshall JM, Taylor CE. Malaria control with transgenic mosquitoes. PLoS Med. 2009 Feb 10; 6(2): e20.

[499] Al-Mashhadani HM, Davidson G, Curtis CF. A genetic study of the susceptibility of Anopheles gambiae to Plasmodium berghei. Trans R Soc Trop Med Hyg. 1980; 74(5):585–594.

[500] Dame DA, Curtis CF, Benedict MQ, Robinson AS, Knols BG. Historical applications of induced sterilisation in field populations of mosquitoes. Malar J. 2009 Nov 16; 8 Suppl 2: S2.

[501] Robinson AS, Knols BG, Voigt G, Hendrichs J. Conceptual framework and rationale. Malar J. 2009 Nov 16; 8 Suppl 2: S1.

[502] Helinski ME, Hassan MM, El-Motasim WM, Malcolm CA, Knols BG, El-Sayed B. Towards a sterile insect technique field release of Anopheles arabiensis mosquitoes in Sudan: irradiation, transportation, and field cage experimentation. Malar J. 2008 Apr 25; 7: 65.

[503] Chaccour C, Lines J, Whitty CJ. Effect of ivermectin on Anopheles gambiae mosquitoes fed on humans: the potential of oral insecticides in malaria control. J Infect Dis. 2010 Jul 1; 202(1): 113–6.

[504] Deparis X, Frere B, Lamizana M, N'Guessan R, Leroux F, Lefevre P, Finot L,

Hougard JM, Carnevale P, Gillet P, Baudon D. Efficacy of permethrin-treated uniforms in combination with DEET topical repellent for protection of French military troops in Côte d'Ivoire. J Med Entomol. 2004 Sep; 41(5): 914–21.

[505] Okell LC, Drakeley CJ, Bousema T, Whitty CJ, Ghani AC. Modelling the impact of artemisinin combination therapy and long-acting treatments on malaria transmission intensity. PLoS Med. 2008 Nov 25; 5(11): e226;

[506] Drakeley CJ, Akim NI, Sauerwein RW, Greenwood BM, Targett GA. Estimates of the infectious reservoir of Plasmodium falciparum malaria in The Gambia and in Tanzania. Trans R Soc Trop Med Hyg. 2000 Sep–Oct; 94(5): 472–6.

[507] Ladhani S, Garbash M, Whitty CJ, Chiodini PL, Aibara RJ, Riordan FA, Shingadia D. Prospective, national clinical and epidemiologic study on imported childhood malaria in the United Kingdom and the Republic of Ireland. Pediatr Infect Dis J. 2010 May; 29(5): 434–8.

[508] WHO. Guidelines for the treatment of malaria, second edition. 2010. Geneva: WHO.

[509]Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O, Saganda K, Shao J, Kitua A, Olomi R, Greenwood BM, Whitty CJ. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ. 2004 Nov 20; 329(7476): 1212.

[510] Amexo M, Tolhurst R, Barnish G, Bates I. Malaria misdiagnosis: effects on the poor and vulnerable. Lancet. 2004 Nov 20–26; 364(9448): 1896–8.

[511] Chandramohan D, Jaffar S, Greenwood B. Use of clinical algorithms for diagnosing malaria. Trop Med Int Health. 2002 Jan; 7(1): 45–52.

[512] Gwer S, Newton CR, Berkley JA. Over-diagnosis and co-morbidity of severe malaria in African children: a guide for clinicians. Am J Trop Med Hyg. 2007 Dec; 77(6 Suppl): 6–13.

[513] Berkley JA, Maitland K, Mwangi I, Ngetsa C, Mwarumba S, Lowe BS, Newton CR, Marsh K, Scott JA, English M. Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study. BMJ. 2005 Apr 30; 330(7498): 995.

[514] Nadjm B, Amos B, Mtove G, Ostermann J, Chonya S, Wangai H, Kimera J, Msuya W, Mtei F, Dekker D, Malahiyo R, Olomi R, Crump JA, Whitty CJ, Reyburn H. WHO guidelines for antimicrobial treatment in children admitted to hospital in an area of intense Plasmodium falciparum transmission: prospective study. BMJ. 2010 Mar 30; 340: c1350. doi: 10.1136/bmj.c1350.

[515] Lubell Y, Reyburn H, Mbakilwa H, Mwangi R, Chonya K, Whitty CJ, Mills A. The cost-effectiveness of parasitologic diagnosis for malaria-suspected patients in an era of combination therapy. Am J Trop Med Hyg. 2007 Dec; 77(6 Suppl): 128–32.

[516] Zurovac D, Midia B, Ochola SA, English M, Snow RW. Microscopy and outpatient malaria case management among older children and adults in Kenya. Trop Med Int Health. 2006 Apr; 11(4): 432–40.

[517] Bates I, Bekoe V, Asamoa-Adu A. Improving the accuracy of malaria-related laboratory tests in Ghana. Malar J. 2004 Nov 1; 3: 38.

[518] Mundy CJ, Bates I, Nkhoma W, Floyd K, Kadewele G, Ngwira M, Khuwi A, Squire SB, Gilks CF. The operation, quality and costs of a district hospital laboratory service in Malawi. Trans R Soc Trop Med Hyg. 2003 Jul–Aug; 97(4): 403–8.

[519] Reyburn H, Ruanda J, Mwerinde O, Drakeley C. The contribution of microscopy to

targeting antimalarial treatment in a low transmission area of Tanzania. Malar J. 2006 Jan 20; 5: 4.

[520] Sarkinfada F, Aliyu Y, Chavasse C, Bates I. Impact of introducing integrated quality assessment for tuberculosis and malaria microscopy in Kano, Nigeria. J Infect Dev Ctries. 2009 Feb 28; 3(1): 20–7.

[521] Hemme F, Gay F. Internal quality control of the malaria microscopy diagnosis for 10 laboratories on the Thai-Myanmar border. Southeast Asian J Trop Med Public Health. 1998 Sep; 29(3): 529–36.

[522] Whitty CJM, Armstrong M, Behrens RH. Self-testing for falciparum malaria with antigen-capture cards by travelers with symptoms of malaria. Am J Trop Med Hyg. 2000 Nov–Dec; 63(5–6): 295–7.

[523] See: www.wpro.who.int/sites/rdt

[524] Chiodini PL, Bowers K, Jorgensen P, Barnwell JW, Grady KK, Luchavez J, Moody AH, Cenizal A, Bell D. The heat stability of Plasmodium lactate dehydrogenase-based and histidine-rich protein 2-based malaria rapid diagnostic tests. Trans R Soc Trop Med Hyg. 2007 Apr; 101(4): 331–7.

[525] Fernandes de Oliveira MR, de Castro Gomes A, Toscano CM. Cost effectiveness of OptiMal(R) rapid diagnostic test for malaria in remote areas of the Amazon Region, Brazil. Malar J. 2010 Oct 11; 9(1): 277.

[526] Bell D, Peeling RW; WHO-Regional Office for the Western Pacific/TDR. Evaluation of rapid diagnostic tests: malaria. Nat Rev Microbiol. 2006 Sep; 4(9 Suppl): S34–8.

[527] See: www.wpro.who.int/sites/rdt

[528] Ansah EK, Narh-Bana S, Epokor M, Akanpigbiam S, Quartey AA, Gyapong J, Whitty CJ. Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana. BMJ. 2010 Mar 5; 340: c930. doi: 10.1136/bmj.c930.

[529] Bisoffi Z, Sirima BS, Angheben A, Lodesani C, Gobbi F, Tinto H, Van den Ende J. Rapid malaria diagnostic tests vs. clinical management of malaria in rural Burkina Faso: safety and effect on clinical decisions. A randomised trial. TropMed Int Health. 2009 May; 14(5): 491–8.

[530] Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakeley C, Whitty CJ. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. BMJ. 2007 Feb 24; 334(7590): 403.

[531] Skarbinski J, Ouma PO, Causer LM, Kariuki SK, Barnwell JW, Alaii JA, de Oliveira AM, Zurovac D, Larson BA, Snow RW, Rowe AK, Laserson KF, Akhwale WS, Slutsker L, Hamel MJ. Effect of malaria rapid diagnostic tests on the management of uncomplicated malaria with artemether-lumefantrine in Kenya: a cluster randomised trial. Am J Trop Med Hyg. 2009 Jun; 80(6): 919–26.

[532] Ssekabira U, Bukirwa H, Hopkins H, Namagembe A, Weaver MR, Sebuyira LM, Quick L, Staedke S, Yeka A, Kiggundu M, Schneider G, McAdam K, Wabwire-Mangen F, Dorsey G. Improved malaria case management after integrated team-based training of health care workers in Uganda. Am J Trop Med Hyg. 2008 Dec; 79(6): 826–33

[533] Msellem MI, Mårtensson A, Rotllant G, Bhattarai A, Strömberg J, Kahigwa E, Garcia M, Petzold M, Olumese P, Ali A, Björkman A. Influence of rapid malaria diagnostic tests on treatment and health outcome in fever patients, Zanzibar: a crossover validation study. PLoS Med. 2009 Apr 28; 6(4): e1000070.

[534] Yukich J, D'Acremont V, Kahama J, Swai N, Lengeler C. Cost savings with rapid diagnostic tests for malaria in low-transmission areas: evidence from Dar es Salaam, Tanzania. Am J Trop Med Hyg. 2010 Jul; 83(1): 61–8.

[535] Lubell Y, Reyburn H, Mbakilwa H, Mwangi R, Chonya S, Whitty CJ, Mills A. The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. BMJ. 2008 Jan 26; 336(7637): 202–5.

[536] D'Acremont V, Lengeler C, Mshinda H, Mtasiwa D, Tanner M, Genton B. Time to move from presumptive malaria treatment to laboratory-confirmed diagnosis and treatment in African children with fever. PLoS Med. 2009 Jan 6; 6(1): e252.

[537] Joshi R, Colford JM Jr, Reingold AL, Kalantri S. Nonmalarial acute undifferentiated fever in a rural hospital in central India: diagnostic uncertainty and overtreatment with antimalarial agents. Am J Trop Med Hyg. 2008 Mar; 78(3): 393–9.

[538] Ansah EK, Narh-Bana S, Epokor M, Akanpigbiam S, Quartey AA, Gyapong J, Whitty CJ. Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana. BMJ. 2010 Mar 5; 340: c930. doi: 10.1136/bmj.c930.

[539] Yeboah-Antwi K, Pilingana P, Macleod WB, Semrau K, Siazeele K, Kalesha P, Hamainza B, Seidenberg P, Mazimba A, Sabin L, Kamholz K, Thea DM, Hamer DH. Community case management of fever due to malaria and pneumonia in children under five in Zambia: a cluster randomised controlled trial. PLoS Med. 2010 Sep 21; 7(9): e1000340.

[540] Ansah EK, Narh-Bana S, Epokor M, Akanpigbiam S, Quartey AA, Gyapong J, Whitty CJ. Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only

presumptive treatment is available: a randomised controlled trial in Ghana. BMJ. 2010 Mar 5; 340: c930. doi: 10.1136/bmj.c930.

[541] Goodman CA, Mutemi WM, Baya EK, Willetts A, Marsh V. The cost-effectiveness of improving malaria home management: shopkeeper training in rural Kenya. Health Policy Plan. 2006 Jul; 21(4): 275–88.

[542] Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakeley C, Whitty CJ. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. BMJ. 2007 Feb 24; 334(7590): 403.

[543] Chinkhumba J, Skarbinski J, Chilima B, Campbell C, Ewing V, San Joaquin M, Sande J, Ali D, Mathanga D. Comparative field performance and adherence to test results of four malaria rapid diagnostic tests among febrile patients more than five years of age in Blantyre, Malawi. Malar J. 2010 Jul 20; 9: 209.

[544] Zurovac D, Ndhlovu M, Rowe AK, Hamer DH, Thea DM, Snow RW. Treatment of paediatric malaria during a period of drug transition to artemether-lumefantrine in Zambia: cross sectional study. BMJ. 2005 Oct 1; 331(7519): 734.

[545] Hamer DH, Ndhlovu M, Zurovac D, Fox M, Yeboah-Antwi K, Chanda P, Sipilinyambe N, Simon JL, Snow RW. Improved diagnostic testing and malaria treatment practices in Zambia. JAMA. 2007 May 23; 297(20): 2227–31.

[546] Gething PW, Kirui VC, Alegana VA, Okiro EA, Noor AM, Snow RW. Estimating the number of paediatric fevers associated with malaria infection presenting to Africa's public health sector in 2007. PLoS Med. 2010 Jul 6; 7(7): e1000301.

[547] Chandler CI, Chonya S, Boniface G, Juma K, Reyburn H, Whitty CJ. The importance of context in malaria diagnosis and treatment decisions – a quantitative analysis of observed clinical encounters in Tanzania. Trop Med Int Health. 2008 Sep; 13(9): 1131–42.

[548] Chandler CI, Jones C, Boniface G, Juma K, Reyburn H, Whitty CJ. Guidelines and mindlines: why do clinical staff over-diagnose malaria in Tanzania? A qualitative study. Malar J. 2008 Apr 2; 7: 53.

[549] Rowe AK, de León GF, Mihigo J, Santelli AC, Miller NP, Van-Dúnem P. Quality of malaria case management at outpatient health facilities in Angola. Malar J. 2009 Dec 2; 8(1): 275.

[550] WHO. Guidelines for the Treatment of Malaria. Second Edition. WHO 2010.

[551] Laufer MK, Thesing PC, Eddington ND, Masonga R, Dzinjalamala FK, Takala SL, Taylor TE, Plowe CV. Return of chloroquine antimalarial efficacy in Malawi. N Engl J Med. 2006 Nov 9; 355(19): 1959–66.

[552] WHO. Treatment of malaria. 2010; 2nd ed. Geneva: WHO.

[553] Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database Syst Rev. 2009 Jul 8; (3): CD007483.

[554] WHO. Global report on antimalarial efficacy and drug resistance: 2000-2010. WHO: Geneva. 2010.

[555] Zwang J, Olliaro P, Barennes H, Bonnet M, Brasseur P, Bukirwa H, et al. Efficacy of artesunate-amodiaquine for treating uncomplicated falciparum malaria in sub-Saharan Africa: a multi-centre analysis. Malar J. 2009 Aug 23; 8: 203.

[556] Uhlemann AC, Krishna S. Antimalarial multi-drug resistance in Asia: mechanisms and assessment. Curr Top Microbiol Immunol. 2005; 295: 39–53.

[557] Dondorp AM, Yeung S, White L, Nguon C, Day NP, Socheat D, von Seidlein L. Artemisinin resistance: current status and scenarios for containment. Nat Rev Microbiol. 2010 Apr; 8(4): 272–80.

[558] Roper C, Pearce R, Nair S, Sharp B, Nosten F, Anderson T. Intercontinental spread of pyrimethamine-resistant malaria. Science. 2004 Aug 20; 305(5687): 1124.

[559] Korsinczky M, Chen N, Kotecka B, Saul A, Rieckmann K, Cheng Q. Mutations in Plasmodium falciparum cytochrome b that are associated with atovaquone resistance are located at a putative drug-binding site. Antimicrob Agents Chemother. 2000 Aug; 44(8): 2100–8.

[560] Mutabingwa TK, Anthony D, Heller A, Hallett R, Ahmed J, Drakeley C, Greenwood BM, Whitty CJ. Amodiaquine alone, amodiaquine+sulfadoxine-pyrimethamine, amodiaquine+artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian children: a four-arm randomised effectiveness trial. Lancet. 2005 Apr 23–29; 365(9469): 1474–80.

[561] Bassat Q, Mulenga M, Tinto H, Piola P, Borrmann S, Menéndez C, Nambozi M, Valéa I, Nabasumba C, Sasi P, Bacchieri A, Corsi M, Ubben D, Talisuna A, D'Alessandro U. Dihydroartemisinin-piperaquine and artemether-lumefantrine for treating uncomplicated malaria in African children: a randomised, non-inferiority trial. PLoS One. 2009 Nov 17; 4(11): e7871.

[562] Arinaitwe E, Sandison TG, Wanzira H, Kakuru A, Homsy J, Kalamya J, Kamya MR, Vora N, Greenhouse B, Rosenthal PJ, Tappero J, Dorsey G. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for falciparum malaria: a longitudinal, randomised trial in young Ugandan children. Clin Infect Dis. 2009 Dec 1; 49(11): 1629–37.

[563] Mbacham WF, Evehe MS, Netongo PM, Ateh IA, Mimche PN, Ajua A, Nji AM, Irenee D, Echouffo-Tcheugui JB, Tawe B, Hallett R, Roper C, Targett G, Greenwood B. Efficacy of amodiaquine, sulphadoxine-pyrimethamine and their combination for the treatment of uncomplicated Plasmodium falciparum malaria in children in Cameroon at the time of policy change to artemisinin-based combination therapy. Malar J. 2010 Jan 27; 9： 34.

[564] Tagbor H, Bruce J, Ord R, Randall A, Browne E, Greenwood B, Chandramohan D. Comparison of the therapeutic efficacy of chloroquine and sulphadoxine-pyremethamine in children and pregnant women. Trop Med Int Health. 2007 Nov; 12(11): 1288–97.

[565] Sutanto I, Endawati D, Ling LH, Laihad F, Setiabudy R, Baird JK. Evaluation of chloroquine therapy for vivax and falciparum malaria in southern Sumatra, western Indonesia. Malar J. 2010 Feb 12; 9: 52.

[566] Leslie T, Mayan MI, Hasan MA, Safi MH, Klinkenberg E, Whitty CJ, Rowland M. Sulfadoxine-pyrimethamine, chlorproguanil-dapsone, or chloroquine for the treatment of Plasmodium vivax malaria in Afghanistan and Pakistan: a randomised controlled trial. JAMA. 2007 May 23; 297(20): 2201–9.

[567] Douglas NM, Anstey NM, Angus BJ, Nosten F, Price RN. Artemisinin combination therapy for vivax malaria. Lancet Infect Dis. 2010 Jun; 10(6): 405–16.

[568] Baird JK. Resistance to therapies for infection by Plasmodium vivax. Clin Microbiol Rev. 2009 Jul; 22(3): 508-34.

[569] Beutler E, Duparc S; G6PD Deficiency Working Group. Glucose-6-phosphate dehydrogenase deficiency and antimalarial drug development. Am J Trop Med Hyg. 2007 Oct; 77(4): 779–89.

[570] Tantular IS, Iwai K, Lin K, Basuki S, Horie T, Htay HH, Matsuoka H, Marwoto H, Wongsrichanalai C, Dachlan YP, Kojima S, Ishii A, Kawamoto F. Field trials of a rapid test for G6PD deficiency in combination with a rapid diagnosis of malaria. Trop Med Int Health. 1999 Apr; 4(4): 245–50.

[571] Tinley KE, Loughlin AM, Jepson A, Barnett ED. Evaluation of a rapid qualitative enzyme chromatographic test for glucose-6-phosphate dehydrogenase deficiency. Am J Trop Med Hyg. 2010 Feb; 82(2): 210–4.

[572] Clark RL. Embryotoxicity of the artemisinin antimalarials and potential consequences for use in women in the first trimester. Reprod Toxicol. 2009 Nov; 28(3): 285–96.

[573] Ward SA, Sevene EJ, Hastings IM, Nosten F, McGready R. Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance. Lancet Infect Dis. 2007 Feb; 7(2): 136–44.

[574] McGready R, Tan SO, Ashley EA, Pimanpanarak M, Viladpai-Nguen J, Phaiphun L, Wüstefeld K, Barends M, Laochan N, Keereecharoen L, Lindegardh N, Singhasivanon P, White NJ, Nosten F. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated plasmodium falciparum treatment in pregnancy. PLoS Med. 2008 Dec 23; 5(12): e253.

[575] Mutabingwa TK, Muze K, Ord R, Briceño M, Greenwood BM, Drakeley C, Whitty CJ. Randomised trial of artesunate+amodiaquine, sulfadoxine-pyrimethamine+amodiaquine, chlorproguanal-dapsone and SP for malaria in pregnancy in Tanzania. PLoS One. 2009; 4(4): e5138.

[576] Manyando C, Mkandawire R, Puma L, Sinkala M, Mpabalwani E, Njunju E, Gomes M, Ribeiro I, Walter V, Virtanen M, Schlienger R, Cousin M, Chipimo M, Sullivan FM. Safety of artemether-

lumefantrine in pregnant women with malaria: results of a prospective cohort study in Zambia. Malar J. 2010 Sep 1; 9: 249.

[577] Nosten F, McGready R, d'Alessandro U, Bonell A, Verhoeff F, Menendez C, Mutabingwa T, Brabin B. Antimalarial drugs in pregnancy: a review. Curr Drug Saf. 2006 Jan; 1(1): 1-15.

[578] Dondorp A, Nosten F, Stepniewska K, Day N, White N; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet. 2005 Aug

27–Sep 2; 366(9487): 717–25.

[579] Dondorp AM, Fanello CI, Hendriksen IC et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010 Nov 13; 376(9753): 1647–57.

[580] Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T, Babiker A, Baiden F, Yunus EB, Binka F, Clerk C, Folb P, Hassan R, Hossain MA, Kimbute O, Kitua A, Krishna S, Makasi C, Mensah N, Mrango Z, Olliaro P, Peto R, Peto TJ, Rahman MR, Ribeiro I, Samad R, White NJ; Study 13 Research Group. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet. 2009 Feb 14; 373(9663): 557–66. Epub 2008 Dec 6.

[581] Gomes M, Ribeiro I, Warsame M, Karunajeewa H, Petzold M. Rectal artemisinins for malaria: a review of efficacy and safety from individual patient data in clinical studies. BMC Infect Dis. 2008 Mar 28; 8: 39.

[582] Karunajeewa HA, Manning L, Mueller I, Ilett KF, Davis TM. Rectal administration of artemisinin derivatives for the treatment of malaria. JAMA. 2007 Jun 6; 297(21): 2381–90.

[583] Simba DO, Kakoko DC, Warsame M, Premji Z, Gomes MF, Tomson G, Johansson E. Understanding caretakers' dilemma in deciding whether or not to adhere with referral advice after pre-referral treatment with rectal artesunate. Malar J. 2010 May 12; 9: 123.

[584] Smith DL, Klein EY, McKenzie FE, Laxminarayan R. Prospective strategies to delay the evolution of anti-malarial drug resistance: weighing the uncertainty. Malar J. 2010 Jul 23; 9: 217.

[585] Luzzatto L. The rise and fall of the antimalarial Lapdap: a lesson in pharmacogenetics. Lancet. 2010 Aug 28; 376(9742): 739–41.

[586] Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. Blood Cells Mol Dis. 2009 May–Jun; 42(3): 267–78.

[587] Beutler E, Duparc S; G6PD Deficiency Working Group. Glucose-6-phosphate dehydrogenase deficiency and antimalarial drug development. Am J Trop Med Hyg. 2007 Oct; 77(4): 779–89.

[588] Vale N, Moreira R, Gomes P. Primaquine revisited six decades after its discovery. Eur J Med Chem. 2009 Mar; 44(3): 937–53.

[589] See: www.mmv.org/

[590] See: www.dndi.org/

[591] Alba S, Dillip A, Hetzel MW, Mayumana I, Mshana C, Makemba A, Alexander M, Obrist B, Schulze A, Kessy F, Mshinda H, Lengeler C. Improvements in access to malaria treatment in Tanzania following community, retail sector and health facility interventions – a user perspective. Malar J. 2010 Jun 15; 9: 163.

[592] Simba DO, Warsame M, Kakoko D, Mrango Z, Tomson G, Premji Z, Petzold M. Who gets prompt access to artemisinin-based combination therapy? A prospective community-based study in children from rural Kilosa, Tanzania. PLoS One. 2010 Aug 10; 5(8). pii: e12104.

[593] Nonvignon J, Aikins MK, Chinbuah MA, Abbey M, Gyapong M, Garshong BN, Fia S, Gyapong JO. Treatment choices for fevers in children under-five years in a rural Ghanaian district. Malar J. 2010 Jun 28; 9: 188.

[594] Gething PW, Kirui VC, Alegana VA, Okiro EA, Noor AM, Snow RW. Estimating the number of paediatric fevers associated with malaria infection presenting to Africa's public health sector in 2007. PLoS Med. 2010 Jul 6; 7(7): e1000301.

[595] Mustafa HS, Malik EM, Tuok HT, Mohamed AA, Julla AI, Bassili A. Malaria preventive measures, health care seeking behaviour and malaria burden in different epidemiological settings in Sudan. Trop Med Int Health. 2009 Dec; 14(12): 1488–95.

[596] Chaturvedi HK, Mahanta J, Pandey A. Treatment-seeking for febrile illness in north-east India: an epidemiological study in the malaria endemic zone. Malar J. 2009 Dec 17; 8(1): 301.

[597] Hwang J, Graves PM, Jima D, Reithinger R, Kachur SP; Ethiopia MIS Working Group. Knowledge of malaria and its association with malaria-related behaviours – results from the Malaria Indicator Survey, Ethiopia, 2007. PLoS One. 2010 Jul 21; 5(7): e11692.

[598] Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T, Babiker A, Baiden F, Yunus EB, Binka F, Clerk C, Folb P, Hassan R, Hossain MA, Kimbute O, Kitua A, Krishna S, Makasi C, Mensah N, Mrango Z, Olliaro P, Peto R, Peto TJ, Rahman MR, Ribeiro I, Samad R, White NJ; Study 13 Research Group. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet. 2009 Feb 14; 373(9663): 557–66.

[599] Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O, Saganda K, Shao J, Kitua A, Olomi R, Greenwood BM, Whitty CJ. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ. 2004 Nov 20; 329(7476): 1212.

[600] Nonvignon J, Aikins MK, Chinbuah MA, Abbey M, Gyapong M, Garshong BN, Fia S, Gyapong JO. Treatment choices for fevers in children under-five years in a rural Ghanaian district. Malar J. 2010 Jun 28; 9: 188.

[601] Chuma J, Okungu V, Molyneux C. Barriers to prompt and effective malaria treatment among the poorest population in Kenya. Malar J. 2010 May 27; 9: 144.

[602] Al-Taiar A, Jaffar S, Assabri A, Al-Habori M, Azazy A, Al-Gabri A, et al. Who develops severe malaria? Impact of access to healthcare, socio-economic and environmental factors on children in Yemen: a case-control study. Trop Med Int Health. 2008 Jun; 13(6): 762–70.

[603] Okeke TA, Okeibunor JC. Rural-urban differences in health-seeking for the treatment of childhood malaria in south-east Nigeria. Health Policy. 2010 Apr; 95(1): 62–8.

[604]Davy CP, Sicuri E, Ome M, Lawrence-Wood E, Siba P, Wavi G, Mueller I, Conteh L. Seeking treatment for symptomatic malaria in Papua New Guinea. Malar J. 2010 Oct 6; 9(1): 268.

[605] Huicho L, Scherpbier RW, Nkowane AM, Victora CG; Multi-Country Evaluation of IMCI Study Group. How much does quality of child care vary between health workers with differing durations of training? An observational multicountry study. Lancet. 2008 Sep 13; 372(9642): 910–6.

[606] Arifeen SE, Hoque DM, Akter T, Rahman M, Hoque ME, Begum K, et al. Effect of the Integrated Management of Childhood Illness strategy on childhood mortality and nutrition in a rural area in Bangladesh: a cluster randomised trial. Lancet. 2009 Aug 1; 374(9687): 393–403.

[607] Pagnoni F. Malaria treatment: no place like home. Trends Parasitol. 2009 Mar; 25(3): 115–9.

[608] Hopkins H, Talisuna A, Whitty CJ, Staedke SG. Impact of home-based management of malaria on health outcomes in Africa: a systematic review of the evidence. Malar J. 2007 Oct 8; 6: 134.

[609] Ajayi IO, Browne EN, Bateganya F, Yar D, Happi C, Falade CO, Gbotosho GO, Yusuf B, Boateng S, Mugittu K, Cousens S, Nanyunja M, Pagnoni F. Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: a report from three study sites in sub-Saharan Africa. Malar J. 2008 Sep 27; 7: 190.

[610] Sirima SB, Konaté A, Tiono AB, Convelbo N, Cousens S, Pagnoni F. Early treatment of childhood fevers with pre-packaged antimalarial drugs in the home reduces severe malaria morbidity in Burkina Faso. Trop Med Int Health. 2003 Feb; 8(2): 133–9

[611] Staedke SG, Mwebaza N, Kamya MR, Clark TD, Dorsey G, Rosenthal PJ, Whitty CJ. Home management of malaria with artemether-lumefantrine compared with standard care in urban Ugandan children: a randomised controlled trial. Lancet. 2009 May 9; 373(9675): 1623–31.

[612] Nsungwa-Sabiiti J, Peterson S, Pariyo G, Ogwal-Okeng J, Petzold MG, Tomson G. Home-based management of fever and malaria treatment practices in Uganda. Trans R Soc Trop Med Hyg. 2007 Dec; 101(12): 1199–207.

[613] Lubell Y, Mills AJ, Whitty CJ, Staedke SG. An economic evaluation of home management of malaria in Uganda: an interactive Markov model. PLoS One. 2010 Aug 27; 5(8): e12439.

[614] Onwujekwe O, Chukwuogo O, Ezeoke U, Uzochukwu B, Eze S. Asking people directly about preferred health-seeking behaviour yields invalid response: an experiment in south-east Nigeria. J Public Health (Oxf). 2010 Aug 25.

[615] Deressa W, Ali A. Malaria-related perceptions and practices of women with children under the age of five years in rural Ethiopia. BMC Public Health. 2009 Jul 23; 9: 259.

[616] Okeke TA, Okeibunor JC. Rural-urban differences in health-seeking for the treatment of childhood malaria in south-east Nigeria. Health Policy. 2010 Apr; 95(1): 62–8.

[617] Chaturvedi HK, Mahanta J, Pandey A. Treatment-seeking for febrile illness in north-east India: an epidemiological study in the malaria endemic zone. Malar J. 2009 Dec 17; 8(1): 301.

[618] Ahmed SM, Haque R, Haque U, Hossain A. Knowledge on the transmission, prevention and treatment of malaria among two endemic populations of Bangladesh and their health-seeking behaviour. Malar J. 2009 Jul 29; 8: 173.

[619] Abuya T, Fegan G, Rowa Y, Karisa B, Ochola S, Mutemi W, Marsh V. Impact of ministry of health interventions on private medicine retailer knowledge and practices on anti-malarial treatment in Kenya. Am J Trop Med Hyg. 2009 Jun; 80(6): 905–13.

[620] Tawfik Y, Nsungwa-Sabitii J, Greer G, Owor J, Kesande R, Prysor-Jones S. Negotiating improved case management of childhood illness with formal and informal private practitioners in Uganda. Trop Med Int Health. 2006 Jun; 11(6): 967–73.

[621] Wiseman V, Onwujekwe O, Matovu F, Mutabingwa TK, Whitty CJ. Differences in willingness to pay for artemisinin-based combinations or monotherapy: experiences from the United Republic of Tanzania. Bull World Health Organ. 2005 Nov; 83(11): 845–52.

[622] Chuma J, Okungu V, Molyneux C. Barriers to prompt and effective malaria treatment among the poorest population in Kenya. Malar J. 2010 May 27; 9: 144.

[623] Chuma J, Abuya T, Memusi D, Juma E, Akhwale W, Ntwiga J, Nyandigisi A, Tetteh G, Shretta R, Amin A. Reviewing the literature on access to prompt and effective malaria treatment in Kenya: implications for meeting the Abuja targets. Malar J. 2009 Oct 28; 8: 243.

[624] Ansah EK, Narh-Bana S, Asiamah S, Dzordzordzi V, Biantey K, Dickson K, Gyapong JO, Koram KA, Greenwood BM, Mills A, Whitty CJ. Effect of removing direct payment for health care on utilisation and health outcomes in Ghanaian children: a randomised controlled trial. PLoS Med. 2009 Jan 6; 6(1): e1000007.

[625] Kenneth J. Arrow, Claire B. Panosian, and Hellen Gelband, Editors Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance. Instutute of Medicine, Washington, 2004

[626] All Party Parliamentary Malaria Group Report: The Right Drug at the Right Time: Affordable Medicines Facility-Malaria (AMFm). London 2007.

[627] Sabot OJ, Mwita A, Cohen JM, Ipuge Y, Gordon M, Bishop D, Odhiambo M, Ward L, Goodman C. Piloting the global subsidy: the impact of subsidised artemisinin-based combination therapies distributed through private drug shops in rural Tanzania. PLoS One. 2009 Sep 2; 4(9): e6857

[628] Cohen JM, Sabot O, Sabot K, Gordon M, Gross I, Bishop D, Odhiambo M, Ipuge Y, Ward L, Mwita A, Goodman C. A pharmacy too far? Equity and spatial distribution of outcomes in the delivery of subsidised artemisinin-based combination therapies through private drug shops. BMC Health Serv Res. 2010 Jul 2; 10 Suppl 1: S6.

[629] Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakeley C, Whitty CJ. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. BMJ. 2007 Feb 24; 334(7590): 403.

[630] Hamer DH, Ndhlovu M, Zurovac D, Fox M, Yeboah-Antwi K, Chanda P, et al. Improved diagnostic testing and malaria treatment practices in Zambia. JAMA. 2007 May 23; 297(20): 2227–31.

[631] Nomhwange TI, Whitty CJ. Diagnosis of malaria in children's outpatient departments in Abuja, Nigeria. Trop Doct. 2009 Apr; 39(2): 90–2.

[632] Amin AA, Hughes DA, Marsh V, Abuya TO, Kokwaro GO, Winstanley PA, Ochola SA, Snow RW. The difference between effectiveness and efficacy of antimalarial drugs in Kenya. Trop Med Int Health. 2004 Sep; 9(9): 967–74.

[633] Souares A, Lalou R, Sene I, Sow D, Le Hesran JY. Adherence and effectiveness of drug combination in curative treatment among children suffering uncomplicated malaria in rural Senegal. Trans R Soc Trop Med Hyg. 2008 Aug; 102(8): 751–8.

[634] Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, Ruzagira E, Babigumira J, Kigozi I, Kiguli J, Kyomuhendo J, Ferradini L, Taylor W, Checchi F, Guthmann JP. Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated Plasmodium falciparum malaria in Mbarara,Uganda: a randomised trial. Lancet. 2005 Apr 23–29; 365(9469): 1467–73.

[635] Depoortere E, Guthmann JP, Pressé J, Sipilanyambe N, Nkandu E, Balkan S, de Pécoulas PE, Legros D. Efficacy and effectiveness of the combination of sulfadoxine/pyrimethamine and a 3-day course of artesunate for the treatment of uncomplicated falciparum malaria in a refugee settlement in Zambia. Trop Med Int Health. 2005 Feb; 10(2): 139–45.

[636] Le NB, Pham TY, Nguyen BN, Dang CT, Pham TL, Le DC. Efficacy and effectiveness of five day treatment of uncomplicated falciparum with artemisinin or artesunate in Vietnam. Southeast Asian J Trop Med Public Health. 1999 Mar; 30(1): 3–6

[637] Kabanywanyi AM, Lengeler C, Kasim P, King'eng'ena S, Schlienger R, Mulure N, Genton B. Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania. Malar J. 2010 Feb 11; 9: 48.

[638] Orton L, Barnish G. Unit-dose packaged drugs for treating malaria. Cochrane Database Syst Rev. 2005 Apr 18; (2): CD004614.

[639] Dondorp AM, Newton PN, Mayxay M, Van Damme W, Smithuis FM, Yeung S, Petit A, Lynam AJ, Johnson A, Hien TT, McGready R, Farrar JJ, Looareesuwan S, Day NP, Green MD, White NJ. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. Trop Med Int Health. 2004 Dec; 9(12): 1241–6.

[640] Newton PN, Fernández FM, Plançon A, Mildenhall DC, Green MD, Ziyong L, et al. collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. PLoS Med. 2008 Feb; 5(2): e32.

[641] Bate R, Hess K. Anti-malarial drug quality in Lagos and Accra – a comparison of various quality assessments. Malar J. 2010 Jun 11; 9: 157.

[642] Newton PN, McGready R, Fernandez F, Green MD, Sunjio M, Bruneton C, Phanouvong S, Millet P, Whitty CJ, Talisuna AO, Proux S, Christophel EM, Malenga G, Singhasivanon P, Bojang K, Kaur H, Palmer K, Day NP, Greenwood BM, Nosten F, White NJ. Manslaughter by fake artesunate in Asia – will Africa be next? PLoS Med. 2006 Jun; 3(6): e197.

[643] U.S. Pharmacopeia. Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda. USP:Maryland. 2009.

[644] Taylor RB, Shakoor O, Behrens RH, Everard M, Low AS, Wangboonskul J, Reid RG, Kolawole JA. Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. Lancet. 2001 Jun 16; 357(9272): 1933–6.

[645] Chizema-Kawesha E, Miller JM, Steketee RW, Mukonka VM, Mukuka C, Mohamed AD, Miti SK, Campbell CC. Scaling up malaria control in Zambia: progress and impact 2005–2008. Am J Trop Med Hyg. 2010 Sep; 83(3): 480–8.

[646] Otten M, Aregawi M, Were W, Karema C, Medin A, Bekele W, Jima D, Gausi K, Komatsu R, Korenromp E, Low-Beer D, Grabowsky M. Initial evidence of reduction of malaria cases and deaths in

Rwanda and Ethiopia due to rapid scale-up of malaria prevention and treatment. Malar J. 2009 Jan 14; 8: 14.

[647] Ceesay SJ, Casals-Pascual C, Erskine J, Anya SE, Duah NO, Fulford AJ, Sesay SS, Abubakar I, Dunyo S, Sey O, Palmer A, Fofana M, Corrah T, Bojang KA, Whittle HC, Greenwood BM, Conway DJ. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. Lancet. 2008 Nov 1; 372(9649): 1545–54.

[648] Dondorp AM, Fanello CI, Hendriksen IC et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010 Nov 13; 376(9753): 1647–57.

[649] Nadjm B, Amos B, Mtove G, Ostermann J, Chonya S, Wangai H, Kimera J, Msuya W, Mtei F, Dekker D, Malahiyo R, Olomi R, Crump JA, Whitty CJ, Reyburn H. WHO guidelines for antimicrobial treatment in children admitted to hospital in an area of intense Plasmodium falciparum transmission: prospective study. BMJ. 2010 Mar 30; 340: c1350. doi: 10.1136/bmj.c1350.

[650] Mackenzie G, Ceesay SJ, Hill PC, Walther M, Bojang KA, Satoguina J, Enwere G, D'Alessandro U, Saha D, Ikumapayi UN, O'Dempsey T, Mabey DC, Corrah T, Conway DJ, Adegbola RA, Greenwood BM. A decline in the incidence of invasive non-typhoidal Salmonella infection in The Gambia temporally associated with a decline in malaria infection. PLoS One. 2010 May 11; 5(5): e10568.

[651] Cheema B, Molyneux EM, Emmanuel JC, M'baya B, Esan M, Kamwendo H, Kalilani-Phiri L, Boele van Hensbroek M. Development and evaluation of a new paediatric blood transfusion protocol for Africa. Transfus Med. 2010 Jun; 20(3): 140–51.

[652] Al-Taiar A, Jaffar S, Assabri A et al. Severe malaria in children in Yemen: two site observational study. *BMJ*. 2006; 333:827.

[653] Akech S, Ledermann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. BMJ. 2010 Sep 2; 341: c4416. doi: 10.1136/bmj.c4416.

[654]Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T, Babiker A, Baiden F, Yunus EB, Binka F, Clerk C, Folb P, Hassan R, Hossain MA, Kimbute O, Kitua A, Krishna S, Makasi C, Mensah N, Mrango Z, Olliaro P, Peto R, Peto TJ, Rahman MR, Ribeiro I, Samad R, White NJ; Study 13 Research Group. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet. 2009 Feb 14; 373(9663): 557–66.

[655] E.g. Centers for Disease control and Prevention. CDC Health Information for Travel 2010. Atlanta: US Department of Health and Human Services Public Health Service. 2009.

[656] Menon A, Snow RW, Byass P, Greenwood BM, Hayes RJ, N'Jie AB. Sustained protection against mortality and morbidity from malaria in rural Gambian children by chemoprophylaxis given by village health workers. Trans R Soc Trop Med Hyg.1990 Nov–Dec; 84(6): 768–72.

[657] Cairns M, Gosling R, Gesase S, Mosha J, Greenwood B, Chandramohan D. Mode of action and choice of antimalarial drugs for intermittent preventive treatment in infants. Trans R Soc Trop Med Hyg. 2009 Dec; 103(12): 1199–201.

[658] Odhiambo FO, Hamel MJ, Williamson J, et al. Intermittent Preventive Treatment in Infants for the Prevention of Malaria in Rural Western Kenya: A Randomized, Double-Blind Placebo-Controlled Trial. PLoS ONE 5(4): e10016. doi:10.1371/journal.pone.0010016.

[659] Garner P, Gülmezoglu AM. Drugs for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2006; 4: CD000169.

[660] Mbaye A, Richardson K, Balajo B, Dunyo S, Shulman C, et al. A randomised, placebo-controlled trial of intermittent preventive treatment with sulphadoxine-pyrimethamine in Gambian multigravidae. Trop Med Int Health 2006; 11: 992–1002

[661] Njagi JK, Magnussen P, Estambale B, Ouma J, Mugo B. Prevention of anaemia in pregnancy using insecticide-treated bednets and sulfadoxinepyrimethamine in a highly malarious area of Kenya: a randomised controlled trial. Trans R Soc Trop Med Hyg2003; 97: 277–282.

[662] Greenwood BM, Greenwood AM, Snow RW, Byass P, Bennett S, et al. The effects of malaria chemoprophylaxis given by traditional birth attendants on the course and outcome of pregnancy. Trans R Soc Trop Med Hyg 1989; 83: 589–594.

[663] Mene´ndez C, Bardajı´ A, Sigauque B, Sanz S, Aponte JJ, et al. Malaria Prevention with IPTp during Pregnancy Reduces Neonatal Mortality. PLoS ONE 2010; 5(2): e9438. oi: 10.1371/journal.pone.0009438

[664] Clerk CA, Bruce J, Affipunguh PK, Mensah N, Hodgson A, Greenwood B, Chandramohan D. A randomised, controlled trial of intermittent preventive treatment with sulfadoxine-pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. J Infect Dis. 2008 Oct 15; 198(8): 1202–11.

[665] Oduro AR, Fryauff DJ, Koram KA, Rogers WO, Anto F, Atuguba F, et al. Sulfadoxine-pyrimethamine-based intermittent preventive treatment, bed net use, and antenatal care during pregnancy: demographic trends and impact on the health of newborns in the Kassena Nankana District, northeastern Ghana. Am J Trop Med Hyg. 2010 Jul; 83(1): 79–89.

[666] Menéndez C, Bardají A, Sigauque B, Sanz S, Aponte JJ, Mabunda S, Alonso PL. Malaria prevention with IPTp during pregnancy reduces neonatal mortality. PLoS One. 2010 Feb 26; 5(2): e9438.

[667] Hommerich L, von Oertzen C, Bedu-Addo G, Holmberg V, Acquah PA, Eggelte TA, Bienzle U, Mockenhaupt FP. Decline of placental malaria in southern Ghana after the implementation of intermittent preventive treatment in pregnancy. Malar J. 2007 Nov 8; 6: 144.

[668] Menéndez C, Bardají A, Sigauque B, Romagosa C, Sanz S, Serra-Casas E, Macete E, Berenguera A, David C, Dobaño C, Naniche D, Mayor A, Ordi J, Mandomando I, Aponte JJ, Mabunda S, Alonso PL. A randomised placebo-controlled trial of intermittent preventive treatment in pregnant women in the context of insecticide treated nets delivered through the antenatal clinic. PLoS One. 2008 Apr 9; 3(4): e1934.

[669] Parise ME, Ayisi JG, Nahlen BL, Schultz LJ, Roberts JM, et al. (1998) 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. Am J Trop Med Hyg 59: 813–822.

[670] Ter Kuile F, van Eijk A, Filler S. Effect of Sulfadoxine-Pyrimethamine Resistance on the efficacy of Intermittent Preventive Therapy for Malaria Control during Pregnancy. JAMA. June 20 2007; 297/23.

[671] Hamer DH, Mwanakasale V, Macleod WB, Chalwe V, Mukwamataba D, Champo D, et al. Two-dose versus monthly intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine in HIV-seropositive pregnant Zambian women. J Infect Dis. 2007 Dec 1; 196(11): 1585–94.

[672] Filler SJ, Kazembe P, Thigpen M, Macheso A, Parise ME, Newman RD, et al. Randomised trial of 2-dose versus monthly sulfadoxine-pyrimethamine intermittent preventive treatment for malaria in HIV-positive and HIV-negative pregnant women in Malawi. J Infect Dis. 2006 Aug 1; 194(3): 286–93.

[673] WHO. Guidelines for the Treatment of Malaria. Second Edition. WHO: Geneva 2010.

[674] Newman RD, A. Hailemariam D. Jimma A et al. Burden of malaria during pregnancy in areas of stable and unstable transmission in Ethiopia during a nonepidemic year. J. Infect. Dis 2003; 187:1765-1772.

[675] Mbaye A, Richardson K, Balajo B, Dunyo S, Shulman C, Milligan P, Greenwood B, Walraven G. A randomised, placebo-controlled trial of intermittent preventive treatment with sulphadoxine-pyrimethamine in Gambian multigravidae. Trop Med Int Health. 2006 Jul; 11(7): 992–1002.

[676] Mutabingwa TK, Muze K, Ord R, Briceño M, Greenwood BM, Drakeley C, Whitty CJ. Randomised trial of artesunate+amodiaquine, sulfadoxine-pyrimethamine+amodiaquine, chlorproguanal-dapsone and SP for malaria in pregnancy in Tanzania. PLoS One. 2009; 4(4): e5138.

[677] Tagbor H, Bruce J, Ord R, Randall A, Browne E, Greenwood B, Chandramohan D. Comparison of the therapeutic efficacy of chloroquine and sulphadoxine-pyremethamine in children and pregnant women. Trop Med Int Health. 2007 Nov; 12(11): 1288–97. Epub 2007 Oct 22.

[678] Briand V, Bottero J, Noël H, Masse V, Cordel H, Guerra J, et al. Intermittent treatment for the prevention of malaria during pregnancy in Benin: a randomised, open-label equivalence trial comparing sulfadoxine-pyrimethamine with mefloquine. J Infect Dis. 2009 Sep 15; 200(6): 991–1001.

[679] Schellenberg D, Menendez C, Aponte JJ, Kahigwa E, Tanner M, Mshinda H, Alonso P. Intermittent preventive antimalarial treatment for Tanzanian infants: follow-up to age 2 years of a randomised, placebo-controlled trial. Lancet. 2005 Apr 23–29; 365(9469): 1481–3.

[680] Aponte JJ, Schellenberg D, Egan A, Breckenridge A, Carneiro I, Critchley J, et al. Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised,placebo-controlled trials. Lancet. 2009 Oct 31; 374(9700): 1533–42.

[681] Armstrong Schellenberg JR, Shirima K, Maokola W, Manzi F, Mrisho M, Mushi A, et al. Community effectiveness of intermittent preventive treatment for infants (IPTi) in rural southern Tanzania. Am J Trop Med Hyg. 2010 May; 82(5): 772–81.

[682] Conteh L, Sicuri E, Manzi F, Hutton G, Obonyo B, Tediosi F, et al. The cost-effectiveness of intermittent preventive treatment for malaria in infants in Sub-Saharan Africa. PLoS One. 2010 Jun 15; 5(6): e10313.

[683] Chandramohan D, Owusu-Agyei S, Carneiro I, Awine T, Amponsa-Achiano K, Mensah N, et al. Cluster randomised trial of intermittent preventive treatment for malaria in infants in area of high, seasonal transmission in Ghana. BMJ. 2005 Oct 1; 331(7519): 727–33.

[684] Chandramohan D, Webster J, Smith L, Awine T, Owusu-Agyei S, Carneiro I. Is the Expanded Programme on Immunisation the most appropriate delivery system for intermittent preventive treatment of malaria in West Africa? Trop Med Int Health. 2007 Jun; 12(6): 743–50.

[685] Schellenberg D, Menendez C, Aponte JJ, Kahigwa E, Tanner M, Mshinda H, Alonso P. Intermittent preventive antimalarial treatment for Tanzanian infants: follow-up to age 2 years of a randomised, placebo-controlled trial. Lancet. 2005 Apr 23–29; 365(9469): 1481–3.

[686] See: www.ipti-malaria.org

[687] Greenwood B. Anti-malarial drugs and the prevention of malaria in the population of malaria endemic areas. Malaria Journal 2010; 9(Suppl 3):S2.

[688] Clarke SE, Jukes MC, Njagi JK, et al. Effect of intermittent preventive treatment of malaria on health and education in schoolchildren: a cluster-randomised, double blind, placebo-controlled trial. Lancet 2008: 372:127-138.

[689] Barger B, Maiga H, Traore OB, et al. Intermittent preventive treatment using artemisinin-based combination therapy reduces malaria morbidity among school-aged children in Mali. Trop Med Int Health 2009; 14:784-791.

[690] Kweku M, Liu D, Adjuik M, Binka F, Seidu M, Greenwood B, Chandramohan D.Seasonal intermittent preventive treatment for the prevention of anaemia and malaria in Ghanaian children: a randomised, placebo controlled trial. PLoS One. 2008; 3(12): e4000.

[691] Barger B, Maiga H, Traore OB, Tekete M, Tembine I, Dara A, Traore ZI, Gantt S, Doumbo OK, Djimde AA. Intermittent preventive treatment using artemisinin-based combination therapy reduces malaria morbidity among school-aged children in Mali. Trop Med Int Health. 2009 Jul; 14(7): 784–91.

[692] Cisse B, Cairns M, Faye E, NDiaye O, Faye B, Cames C, Cheng Y, NDiaye M, Lô AC, Simondon K, Trape JF, Faye O, NDiaye JL, Gaye O, Greenwood B, Milligan P. Randomised trial of piperaquine with sulfadoxine-pyrimethamine or dihydroartemisinin for malaria intermittent preventive treatment in children. PLoS One. 2009 Sep 28; 4(9): e7164.

[693] Conteh L, Patouillard E, Kweku M, Legood R, Greenwood B, Chandramohan D. Cost effectiveness of seasonal intermittent preventive treatment using amodiaquine and artesunate or sulphadoxine-pyrimethamine in Ghanaian children. PLoS One. 2010 Aug 17; 5(8). pii: e12223.

[694] Temperley M, Mueller DH, Njagi JK, Akhwale W, Clarke SE, Jukes MC, Estambale BB, Brooker S. Costs and cost-effectiveness of delivering intermittent preventive treatment through schools in western Kenya. Malar J. 2008 Sep 30; 7: 196.

[695] Kweku M, Webster J, Adjuik M, Abudey S, Greenwood B, Chandramohan D. Options for the delivery of intermittent preventive treatment for malaria to children: a community randomised trial. PLoS One. 2009 Sep 30; 4(9): e7256

[696] Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, Hinsley W, et al. Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies. PLoS Med. 2010 Aug 10; 7(8). pii: e1000324.

[697] White NJ. The role of anti-malarial drugs in eliminating malaria. Malar J. 2008 Dec 11; 7 Suppl 1: S8.

[698] von Seidlein L, Greenwood BM. Mass administrations of antimalarial drugs. Trends Parasitol. 2003 Oct;19(10):452-60.

[699] Song J, Socheat D, Tan B, Dara P, Deng C, Sokunthea S, Seila S, Ou F, Jian H, Li G. Rapid and effective malaria control in Cambodia through mass administration of artemisinin-piperaquine. Malar J. 2010 Feb 23; 9: 57.

[700] von Seidlein L, Walraven G, Milligan PJ, Alexander N, Manneh F, Deen JL, et al. The effect of mass administration of sulfadoxine-pyrimethamine combined with artesunate on malaria incidence: a double-blind, community-randomised, placebo-controlled trial in The Gambia. Trans R Soc Trop Med Hyg. 2003 Mar–Apr; 97(2): 217-25.

[701] Shekalaghe SA, ter Braak R, Daou M, Kavishe R, van den Bijllaardt W, van den Bosch S, Koenderink JB, Luty AJ, Whitty CJ, Drakeley C, Sauerwein RW, Bousema T. In Tanzania, hemolysis after a single dose of primaquine coadministered with an artemisinin is not restricted to glucose-6-phosphate dehydrogenase-deficient (G6PD A-) individuals. Antimicrob Agents Chemother. 2010 May; 54(5): 1762–8.

[702] Sanjoaquin MA, Molyneux ME: Malaria and vitamin A deficiency in African children: a vicious circle? Malar J 2009, 8: 134.

[703] Shankar AH, Genton B, Semba RD, Baisor M, Paino J, Tamja S, et al: Effect of vitamin A supplementation on morbidity due to Plasmodium falciparum in young children in Papua New Guinea: a randomised trial. Lancet 1999, 354: 203–209.

[704] Ross DA, Dollimore N, Smith PG et al. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. The Lancet 1993; 342(8862):7-12.

[705] SanJoaquin MA, Molyneux ME. Malaria and vitamin A deficiency in African children: a vicious circle? Malaria Journal 2009, 8:134.

[706] Black RE: Zinc deficiency, infectious disease and mortality in the developing world. J Nutr 2003, 133: 1485S–1489S.

[707] Richard SA, Zavaleta N, Caulfield LE, Black RE, Witzig RS, Shankar AH: Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon. Am J Trop Med Hyg 2006, 75: 126–132.

[708]Shankar AH: Nutritional modulation of malaria morbidity and mortality. J Infect Dis 2000, 182 Suppl 1: S37–53.

[709] Muller O, Becher, H, Van Zweeden AB et al. Effect of zinc supplementation on malaria and other causes of morbidity in west African children: randomised, placebo-controlled trial. BMJ, 2001; 322: 1567

[710] Sazawal S, Black RE, Ramsan M, Chwaya HM, Dutta A, Dhingra U, et al. Effect of zinc supplementation on mortality in children aged 1–48 months: a community-based randomised placebo-controlled trial. Lancet 2007, 369: 927–934.

[711] Zeba AN, Sorgho H, Rouamba N, Zongo I, Rouamba J, Guiguemde RT, et al. Major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children in Burkina Faso: a randomised double blind trial. Nutr J 2008, 7: 7.

[712] Sazawal S, Black RE, Ramsan M et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria

transmission setting: community-based, randomised, placebo-controlled trial. The Lancet 2006; 367(9505):133-143.

[713] WHO. Conclusions and recommendations of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malariaendemic areas. Food and Nutrition Bulletin 2006; 28(4):s621-s631.

[714] Ojukwu JU, Okebe JU, Yahav D, Paul M. Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. Cochrane Database of Systematic Reviews 2009; Issue 3. Art. No.: CD006589. DOI: 10.1002/14651858.CD006589.pub2.

[715] Richard SA, Zavaleta N, Caulfield LE, Black RE, Witzig RS, Shankar AH: Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon. Am J Trop Med Hyg 2006, 75: 126–132.

[716] Berkley JA, Bejon P, Mwangi T, Gwer S, Maitland K, Williams TN, et al. HIV infection, malnutrition, and invasive bacterial infection among children with severe malaria. Clin Infect Dis. 2009 Aug 1; 49(3): 336–43.

[717] Gamble CL, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD003755. DOI: 10.1002/14651858.CD003755.pub2

[718] WHO. Guidelines for the Treatment of Malaria. Second Edition. WHO 2010.

[719] Bremen et al. Conquering malaria. In Jamison et al (eds). Disease Control Priorities in Developing Countries. DCPP. Oxford University Press/World Bank. 2006.

[720] Anon. As challenges change so does science. Science. 14 May 2010; 328.

[721] Personal communication, Dr Kara Hanson, Malaria in Pregnancy Consortium.

[722] Reithinger R, Kamya MR, Whitty CJ, Dorsey G, Vermund SH. Interaction of malaria and HIV in Africa. BMJ. 2009 Jun 3; 338: b2141.

[723] Modjarrad K, Vermund SH. Effect of treating co-infections on HIV-1 viral load: a systematic review. Lancet Infect Dis. 2010 Jul; 10(7): 455–63.

[724] Brahmbhatt H, Sullivan D, Kigozi G, Askin F, Wabwire-Mangenm F, Serwadda D, et al. Association of HIV and malaria with mother-to-child transmission, birth outcomes, and child mortality. J Acquir Immune Defic Syndr. 2008 Apr 1; 47(4): 472–6.

[725] Cohee L, Mills LA, Kagaayi J, Jacobs I, Galiwango R, Ludigo J, et al. High retention and appropriate use of insecticide-treated nets distributed to HIV-affected households in Rakai, Uganda: results from interviews and home visits. Malar J. 2009 Apr 22; 8: 76.

[726] Mermin J, Lule J, Ekwaru, JP. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. AIDS 2004. 364(9443): 1428–34.

[727] Campbell J, Moore D, Degerman R, et al. Abstract 33: HIV-infected Ugandans on HAART with CD4 counts >200 cells/mm3 who discontinue cotrimoxazole have increased risk of malaria and diarrhea. 16th Conference on Retroviruses and Opportunistic Infections. 2009 8–11 February; Montreal, Canada.

[728] Kamya MR, Gasasira AF, Achan J et al. Effects of trimethoprim-sulfamethoxazole and insecticide-treated bednets on malaria among HIV-infected Ugandan children. AIDS 2007; 21(15): 2059–66.

[729] Mermin J et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. Lancet 2006; 367(9518): 1256–61.

[730] WHO. Malaria and HIV interactions and their implications for public health policy. Report of a technical consultation, June 2004.

[731] Hamer DH. Two-dose versus monthly intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine in HIV-seropositive pregnant Zambian women. J Infect Dis 2007; 196: 1585–1594.

[732] Shah SN et al. HIV-1 immunosuppression and antimalarial efficacy: sulfadoxine-pyrimethamine for the treatment of uncomplicated malaria in HIV-infected adults in Siaya, Kenya. J Infect Dis 194: 1519–1528, 2006.

[733] Gasasira AF, Kamya MR, Achan J, Mebrahtu T, Kalyango JN, Ruel T, C et al. High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. Clin Infect Dis. 2008 Apr 1; 46(7): 985–91.

[734] Khoo S et al. The potential for interactions between antimalarial and antiretroviral drugs. AIDS 19(10): 995–1005, 2005.

[735] Reilley B, Abeyasinghe R, Pakianathar MV. Barriers to prompt and effective treatment of malaria in northern Sri Lanka. Trop Med Int Health. 2002 Sep; 7(9): 744–9.

[736] Rajakaruna RS, Alifrangis M, Amerasinghe PH, Konradsen F. Pre-elimination stage of malaria in Sri Lanka: assessing the level of hidden parasites in the population. Malar J. 2010 Jan 20; 9: 25.

[737] Matthys B, Sherkanov T, Karimov SS, Khabirov Z, Mostowlansky T, Utzinger J, Wyss K. History of malaria control in Tajikistan and rapid malaria appraisal in an agro-ecological setting. Malar J. 2008 Oct 26; 7: 217.

[738] Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Ann Trop Med Parasitol. 2001 Dec; 95(8): 741–54.

[739] See: www.who.int/malaria/publications/atoz/9789241563697/en/index.html

[740] Nyarango PM, Gebremeskel T, Mebrahtu G, Mufunda J, Abdulmumini U, Ogbamariam A, et al. A steep decline of malaria morbidity and mortality trends in Eritrea between 2000 and 2004: the effect of combination of control methods. Malar J. 2006 Apr 24; 5: 33.

[741] O'Meara WP, Mangeni JN, Steketee R, Greenwood B. Changes in the burden of malaria in sub-Saharan Africa. Lancet Infect Dis. 2010 Aug; 10(8): 545–55.

[742] Kolaczinski J, Graham K, Fahim A, Brooker S, Rowland M. Malaria control in Afghanistan: progress and challenges. Lancet. 2005 Apr 23–29; 365(9469): 1506–12.

[743] Howard N, Shafi A, Jones C, Rowland M. Malaria control under the Taliban regime: insecticide-treated net purchasing, coverage, and usage among men and women in eastern Afghanistan. Malar J. 2010 Jan 6; 9: 7.

[744] Pinto A, Saeed M, El Sakka H, Rashford A, Colombo A, Valenciano M, Sabatinelli G. Setting up an early warning system for epidemic-prone diseases in Darfur: a participative approach. Disasters. 2005 Dec; 29(4): 310–22.

[745] Bonnet M, Broek I, van Herp M, Urrutia PP, van Overmeir C, Kyomuhendo J, et al. Varying efficacy of artesunate+amodiaquine and artesunate+sulphadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria in the Democratic Republic of Congo: a report of two in-vivo studies. Malar J. 2009 Aug 10; 8: 192.

[746] Rowland M, Rab MA, Freeman T. Afghan refugees and the temporal and spatial distribution of malaria in Pakistan. Soc Sci Med. 2002 Dec; 55(11): 2061–72.

[747] Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Annals of Tropical Medicine & Parasitology 2001; 95, 741-754.

[748] Otten M, Aregawi M, Were W, Karema C, Medin A, Bekele W, Jima D, Gausi K, Komatsu R, Korenromp E, Low-Beer D, Grabowsky M. Initial evidence of reduction of malaria cases and deaths in Rwanda and Ethiopia due to rapid scale-up of malaria prevention and treatment. Malar J. 2009 Jan 14; 8: 14.

[749] Rowe AK, Kachur SP, Yoon SS, Lynch M, Slutsker L, Steketee RW. Caution is required when using health facility-based data to evaluate the health impact of malaria control efforts in Africa. Malar J. 2009 Sep 3; 8: 209.

[750] Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Annals of Tropical Medicine & Parasitology 2001; 95, 741-754.

[751] World Health Organization: Guiding principles for malaria control in acute and chronic phase emergencies in Africa. 2004. DIP/MAL/05.08.

[752] Rowland M, Webster J, Padshah S et al.Prevention of malaria in Afghanistan through social marketing of insecticide-treated nets: evaluation of coverage and effectiveness by cross-sectional surveys and passive surveillance. Tropical Medicine and International Health, 2002 7 (10): 813–822

[753] Graham K, Mohammad N, Rehman H, Nazari A, Ahmad M, Kamal M, et al. Insecticide-treated plastic tarpaulins for control of malaria vectors in refugee camps. Med Vet Entomol. 2002 Dec; 16(4): 404–8.

[754] Kolaczinski J, Webster J. Malaria control in complex emergencies: the example of East Timor. Trop Med Int Health. 2003; 8(1):48-55.

[755] Rowland M, Rab MA, Freeman T. Afghan refugees and the temporal and spatial distribution of malaria in Pakistan. Soc Sci Med. 2002 Dec; 55(11): 2061–72.

[756] Hawkins, Michael. Use and limitations of malaria rapid diagnostic testing by community health workers in war-torn Democratic Republic of Congo. Malaria Journal 2009, 8: 308

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

[758] WHO: Malaria Early Warning Systems: Concepts, Indicators and Partners. A Framework for Field Research in Africa. 2001.

[759] Anderson et al. Micro-Satellite and In Situ Ground Sensor Network For Combating Malaria. Available at: www.aidharmonization.org; 2003.

[760] Adimi et al. Towards malaria risk prediction in Afghanistan using remote sensing. Mal Jnl 2010; 9: 125.

[761] Lengeler et al. Quick Wins Versus Sustainability: options for the upscaling of insecticide-treated nets. Am J Trop Med Hyg 2007; 77.

[762] Yukich et al. Costs and Cost-effectiveness of Vector Control in Eritrea using ITNs. Malar J; 2009; 8(51).

[763] Rowland M et al. Prevention of malaria in Afghanistan through social marketing of insecticide-treated nets: evaluation of coverage and effectiveness by cross-sectional surveys and passive surveillance. Tropical Medicine and International Health, 2002; 7 (10): 813–822

[764] Spencer S et al. Malaria in camps for internally-displaced persons in Uganda: evaluation of an insecticide-treated bednet distribution programme. Transactions of the Royal Society of Tropical Medicine and Hygiene 2004 Dec; 98(12): 719–27.

[765] Rowland M, Hewitt S, Durrani N et al. Sustainability of pyrethroid impregnated bed nets for malaria control in Afghan communities. Bulletin of the World Health Organisation 1997; 75: 23-29.

[766] Rowland M, Webster J, Saleh P, et al. Prevention of malaria in Afghanistan through social marketing of insecticide treated nets: evaluation of coverage and effectiveness by cross-sectional surveys and passive surveillance. Tropical Medicine & International Health 2002; 7:813-822.

[767] Graham K, Mohammad N, Rehman H, et al. Insecticide treated plastic tarpaulins for control of malaria vectors in refugee camps. Med Vet Entomol 2002; 16:404-408.

[768] Hewitt S, Rowland M, Nasir M, et al. Pyrethroid sprayed tents for malaria control: an entomological evaluation in Pakistan's North West Frontier Province. Medical & Veterinary Entomology 1995; 9:344-352.

[769] Bouma MJ, Parvez SD, Nesbit R, Winkler AMF. Malaria control using permethrin applied to tents of nomadic Afghan refugees in northern Pakistan. Bull World Health Organ 1996; 74:413-421.

[770] Spencer S et al. Malaria in camps for internally-displaced persons in Uganda: evaluation of an insecticide-treated bednet distribution programme. Transactions of the Royal Society of Tropical Medicine and Hygiene 2004 Dec; 98(12): 719–27.

[771] S Hoibak, A Scifo, J-B Bouvier, R Allan. Impact Of Integrated Malaria Control Amongst Communities Displaced by Conflict on the Chad/Darfur, Sudan Border. Available at:

www.thementorinitiative.org/images/stories/MENTOR/media/publications/poster_mim_chad.pdf; 2009.

[772] Protopopoff (2007) Vector control in a malaria epidemic occurring within a complex emergency situation in Burundi Mal Jnl, 6: 93,

[773] World Health Organization. Malaria control in complex emergencies An Inter-Agency Field Handbook. WHO: Geneva. 2005.

[774] Howard, N et al. Socio-economic factors associated with the purchasing of insecticide-treated nets in Afghanistan and their implications for social marketing. Tropical Medicine and International Health, 2003 8 (12): 1043–1050.

[775] Martins JS, Zwi AB, Martins N, Kelly PM. Malaria control in Timor-Leste during a period of political instability: what lessons can be learned? Conflict and Hlth 2009; 3: 11.

[776] Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Annals of Tropical Medicine & Parasitology 2001; 95, 741-754.

[777] Charlwood JD, Qassim M, Elnsur EI et al. The impact of indoor residual spraying with malathion on malaria in refugee camps in eastern Sudan. Acta Tropica 2001; 80: 1–8.

[778] Graham K, Mohammad N, Rehman H et al. Comparison of three pyrethroid treatments of top-sheets for malaria control in emergencies: entomological and user acceptance studies in an Afghan refugee camp in Pakistan. Med Vet Entomology 2002; 16 (2): 199–206.

[779] Rowland M, Durrani N, Hewitt S et al. Permethrin-treated chaddars and top-sheets: appropriate technology for protection against malaria in Afghanistan and other complex emergencies. Trans R Soc Trop Med Hyg 1999; 93: 465–72.

[780] Graham K, Mohammad N, Rehman H et al. Insecticide-treated plastic tarpaulins for control of malaria vectors in refugee camps. Med Vet Entomology 2002; 16 (4) : 404–408.

[781] Graham K, Mohammad N, Rehman H et al. Comparison of three pyrethroid treatments of top-sheets for malaria control in emergencies: entomological and user acceptance studies in an Afghan refugee camp in Pakistan. Med Vet Entomology 2002; 16 (2): 199–206.

[782] Rowland M, Durrani N, Hewitt S. Permethrin-treated chaddars and top-sheets: appropriate technology for protection against malaria in Afghanistan and other complex emergencies. Trans R Soc Trop Med Hyg 1999; 93: 465–72.

[783] Hawkins, M. Use and limitations of malaria rapid diagnostic testing by community health workers in war-torn Democratic Republic of Congo. Malaria Journal 2009, 8: 308.

[784] Zwi AB, Martins J, Grove NJ, Wayte K, Martins N, Kelly P. Timor-Leste Health Sector Resilience and Performance in a Time of Instability. Sydney: The University of New South Wales; 2007.

[785] Lee CI, Smith SL, Shwe EK et al. Internally displaced human resources for health: villager health worker partnerships to scale up a malaria control programme in active conflict areas of eastern Burma. Glob Public Health. 2009; 4(3).

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

[787] This section was undertaken by Kara Hanson, April Baller, Jayne Webster, Kristian Schultz Hansen of the London School of Hygeine and Tropical Medicine.

[788] Webster J, Hill J, Lines J, Hanson K. Delivery systems for insecticide treated and untreated mosquito nets in Africa: categorisation and outcomes achieved. Health Policy and Planning 2007; 22(5): 277–93

[789] Kilian A, Wijayanandana N, Ssekitoleeko J. Review of delivery strategies for insecticide treated mosquito nets – are we ready for the next phase of malaria control efforts? TropIKA.net, March 2009; 1(1).

[790] Hanson K, Kikumbih N, Armstrong Schellenberg JRM, Mponda H, Nathan R, Mills A, et al. Cost effectiveness of social marketing of insecticide-treated nets in Tanzania. Bulletin of the WHO. 2003; 81(4): 269–76.

[791] Webster J, Kweku M, Dedzo M, Tinkorang K, Bruce J, Lines J, Chandramohan D, Hanson K, 2010. Evaluating delivery systems: Complex evaluations and plausibility inference. Am J Trop Med Hyg. 2010 Apr; 82(4): 672–7.

[792] Hanson K, Marchant T, Nathan R, Mponda H, Jones C, Bruce J, et al. A national voucher programme for insecticide treated nets in Tanzanzia: Effects on household ownership and use among target groups after three years of implementation. British Medical Journal 2009; 338: b2434 doi: 10: 1136/bmj/b2434.

[793] World Bank. World Development Report: Investing in Health. Washington DC: The World Bank; 1993.

[794] WHO. Investing in Health Research and Development. Report of the Ad Hoc committee on health research relating to future intervention options Geneva: WHO; 1996.

[795] Conteh L, Sicuri E, et al. The cost-effectiveness of intermittent preventive treatment for malaria in infants in Sub-Saharan Africa. PloS one 2010; 5(6): 1–7.

[796] Lomborg B, ed. Global Crises, Global Solutions. Cambridge UK: Cambridge University Press; 2004.

[797] Goodman CA, Coleman PG, Mills AJ. The cost-effectiveness of antenatal malaria prevention in sub-Saharan Africa. Am J Trop Med Hyg 2001; 64(1–2)S: 45–56.

[798] Goodman CA, Coleman PG, et al. Cost-effectiveness of malaria control in sub-Saharan Africa. Lancet 1999; 354(9176): 378–385.

[799] Wiseman V, Hawley WA, ter Kuile FO, Phillips-Howard PA, Vulule JM, Hahlen BL, Mills AJ. The cost-effectivenes of permethrin-treated bednets in an area of intense malaria transmission in western Kenya. Am J Trop Med Hyg 2003; 68(4 Suppl): 161–7.

[800] Bhatia MR, Fox-Rushby J, et al. Cost-effectiveness of malaria control interventions when malaria mortality is low: Insecticide-treated nets versus in-house residual spraying in India. Social Science and Medicine 2004; 59(3): 525–539.

[801] Lengeler C. Insecticide-treated bednets and curtains for malaria control Cochrane Database Systematic Reviews 2004; (2): CD000363.

[802] Hanson K, Kikumbih N, et al. Cost-effectiveness of social marketing of insecticide-treated nets for malaria control in the United Republic of Tanzania. Bulletin of the World Health Organization 2003; 81(4): 269–276.

[803] Kikumbih N, Hanson K, Mills A, Mponda H, Armstrong Schellenberg J. The economics of social marketing: the case of mosquito nets in Tanzania. Social Science and Medicine 2005; 60: 369–381.

[804] Stevens W, Wiseman V, et al. The costs and effects of a nationwide insecticide-treated net programme: the case of Malawi. Malaria Journal 2005; 4(22): (10 May 2005).

[805] Mueller DH, Wiseman V, et al. Cost-effectiveness analysis of insecticide-treated net distribution as part of the Togo Integrated Child Health Campaign. Malaria Journal 2008; 7(73).

[806] Kolaczinski JH, Kolaczinski K, et al. Costs and effects of two public sector delivery channels for long-lasting insecticidal nets in Uganda. Malaria Journal 2010; 9: 102.

[807] Yukich JO, Lengeler C, et al. Costs and consequences of large-scale vector control for malaria. Malaria Journal 2008; 7: 258.

[808] Mulligan J-A, Yukich J, Hanson K. Costs and effects of the Tanzanian national voucher scheme for insecticide-treated nets. Malaria Journal 2008; 7: 32.

[809] Kolaczinski JH, Kolaczinski K, et al. Costs and effects of two public sector delivery channels for long-lasting insecticidal nets in Uganda. Malaria Journal 2010; 9: 102.

[810] Stevens W, Wiseman V, et al. The costs and effects of a nationwide insecticide-treated net programme: the case of Malawi. Malaria Journal 2005; 4(22).

[811] Mueller DH, Wiseman V, et al. Cost-effectiveness analysis of insecticide-treated net distribution as part of the Togo Integrated Child Health Campaign. Malaria Journal 2008; 7(73).

[812] Yukich JO, Lengeler C, et al. Costs and consequences of large-scale vector control for malaria. Malaria Journal 2008; 7: 258.

[813] Ibid.

[814] Ibid.

[815] Ibid.

[816] Ibid.

[817] Mulligan J-A, Yukich J, Hanson K. Costs and effects of the Tanzanian national voucher scheme for insecticide-treated nets. Malaria Journal 2008; 7: 32.

[818] Kolaczinski JH, Kolaxzinski K, Kyabayinze D, Strachan D, Termperley M, Wijayanandana N, Kilian A. Costs and effects of two public sector delivery channels for long-lasting insecticidal nets in Uganda. Malaria Journal 2010; 9: 102.

[819] De Allegri M, Marschall P, et al. Comparative cost analysis of insecticide-treated net delivery strategies: sales supported by social marketing and free distribution through antenatal care. Health Policy and Planning 2010; 25(1): 28–38.

[820] Kilian A, Wijayanandana N, Ssekitoleeko J. Review of delivery strategies for insecticide treated mosquito nets-are we ready for the next phase of malaria control efforts? TropIKA.net Journal 2010; 1(1).

[821] Kilian A. 2009. Op cit.

[822] Kilian A. 2009. Op cit.

[823] Mueller DH, Wiseman V, et al. Cost-effectiveness analysis of insecticide-treated net distribution as part of the Togo Integrated Child Health Campaign. Malaria Journal 2008; 7(73).

[824] Rowland M, Durrani N, et al. Control of malaria in Pakistan by applying deltamethrin insecticide to cattle: a community-randomised trial. Lancet 2001; 357(9271): 1837–1841.

[825] Kroeger, A., C. Ayala, et al. Unit costs for house spraying and bednet impregnation with residual insecticides in Colombia: a management tool for the control of vector-borne disease. Annals of Tropical Medicine and Parasitology 2002; 96(4): 405–416.

[826] Yukich J, Lengeler C, Tediosi F, et al. Costs and consequences of large-scale vector control for malaria. Malaria Journal 2008; 7: 258.

[827] Morel CM, Lauer JA, et al. Achieving the millennium development goals for health: Cost effectiveness analysis of strategies to combat malaria in developing countries. BMJ 2005; 331(7528): 1299–1302.

[828] Goodman CA, Coleman PG, et al. Cost-effectiveness of malaria control in sub-Saharan Africa. Lancet 1999; 354(9176): 378–385.

[829] Yukich J, Lengeler C, Tediosi F, et al. Costs and consequences of large-scale vector control for malaria. Malaria Journal 2008; 7: 258.

[830] Yukich et al. 2008. op cit.

[831] Yukich et al. 2008. op cit.

[832] Guyatt HL, Corlett SK, et al. Malaria prevention in highland Kenya: indoor residual house-spraying vs. Insecticide treated bednets. Tropical Medicine and International Health 2002; 7(4): 298–303.

[833] Guyatt HL, Kinnear J, et al. A comparative cost analysis of insecticide-treated nets and indoor residual spraying in highland Kenya. Health Policy and Planning 2002; 17(2): 144–153.

[834]Kroeger A, Ayala C, et al. Unit costs for house spraying and bednet impregnation with residual insecticides in Colombia: a management tool for the control of vector-borne disease. Annals of Tropical Medicine and Parasitology 2002; 96(4): 405–416.

[835]Conteh L, Sharp BL, et al. The cost and cost-effectiveness of malaria vector control by residual insecticide house-spraying in southern Mozambique: A rural and urban analysis. Tropical Medicine and International Health 2004; 9(1): 125–132.

[836]Rowland M, Durrani N, et al. Control of malaria in Pakistan by applying deltamethrin insecticide to cattle: a community-randomised trial. Lancet 2001; 357(9271): 1837–1841.

[837]Konradsen F, Steele P, et al. Cost of malaria control in Sri Lanka. Bulletin of the World Health Organization 1999; 77(4): 301–309.

[838]Morel CM, Lauer JA, et al. Achieving the millennium development goals for health: Cost effectiveness analysis of strategies to combat malaria in developing countries. BMJl 2005; 331(7528): 1299–1302.

[839] Goodman C A, Coleman PG et al. Cost-effectiveness of malaria control in sub-Saharan Africa. Lancet 1999; 354(9176): 378–385.

[840] Goodman C, Coleman PG, Mill A. The cost-effectiveness of antenatal malaria prevention in sub-Saharan Africa. Am J Trop Med Hyg 2001; 64(1–2)S: 45–56.

[841] Breman JG, Mills A, Snow RW, Mulligan J, Lengeler C, Mendis K, et al. Conquering malaria. In. Jamison DT et al. eds. Disease control priorities in developing countries, 2nd edition. Washington DC: The World Bank and Oxford University Press; 2006

[842] Mbonye AK, Hansen KS, Bygbjerg I, Magnussen P. Intermittent preventive treatment of malaria in pregnancy: the incremental cost-effectiveness of a new delivery system in Uganda. Trans Roy Soc Trop Med Hyg 2008; 102: 685–693.

[843] Conteh, L. Cost Effectiveness of Seasonal Intermittent Preventive Treatment Using Amodiaquine and Artesunate or Sulphadoxine-Pyrimethamine in Ghanaian Children. PLOS-One 2010; 5(8): e12223.

[844] Temperley M , Mueller DH, et al. Costs and cost-effectiveness of delivering intermittent preventive treatment through schools in western Kenya. Malaria Journal 2008; 7(196).

[845] Conteh L, Sicuri E, et al. The cost-effectiveness of intermittent preventive treatment for malaria in infants in Sub-Saharan Africa. PloS one 2010; 5(6): 1–7.

[846]Hutton G, Schellenberg D, et al. Cost-effectiveness of malaria intermittent preventive treatment in infants (IPTi) in Mozambique and the United Republic of Tanzania. Bulletin of the World Health Organization 2009; 87(2): 123–129.

[847] WHO. Guidelines for the treatment of malaria, 2nd ed. Geneva: WHO.

[848] Wiseman V, Kim M, et al. Cost-effectiveness study of three antimalarial drug combinations in Tanzania. PLoS Medicine / Public Library of Science 2006; 3(10): e373.

[849] Agnamey P, Brasseur P, et al. Economic evaluation of a policy change from single-agent treatment for suspected malaria to artesunate-amodiaquine for microscopically confirmed uncomplicated falciparum malaria in the Oussouye District of south-western Senegal. Tropical Medicine and International Health 2005; 10(9): 926–933.

[850] Muheki C, McIntyre D et al. Artemisinin-based combination therapy reduces expenditure on malaria treatment in KwaZulu Natal, South Africa. Tropical Medicine and International Health 2004; 9(9): 959–966.

[851] Chanda P, Masiye F, et al. A cost-effectiveness analysis of artemether lumefantrine for treatment of uncomplicated malaria in Zambia. Malaria Journal 2007; 6(21).

[852] Agnamey et al. op cit.

[853] Muheki C, McIntyre D et al. Artemisinin-based combination therapy reduces expenditure on malaria treatment in KwaZulu Natal, South Africa. Tropical Medicine and International Health 2004; 9(9): 959–966.

[854] Lubell Y, Yeung S, et al. Cost-effectiveness of artesunate for the treatment of severe malaria. Tropical Medicine and International Health 2009; 14(3): 332–337.

[855] Available at: www.actwatch.info

[856] International Drug Price Indicator Guide, Available at: www.erc.msh.org

[857] Institute of Medicine. Saving Lives, Buying Time: Economics of malaria drugs in an age of resistance. Washington DC: Institute of Medicine; 2004.

[858]Yeung S, Van Damme W, Socheat D, White NJ, Mills A. Cost of increasing access to artemisinin combination therapy: the Cambodian experience. Malaria Journal 2008; 7: 84.

[859] English M, Reyburn H, Goodman C, Snow RW. Abandoning presumptive antimalarial treatment for febrile children aged under five years: A case of running before we can walk? PLOS Medicine 2009; 6(1): 7–9.

[860]Yukich, J., V. D'Acremont, et al. Cost savings with rapid diagnostic tests for malaria in low-transmission areas: Evidence from Dar es Salaam, Tanzania. American Journal of Tropical Medicine and Hygiene 2010; 83(1): 61–68.

[861] Ly AB, Tall A, et al. 2010. Use of HRP-2-based rapid diagnostic test for Plasmodium falciparum malaria: assessing accuracy and cost-effectiveness in the villages of Dielmo and Ndiop, Senegal. Malaria Journal 9: 153.

[862]Mosha JF, Conteh L, et al. Cost implications of improving malaria diagnosis: findings from north-eastern Tanzania.[Erratum appears in PLoS One 2010; 5(1).

[863]Zikusooka CM, McIntyre D, et al. Should countries implementing an artemisinin-based combination malaria treatment policy also introduce rapid diagnostic tests? Malaria Journal 2008; 7(176).

[864] Rolland E, Checchi F, et al. Operational response to malaria epidemics: are rapid diagnostic tests cost-effective? Tropical Medicine and International Health 2006; 11(4): 398–408.

[865] Ly et al. Op cit.

[866] Yukich et al. Op cit.

[867] Uzochukwu BSC, Obikeze EN, et al. Cost-effectiveness analysis of rapid diagnostic test, microscopy and syndromic approach in the diagnosis of malaria in Nigeria: Implications for scaling-up deployment of ACT. Malaria Journal 2009; 8(1).

[868] Zikusooka et al. Op cit.

[869]Shillcutt S, Morel C, et al. Cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa in an era of combination therapy. Bulletin of the World Health Organization 2008; 86(2): 101–110.

[870]Lubell Y, Hopkins H, Whitty CJ, Staedke G, Mills A. An interactive model for the assessment of the economic costs and benefits of different rapid diagnostic tests for malaria. Malaria Journal 2008; 7: 21.

[871] Lubell Y, Reyburn H, et al. The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. BMJ 2008; 336(7637): 202–205.

[872] Ly et al. op cit.

[873] Yukich J, D'Acremont V, et al. Cost savings with rapid diagnostic tests for malaria in low-transmission areas: Evidence from Dar es Salaam, Tanzania. American Journal of Tropical Medicine and Hygiene 2010; 83(1): 61–68.

[874] Uzochukwu BSC, Obikeze EN, et al. Cost-effectiveness analysis of rapid diagnostic test, microscopy and syndromic approach in the diagnosis of malaria in Nigeria: Implications for scaling-up deployment of ACT. Malaria Journal 2009; 8(1).

[875] Willcox ML, Sanogo F, et al. Rapid diagnostic tests for the home-based management of malaria, in a high-transmission area. Annals of Tropical Medicine and Parasitology 2009; 103(1): 3–16.

[876] Yukich et al. 2010. Op cit.

[877] Ly et al. Op cit.

[878] Uzochukwu et al. Op cit.

[879] Hawkes M, Katsuva JP, et al. Use and limitations of malaria rapid diagnostic testing by community health workers in war-torn Democratic Republic of Congo. Malaria Journal 2009; 8(1).

[880] Zikusooka et al. op cit.

[881] Zikusooka et al. op cit.

[882] Shillcutt et al. op cit.

[883] Lubell Y, Hopkins H, Whitty CJM, Staedke SG, Mills A. 2008. An interactive model for the assessment of the economic costs and benefits of different rapid diagnostic tests for malaria. Malaria Journal, 7: 21.

[884] Lubell et al. BMJ 2008 op cit.

[885] In Zambia, where parasitological diagnosis using microscopy and RDTs is routine practice, antimalarials were provided to over one-third of patients with a negative test (Hamer DH, Ndhlovu M, Zurovac D, Fox M, Yeboah-Antwi K, Chanda P, Sipilinyambe N, Simon JL, Snow RW. 2007. Improved diagnostic testing and malaria treatment practices in Zambia. JAMA 297(20): 2227–2231); and in Tanzania a randomised trial of RDTs vs. microscopy found that in a low transmission setting over 90% of antimalarials were given to patients with a negative test (either type)(Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakeley C, Whitty CJ. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. BMJ 2007, 334(7590): 403)

[886] Goodman C, Brieger W, Unwin A, Meek S, Greer G. Medicine sellers and malaria treatment in sub-Saharan Africa: what do they do and how can their practice be improved. American Journal of Tropical Medicine and Hygiene 2007; 77(6 Suppl): 203–18.

[887] Conteh et al. 2010. PLOS-one. op cit.

[888] Mills A, Shillcutt S. 2004. The Challenge of Communicable Disease. In Global Crises, Global Solutions. Ed. Lomborg B. Cambridge UK: Cambridge University Press.

[889] Mills A, Lubell Y, Hanson K. 2008. Malaria eradication: the economic, financial and institutional challenge. Malaria Journal 7(suppl 1): S11.

[890] Sabot O, Cohen JM, Hsiang MS, Kahn GJ, Basu S, Tang L, et al. 2010. The costs and financial feasibility of malaria elimination. Lancet. DOI: 10.10.16/S0140-6736(10)61355-4. .

[891] Lines J, Lengeler C, et al. 2003. Scaling-up and sustaining insecticide-treated net coverage. Lancet Infectious Diseases 3: 465–466.

[892] Bonner K, Mwita A, McElroy P, Omari S, Mnzava A, Lengeler C, et al. Design, Implementation, and Evaluation of a National Campaign to Distribute 9 Million Free LLINs to Children under 5 Years in Tanzania. Unpublished manuscript.

[893] Government of Tanzania. Budget estimates.

[894] Nick Brown, NMCP Tanzania, personal communication.

[895] Sharma S, Pathak S. Malaria vaccine: a current perspective. J Vector Borne Dis. 2008 Mar; 45(1): 1–20.

[896] Richards JS, Beeson JG. The future for blood-stage vaccines against malaria. Immunol Cell Biol. 2009 Jul; 87(5): 377–90

[897] Graves PM, Gelband H. Vaccines for preventing malaria (blood-stage). Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006199; Graves PM, Gelband H. Vaccines for preventing malaria (SPf66). Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005966; Graves PM, Gelband H. Vaccines for preventing malaria (pre-erythrocytic). Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006198. DOI: 10.1002/14651858.CD006198; Ogutu et al. Blood stage malaria vaccine eliciting high antigen-specific antibody concentrations confers no protection to young children in Western Kenya. PLoS One. 2009; 4(3): e4708.

[898] Ballou WR. The development of the RTS,S malaria vaccine candidate: challenges and lessons. Parasite Immunol. 2009 Sep; 31(9): 492–500; Vekemans J, Leach A, Cohen J. Development of the RTS,S/AS malaria candidate vaccine. Vaccine. 30 December 2009; 27, supp. 6: G67-G71; Graves PM, Gelband H. Vaccines for preventing malaria (pre-erythrocytic). Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006198. DOI: 10.1002/14651858.CD006198.

[899] Such as: Lell B et al. A randomised trial assessing the safety and immunogenicity of AS01 and AS02 adjuvanted RTS,S malaria vaccine candidates in children in Gabon. PLoS One. 2009 Oct 27; 4(10): e7611; Bojang K et al. Five-year safety and immunogenicity of GlaxoSmithKline's candidate malaria vaccine RTS,S/AS02 following administration to semi-immune adult men living in a malaria-endemic region of The Gambia. Hum Vaccin. Apr 2009; 5(4): 242–7, epub 2009 Apr 22; Sacarlal J, et al. Long-term safety and efficacy of the RTS,S/AS02A malaria vaccine in Mozambican children. J Infect Dis. 2009 Aug 1; 200(3): 329–36; Bejon P et al. Efficacy of RTS,S/AS01E Vaccine against Malaria in Children 5 to 17 Months of Age. New England Jnl of Medicine 2008; 359: 2521–2532; Aponte JJ, et al. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. Lancet 370 (9598): 1543–51 2007.

[900] PG, Milligan PJ. Malaria vaccine: 3 or 6 months' protection? Lancet. 2005 Feb 5–11; 365(9458): 472–3.

[901] Moorthy VS, Ballou WR. Immunological mechanisms underlying protection mediated by RTS,S: a review of the available data. Malar J. 2009 Dec 30; 8(1): 312. Casares S, Brumeanu TD, Richie TL. The RTS,S malaria vaccine. Vaccine. 2010 May 27. [Epub ahead of print]

[902] Malaria vaccine enters phase III clinical trials, Published online 27 May 2009, Nature, doi: 10.1038/news.2009.517

[903] Ibid.

[904] Available at: www.who.int/vaccine_research/diseases/soa_parasitic/en/index4.html

[905] Abdulla S et al. Safety and Immunogenicity of RTS,S/AS02D Malaria Vaccine in Infants. New England Jnl of Medicine 2008; 359: 2521–2532.

[906] Audran R, Lurati-F, Genton B et al. The synthetic Plasmodium falciparum circumsporozoite peptide PfCS102 as a malaria vaccine candidate: a randomised controlled phase I trial. PLoS One. 2009 Oct 2; 4(10): e7304.

[907] Thera MA, Doumbo OK, Coulibaly D et al. Safety and immunogenicity of an AMA-1 malaria vaccine in Malian adults: results of a phase 1 randomised controlled trial. PLoS One. 2008 Jan 23; 3(1): e1465; Thera MA, Doumbo OK, Coulibaly D et al. Safety and immunogenicity of an AMA1 malaria vaccine in Malian children: results of a phase 1 randomised controlled trial. PLoS One. 2010 Feb 4; 5(2): e9041.

[908] Esen M, Kremsner PG, Schleucher R et al. Safety and immunogenicity of GMZ2 – a MSP3-GLURP fusion protein malaria vaccine candidate. Vaccine. 2009 Nov 16; 27(49): 6862–8.

[909] Lusingu JP, Gesase S, Msham S et al. Satisfactory safety and immunogenicity of MSP3 malaria vaccine candidate in Tanzanian children aged 12–24 months. Malar J. 2009 Jul 17; 8: 163.

[910] Arévalo-Herrera M, Chitnis C, Herrera S. Current status of Plasmodium vivax vaccine. Hum Vaccin. Jan 2010; 6(1): 124-32, 2010.

[911] Herrera S, Corradin G, Arévalo-Herrera M. An update on the search for a Plasmodium vivax vaccine. Trends Parasitol. Mar; 23(3): 122-8 2007; Arévalo-Herrera M, Chitnis C, Herrera S. Current status of Plasmodium vivax vaccine. Hum Vaccin. Jan 2010; 6(1): 124–32, 2010.

[912] Tuikue Ndam N, Deloron P. Towards a vaccine against pregnancy-associated malaria. Parasite. 2008 Sep; 15(3): 515–21.

[913] Salanti A et al. Several domains from VAR2CSA can induce Plasmodium falciparum adhesion-blocking antibodies. Malaria Journal 2010, 9: 11.

[914] Gamain B et al. Pregnancy-associated malaria: parasite binding, natural immunity and vaccine development. Int J Parasitol. 2007 Mar; 37(3–4): 273–83.

[915] Such as: Avril M et al. Optimising expression of the pregnancy malaria vaccine candidate, VAR2CSA in Pichia pastoris. Malar J. 2009 Jun 29; 8: 143; Avril et al M. Immunisation with VAR2CSA-DBL5 Recombinant Protein Elicits Broadly Cross-Reactive Antibodies to Placental Plasmodium falciparum-Infected Erythrocytes. Infection and Immunity. May 2010;78/5: 2248–2256.

[916] Srivastava A et al. Full-length extracellular region of the var2CSA variant of PfEMP1 is required for specific, high-affinity binding to CSA. PNAS. March 16 2010; 107/11: 4884–4889; Khunrae P. Full-Length Recombinant Plasmodium falciparum VAR2CSA Binds Specifically to CSPG and Induces Potent Parasite Adhesion-Blocking Antibodies. Journal of Molecular Biology. 2 April 2010; 397/3: 826–834.

[917] Greenwood B. Can malaria be eliminated? Trans R Soc Trop Med Hyg. 2009 Apr; 103 Suppl 1: S2-5; Sutherland CJ. Surface antigens of Plasmodium falciparum gametocytes – A new class of transmission-blocking vaccine targets? Molecular and Biochemical Parasitology. August 2009; 166/2: 93–98; Dinglasan R, Jacobs-Lorena M. Flipping the paradigm on malaria transmission-blocking vaccines. Trends in Parasitology. August 2008; 24/8: 364–370.

[918] Kappe SH et al. That was then but this is now: malaria research in the time of an eradication agenda. Science. 2010 May 14; 328(5980): 862–6; Chowdhury DR et al. A Potent Malaria Transmission Blocking Vaccine Based on Codon Harmonised Full Length Pfs48/45 Expressed in Escherichia coli. PLoS ONE 4(7): e6352; Saul A. Mosquito stage, transmission blocking vaccines for malaria. Curr Opin Infect Dis. 2007 Oct; 20(5): 476–81.

[919] Wu Y et al. Phase 1 Trial of Malaria Transmission Blocking Vaccine Candidates Pfs25 and Pvs25 Formulated with Montanide ISA 51. PLoS ONE. 2008; 3(7): e2636.

[920] Saul A. Mosquito stage, transmission blocking vaccines for malaria. Curr Opin Infect Dis. 2007 Oct; 20(5): 476–81; Targett B, Greenwood B. Malaria vaccines and their potential role in the elimination of malaria. Malaria Journal 2008, 7 (Supp 1): s10.

[921] Richards JS, Beeson JG. The future for blood-stage vaccines against malaria. Immunol Cell Biol. 2009 Jul; 87(5): 377–90.

[922] Tediosi F. Simulation of the cost-effectiveness of malaria vaccines. Malaria Journal 2009, 8: 127 doi: 10.1186/1475-2875-8-127; Penny MA et al. What should vaccine developers ask? Simulation of the effectiveness of malaria vaccines. PLoS One. 2008 Sep 11; 3(9): e3193; Koram KA, Gyan BA. Malaria vaccine development: an endemic country perspective. Hum Vaccin. 2010 Jan; 6(1): 12–6; Moorthy V. Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine. 2007 Jul 9; 25(28): 5115–23; Moree M, Ewart S. Policy Challenges in Malaria Vaccine Introduction, Am. J. Trop. Med. Hyg., 71(2 suppl), 2004, pp. 248–252.

[923] Penny MA et al. What should vaccine developers ask? Simulation of the effectiveness of malaria vaccines. PLoS One. 2008 Sep 11; 3(9): e3193.

[924] Greenwood B and Targett G. Do we still need a malaria vaccine? Parasite Immunol. 2009 Sep; 31(9): 582–6

[925] Takala SL, Plowe CV. Genetic diversity and malaria vaccine design, testing and efficacy: preventing and overcoming 'vaccine resistant malaria'. Parasite Immunol. 2009 Sep; 31(9): 560–73; Guinovart C, Alonso PL. Methods for determining vaccine efficacy and effectiveness and the main barriers to developing a fully deployable malaria vaccine. Am J Trop Med Hyg. 2007 Dec; 77(6 Suppl): 276–81; O'Meara WP, Hall BF, McKenzie FE. Malaria vaccine efficacy: the difficulty of detecting and diagnosing malaria. Malar J. Mar 26; 6: 36 2007; Small DS, Cheng J, Ten Have TR. Evaluating the Efficacy of a Malaria Vaccine. Int J Biostat. 2010 Feb 22; 6(2): Article4; Todryk S, Bejon P. Malaria vaccine development: lessons from the field. Eur J Immunol. 2009 Aug; 39(8): 2007–10; Moorthy V. Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine. 2007 Jul 9; 25(28): 5115–23; Girard M et al. A review of human vaccine research and development: Malaria. Vaccine 25 (2007) 1567–1580.

[926] Sharma S, Pathak S. Malaria vaccine: a current perspective. J Vector Borne Dis. 2008 Mar; 45(1): 1–20

[927] Guinovart C, Alonso PL. Methods for determining vaccine efficacy and effectiveness and the main barriers to developing a fully deployable malaria vaccine. Am J Trop Med Hyg. 2007 Dec; 77(6 Suppl): 276–81

[928] Ogutu B et al. Sustainable development of a GCP-compliant clinical trials platform in Africa: the Malaria Clinical Trials Alliance perspective. Malaria Journal 2010, 9: 103.

[929] Koram KA, Gyan BA. Malaria vaccine development: an endemic country perspective. Hum Vaccin. 2010 Jan; 6(1): 12–6

[930] Moorthy V. Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine. 2007 Jul 9; 25(28): 5115–23

[931] Berndt E et al. Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. Health Economics. 16/5: 491 – 511.

[932] Dr Bhargavi RAO, Imperial College London, assisted in the preparation of this section.

[933] WHO 2009: World Malaria Report 2009. Geneva: WHO.

[934] WHO 2009: World Malaria Report 200. Geneva: WHO.

[935] Patoulliard E, Hanson K, Goodman C. Retail sector distribution chains for malaria treatment in the developing world: a review of the literature. Malaria Journal. 2010; 9: 50.

[936] Webster J, Chanramohan D, Hanson K. Methods for evaluating delivery systems for scaling up malaria control intervention. BMC Health Services Research. 2010; 10(Suppl 1): S8.

[937] WHO. Everybody's business: strengthening health systems to improve health outcomes: WHO's framework for action. 2007. Geneva: WHO.

[938] Moerman F, Lengeler C, Chimumbwa J. Tallisuna A, Erhart A, et al. The contribution of health-care services to a sound and sustainable malaria-control policy. Lancet Infectious Diseases. 2003; 3: 99–102.

[939] Tanner M, Lengeler Ch, Lorenz N. From the efficacy of disease control tools to community effectiveness. . Transactions of the Royal Society of Tropical Medicine and Hygiene 1993; 87: 518–523

[940] Smith T. Beyond efficacy trials: what more do we need to know about the effects of vaccines?' presentation MALVAC June 2008.

[941] Rao B. Barriers to Effectiveness: Artemisinin Combination Therapies and the health system. 2010.

[942] Sktekette R, Siplanyambe N, Chimumbwa J, Banda J, Mohamed A, et al. National Malaria control and scaling up for impact: the Zambia experience through 2006. Am J Trop Med Hyg 79(1), 2008, 45–52.

[943] Sabot OJ, Mwita A, Cohen JM, Ipuge Y, Gordon M, Bishop D, Odhiambo M, Ward L, Goodman C. Piloting the global subsidy: the impact of subsidised artemisinin-based combination therapies distributed through private drug shops in rural Tanzania. PLoS One 2009; 4: e6857.

[944] Chuma J, Abuya T, Memusi D, Juma E, Willis Akhwale, Ntwiga J, Nyandigisi A, Tetteh G, Shretta R, Amin A. Reviewing the literature on access to prompt and effective malaria treatment in Kenya: implications for meeting the Abuja targets. Malaria Journal 2009; 8: 243

[945] Rutebemberwa E, Pariyo G, Peterson S, Tomson G, Kallander K. Utilisation of public or private health care providers by febrile children after user fee removal in Uganda. Malaria Journal. 2009; 8: 45.

[946] Moerman F, Lengeler C, Chimumbwa J, Talisuna A, Ernhart A, Coosemans M, D'Alessandro U. The contribution of health-care services to a sound and sustainable malaria-control policy. Lancet Infectious Disease. 2003; 3: 99–102.

[947] Goodman C, Brieger W, UnwinA, Mills A, Meek S, Greer G. Medicine sellers and malaria treatmen in sub-Saharan Africa: What do they do and how can their practice be improved? Am J Trop Med Hyg. 2007; 77(supl6): 203–218.

[948] Patoulliard E, Hanson K, Goodman C. Retail sector distribution chains for malaria treatment in the developing world: a review of the literature. Malaria Journal 2010, 9: 50

[949] Chuma J, Abuya T, Memusi D, Juma E, Willis Akhwale, Ntwiga J, Nyandigisi A, Tetteh G, Shretta R, Amin A. Reviewing the literature on access to prompt and effective malaria treatment in Kenya: implications for meeting the Abuja targets. Malaria Journal 2009; 8: 243

[950] Noor A, Rage I, Moonen B, Snow R. Health service providers in Somalia: their readiness to provide malaria case management. Malaria Journal 2009 8: 100.

[951] Kangana, Short report.[951] Kangwana BB, Njogu J, Wasunna B, Kedenge SV, Memusi DN, Goodman CA, Zurovac D, Snow RW. Malaria drug shortages in Kenya: a major failure to provide access to effective treatment. American Journal of Tropical Medicine and Hygiene 2009; 80: 737–738.

[952] Patouillard E, Goodman C, Hanson K, Mills A. Can working with the private for-profit sector improve utilisation of quality health services by the poor? A systematic review of the literature. Int J for Equity in Health. Nov 2007.

[953] Abuya T, Fegan G, Amin A, Akhwale W, Noor A, Snow R, Marsh V. Evaluating different dimensions of programme effectiveness for private medicine retailer malaria control interventions in Kenya. PLoS One 5(1). 2010.

[954] Noor A, Rage I, Moonen B, Snow R. Health service providers in Somalia: their readiness to provide malaria case management. Malaria Journal 2009 8: 100

[955] Uzochukwu B, Chiegboka L, Enwereuzo C, Nwosu U, Okorafor D. Examining appropriate diagnosis and treatment of malaria: availability and use of rapid diagnostic tests and demonstrate less quality assurance and adherence to treatment guidelines within the private sector as compared with public sector facilities.

[956] Patouillard E, Goodman C, Hanson K, Mills A. Can working with the private for-profit sector improve utilisation of quality health services by the poor? A systematic review of the literature. Int J for Equity in Health. Nov 2007

[957] Alba S., Hetzel MW, Goodman C, DilipDillip A, Liana J, Mshinda H, Lengeler C: Improvements in access. to malaria treatment in Tanzania after switch to artemisinin combination therapy and the introduction of accredited drug dispensing outlets – a provider perspective. Malaria Journal 2010 , 9: 164.

[958] Uzochukwu B, Chiegboka L, Enwereuzo C, Nwosu U, Okorafor D. Examining appropriate diagnosis and treatment of malaria: availability and use of rapid diagnostic tests and Artemisinin-based combination therapy in public and private health facilities in south east Nigeria. BMC Public Health 2010; 10: 486

[959] Zurovac D, Tibenderana J, Nankabirwa J, Ssekitooleko J, Njogu J et al. Malaria case-management under artemether-lumefantrine treatment policy in Uganda. Malaria Journal 2008, 7: 181.

[960] Crisp N, Gawanas B, Sharp I, Task Force for Scaling up Education and Training for Health Workers, Training the health workforce: scaling up, saving lives. Lancet 2008; 371: 689–91.

[961] Chopra M, Munro S, Lavis J, Vist G, Bennett S. Effects of policy options for human resources for health: an analysis of systematic reviews. Lancet 2008; 371: 668–74.

[962] McCoy D, Bennett S, Witter S, Pond B, Baker B, Gow J et al. Salaries and incomes of health workers in sub-Saharan Africa. Lancet 2008: 371: 675–81.

[963] Crisp N, Gawanas B, Sharp I, Task Force for Scaling up Education and Training for Health Workers, Training the health workforce: scaling up, saving lives. Lancet 2008; 371: 689–91.

[964] Chopra M, Munro S, Lavis J, Vist G, Bennett S. Effects of policy options for human resources for health: an analysis of systematic reviews. Lancet 2008; 371: 668–74.

[965] Rowa Y, Abuya T, Mutemi W, Factors influencing implementation of the ministry of health-led private medicine retailer programmes on malaria in Kenya. BMC 2010; 10: 93

[966] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 80(3) 2009. p. 326–335.

[967] Goodman C, Brieger W, UnwinA, Mills A, Meek S, Greer G. Medicine sellers and malaria treatmen in sub-Saharan Africa: What do they do and how can their practice be improved? Am J Trop Med Hyg 77(supl6) 2007 203–218.

[968] Patouillard E, Goodman C, Hanson K, Mills A. Can working with the private for-profit sector improve utilisation of quality health services by the poor? A systematic review of the literature. Int J for Equity in Health. Nov 2007.

[969] Otten M, Aregawi M, Were W, Karema C. Initial evidence of reduction of malaria cases and deaths in Rwanda and Ethiopia due to rapid scale-up of malaria prevention and treatment. Malaria Journal 2009 8: 14.

[970] Sktekette R, Siplanyambe N, Chimumbwa J, Banda J, Mohamed A, et al. National Malaria control and scaling up for impact: the Zambia experience through 2006. Am J Trop Med Hyg 79(1), 2008, 45–52.

[971] Otten M, Aregawi M, Were W, Karema C. Initiatial evidence of reduction of malaria cases and deaths in Rwanda and Ethiopia due to rapid scale-up of malaria prevention and treatment. Malaria Journal 2009 8: 14.

[972] Teklehaimanot H, Heklehaimanot A, Kiszewski A, Rampao H, Sachs J. Malaria in Sao Tome and Principe: On the brink of elimination after three years of effective antimalarial measures. Am J Trop Med Hyg. 80(1) 2009 pp133–140.

[973] Bhattarai Achuyt, Ali Abdullah Impact of Artemisinin-Based Combination Therapy and Insecticide-Treated Nets on malaria burden in Zanzibar. PLoS Med 4(11): e309. doi: 10.1371/journal.pmed.0040309.

[974] Amin A, Marsh V, Noor A, Ochola S, Snow R. The use of formal and informal curative services in the management of paediatric fevers. Tropical Medicine and International Health. 2003; 8/12): 1143–1152.

[975] Guyatt HL, Snow RW: The management of fevers in Kenyan children and adults in an area of seasonal malaria transmission. Trans R Soc Trop Med Hyg 2004, 98: 111–115.

[976] Noor AM, Zurovac D, Hay SI, Ochola SA, Snow RW: Defining equity in physical access to clinical services using geographical information systems as part of malaria planning and monitoring in Kenya. Trop Med Int Health 2003, 8: 917–926.

[977] Al-Taiar A, Jaffar S, Assabri A, Al-Habori M, Azazy A, et al. Who develops severe malaria? Impact of access to healthcare, socio-economic and environmental factors on children in Yemen: a case-control study. Trop Med Int Health. 2008.

[978] O'Meara W, Noor A, Gatakaa H, Tsofa B, McKenzie F et al. The impact of primary healthcare on malaria morbidity – defining access by disease burden. Trop Med Int Health 2009 Jan 14(1): 29–35.

[979] Noor AM, Zurovac D, Hay SI, Ochola SA, Snow RW: Defining equity in physical access to clinical services using geographical information systems as part of malaria planning and monitoring in Kenya. Trop Med Int Health 2003, 8: 917–926.

[980] Greenwood BM, Bojang K, Whitty CJ, Targett GA: Malaria. Lancet 2005, 365: 1487–1498

[981] O'Meara W, Noor A, Gatakaa H, Tsofa B, McKenzie F et al. The impact of primary healthcare on malaria morbidity – defining access by disease burden. Trop Med Int Health 2009 Jan 14(1): 29–35.

[982] Chuma J, Abuya T, Memusi D, Juma E, Willis Akhwale, Ntwiga J, Nyandigisi A, Tetteh G, Shretta R, Amin A. Reviewing the literature on access to prompt and effective malaria treatment in Kenya: implications for meeting the Abuja targets. Malaria Journal 2009; 8: 243

[983] Patoulliard E, Hanson K, Goodman C. Retail sector distribution chains for malaria treatment in the developing world: a review of the literature. Malaria Journal 2010, 9: 50.

[984] Patoulliard E, Hanson K, Goodman C. Retail sector distribution chains for malaria treatment in the developing world: a review of the literature. Malaria Journal 2010, 9: 50

[985] More information available at: deliver.jsi.com/dhome

[986]Orton L, Barnish G. Unit-dose packaged drugs for treating malaria. Cochrane Database Syst Rev. 2005, Issue 2. Art. No.: CD004614. DOI: 10.1002/14651858.CD004614.pub2.

[987] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 80(3) 2009. pp326–335.

[988] Patouillard E, Goodman C, Hanson K, Mills A. Can working with the private for-profit sector improve utilisation of quality health services by the poor? A systematic review of the literature. Int J for Equity in Health. Nov 2007.

[989] Pongtavornpinyo W, Yeung S, Hastings I, Dundorp A, Day N, White N. Spread of anti-malarial drug resistance: Mathematical model with implications for ACT drug policies. Malaria Journal 2008; 7: 299.

[990] Pongtavornpinyo W, Yeung S, Hastings I, Dundorp A, Day N, White N. Spread of anti-malarial drug resistance: Mathematical model with implications for ACT drug policies. Malaria Journal 2008; 7: 299.

[991] Dange C, Kafle K, Karke S, Rajubhandari V, Humagain B. Effect of regulator intervenitn on drug availability in Nepal. 2004: Proceedings of International Conferences on Improving the Use of Medicines.

[992] Goodman C, Brieger W, UnwinA, Mills A, Meek S, Greer G. Medicine sellers and malaria treatmen in sub-Saharan Africa: What do they do and how can their practice be improved? Am J Trop Med Hyg 77(supl6) 2007 203–218.

[993] Enserik M. Malaria's drug miracle in danger. Science 2010. 328. p. 844–846.

[994] Beer N, Ali AS, Rotllant G, Abass AK, Omari RS, Al-mafazy AH, et al: Adherence to artesunate-amodiaquine combination therapy for uncomplicated malaria in children in Zanzibar, Tanzania. Trop Med Int Health 2009, 14: 1-9.

[995] Zurovac D, Njogu J, Akhwale WS, Hamer DH, Snow RW: Translation of artemether-lumefantrine treatment policy into paediatric clinical practice: an early experience from Kenya. Trop Med Int Health 2008, 13: 99-107

[996] Zurovac D, Tibenderana JK, Nankabirwa J, Ssekitooleko J, Njogu JN, Rwakimari JB, Meek S, Talisuna A, Snow RW: Malaria case-management under artemether-lumefantrine treatment policy in Uganda. Malar J 2008, 7: 181

[997] Wasunna B, Zurovac D, Bruce J, Jones C, Webster J, Snow RW. Health worker performance in the management of paediatric fevers following in-service training and exposure to job aids in Kenya. Malaria Journal 2010, 9: 261

[998] Amaral J, Victora C. The effect of training in Integrated Management of Childhood Illness (IMCI) on the performance and healthcare quality of pediatric healthcare workers: a systematic review. Rev. Bras. Saude Mater. Infant. Jan/Mar 2008; 8/2 Recife.

[999] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 2009; 80(3): 326–335.

[1000] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 2009; 80(3): 326–335.

[1001] Huicho L, Scherpbier RW, Nkowane AM, Victora CG: How much does quality of child care vary between health workers with differing durations of training? An observational multicountry study. Lancet. 2008; 372(9642): 910–916.

[1002] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 2009; 80(3): 326–335.

[1003] WHO/AFRO. Making an impact on child health: a framework for scaling up RBM and IMCI implementation in countries. Harare. January 2001.

[1004] Patouillard E, Goodman C, Hanson K, Mills A. Can working with the private for-profit sector improve utilisation of quality health services by the poor? A systematic review of the literature. Int J for Equity in Health. Nov 2007.

[1005] Bhutta Z, Lassi Z, Pariyo G. and Huicho, L. Global Experience of community health workers for delivery of health related millennium development goals: a systematic review, country case studies, and recommendations for integration into national health systems. 2010. Geneva: WHO/Global Health Workforce Alliance.

[1006] Haines A, Sanders D, Lehmann U, Rowe AK, Lawn JE, Jan S, Walker DG, Bhutta Z. Achieving child survival goals: potential contribution of community health workers. Lancet 2007; 369: 2121–2131

[1007] Staedke SG, Mwebaza N, Kamya MR, Clark TD, Dorsey G, Rosenthal PG, Whitty CJ. Home Management of malaria with artemether-lumefantrine compared with standard care in urban Ugandan children: a randomised controlled trial. Lancet 2009; 373: 1623–1631

[1008] Uneke C. Impact of home management of Plasmodium falciparum malaria on childhood malaria control in sub-Saharan Africa. 2009. Tropical biomedicine 26(2): 182–199.

[1009] Hopkins H, Talisuna A, Whitty C, Staedke S. Impact of home-based management of malaria on health outcomes in Africa: a systematic review of the evidence. Malaria Journal 2007, 6: 134.

[1010] Walt G. Commentary: lay health workers in primary and community health care. International Journal of Epidemiology 2005; 34; 1251

[1011] Yasuoka J, Poudel KC, Poudel-Tandukar K, Nguon C, Socheat D, Masamine J. Assessing the quality of service of village malaria workers to strengthen community-based malaria control in Cambodia. Malaria Journal 2010; 9: 109

[1012] Yeboah-Antwi K, Pilingana P, Macleod WB, Semrau K, Siazeele K, et al. Community Case Management of Fever Due to Malaria and Pneumonia in Children Under Five in Zambia: A Cluster Randomised Controlled Trial. PLoS Med 2010; 7(9): e1000340. doi: 10.1371/journal.pmed.1000340.

[1013] Onwujekwe O, Uzochukwu B, Ojukwu J, Dike N, Shu E. Acta Trop 2007; 101 (2): 95–105 Feasibility of a community health worker strategy for providing near and appropriate treatment of malaria in southeast Nigeria: an analysis of activities, costs and outcomes. BMC Public Health 2010; 10: 486

[1014] Bhutta Z, Lassi Z, Pariyo G. and Huicho, L. Global Experience of community health workers for delivery of health related millennium development goals: a systematic review, country case studies, and recommendations for integration into national health systems. 2010. Geneva: WHO/Global Health Workforce Alliance.

[1015] Chopra M, Munro S, Lavis J, Vist G, Bennett S. Effects of policy options for human resources for health: an analysis of systematic reviews. Lancet 2008; 371: 668–74.

[1016] Njogu J, Akhwale W, Hamer D, Zurovac D. Health facility and health worker readiness to deliver new national treatment policy for malaria in Kenya. East African Medical Journal. 85(5) 5 May 2008.

[1017] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 80: 3 2009. 326–335.

[1018] Meek S, Hill J, Webster J. The evidence base for interventions to reduce malaria mortality in low and middle-income countries. Working Group 5 of CMH. 2001. Commission on Macroeconomics and Health.

[1019] Crisp N, Gawanas B, Sharp I, Task Force for Scaling up Education and Training for Health Workers, Training the health workforce: scaling up, saving lives. Lancet 2008; 371: 689–91.

[1020] Lewin, S, Babigumira S, Bosch-Capblanch W et al. Lay health workers in primary and community healthcare: human resource implications from a systematic review of trials. Cape Town, South Africa: MRC, South Africa 2006.

[1021] Southall D, Cham M, Sey O. Health workers lost to international bodies in poor countries. Lancet 376(9740) 498–99.

[1022] Afenyadu et al. Improving access to early treatment of malaria: a trial with primary school teachers as care providers. Trop Med Int Health. 2005 Oct; 10(10)

[1023] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 80: 3 2009. 326–335.

[1024] Eke, Enwereji. Diagnosis of malaria by community health workers in Nigeria. East Afr J Public Health. 2009 Apr; 6(1): 15–6.

[1025] Kamanga et al. Rural health centres, communities and malaria case detection in Zambia using mobile telephones: a means to detect potential reservoirs of infection in unstable transmission conditions. Malar J. 2010 Apr 15; 9: 96

[1026] Crisp N, Gawanas B, Sharp I, Task Force for Scaling up Education and Training for Health Workers, Training the health workforce: scaling up, saving lives. Lancet 2008; 371: 689–91.

[1027] Bosch-Capblanch X, Garner P. Systematic review: primary health supervision in developing countries. 2008 13(3) 369–383.

[1028] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 80: 3 2009. 326–335.

[1029] Ibid.

[1030] McCoy D, Bennett S, Witter S, Pond B, Baker B, Gow J et al. Salaries and incomes of healthworkers in sub-Saharan Africa. Lancet 2008: 371: 675–81.

[1031] Chopra M, Munro S, Lavis J, Vist G, Bennett S. Effects of policy options for human resources for health: an analysis of systematic reviews. Lancet 2008; 371: 668–74.

[1032] Njogu J, Akhwale W, Hamer D, Zurovac D. Health facility and health worker readiness to deliver new national treatment policy for malaria in Kenya. East African Medical Journal. 85(5) 5 May 2008.

[1033] Noor A, Rage I, Moonen B, Snow R. Health service providers in Somalia: their readiness to provide malaria case-management. Malaria Journal 2009, 8: 100.

[1034] McCoy D, Bennett S, Witter S, Pond B, Baker B, Gow J et al. Salaries and incomes of healthworkers in sub-Saharan Africa. Lancet 2008: 371: 675–81.

[1035] Smith L, Jones C, Meek S, Webster J. Review: Provider practice and user behaviour interventions to improve prompt and effective treatment of malaria: Do we know what works? Am J Trop Med Hyg. 80: 3 2009. 326–335.

[1036] Kabene SM, Orchard C Howard JM, Soriano MA, Leduc R. The importance of human resources management in health care: a global context. Human Resources for Health 2006; 4: 20.

[1037] WHO: World Health Report 2000. Health Systems: Improving Performance. 2000. Geneva: WHO.

[1038] Ibid.

[1039] Kabene SM, Orchard C Howard JM, Soriano MA, Leduc R. The importance of human resources management in health care: a global context. Human Resources for Health 2006; 4: 20.

[1040] Ibid.

[1041] Bremen JG, Allilio M, Mills A. Conquering the Intolerable Burden of Malaria: What's New, What's Needed: A Summary. Am J Trop Med 2004; 71(Suppl 2): 1–15

[1042] De Savigny D, Binka F. Monitoring the Future Impact of Malaria Burden in Sub-Saharan Africa. AM J Trop Med 2004; 71(Suppl 2); 224–231

[1043] Agyepong I, Kengeya-Kayondo J, 2004. Providing practical estimatesof the malaria burden for health planners in resourcepoor communities. Am J Trop Med Hyg 71 (Suppl 2): 162–167.

[1044] Bremen JG, Allilio M, Mills A. Conquering the Intolerable Burden of Malaria: What's New, What's Needed: A Summary. Am J Trop Med 2004; 71(Suppl 2): 1–15

[1045] De Savigny D, Binka F. Monitoring the Future Impact of Malaria Burden in Sub-Saharan Africa. AM J Trop Med 2004; 71(Suppl 2); 224–231

[1046] Agyepong I, Kengeya-Kayondo J, 2004. Providing practical estimates of the malaria burden for health planners in resource poor communities. Am J Trop Med Hyg 71 (Suppl 2): 162–167.

[1047] Larson BA, Amin AA, Noor AM, Zurovac D, Snow RW: The cost of uncomplicated childhood fevers to Kenyan households: implications for reaching international access targets. BMC Public Health 2006, 6: 314

[1048] Chuma J, Abuya T, Memusi D, Juma E, Willis Akhwale, Ntwiga J, Nyandigisi A, Tetteh G, Shretta R, Amin A. Reviewing the literature on access to prompt and effective malaria treatment in Kenya: implications for meeting the Abuja targets. Malaria Journal 2009; 8: 243

[1049] Cohen J, Sabot O, Sabot K, Gordon M, Gorss I, Bishop I, et al. A pharmacy too far? Equity and spatial distribution of outcomes in the delivery of subsidised artemisinin-based combination therapies through private drug shops. BMC Health Services Research 2010, 10 (Suppl1): S6.

[1050] Laxminarayan R, Gelband H. A global subsidy: Key to affordable drugs for malaria? Health Affairs: Jul/Aug 2009; 28,4. 949–961.

[1051] Sabot OJ, Mwitwa A, Cohen JM, Ipuge Y, Gordon M, Bishop D, et al. Piloting the global subsidy: the impact of subsidised Artemisinin-based combination therapies distributed through private drug shops in rural Tanzania. Plos One 2009; 2 (4): e6857

[1052] Matowe L, Adeyi O. The quest for universal access to effective malaria treatment: how can the AMFm contribute?.Malaria Journal 2010 9: 274

[1053] Steketee RW, Eisele TP (2009) Is the Scale Up of Malaria Intervention Coverage Also Achieving Equity? PLoS ONE 4(12): e8409. doi: 10.1371/journal.pone.0008409

[1054] Barat L, Plamer N, Basu S, Worrall E, Hanson K, Mills A. Do malaria control interventions reach the poor? A view through the equity lens. Am J Trop Med Hyg 71(Suppl 2), 2004: 174–178.

[1055] Steketee RW, Eisele TP Op. Cit.

[1056] Gwatkin D. Millennium Development Goals for Health? An Inquiry into the possibility of progress that fails to reach the poor. World Bank, HNP Discussion paper. 2002.

[1057] Nathan R, Masanja H, Mshinda H, Schellenberg J, Savingny D, Lengeler C et al. Mosquito nets and the poor: can social marketing redress inequities in access? Trop Med and Int Health, 2004, 9(10): 1121–1126.

[1058] Schellenberg J, Victoria C, Mushi A, De Savigny D, Schellenberg D, Mshinda H et al. Inequities among the very poor: health care for children in rural southern Tanzania. Lancet. 2003; 361: 561–564.

[1059] Barat L, Plamer N, Basu S, Worrall E, Hanson K, Mills A. Do malaria control interventions reach the poor? A view through the equity lens. Am J Trop Med Hyg. 2004; 71(Suppl 2): 174–178.

[1060] Steketee RW, Eisele TP Op. Cit.

[1061] Worral E, Basu S, Hanson K. Is malaria a disease of poverty? A review of the literature. Trop Med and Int Health 2005. 10(10) 1047–1059.

[1062] Barat L et al. Op cit.

[1063] Steketee RW, Eisele TP. Is the Scale Up of Malaria Intervention Coverage Also Achieving Equity? PLoS ONE 2009; 4(12): e8409. doi: 10.1371/journal.pone.0008409

[1064] Webster J, Lines J, Bruce J, Armstrong Schellenberg JR, Hanson K. Which delivery systems reach the poor? A review of equity of coverage of ever-treated nets, never-treated nets, and immunisation to reduce child mortality in Africa. Lancet Infect Dis 2005; 5: 709–717.

[1065] Noor AM, Amin AA, Akhwale WS, Snow RW. Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children. PLoS Med 2007; 4: e255..

[1066] Grabowsky M, Farrell N, Hawley W, Chimumbwa J, Hoyer S, et al. Integrating insecticide-treated bednets into a measles vaccination campaign achieves high, rapid and equitable coverage with direct and voucher-based methods. Trop Med Int Health 2005; 10: 1151–1160..

[1067] Matovu F, Goodman C, Wiseman V, Mwengee W. How equitable is bed net ownership and utilisation in Tanzania? A practical application of the principles of horizontal and vertical equity. Malar J 2009; 8: 109.

[1068] Curtis C, Maxwell C, Lemnge M, Kilama WL, Steketee RW, et al. Scaling-up coverage with insecticide-treated nets against malaria in Africa: who should pay? Lancet Infect Dis 2003; 3: 304–307..

[1069] Steketee RW, Eisele TP. Is the Scale Up of Malaria Intervention Coverage Also Achieving Equity? PLoS ONE 2009; 4(12): e8409. doi: 10.1371/journal.pone.0008409

[1070] Steketee RW, Eisele TP. Is the Scale Up of Malaria Intervention Coverage Also Achieving Equity? PLoS ONE 2009; 4(12): e8409. doi: 10.1371/journal.pone.0008409

[1071] Webster J, Hill J, Lines J, Hanson K. Delivery systems for insecticide treated and untreated mosquito nets in Africa: categorisation and outcomes achieved. Health Policy Plan 2007; 22: 277–293..

[1072] Noor AM, Amin AA, Akhwale WS, Snow RW. Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children. PLoS 2007; Med 4: e255...

[1073] Noor AM, Mutheu JJ, Tatem AJ, Hay SI, Snow RW (2009) Insecticide-treated net coverage in Africa: mapping progress in 2000–07. Lancet 373: 58–67.

[1074] Ibid.

[1075] Nathan R, Masanja H, Mshinda H, Schellenberg J, Savingny D, Lengeler C et al. Mosquito nets and the poor: can social marketing redress inequities in access? Trop Med and Int Health, 2004, 9(10): 1121–1126.

[1076] Roll Back Malaria Partnership, 2008. Global malaria action plan. Available at: www.rbm.who.int/gmap/index.html.

[1077] WHO World Malaria Report 2009. World health Organisation: geneva. 2009.

[1078] Muula, AS, Rudatsibira, E, Siziya, S, Mataya, RH Estimated financinal and human resources requirements for the treatment of malaria in Malawi; Malar J 2007, 6: 168

[1079] Laxminarayan et al. A global subsidy: key to affordable drugs for malaria? Hlth Aff. 2009 Jul–Aug; 28(4)

[1080] Watts 'An extra dollar can go a long way'. BMJ 2004: 1126 13 Nov

[1081] White NJ. Qinghaosu (artemisinin): the price of success. Science. 2008 Apr 18; 320(5874): 330–4.

[1082] WHO. World Malaria Report 2009. Geneva: WHO.

[1083] Okell LC, Drakeley CJ, Bousema T, Whitty CJ, Ghani AC. Modelling the impact of artemisinin combination therapy and long-acting treatments on malaria transmission intensity. PLoS Med. 2008 Nov 25; 5(11): e226;

[1084] White NJ. The role of anti-malarial drugs in eliminating malaria. Malar J. 2008 Dec 11; 7 Suppl 1: S8.

[1085] Dundorp A, Yeung S, White L, Nquon C, Day N, Socheat D. et al. Artemesinin resistance: current status and scenarios for containment Nature reviews: Microbiology. April 2010; 8: 272–280.

[1086] Noedl H, Se Y, Schaecher K, Smith BL. Socheat, Fukuda M. Evidence of artemisinin-resistant malaria in Western Cambodia. N Engl J Med 2008; 359: 2619–20.

[1087] Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med. 2009; 361: 455–67.

[1088] Carrara VI, Zwang J, Ashley EA, Price RN, Stepniewska K, Barends M, Brockman A, Anderson T, McGready R, Phaiphun L, Proux S, van Vugt M, Hutagalung R, Lwin KM, Phyo AP, Preechapornkul P, Imwong M, Pukrittayakamee S, Singhasivanon P, White NJ, Nosten F. Changes in the treatment responses to artesunate-mefloquine on the northwestern border of Thailand during 13 years of continuous deployment. PLoS One. 2009; 4(2): e4551.

[1089] WHO (2010). Progress on the containment of artemisinin tolerant malaria parasites in South-East Asia (ARCE) Initiative. 28 April 2010.

[1090] Plowe, C. The evolution of drug resistant malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009; 1035, S11–14.

[1091] Kublin J, Cortese JF, Mbindo Njunju E et al. Reemergence of Chloroquine-Sensitive Plasmodium falciparum Malaria after Cessation of Chloroquine Use in Malawi. J Infectious Diseases. Jun 15, 2003; 187/12: 1870–1875.

[1092] Mita T, Kaneko A, Lum KJ et al. Recovery of chloroquine sensitivity and low prevalence of the plasmodium falciparum chloroquine resistance transporter gene mutation k76t following the discontinuance of chloroquine use in Malawi. Am. J. Trop. Med. Hyg. 2003; 68(4): 413–415.

[1093] Roper C, Pearce R, Nair S, Sharp B, Nosten F, Anderson T. Intercontinental spread of pyrimethamine-resistant malaria. Science. 2004 Aug 20; 305 (5687): 1124.

[1094] Pearce RJ, Pota H, Evehe MS, Bâ el-H, Mombo-Ngoma G, Malisa AL, et al. Multiple origins and regional dispersal of resistant dhps in African Plasmodium falciparum malaria. PLoS Med. 2009 Apr 14; 6(4): e1000055.

[1095] Clyde DF. Drug resistance of malaria parasites in Tanzania. East Afr Med J. 1966 Oct; 43(10): 405–8.

[1096] Roper C, Pearce R, Bredenkamp B, Gumede J, Drakeley C, Mosha F, et al. Antifolate antimalarial resistance in southeast Africa: a population-based analysis. Lancet. 2003 Apr 5; 361(9364): 1174–81.

[1097] Clyde DF, Dawkins AT Jr, Heiner GG, McCarthy VC, Hornick RB. Characteristics of four new drug-resistant strains of Plasmodium falciparum from South-East Asia. Mil Med. 1969 Sep; 134(10): 787–94.

[1098] White NJ. Antimalarial drug resistance. J Clin Invest. 2004 Apr; 113(8): 1084–92.

[1099] Dundorp AM, Yeung S, White L, Nguon C, Day N, Socheat D, et al. Artemisinin resistance: current status and scenarios for containment. Nature Reviews Microbiology. April 2010; 8: 272–280.

[1100] Mackinnon M, Marsh K. The selection landscape of malaria parasites. Science. 14 May 2010; 328: 866–871.

[1101] White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, Kokwaro G, Ouma J, Hien TT, Molyneux ME, Taylor TE, Newbold CI, Ruebush TK 2nd, Danis M, Greenwood BM, Anderson RM, Olliaro P. Averting a malaria disaster. Lancet. 1999 Jun 5; 353(9168): 1965–7.

[1102] Peters W. Prevention of drug resistance in rodent malaria by the use of drug mixtures. Bull World Health Organ. 1974; 51(4): 379–83.

[1103] Pongtavornpinyo W, Yeung S, Hastings I, Dundorp A, Day N, White N. Spread of anti-malarial drug resistance: Mathematical model with implications for ACT drug policies. Malaria Journal 2008; 7: 299.

[1104] Dundorp AM, Yeung S, White L, Nguon C, Day N, Socheat D, et al. Artemisinin resistance: current status and scenarios for containment. Nature Reviews Microbiology. April 2010; 8: 272–280.

[1105] Plowe, C. The evolution of drug resistant malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009; 1035, S11-14; Pearce R, Pota H, Evehe MS, Ba E, Mombo-Ngoma G, Malisa A et al. Multiple origins and regional dispersal of resistant dhps in African Plasmodium falciparum malaria. Plos Medicine 2009; 6(4).

[1106] Pearce R, Pota H, Evehe MS, Ba E, Mombo-Ngoma G, Malisa A et al. Multiple origins and regional dispersal of resistant dhps in African Plasmodium falciparum malaria. Plos Medicine 2009; 6(4).

[1107] Enserink M. Malaria's drug miracle in danger. Science 2010; 328: 844–846.

[1108] www.malariaconsortium.org/resistance/the_containment_project.htm

[1109] WHO (2010). Progress on the containment of artemisinin tolerant malaria parasites in South-East Asia (ARCE) Initiative. 28 April 2010.

[1110] Maude RJ, Pontavornpinyo W, Saralamba S, Aguas R, Yeung S, Dondorp AM et al. The last man standing is the most resistant: eliminating artemisinin-resistant malaria in Cambodia. Malar J. 2009; 8: e31.

[1111] Enserink M. Malaria's drug miracle in danger. Science 2010; 328: 844–846.

[1112] Plow C, Rober C, Barnwell J, Happi C, Joshi H, Mbacham W, et al. World Antimalarial Resistance Network (WARN) III: Molecular markers for drug resistant malaria. Malaria Journal 2007; 6: 121.

[1113] Humphreys GS, Merinopoulos I, Ahmed J et al. Amodiaquine and artemether-lumefantrine select distinct alleles of the Plasmodium falciparum mdr1 gene in Tanzanian children treated for uncomplicated malaria. Antimicrob Agents Chemother 2007; 51(3):991-7.

[1114] Kelly-Hope L, Ranson H, Hemingway, J. Lessons from the past: managing insecticide resistance in malaria control and eradication programmes. Lancet Infectious Disease 2008; 8: 387–89.

[1115] WHO, Regional Office for Africa. Atlas of insecticide resistance in malaria vectors of the World Health Organization African region. African Network for vector resistance. October 2005.

[1116] Nauen, R. Insecticide resistance in public health pests: A challenge for effective vector control. Public Health Journal 2006; 18: 9–15.

[1117] Chapin G, Wasserstrom R. Agricaulrual production and malaria resurgence in Central America and India. Nature 1981; 293: 181–185.

[1118] Kelly-Hope L, Ranson H, Hemingway, J. Lessons from the past: managing insecticide resistance in malaria control and eradication programmes. Lancet Infectious Disease 2008; 8: 387–89.

[1119] Nauen, R. Insecticide resistance in disease vectors of public health importance. Pest Management Science 2007; 63: 628–633.

[1120] Ranson H, Abdallah H, Badolo A et al. Insecticide resistance in Anopheles gambiae: data from the first year of a multi-country study highlight the extent of the problem. Malaria Journal 2009, 8: 299.

[1121] Nauen, R. Insecticide resistance in disease vectors of public health importance. Pest Management Science 2007; 63: 628–633.

[1122] Ranson H et al. Op cit.

[1123] Nauen R. Insecticide resistance in disease vectors of public health importance. Pest Management Science 2007; 63: 628–633.

[1124] Ranson H et al. Op cit.

[1125] WHO Regional Office for Africa. Atlas of insecticide resistance in malaria vectors of the WHO African region. African Network for vector resistance. October 2005

[1126] Coleman M, Sharp B, Seochara I, Hemmingway J. Developing an evidence-based decision support system for rational insecticide choice in the control of African malaria vectors. Journal of medical entomology 2006; 43(4): 663–668

[1127] Ranson H, N'Guessan RN, Lines J et al. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends in Parasitology 2010. Article in press: doi: 10.1016/j.pt.2010.08.004.

[1128] Nauen, R. Insecticide resistance in disease vectors of public health importance. Pest Management Science 2007; 63: 628–633.

[1129] Wood OR, Hanrahan S, Coetzee M et al. Cuticle thickening associated with pyrethroid resistance in the major malaria vector Anopheles funestus. Parasites and Vectors 2010, 3: 67.

[1130] Ranson H, N'Guessan RN, Lines J et al. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends in Parasitology 2010. Article in press: doi: 0.1016/j.pt.2010.08.004.

[1131] Ranson H, N'Guessan RN, Lines J et al. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends in Parasitology 2010. Article in press: doi: 0.1016/j.pt.2010.08.004.

[1132] WHO, Global Malaria Programme. Development of a Global Strategy against insecticide resistance in malaria vectors.

[1133] Rodriguez A, Penilla R, Rodriguez M, Hemingway J. A Mexican trial shows sustainability. Public Health Journal 2006; 18.

[1134] Oxborough M, Mosha FW, Matowo J, etal. Mosquitoes and bednets: testing the spatial positioning of insecticide on nets and the rationale behind combination insecticide treatments. Annals of Tropical Medicine & Parasitology 2008; 102: 717–727.

[1135] Asidi AN, N'Guessan R, Koffi AA, et al. Experimental hut evaluation of bed nets treated with an organophosphate (chlorpyrifos methyl) or a pyrethroid (lambdacyhalothrin) alone and in combination against insecticide resistant *A.gambiae* and *C.quinquefasciatus* mosquitoes. Malaria Journal 2005; 4: 25.

[1136] Tungu P, Magesa S, Maxwell C, et al. Evaluation of PermaNet 3.0 a deltamethrin-PBO combination net against *Anopheles gambiae* and pyrethroid resistant *Culex quinquefasciatus* mosquitoes: an experimental hut trial in Tanzania. Malaria Journal 2010; 9:21.

[1137] N'Guessan R, Asidi A, Boko P, et al. An experimental hut evaluation of PermaNet® 3.0, a deltamethrin–piperonyl butoxide combination net, against pyrethroid-resistant Anopheles gambiae and Culex quinquefasciatus mosquitoes in southern Benin. Transactions of the Royal Society of Tropical Medicine and Hygiene 2010; 104: 758–765.

[1138] Tungu P, Magesa S, Maxwell C, Malima R, Masue D, Sudi W, et al. Evaluation of PermaNet 3.0 a deltamethrin-PBO combination net against Anopheles gambiae and pyrethroid resistant Culex quinquefasciatus mosquitoes: an experimental hut trial in Tanzania. Malaria Journal 2010; 9: 21

[1139] Pennetier C, Corbel V, Hougard J. Combination of a non-pyrethroid insecticide and a repellent: a new appreoach for controlling knockdown-reisstant mosquitoes. Am J Trop Med Hyg 2005; 72: 739–744

[1140] Pennetier C, Costantini C, Corbal V, Licciardi S, Dabire R, Lapied B, et al. Mixture for controlling insecticide resistant malaria vectors. Emerging Infectious Diseases. 2008; (14)11: 1707–14

[1141] WHO, Global Malaria Programme. Development of a Global Strategy against insecticide resistance in malaria vectors. www.rollbackmalaria.org/partnership/wg/wg_itn/.../5winwgSession4-3.pdf

[1142] R N'Guessan, P Boko, A Odjo, B Knols, M Akogbeto, M Rowland. Control of pyrethroid-resistant Anopheles gambiae and Culex quinquefasciatus mosquitoes with chlorfenapyr in Benin. Tropical Medicine and International Health 2009; 14:389–395.

[1143] Djenontin A, Chabi J, Baldet T, Irish S, Pennetier C, Hougard J et al. Managing insectide resistance in malaria vectors by combining carbamate-treated plastic wall sheeting with pyrethroid-treated bed nets. Malaria Journal October 2009; 8: 233

[1144] Current status of pyrethroid resistance in African malaria vetors and its operational significance. (Lines J, upublished, WHO)

[1145] N'Guessan R, Corbel V, Akogbéto M, Rowland M. Reduced Efficacy of Insecticide Treated Nets and Indoor Residual Spraying for Malaria Control in Pyrethroid Resistance Area, Benin. Emerging Infectious Diseases 2007; 13: 199–206.

[1146] Henry M, Assi S, Rogier C, Dossou-Yovo J, Chandre F, Guillet P et al. Protective efficacy of lambda-cyhalorhrin treated nets in Anopheles gambiae pyrethroid resitance areas of Cote d'Ivoire. Am J Trop Med Hyg 2005, 73(5): 859–864.

[1147] Corbel V, N'Guessan RN, Brengues C, et al. Multiple insecticide resistance mechanisms in *Anopheles gambiae* and *Culex quinquefasciatus* from Benin, West Africa. Acta Tropica 2007; 101(3): 207-216 .

[1148] Pennetier C, Costantini C, Corbal V, Licciardi S, Dabire R, Lapied B, et al. Mixture for controlling insecticide resistant malaria vectors. Emerging Infectious Diseases. 2008; (14)11: 1707–14

[1149] Zaim M, Guillet P. Altnerative insecticides: an urgent need. Trends Parasitol. 2002; 18: 161–3

[1150] IVCC Business Plan: A global partnership. Working together to save lives. July 2009.

[1151] Rowland M, N'Guessan R. Pyrethroid resistance in the African malaria vector *Anopheles gambiae* and potential of alternative insecticides for indoor residual spraying and use on mosquito nets. In: Advances in human vector control, Marshall Clark J, editor. American Chemical Society Symposium Series 1014; 2009. p. 13-26.

[1152] N'Guessan R, Boko P, Odjo A, et al. Chlorfenapyr: a pyrrole insecticide for the control of pyrethroid or DDT resistant *Anopheles gambiae* (Diptera: Culicidae) mosquitoes. Acta Tropica 2007; 102:69-79.

[1153] N'Guessan R, Corbel V, Bonnet J, et al. Evaluation of indoxacarb, an oxadiazine insecticide for the control of pyrethroid resistant *Anopheles gambiae* s.s. (Diptera: Culicidae). J. Medical Entomology 2007; 44: 270-276.

[1154] Mosha FW, Lyimo IN, Oxborough RM, et al. Experimental hut evaluation of the pyrrole insecticide chlorfenapyr on bed nets for the control of Anopheles arabiensis and Culex quinquefasciatus. Tropical Medicine and International Health 2008; 13: 644–652.

[1155] 113. R N'Guessan, P Boko, A Odjo, B Knols, M Akogbeto, M Rowland (2009). Control of pyrethroid-resistant Anopheles gambiae and Culex quinquefasciatus mosquitoes with chlorfenapyr in Benin. Tropical Medicine and International Health 2009; 14: 389–395.

[1156] N'Guessan R, Boko P, Odjo A, et al. Control of pyrethroid and DDT-resistant *Anopheles gambiae* by application of indoor residual spraying or mosquito nets treated with a long-lasting organophosphate insecticide, chlorpyrifos-methyl. Malaria Journal 2009; 9, 44.

[1157] Ranson H, N'Guessan RN, Lines J et al. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends in Parasitology 2010. Article in press: doi: 10.1016/j.pt.2010.08.004.

[1158] Kelly-Hope L, Ranson H, Hemingway, J. Lessons from the past: managing insecticide resistance in malaria control and eradication programmes. Lancet Infectious Disease 2008; 8: 387–89

[1159] This section is based on an edited and updated version of J Lines, CJM Whitty, K Hanson. Prospects for Eradication and Elimination of Malaria: a technical briefing for DFID. 2007. DFID Health Resource Centre.

[1160] Mendis, K., Rietveld, A., Warsame, M., Bosman, A., Greenwood, B. and Wernsdorfer, W. H. (2009), From malaria control to eradication: The WHO perspective. Tropical Medicine and International Health, 14: 802–809. doi: 10.1111/j.

[1161] Richard G A Feachem, Allison A Phillips, Jimee Hwang, Chris Cotter, Benjamin Wielgosz, Brian M Greenwood, Oliver Sabot, Mario Henry Rodriguez, Rabindra R Abeyasinghe, Tedros Adhanom Ghebreyesus, Robert W Snow. Shrinking the malaria map: progress and prospects. Lancet 2010.

[1162] Moonen B, Cohen JM, Snow RW et al. Operational strategies to achieve and maintain malaria elimination. 376/9752: 1592–1603.

[1163] Greenwood BM, Fidock DA, Kyle DE et al. Malaria: progress, perils, and prospects for eradication. J Clin Invest. 2008 April 1; 118(4): 1266–1276; Ferguson HM, Dornhaus A, Beeche A. Ecology: A Prerequisite for Malaria Elimination and Eradication. PLoS Med 7(8): e1000303.

[1164] The Lancet 2010; 376 (9752); 1566-1615.

[1165] Gramiccia G and Beales PF. The recent history of malaria control and eradication pp1335–1378 in Principles and Practice of Malariology, eds. WH Wernsdorfer and Sir I MacGregor, Churchill Livingstone Edinburgh; 1988.

[1166] Barrett S (2004) Eradication versus control: the economics of global infectious disease policies. Bulletin of the World Health Organization 82 639–718.

[1167] Oliver Sabot, Justin M Cohen, Michelle S Hsiang, James G Kahn, Suprotik Basu, Linhua Tang, Bin Zheng, Qi Gao, Linda Zou, Allison Tatarsky, Shahina Aboobakar, Jennifer Usas, Scott Barrett, Jessica L Cohen, Dean T Jamison, Richard G A Feachem Costs and financial feasibility of malaria elimination. Lancet 2010

[1168] Tognotti E. Program to eradicate malaria in Sardinia, 1946–1950. Emerg Infect Dis. 2009 Sep; 15(9): 1460–6.

[1169] Baldari M, Tamburro A, Sabatinelli G, Romi R, Severini C, Cuccagna G, Fiorilli G, Allegri MP, Buriani C, Toti M. Malaria in Maremma, Italy. Lancet. 1998 Apr 25; 351(9111): 1246–7.

[1170] Layton M, Parise ME, Campbell CC, et al. Mosquito-transmitted malaria in New York City, 1993. Lancet 1995; 346: 729–31.

[1171] For lymphatic fialriasis elimination short of eradication should be moderately stable because the worms that cause the disease have a long life cycle: the parasite population will rebound but only very slowly.

[1172] Bhattarai A, Ali AS, Kachur SP, Mårtensson A, Abbas AK, Khatib R, Al-Mafazy AW, Ramsan M, Rotllant G, Gerstenmaier JF, Molteni F, Abdulla S, Montgomery SM, Kaneko A, Björkman A. Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. PLoS Med. 2007 Nov 6; 4(11): e309.

[1173] Jaenisch T, Sullivan DJ, Dutta A, Deb S, Ramsan M, Othman MK, Gaczkowski R, Tielsch J, Sazawal S. Malaria incidence and prevalence on Pemba island before the onset of the successful control intervention on the Zanzibar archipelago. Malar J. 2010 Jan 25; 9: 32.

[1174] www.malariaeliminationgroup.org/sites/default/files/MalariaEliminationZanzibar.pdf

[1175] Matola YG, Mwita U, Masoud AE. Malaria in the islands of Zanzibar and Pemba 11 years after the suspension of a malaria eradication programme. Cent Afr J Med. 1984 May; 30(5): 91–2, 95–6.

[1176] Teklehaimanot HD, Teklehaimanot A, Kiszewski A, Rampao HS, Sachs JD. Malaria in São Tomé and principe: on the brink of elimination after three years of effective antimalarial measures. Am J Trop Med Hyg. 2009 Jan; 80(1): 133–40.

[1177] Lee PW, Liu CT, do Rosario VE, de Sousa B, Rampao HS, Shaio MF. Potential threat of malaria epidemics in a low transmission area, as exemplified by São Tomé and Príncipe. Malar J. 2010 Sep 29; 9: 264.

[1178] It is worth noting that eradication remained the long-term goal: what was dropped was the short-term deadline that had been a key concept in the Campaign's creation.

[1179] Sabot O, Cohen JM, Hsiang MS, et al. Costs and financial feasibility of malaria elimination. Lancet 2010; 376(9752):1604-1615.

[1180] Bradley DJ. Morbidity and mortality at Pare-Taveta, Kenya and Tanzania, 1954–66: the effects of a period of malaria control. In: Feachem RG, Jamison DT, eds. Disease and mortality in sub-Saharan Africa. World Bank, Oxford University Press, 1991: 248–263.

[1181] This in not specific to insecticides. The use of chloroquinised salt in areas where vectors were difficult to target including Cambodia and the Amazon may have contributed to drug resistance emerging.

[1182] Litsios S. The Tomorrow of Malaria. 1996. Pacific Press: New Zealand

[1183] Tatem A, Smith D, Gething P, Kabaria C, Snow R, Hay S. Ranking of elimination feasibility between malaria-endemic countries. Lancet. 2010.

[1184] Ibid.

[1185] Sabot O, Cohen JM, Hsiang MS, Kahn JG, Basu S, Tang L et al. Costs and financial feasibility of malaria elimination. Lancet. 6 November 2010–12 November; 2010376 (9752): 1604–1615.

[1186] Galinski MR, Barnwell JW. Plasmodium vivax: who cares? Malar J. 2008; 7 Suppl 1, S9.

[1187] WHO. Guidelines for the treatment of malaria. 2010 2nd ed. Geneva: WHO.

[1188] Yukich J et al, Schwabe et al, Worrall et al. Presentations at the American Society of Tropical Medicine and Hygiene. November 2007.

[1189] Yukich J, Tediosi F, Lengeler C. Operations, cost and cost-effectiveness of five insecticide-treated net programmes (Eritrea, Malawi, Tanzania, Togo and Senegal) and two indoor residual spraying programmes (Kwa Zulu Natal and Mozambique). 2007. Swiss Tropical Institute: Basil.

[1190] Kisewski et al. Estimated global resources needed to attain international malaria control goals. Bulletin of the WHO. 2007; 85(8): 623–630.

[1191] Sabot O, Cohen JM, Hsiang MS et al. Costs and financial feasibility of malaria elimination. The Lancet 2010; 376 (9752): 1604-1615.

[1192] Dundorp A, Yeung S, White L, Nquon C, Day N, Socheat D. et al. Artemesinin resistance: current status and scenarios for containment Nature reviews: Microbiology. April 2010; 8: 272–280.

[1193] Wirth, D. The parasite genome: biological revelations. Nature Oct 2002; 419: 495–496.

[1194] Malaria: Biology. US Centers for Disease Control (CDC). 2010 Feb 8 updated. Available at: www.cdc.gov/malaria/about/biology/index.html.

[1195] Malaria: Biology. US Centers for Disease Control (CDC). 2010 Feb 8 updated. Available at: www.cdc.gov/malaria/about/biology/index.html.

[1196] Dundorp A, Yeung S, White L, Nquon C, Day N, Socheat D. et al. Artemesinin resistance: current status and scenarios for containment Nature reviews: Microbiology. April 2010; 8: 272–280.

[1197] Westenberger S, McClean C, Chattopadhyay R, Dharia N, Carlton J, Barnwell J, et al. A systems-based analysis of Plasmodium vivax lifecycle transcription from human to mosquito. PLoS Neglected Tropical Diseases, April 2010, 4(4): e653.

[1198] Bremen et al. Conquering malaria. In Jamison et al (eds). Disease Control Priorities in Developing Countries. DCPP. Oxford University Press/World Bank. 2006.

[1199] M Rowland, M Bouma, D Ducornez, N Durrani, J Rozendaal, A Schapira, E Sondorp. Pyrethroid impregnated bed nets for self protection from malaria for Afghan refugees. Transactions of the Royal Society of Tropical Medicine and Hygiene 1996; 90:357–361.

[1200] M. Rowland, J. Webster, P. Saleh, D. Chandramohan, T. Freeman, B. Pearcy, N. Durrani, A. Rab, N. Mohammed. Prevention of malaria in Afghanistan through social marketing of insecticide treated nets: evaluation of coverage and effectiveness by cross-sectional surveys and passive surveillance. Tropical Medicine and International Health 2002; 7: 813–822.

[1201] Crawley J, Chu C, Mtove G, Nosten F. Malaria in children. Lancet Apr 2010; 375: 1468–81.

[1202] RBM. Guidelines For Core Population-Based Indicators. RBM Technical Paper Series No. 1. RBM Partnership, 2009.

[1203] RBM. Guidelines For Core Population-Based Indicators. RBM Technical Paper Series No. 1. RBM Partnership, 2009. p10

[1204] Note – the RBM MERG indicators are mainly recommended for high malaria burden countries of Africa where malaria is a generalised problem. Other settings such as SE Asia or Latin America may require more targeted approaches to M and E.

[1205] RBM. Guidelines For Core Population-Based Indicators. RBM Technical Paper Series No. 1. RBM Partnership, 2009. p15.

[1206] RBM. Guidelines For Core Population-Based Indicators. RBM Technical Paper Series No. 1. RBM Partnership, 2009. p15.

[1207] Rowe AK, Steketee RW, Arnold F, Wardlaw T, Basu S, Bakyaita N, et al. Evaluating the impact of malaria control efforts on mortality in sub-Saharan Africa. Tropical Medicine and International Health. 2007; 12 (12): 1524–1539.

[1208] WHO. World Malaria Report 2009. 2009; p. 6. Geneva: WHO.

[1209] Rowe AK, Steketee RW, Arnold F, Wardlaw T, Basu S, Bakyaita N, et al. Evaluating the impact of malaria control efforts on mortality in sub-Saharan Africa. Tropical Medicine and International Health. 2007; 12 (12): 1524–1539. p1526

[1210] Rowe AK, Steketee RW, Arnold F, Wardlaw T, Basu S, Bakyaita N, et al. Evaluating the impact of malaria control efforts on mortality in sub-Saharan Africa. Tropical Medicine and International Health. 2007; 12 (12): 1524–1539. p1528

[1211] Adapted from: Roll Back Malaria, MEASURE Evaluation, USAID, UNICEF, WHO, MACEPA, CDC. Guidelines for Core Population-Based Indicators. MEASURE Evaluation: Calverton, MD. 2009. p12

[1212] It is also important to note the difference between population wide stats versus stats for populations at risk (dilutes the effect) – RBM targets are for coverage of populations at risk – this is not the whole population in countries where a certain % of the population is NOT at risk of malaria.

[1213] WHO. World Malaria Report 2009. 2009; p. 6. Geneva: WHO.

[1214] USAID. Lantos-Hyde United States Government Malaria Strategy 2009–2014. USAID; Washington; 2010.

[1215] UN. Millennium Development Goals Indicators. Available at: unstats.un.org/unsd/mdg/Host.aspx?Content=Indicators/OfficialList.htm

[1216] See: unstats.un.org/unsd/mdg/Data.aspx

[1217] GFATM. Monitoring and evaluation manual – developing an M and E plan. 2008. Geneva: GFATM. p. 7.

[1218] GFATM. Monitoring and evaluation toolkit – HIV, tuberculosis and Malaria and health systems strengthening, part 2: tools for monitoring programs for HIV, tuberculosis, malaria and health systems strengthening Malaria. 2009; 3rd ed. Geneva: GFATM.

[1219] Rowe AK, Steketee RW, Arnold F, Wardlaw T, Basu S, Bakyaita N, et al. Evaluating the impact of malaria control efforts on mortality in sub-Saharan Africa. Tropical Medicine and International Health. 2007; 12 (12): 1524–1539. p1536.

[1220] WHO. Roll back malaria: framework for monitoring progress and evaluation outcomes and impact. 2000. Geneva: WHO. Available at: rollbackmalaria.org/cmc_upload/0/000/012/168/m_e_en.pdf.

[1221] Rowe et al. Evaluating the impact of malaria control efforts on mortality in sub-Saharan Africa. Tropical Medicine and International Health. 2007; 12 (12): 1524–1539. p1525.

[1222] Chandramohan D, Jaffar S, Greenwood B. Use of clinical algorithms for diagnosing malaria. Trop Med Int Health. 2002 Jan; 7(1): 45–52.

[1223] Nankabirwa J, Zurovac D, Njogu JN, Rwakimari JB, Counihan H, Snow RW, Tibenderana JK. Malaria misdiagnosis in Uganda – implications for policy change. Malar J. 2009 Apr 16; 8: 66.

[1224] Amexo M, Tolhurst R, Barnish G, Bates I. Malaria misdiagnosis: effects on the poor and vulnerable. Lancet. 2004 Nov 20–26; 364(9448): 1896–8.

[1225] WHO. Guidelines for the treatment of malaria. 2010; 2nd ed. Geneva: WHO

[1226] Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerindi O, et al. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ. 2004; 329(7476):1212.

[1227]Joshi R, Colford JM Jr, Reingold AL, Kalantri S. Nonmalarial acute undifferentiated fever in a rural hospital in central India: diagnostic uncertainty and overtreatment with antimalarial agents. Am J Trop Med Hyg. 2008 Mar; 78(3): 393–9.

[1228] Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakely C, et al. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. BMJ 2007; 334:403.

[1229] WHO. Guidelines for the treatment of malaria. 2010; p. xi. Geneva: WHO. 2010.

[1230] Breman J. The ears of the hippopotamus: manifestations, determinants and estimates of the malaria burden. Am. J. Trop. Med. Hyg. 2001; 64 (1.2)S: 1–11.

[1231] Rowe AK, Steketee RW, Arnold F, Wardlaw T, Basu S, Bakyaita N, et al. Evaluating the impact of malaria control efforts on mortality in sub-Saharan Africa. Tropical Medicine and International Health. 2007; 12 (12): 1524–1539.

[1232] WHO. World Malaria Report 2008. Geneva: WHO 2008; Annex 1, p129.

[1233] The concept of R_0 is general for all infectious diseases. A closely related concept specifically for vector-borne diseases R_0 is vectoral capacity. It represents the daily rate of secondary cases arising from one primary case, and consists of all the entomological factors in Macdonald's formula with the human factors removed.

[1234] If p is reduced by half, transmission will decline by a factor $p^{10} = 0.5^{10} = 1/1024 = 0.001$, i.e. a reduction of 99.9%.

[1235] Shah N. Assessing strategy and equity in the elimination of malaria. PLoS Medicine. 2010 7(8).

[1236] Lines J, Schapira A, Smith T. 2008. Tackling malaria today. BMJ 227

[1237] The Lancet 2010; 376 (9752); 1566-1615.

[1238] Moonen B, Cohen JM, Snow RW, et al. Operational strategies to achieve and maintain malaria elimination. Lancet. 2010; 376(9752):1592-603.

[1239] Kappe SH, Vaughan AM, Boddey JA, Cowman AF. That was then but this is now: malaria research in the time of an eradication agenda. Science. 2010;328(5980):862-6.

[1240] Hay SI, Smith DL, Snow RW. Measuring malaria endemicity from intense to interrupted transmission. Lancet Infect Dis. 2008; 8: 369–78.

[1241] Malaria Atlas Project, 2010. Available at: www.map.ox.ac.uk/public-engagement/publicity

[1242] WHO. World Malaria Report 2009. Geneva: WHO.

[1243] Ottesen et al. How is eradication to be defined and what are the biological criteria. In: Dowdle WR, Hopkins DR. Eds. The Eradication of Infectious Diseases, Dahlem Workshop Report. John Wiley and Sons. Chichester, 1997.

[1244] WHO. Informal consultation on malaria elimination: setting up the WHO agenda. Tunis, 25–26 February 2006. Geneva: WHO.

[1245] Kidson C, Indaratna K. Ecology, economics and political will: the vicissitudes of malaria strategies in Asia. Parassitologia,, 40 39–46, 1998

[1246] This section from Schapira A in Lines J, Whitty CM and Hanson K, Prospects for Eradication and Elimination of Malaria- a technical briefing for DFID 2007.

[1247] Schapira A. Prospects for eradication and elimination of malaria: Annexe 2. Opportunities, obstacles and risks for elimination of Plasmodium falciparum malaria in difference countries and regions of the World with currently existing tools. London: Department for International Development; 2007.

[1248] www.who.int/malaria/docs/drugresistance/ReportThaiCam.pdf