

The Control of Malaria 2005-15: progress and priorities towards Eradication

The Sixth Report of the All-Party Parliamentary Group
on Malaria and Neglected Tropical Diseases (APPMG)

**The prize we can grasp –
if we have the will to do so...**



House of Commons
The All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases (APPMG)



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Based on evidence presented during 2008-10

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Chairman: Stephen O'Brien MP

Vice-Chairmen: Dr Evan Harris MP, Lord Rea, David Drew MP

Treasurer: Ashok Kumar MP **Secretary:** Eleanor Laing MP

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Website: www.appmg-malaria.org.uk



Contents

Chairman's Foreword	iv
Abbreviations	vi
Acknowledgements	vii
Executive Summary	viii
I Introduction	I
2 Burden of disease & monitoring malaria	2
3 Tools to control malaria	6
a Preventive strategies	6
i Vector control strategies	6
ii Resistance to insecticides	8
iii In the pipeline	10
b Treatment of malaria – ACTs	11
i Producing artemisinin	11
ii Appropriate formulations	13
iii Drug quality and counterfeit medicines	14
iv Supply chain issues	15
v Diagnosis of malaria	16
vi Affordability of ACTs; the AMFm	20
vii Access	20
viii The threat of resistance	22
4 Financing malaria control	24
5 Leadership, co-ordination, co-operation & advocacy	27
6 Elimination	31
7 Recommendations	34

Chairman's Foreword



House Of Commons

The All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases

I am delighted to introduce the Sixth Report of the APPG on Malaria and Neglected Tropical Diseases. We have been pursuing our active programme month in, month out in Parliament, attracting the very best presenters and practitioners from around the world in understanding the science, developing the control measures and delivering the implementation of these measures most effectively on the ground. In the nearly 6 years that this Group has been running, this Sixth Report attempts to “take stock” of where the control of malaria in all its manifestations globally has progressed to, and what we need to focus on in the coming years in order to achieve elimination area by area (shrinking the map) and dramatically reduce the burden in the high transmission areas through the use of the most efficacious control measures.

Malaria remains a truly global challenge. Although over 85% of global cases and deaths occur in Sub-Saharan Africa, more people live at risk of this potentially life-threatening disease in Central and South East Asia. There is a clear need to remain vigilant about mutations and behavioural variations between different types of malaria parasites and mosquitoes in various parts of the world. To get a real understanding of the development of resistance means that all the lessons that we have learned over the last 5 years point to one inescapable conclusion: in order for the world to win one of its greatest prizes in eradicating malaria in this generation's lifetime we have to sustain the will and the resources to bear down on the world's most widespread but avoidable killer disease.

This Report aims to ensure that there is a greater understanding of both the challenge and the opportunity to control malaria and the enormous encouragement we can take from the progress that has been made over the last 5 years given the focus that has been brought to bear. The APPMG has been glad to play its own role in this effort and I am pleased to have this opportunity to pay tribute not only to my fellow Parliamentarians in the House of Commons and the House of Lords here in the United Kingdom for their continuing interest and commitment to our cause but also to all the political parties as we rise above our political differences to unite in addressing one of today's greatest scourges of mankind. I have been pleased to note the emergence of Parliamentary groupings in an increasing number of countries across Continents focussed on the cause of beating malaria.

I am also extremely grateful to the enormous number of people, be they academic, governmental, international agency, charitable, private sector, professional and scientific groups and many more who have made their time and expertise available to us – as a result, this Sixth Report is as authoritative and timely as the five that have preceded it. I hope it will add weight to our robust advocacy in coercing and sustaining the political will to maintain the resources and aspirations to which we all cleave – to save lives and to remove the burden of disease from hundred of millions of people across the world: a disease which is entirely preventable and treatable.

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The highlights of this report are easily summarised:

- We're making progress in malaria control at a faster rate than ever before.
- We have good tools which can prevent and treat malaria.
- Political will is strong and funding is better than ever before.
- Major obstacles exist
- We need better systems to deliver the tools, especially to the most poor and remote populations.
- There are the first warnings that current tools may not last.
- Funding for research to develop new tools and to purchase commodities and strengthen health systems is uncertain. Just as momentum is building in malaria control, and impact is being demonstrated, a faltering of financial support threatens the progress.
- Minimising the malaria burden not only saves lives, but keeps parents at work, children at school and helps societies achieve prosperity and security.
- There is an urgent need to renew support, to consolidate and expand our "fragile success".

The greatest need is for Collaboration,
Co-ordination, Commitment.

As ever I am very grateful to Susan Dykes for all her hard work in co-ordinating and administrating this APPG and to our sponsors who help sustain the Group: MMV, Malaria Consortium, GSK and Westergaard Fransen amongst others. I am particularly grateful to MMV for their support for this particular Report in covering its printing and distribution costs.

Following the departure of Dr Chris Whitty from the London School of Hygiene and Tropical Medicine to become Head of Research at DFID I had to unearth another author for this Report by drawing together all the information and expertise contained in the presentations to us over the past 8 months. In David Schellenberg, Professor of Malaria and International Health at the London School of Hygiene and Tropical Medicine, we have found another great talent who has given so much of his time and knowledge in agreeing to author this Report. I pay tribute to his outstanding work for which I hope he will get the much wider public recognition that he deserves.

In commending this Report I hope it will reinforce and urge each and every reader to be recommitted to the global battle against malaria – a battle we can win and, for the sake of the millions of lives to be saved and improved, we must win!

Stephen O'Brien MP

Chairman of the All-Party Parliamentary Group
on Malaria and Neglected Tropical Diseases
February 2010



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Abbreviations

ACT	Artemisinin Combination Therapy
AMFm	Affordable Medicines Facility - malaria
APPMG	All Party Parliamentary Malaria Group
CHW	Community Health Workers
DDT	DichloroDiphenylTrichloroethane
EAAM	European Alliance Against Malaria
EDCTP	European and Developing Country Clinical Trial Platform
EU	European Union
FIND	Foundation for Innovative New Diagnostics
GFATM	Global Fund for AIDS, TB and Malaria
GMP	Global Malaria Programme
GNI	Gross National Income
GSK	GlaxoSmithKline
HBMF	Home Based Management of Fever
ICCM	Integrated Community Case Management
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Nets
IVCC	Innovative Vector Control Consortium
LLIN	Long Lasting Insecticide-treated Net
MDG	Millennium Development Goal
MIM	Multilateral Initiative on Malaria
MMV	Medicines for Malaria Venture
MRA	Medicines Regulatory Authority
MVI	Malaria Vaccine Initiative
ODA	Official Development Assistance
PMI	President's Malaria Initiative
PSI	Population Services International
RBM	Roll Back Malaria Partnership
RDT	Rapid Diagnostic Test
SP	Sulphadoxine-pyrimethamine
UNICEF	United Nations Children's Fund
WHO	World Health Organisation
WMR	World Malaria Report

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Executive Summary

Where are we today?

The last five years have seen extraordinary developments in the fight against malaria. After decades of often lonely campaigning, investment in control and research has reached unprecedented levels and there are strong indications that these investments are starting to pay off. Malaria disease and deaths have been shown to be falling in several settings. However, this is a “fragile success” with a need for further investment to consolidate and expand the early gains.

This 6th Report of the All Party Parliamentary Group on Malaria and Neglected Tropical Diseases comes five years after the Group’s first meeting, and five years before the 2015 date set for achieving the Millennium Development Goals (MDGs). Here we review the progress so far and assess priorities for moving towards the ambitious aspirations of the MDGs.

The Problem

- Malaria continues to cause enormous suffering and death in large swathes of the world: 243 million cases and about a million deaths each year.
- Malaria keeps children away from school, impacting educational outputs; keeps workers off the land, impairing food security at the family, community and national levels; and keeps staff away from work, reducing economic productivity.
- Funding for operational research remains woefully inadequate, yet is essential to maximise the impact of existing malaria control tools.
- The threat of resistance to drugs and insecticides must not be underestimated. Resistance to artemisinin, the key component of the first-line choice in malaria treatment, has been confirmed in the same part of south-east Asia where resistance to previous first-line treatments, chloroquine and sulphadoxine-pyrimethamine, was first identified. Many of the gains in malaria will be lost if artemisinin resistance spreads to Africa, where the majority of the malaria burden continues to bite.

Progress to date

- High coverage of key malaria control tools has been attained in some countries and regions and has been associated with reductions in the prevalence of malaria infection, the incidence of clinical disease and the number of children dying. Such encouraging findings have been documented in only a few countries, so far, but the principle is proved: adequate, appropriate investment in malaria control impacts health outcomes and saves lives.
- Gains have been made in malaria control despite the lack of major technological breakthroughs. The mainstay of treatment remains Artemisinin-based Combination Therapy (ACT) and the principle approach to prevention is the Long Lasting Insecticide Treated mosquito Net (LLIN). Nevertheless, more effective deployment of increased resources has allowed higher coverage of these key interventions and has been associated with gains in health and survival.
- The impact of ACTs and LLINs has been greatly enhanced by improved co-ordination and co-operation between governments, bilateral and philanthropic agencies, the development of new and novel financing mechanisms and by clearer and louder advocacy at international and local levels.
- Malaria research has also flourished. As a result of better funding initiatives now exist to co-ordinate the development and evaluation of anti-malarial drugs, insecticides for public health use and the improved utilisation of ACTs. Funding has also facilitated real progress in the development of a malaria vaccine.

Looking Forward

- Ensuring that efficacious tools are available to those who need them requires increased funding for operational research. Only by remedying this shortcoming can the full potential of available interventions be unlocked.
- Increased operational research has the added benefit of strengthening health systems; if we get it right for malaria, we get it right for local health systems and improve the prospects for many other diseases. If the supply chain works for malaria treatments, it is more likely also to work for antibiotics, oral rehydration salts and other life-saving commodities.
- Investment in control needs to increase yet further, in the confidence that it will yield real benefits. The All Party Parliamentary Group on Malaria (APPMG) recognises the leading role played by The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) in the fight against malaria. Some two-thirds of all global financing for malaria prevention, care and treatment is provided by the GFATM. But there is now a funding shortfall which requires countries to increase their pledges and to be held accountable for these pledges.
- The threat of resistance to drugs and insecticides must not be underestimated. It is critically important to plan surveillance for artemisinin resistance in Africa and to determine the scale and content of the response if resistance is identified. It is essential to continue to fund the development of new malaria treatments.

Increased investment in malaria control has the potential to save millions of lives in the coming decade, and more thereafter. Thus helping to attain the MDGs on poverty, primary education, child mortality, maternal health, malaria and helping to develop and improve access to essential drugs. Only with sustained commitment can the early, fragile success be consolidated and expanded, and the full benefits of effective malaria control realised.

1. Introduction

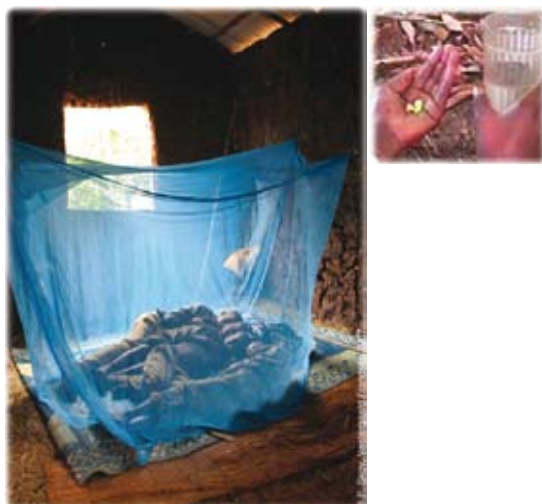
Malaria disappeared from the international agenda for many years, largely as a result of disillusionment following the perceived failure of the global malaria eradication programme (1955-1969). The insecticide DDT had been central to malaria control and eradication efforts, but fell victim to a largely unwarranted fear of its potential adverse health and environmental effects and to the development of resistance. Former colonies gained independence, economic times became difficult and the will to continue to invest in effective malaria control slipped away. Malaria was once more accepted as a way of life.

The 1990s saw recognition of the appalling burden of disease and death exacted by this preventable and treatable disease. This stimulated a flourish of initiatives to finance malaria control and to make anti-malaria interventions available to those most in need. In the last 5 years these efforts have started producing results; investing in malaria control is working.

The World Malaria Report, 2009, states that an estimated 863,000 lives were lost to malaria in 2008, 767,000 of those (89%) in Africa. It predominantly affects the poorest of the poor; the remotest, hardest to reach communities, young children and women in pregnancy. As well as being frequently fatal, malaria keeps children away from school and adults away from work. Care-seeking costs drain household's resources and increase indebtedness. The public health micro- and macro-economic impacts of malaria are enormous.

Just two simple approaches, costing a few dollars per person each year, are all that is available to counter malaria. Nevertheless, if effectively deployed, prompt, effective treatment and vector control, especially with long-lasting insecticide treated mosquito nets (LLIN), can massively reduce the burden of malaria (fig 1.1).

Fig 1.1. ACTs and LLINs can effectively control malaria



The new era of commitment to improve the malaria situation started with a series of meetings in the 1990's, such as the Ministerial Conference on Malaria in Amsterdam (1992) and the Dakar Conference (1997), which led to the formation of the Multilateral Initiative on Malaria. Under the auspices of the WHO, the Roll Back Malaria Partnership was established in 1998 and the Abuja Declaration, in 2000, set internationally recognised targets including the halving of malaria deaths in Africa's people by 2010. Malaria was increasingly acknowledged as a cause of global poverty and included among the United Nations' Millennium Development Goals (MDGs). Although MDG 6 calls specifically for the halting and reversal of the malaria burden by 2015, malaria also affects most of the other MDGs. Effective control of malaria can make a major contribution to the attainment of the MDGs by 2015.

The Global Fund to fight AIDS, tuberculosis and malaria (GFATM) was formed in 2002, creating a means to finance essential commodities for malaria control, with additional mechanisms through the United States' President's Malaria Initiative (PMI) and the World Bank providing important additional funds in more recent years.

Roll Back Malaria's Global Malaria Action Plan (GMAP) is a global framework for action, around which all partners can coordinate their efforts. The goal set for 2010 is to reduce the number of global malaria cases and deaths by 50% compared with the numbers for 2000. The GMAP tells us what it will take to reach the 2010 goal, and how much it will cost.

This sixth report of the All Party Parliamentary Group on Malaria and Neglected Tropical Diseases reviews progress since its first meeting in 2004, with a focus on evidence submitted during 2008-10. The report starts with an overview of changes in the burden of disease in recent years before reviewing the most important currently available tools to prevent and treat malaria, drawing on testimony to highlight the critical issues surrounding deployment of these tools today. Section 4 presents an overview of funding for malaria control and research before considering the issues of leadership, co-ordination and co-operation. Finally, we touch on the prospects for elimination and, ultimately, eradication of this terrible, but eminently preventable, killer.

2. Burden of Disease

Fig 2.1. Estimated numbers of malaria cases (in millions) and deaths (in thousands) by WHO Region, 2008

REGION	CASES				DEATHS			
	Point	Lower	Upper	<i>P. falciparum</i> (%)	Point	Lower	Upper	Under 5 (%)
AFR	208	155	276	98	767	621	902	88
AMR	1	1	1	32	1	1	2	30
EMR	9	7	11	75	52	32	73	77
EUR	0	0	0	4	0	0	0	3
SEAR	24	20	29	56	40	27	55	34
WPR	2	1	2	79	3	2	5	41
Total	243	190	311	93	863	708	1003	85

WHO's 2009 World Malaria Report presents evidence that development aid for health is working. The tremendous increase in funding for malaria control has allowed rapid scale-up of available control tools. Increased coverage has produced marked effects on health, especially the health of children in sub-Saharan Africa. The global momentum for improved malaria control is building.

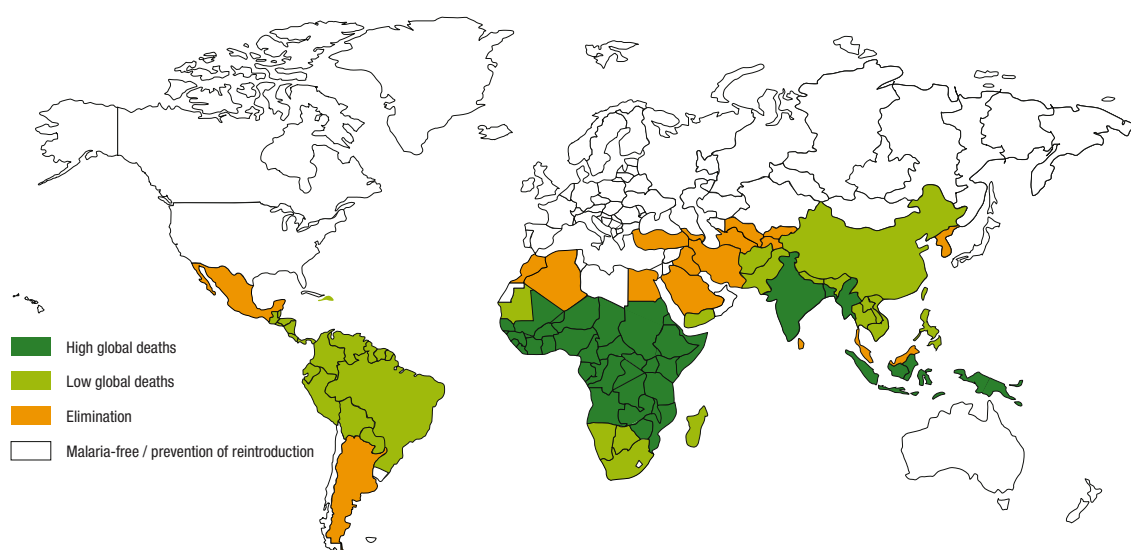
Malaria remains endemic in 108 countries, where it causes a total of approximately 243 million cases and 863,000 deaths per year (fig 2.1). *P. falciparum* infection accounts for 93% of malaria episodes.

The risk of malaria varies between different regions and countries (fig 2.2), and can be separated into unstable risk (i.e. with less than one case per 10,000 people each year) or stable risk, (with more than one case per 10,000 people per year) (fig 2.3). Stable transmission settings are split into three levels of endemicity, based on the prevalence of malaria parasites in children aged

2-10 years. The lowest endemicity class is defined by a parasite prevalence of less than 5%, the intermediate class by parasite prevalence between 5 and 40% and the high endemicity class by a parasite prevalence in this age group above 40%.

WHO suggests that when the prevalence of parasitaemia falls below 5% it may be appropriate to move to a pre-elimination phase, and that when the incidence falls below 1 case per 1000 people per year it may be appropriate to move to the elimination phase, although in practice the transitions will depend on the malaria burden that a programme can realistically handle, including the capacity for effective case notification and follow up. By this reckoning, those countries falling into the unstable transmission category could consider adopting malaria elimination as their target, and those falling into the low endemicity category of stable transmission could move into a pre-elimination phase.

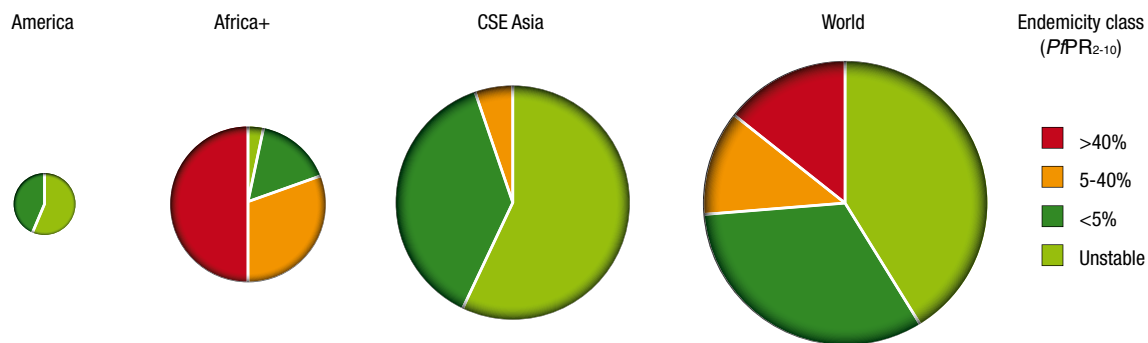
Fig 2.2. Malaria: a disease without borders



Source: World Malaria Report 2008. Geneva, WHO (2006 data)

2. Burden of Disease

Fig 2.3. The risk of malaria varies in different regions



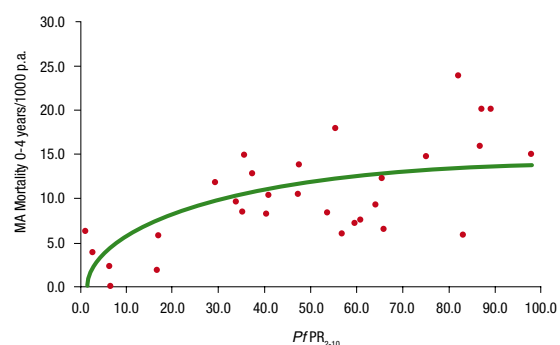
The group was presented evidence showing about 0.9 billion people live at low, unstable risk, most of them in central and south-east Asia (CSE Asia). A further 1.4 billion people live at stable risk, of whom 0.69 billion are in CSE Asia, 0.66 billion in Africa, Yemen, and Saudi Arabia ("Africa+"), and 0.04 billion are in the Americas. All those at stable risk in the Americas are in the lowest endemicity class, as are 88% of those living under stable risk in CSE Asia. High endemicity was widespread only in the "Africa+" region, where 0.35 billion people live at this highest level of risk, and a further 0.20 billion live at intermediate risk, and 0.11 billion live at low stable risk. In summary, about three quarters of people at risk from *P. falciparum* live in areas of unstable or low endemic risk, and only 14% of people at risk of *P. falciparum* infection live in areas of high transmission. Almost all (98%) of those exposed to high transmission live in Africa. Accordingly, it may be technically feasible to eliminate *P. falciparum* from countries with substantial populations at risk, and it is definitely possible to reduce by a very large proportion, the disease and death caused by malaria in much of sub-Saharan Africa.

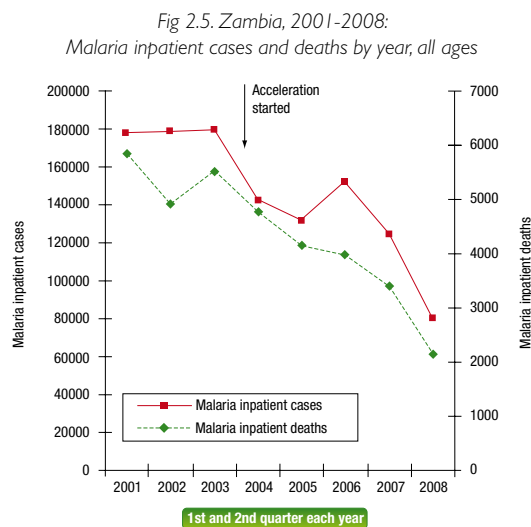
In south-east Asia the population density is high, with half the world's people living within 2,000 miles of Bangkok. Another species of malaria, *P. vivax*, is relatively important in this area. In contrast to *P. falciparum*, *P. vivax* only rarely causes life-threatening illness and death. However, it is more difficult to control because the parasite's life-cycle includes a dormant liver stage which is not killed by the drugs used to treat the acute illness. As a result, weeks, months or even years after a patient has been cured of an acute episode, they may become unwell with malaria when the dormant liver stage awakens. Only one drug, primaquine, is currently available and effective for treatment of the dormant liver form (the hypnozoite), but its safety profile in some people, and protracted treatment course with associated compliance challenges, exacerbate the challenge of effective *P. vivax* control.

In Africa, children under the age of 5 years and women in pregnancy are at particularly high risk of malaria disease and death because of the under-developed and compromised immune systems, respectively: 88% of all malaria deaths are in children under 5 years of age in Africa (fig 2.1, fig 2.4). Malaria continues to be a significant cause of additional, indirect mortality. For example, malaria in pregnancy causes low birth-weight and premature delivery, which together are associated with up to 200,000 infant deaths per year in Africa. Targetting many malaria control activities at children under five years of age and pregnant women could yield important benefits in terms of reduced morbidity and mortality in much of Africa. The enormous number of out-patient malaria cases are an immense burden on health systems. The cost of seeking care and the loss of productivity exacerbate poverty and hunger; and illness episodes in children and their carers keep children away from primary school. Hence, malaria is a factor in MDG 1 (eradication of extreme poverty and hunger), MDG 2 (achievement of primary universal education), MDG 4 (reduction of child mortality), MDG 5 (improvement of maternal health) and MDG 6 (combating HIV/AIDS, TB and Malaria).

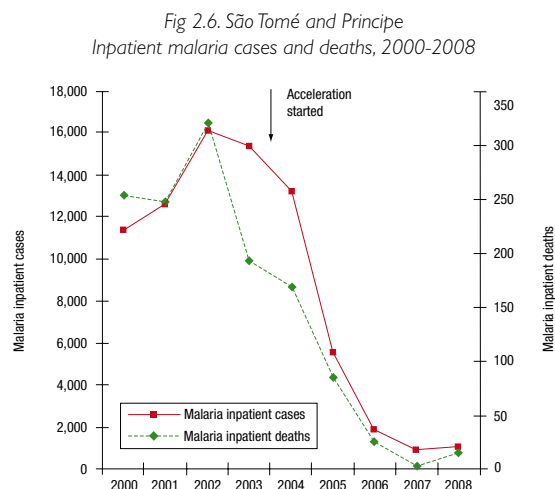
Minimising the malaria burden not only saves lives, but keeps parents at work, children at school and helps societies achieve prosperity and security.

Fig 2.4. Malaria-specific mortality in African children aged 0-4 years per 1000 children p.a. from 31 community-based surveillance studies between 1985-2004



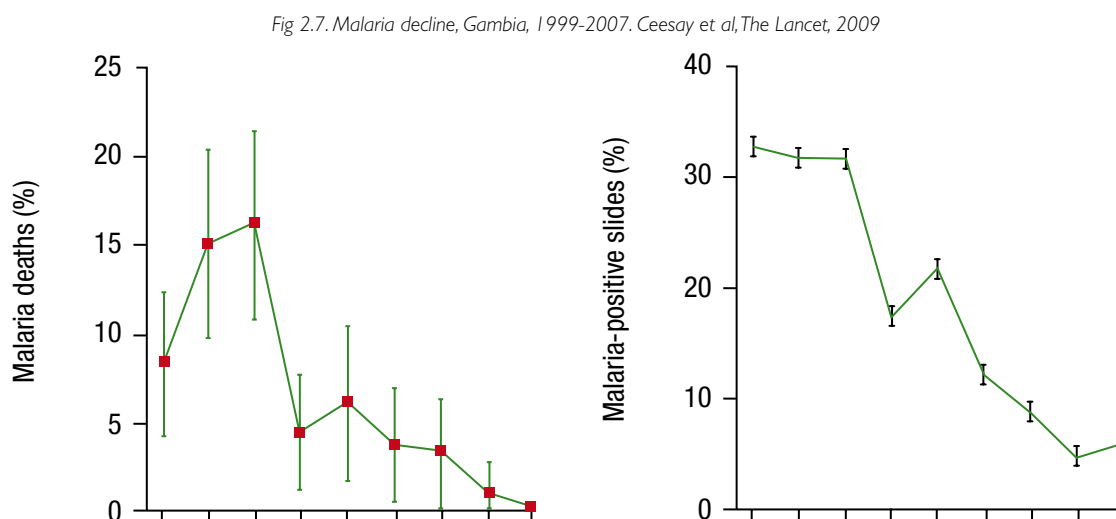


Source: Ministry of Health routine surveillance data



The burden of malaria disease and death thus remains unacceptable, especially as the disease is eminently preventable and treatable. Nevertheless, important progress has been made in a number of countries. For example, there was a 30% decrease in malaria cases between 2000 and 2005 in Burundi, following the introduction of ACTs and ITNs; a 64% decline in malaria mortality since 2001 in Eritrea, following the deployment of ITNs and ACTs; a 90% decline in malaria deaths in the southern provinces of Zambia between 2001-2005, following the implementation of ITNs and ACTs (fig 2.5). Recognising the relatively more benign opportunity island states present, in Sao Tome and Principe, malaria admissions and deaths reduced by over 90% between 2000 and 2008 (fig 2.6). These are major improvements in the malaria situation in some of the 35 high-burden countries in the WHO African region and prove the principle that investing in malaria control works where the burden of disease is heaviest. However, there is a major constraint

on the development of a broad over-view of the malaria situation and that is the poor quality of routine information available from many countries. Data quality is also a challenge in lower transmission countries in Africa, though five countries with reliable data have also demonstrated decreases of over 50% in the number of confirmed cases and deaths due to malaria between 2000 and 2008. Publications from Zanzibar (Tanzania), Bioko island (Equatorial Guinea), The Gambia (fig 2.7) and coastal Kenya also document a decrease in the incidence of disease and an improvement in survival on the basis of relatively robust data from extensive malaria control and evaluation programmes. Thus, the overall picture is that investment in malaria control is producing important benefits in some settings. **But there is a need for continued investment, particularly in higher-burden countries. Improved monitoring of the burden of disease and of progress with control efforts will be enhanced by strengthening of health information systems.**



2. Burden of Disease

Monitoring Malaria

One of the limitations in building a picture of the malaria situation is the weakness of routine health information and the limitations of surveys. Routine health information systems produce an incomplete picture of patients attending the health facilities, with a failure to record a variable proportion of patients attending health facilities, a lack of diagnostic confidence - the vast majority having been based on clinical diagnosis only - and only intermittent returns from many health facilities. Furthermore, routine health information systems fail to reflect the health needs of those not attending the formal system, a serious impediment when the majority of anti-malarial treatments are accessed over the counter at drug shops, and the problems with products sold from small pharmacies or street vendors in the private sector. In addition, data from non-government facilities are often not incorporated into routine health statistics.

Household surveys are increasingly standardised but there remains a need to update and consolidate indicators to ensure that they remain meaningful as malaria control improves. Most surveys are conducted during the dry season, for logistic feasibility, providing only a snapshot of the malaria situation, and one which may tend to underestimate the true burden of malaria (which thrives and spreads better in humid and wet conditions).

The development of serological approaches to assess exposure to malaria offers some hope. The antibodies produced in response to malaria infection do not usually protect against infection but remain present for a considerable time after the infection and can be used to monitor the intensity of transmission and, potentially, the impact of malaria control interventions. The Group heard how the evaluation of a population's serological profile may prove a powerful tool for improving malaria control, for example by facilitating identification of hot spots of continued transmission, for monitoring progress with malaria control and for generating evidence to evaluate whether local transmission of malaria in a setting has been eliminated.

3. Tools to control malaria

Tools to control malaria

Malaria control depends on the early, effective treatment of acute cases and on the deployment of preventive strategies. The mainstays of malaria control thus depend on chemical entities – drugs and insecticides – but the greatest threat to each is resistance. Reducing transmission with insecticides will reduce the need for treatment of cases and hence help to limit the spread of resistance. Investment into the development of new insecticides, monitoring the spread of insecticide resistance and approaches to retard the spread of resistance to insecticides should be an absolute priority. There will continue to be a need for treatment until malaria is eradicated, and the advent of resistance to artemisinin, the mainstay of malaria treatment, is a worrying development that merits a robust, co-ordinated response. Investment is needed to prepare for a future in which we cannot depend on artemisinin derivatives for malaria treatment.

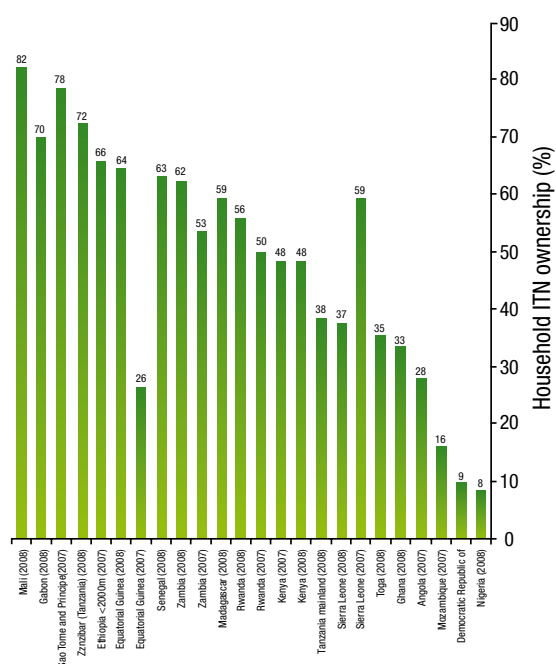
Preventive Strategies

Vector Control Strategies are the mainstay of preventive malaria control activities. Indoor Residual Spraying (IRS) of insecticide has a long history and continues to play a role in malaria control in certain settings. However, the most widely deployed approach to malaria vector control is with Insecticide Treated mosquito Nets (ITNs) and the APPMG heard several pieces of evidence on this topic. ITNs have been shown to prevent over 20% of deaths in children under 5 years of age and have been recommended by WHO for malaria control since the 1990's. Coverage of ITNs has been disappointing, with only 11% children under five years protected by an ITN in the 2005 World Malaria Report and only one country, Eritrea, reaching the Abuja target of 60% at that time. Reasons for the low coverage included lack of manufacturing capacity and lack of resources for procurement, both of which have been addressed to some extent during the last five years. The 2009 World Malaria Report states that "the number of nets needed to cover all persons at risk in high-burden countries in 2008 was approximately 336 million (assuming that one net covers two persons). The cumulative number of LLINs delivered in 2006–2008 by manufacturers was 141 million, which represents 42% of the 336 million needed in 2008 (assuming a lifespan of 3 years)."

Mosquito net manufacturers are responding to the increase in demand. The Global Malaria Action Plan (see page 27) estimates that 300 million LLINs are needed in Africa in 2009/10 alone, but that the industry capacity to produce is about 115 million per year. The manufacturing giant BASF explained how de-bottlenecking and build up of capacity to produce Long Lasting Insecticide treated Nets (LLIN), which was scheduled to take place between 2009 and 2013, has been fast-tracked, with a resultant increase in their production capacity by 50%. This represents a contribution by BASF to the targets of the GMAP, and a response to the call of the UN special envoy for malaria for increased capacity for LLIN.

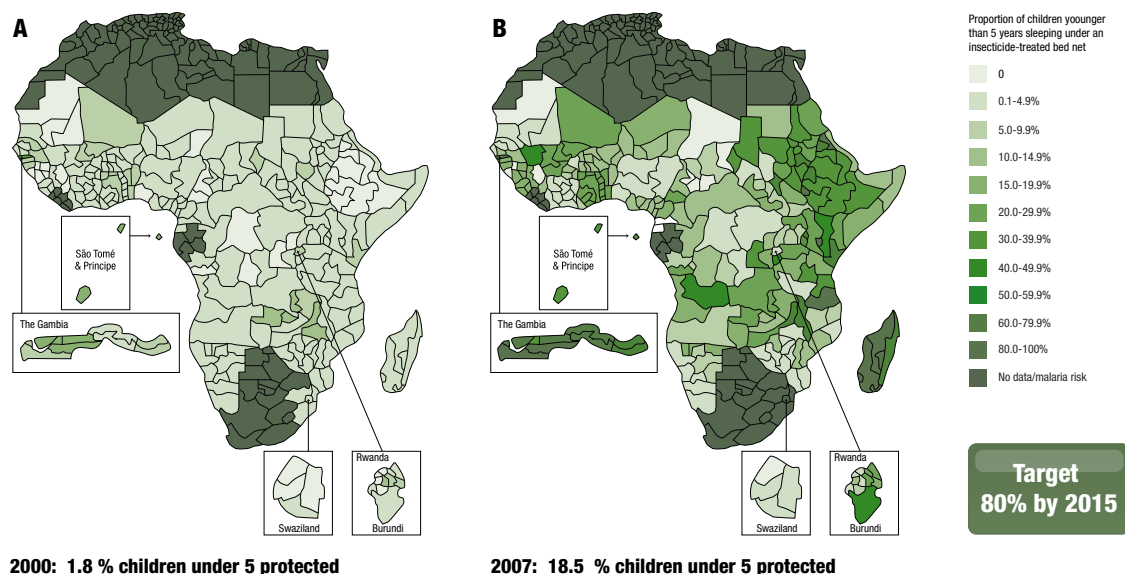
Data from ministries of health indicate that a about 35% of the needed nets have been distributed, resulting in improved coverage (fig 3.1-3.2) and more, major activities are planned in this area. The unnecessarily polarised debate on appropriate approaches to the distribution of ITNs – free mass distribution versus ongoing social marketing - seems to have been resolved by an appreciation of the needs to improve coverage rapidly in settings where it is low ("catch-up") and also to have systems established to maintain supplies of ITNs once coverage levels are high ("keep up").

Fig 3.1. Household ITN ownership 2007–2008, high-burden WHO African Region countries



3. Tools to control malaria

Fig 3.2. Scale-up of use of insecticide treated bednets: Noor et al, Lancet, 2009



A major problem has been low rates of retreatment of conventional nets with insecticide. Given the challenges of increasing net coverage it is not surprising that insecticide re-impregnation every 6-12 months proved very difficult. The last five years have seen the development and introduction of two technologies which ameliorate this challenge; (a) the development of formulations of insecticide which are retained on the net even after it is washed, and (b) the development of long-lasting insecticide treated nets (LLIN), which have insecticide incorporated into the net fibres during the manufacturing process such that the net retains its insecticidal properties for the lifetime of the net (approximately 5 years). So far only a limited number of LLINs are recommended by WHO but these products have tremendous potential to deploy controlled release technology in a ready to use product that retains its insecticidal activity even when washed 20 or more times. Other major manufacturers of LLINs are Sumitomo Chemicals - Olyset Nets, and Vestergaard Frandsen's PermaNet®, ZeroFly®.

Next steps for ITN/LLIN

Improving coverage with mass distributions

The major current challenge is to get nets to those who need them most. Manufacturing capacity is increasing and funds for procurement are available to some extent, but need supplementing. The 2009 World Malaria Report estimates household ITN ownership to be 30%, but ITN use by children under five years was 24% in 2008. Ownership of an ITN does not necessarily equate to ITN usage and there is a need for operational work to close the gap between ownership and usage.

The WHO policy is for universal coverage, as endorsed in 2008 by the UN Secretary General, Ban Ki-Moon, and included in the Roll Back Malaria partnership's Global Malaria Action Plan (see page 27). This means, quite simply, that all ages, all sleeping places and all socioeconomic classes in areas with malaria transmission should be covered by an ITN/LLIN every night. Moving from 30% household ownership to universal coverage is a major challenge requiring massive national-scale campaigns in many countries to reach high coverage rapidly.

Universal Coverage of ITNs

- All ages
- All sleeping places
- All socioeconomic classes
- All areas with malaria transmission
- Every night

In Africa it is estimated that 90 million children did not sleep under an ITN in 2007, but that most of these children lived in just seven countries. Strikingly, 25% of all unprotected children are in Nigeria, (where there is the highest population and thus a cradle of transmission) which estimates that 62 million ITNs will be needed to remedy the situation. Late in 2009 the APPMG was informed that a major grant from the Global Fund will provide half of the ITNs needed in Nigeria. Together with contributions from the World Bank, DfID, USAID, UNITAID, UNICEF and the Nigerian government, plans are taking shape for the largest ever ITN catch-up campaign in history. Impressive though this is, there is a need for additional large-scale efforts to increase coverage in the knowledge that tens or hundreds of thousands of lives will be saved as a result.

Systems to Keep-Up Coverage

It is imperative, however, that the campaigns are complemented by mechanisms to ensure “keep-up” – to maintain coverage – through sustainable delivery systems, once the campaigns are over. Failure to ensure a functional mechanism for ‘keep up’ will result in a progressive decrease in coverage, as indicated by the 2009 Global Malaria Report. Ante-natal and immunisation systems, as well as the power of the private sector, can be harnessed to good effect.

Resistance to insecticide

Insecticide resistance has been reported to the APPMG and there is some evidence that it has a negative impact on malaria control. A major concern is the possibility that, as malaria control is scaled up and insecticides used ever more widely, the resistance situation could deteriorate very rapidly. Although this is by no means certain, the past programmatic experience, plus the damage caused by resistance to political will both internationally and in endemic countries, leads all concerned to address resistance early. **Thus there is an urgent need for new insecticides for malaria control, for research into strategies to sustain the efficacy of existing insecticides and for improved monitoring of insecticide resistance to enable evidence-based decisions on appropriate insecticide selection.**

Resistance to DDT was documented during the previous malaria eradication programme and, having been very successful and saved countless lives, resistance to DDT contributed to a lack of success in some settings. The main driving force of DDT resistance was probably its use for agricultural purposes, which consumed far greater quantities than were used for disease prevention. The APPMG was informed of DDT resistance in Benin, but also recent, more worrying data showing reduced sensitivity to pyrethroids on nets and when used as IRS. The pyrethroids were

developed in the 1970s and remain the only insecticide recommended for use on mosquito nets. Worryingly, no new classes of insecticide have become available for public health use since they were developed. Pyrethroid resistance has been documented in terms of both mosquito killing and the proportion of mosquitoes that had fed, suggesting a loss of the effect of pyrethroids on transmission and for personal protection. Pyrethroid insensitivity has also been clearly documented in Bioko island, Equatorial Guinea, where effective vector control was only possible following adoption of the relatively expensive insecticide carbamate.

Pyrethroid resistance clearly threatens control and elimination ambitions and there is a need to support activities to accelerate the development of new insecticides and reformulate alternative insecticides, for use on LLINs and for IRS, to improve residuality and wash resistance.

The development of new insecticides is thus a priority. The Group was informed of the work of the Innovative Vector Control Consortium (IVCC), funded by the Bill and Melinda Gates Foundation. This product development partnership was created to enable the development of new insecticides for public health vector control, bringing academic researchers and industry together to develop new products, and also working to develop information systems to enable insecticides to be used more effectively.

BASF is working in conjunction with the IVCC and presented information about chlorfenapyr; a new insecticide which so far has not been found to share resistance with other classes of insecticide and has better efficacy against *Culex* mosquitoes than alphacypermethrin. Although mosquitoes in the *Culex* class do not transmit malaria, they are responsible for a large proportion of ‘nuisance biting’. If an insecticide is effective against these nuisance mosquitoes then people may be more likely to use the intervention, with potential for enhanced impact on malaria transmission. There is a need to improve the formulation of chlorfenapyr to sustain its activity but recent results are encouraging. It may be of particular use in combination with other insecticides (such as alphacypermethrin) in a single product.

Another insecticide in the pipeline is primiphos (methyl actellic CS), also developed in conjunction with the IVCC which has supported its evaluation in south Benin. Here it has shown high levels of efficacy (>90% kill after 6 months) in pyrethroid resistant *A. gambiae*.

Insecticides for use as IRS are also being developed, with new modes of action to overcome the growing threat of resistance. New formulations of insecticides for IRS may make long-lasting IRS feasible, which would increase the utility of the approach by reducing the frequency with which the insecticide has to be re-applied (currently 6 monthly).

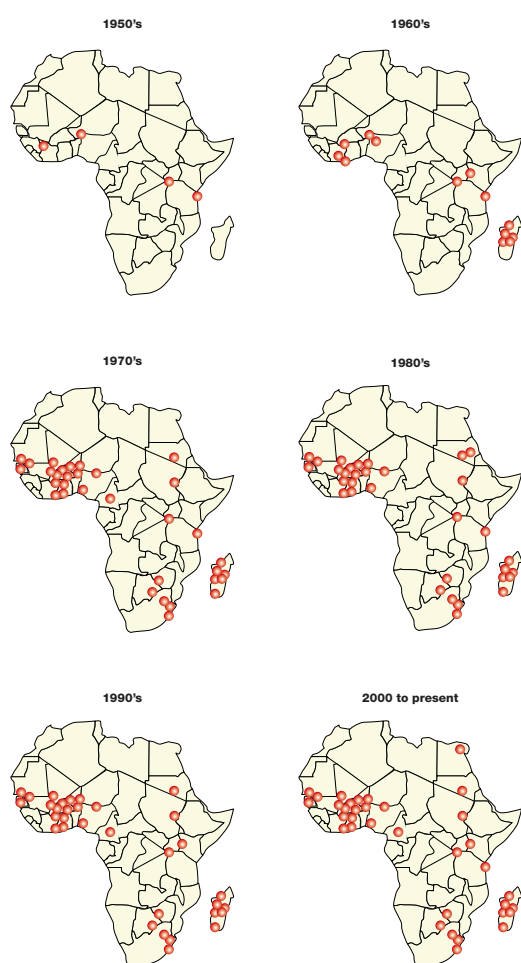
3. Tools to control malaria

Monitoring resistance to insecticide

There is a clear need to map and track the spread of resistance. It is likely that as ITN deployment continues to grow the rate of development and spread of resistance to commonly used insecticides will also increase. This is almost inevitable and emphasises the need for parallel investment in malaria control and research activities.

A rational approach to monitoring insecticide resistance requires agreement of the approach to be used for monitoring, deploying that approach in a systematic and co-ordinated manner and then the compilation of the information generated. Approaches to monitoring insecticide resistance may be based on bioassays, which evaluate the effect of insecticide on live mosquitoes in controlled conditions. This is a cumbersome process but standards have been developed and agreed and this approach is widely deployed. Once the cause of resistance to an insecticide has been understood there are other options, such as biochemical, genetic or protein-based testing, which may offer efficiencies and improved test performance.

Fig 3.3. Sites in Africa reporting insecticide resistance (1950's - 2006)



Source: Coleman et al (2006) J Med Ent 43: 663-668

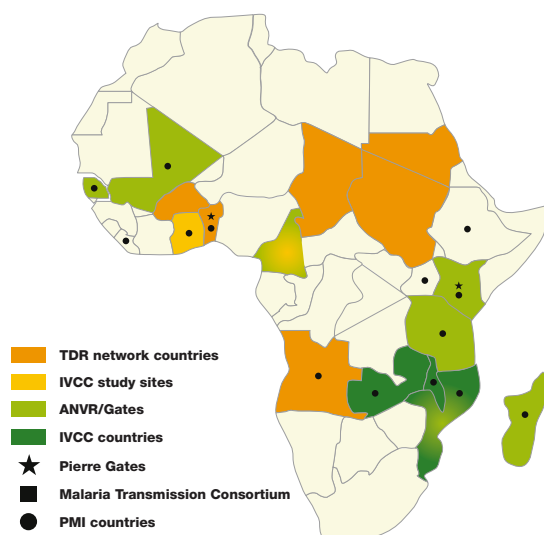
Once appropriate monitoring tests have been identified there is a need to deploy them in a co-ordinated and systematic way which enables the spread of resistance to be tracked. The number of sites evaluating insecticide resistance has increased in the last 50 years (fig 3.3) but investment in grassroots data collection and African field sites is essential.

Various networks are involved in monitoring and evaluation of insecticide-based malaria control programmes (fig 3.4) but there is a need for overall compilation of information, which is not a trivial undertaking. The Group was informed of the efforts of Vestergaard Frandsen in compiling country resistance packages, linked to mapping software, which enables identification of geographic gaps in monitoring and the identification of areas with multi-resistant mosquitoes which can facilitate the development of new products.

Monitoring for resistance should be seen as part of Good Practice in the deployment of any insecticidal intervention, including ITNs, and should be seen as the responsibility of the vector control implementing agency. Funders should regard it as mandatory and look for mechanisms to facilitate sub-regional coordination of monitoring activities.

Recent years have seen the development of novel partnerships, such as the Innovative Vector Control Consortium, a public/private partnership co-ordinating the development of novel vector control chemicals and working to improve the delivery of insecticides through better formulations and decision support systems for vector control. Such initiatives have enormous potential and merit sustained support.

Fig 3.4. Monitoring and Evaluation of Insecticide based malaria control programmes



Preventive strategies in the pipeline

Intermittent Preventive Treatment (IPT) is the administration of a treatment dose of an anti-malarial at pre-defined times, regardless of the presence of malaria parasites. Routine health contacts are used to deliver the IPT, and there is no attempt at diagnostic testing. Only IPT in pregnancy (IPTp) is currently recommended by WHO, involving administration of a treatment dose of anti-malarial when women attend routine ante-natal clinics. Recent work on IPT for infants (IPTi) is likely to lead to its inclusion as a recognised WHO strategy for malaria control, although the lack of available, efficacious, long-acting anti-malarials may reduce the potential of this strategy. IPT approaches are also being evaluated for children under five years of age in intensely seasonal transmission settings, in school children and following discharge from hospital. There is a need to develop new, high efficacy, long half life anti-malarial drugs for use in IPT strategies.

Other developments in malaria prevention include **house screening** to prevent entry of mosquitoes into houses and thus protect from mosquito bites, and attempts to **control mosquito larvae**, which have been shown to reduce populations of adult mosquitoes but not necessarily to have an impact on the health of local people. However, most attention and research investment in preventive strategies has been focussed on the development of a **vaccine**. Encouragingly, the group was informed that RTSs, jointly developed by the Malaria Vaccine Initiative (MVI) and GSK, has entered a phase three clinical trial which, if successful, will be the last step before file submission to regulatory authorities of the vaccine for routine use in sub-Saharan Africa.

Development of a malaria vaccine

The scientific challenges to the development of a malaria vaccine lie in the complexity of the Plasmodium parasite. So far, no vaccine is in human use against a whole parasite. *P. falciparum* has approximately 6,000 genes, many more than a virus, and it's unclear in the midst of such complexity, how best to induce a protective immune response. An ongoing problem has been the lack of a surrogate marker of immune protection, meaning that the only way to assess whether a potential vaccine is likely to work is by means of clinical efficacy trials. To be confident that a vaccine is safe and works sufficiently well to be deployed as part of an integrated malaria control strategy, it is necessary to conduct a series of increasingly large efficacy trials. These are costly, complex and require committed collaboration between vaccine developers, funders and clinical trial sites in Africa. All this is required to develop a vaccine for which there will be a limited market, if any, in developed countries and where target countries are the poorest in the world; this is a high-risk, high-level investment. Nevertheless, with major support from the Bill and Melinda Gates Foundation, a collaboration between MVI, GSK and 11 clinical trial centres in seven African countries, plus a variety of Northern institutions, has initiated a Phase 3 trial to support licensure of the world's first potential malaria vaccine.

Several other approaches to making a malaria vaccine are being supported, one of which depends on the growth, harvesting and irradiation of malaria sporozoites, the form of parasite inoculated by the mosquito. Such pioneering work is expensive and takes time but, if successful, could yield enormous benefits.

The malaria vaccine world agreed a goal for 2015 of producing a vaccine with 50% efficacy against severe disease which lasts more than one year. Vaccines are shaping up to be another tool to help achieve malaria control as part of integrated malaria control packages. Even the most successful vaccine imaginable today is not likely to be a magic bullet and would only ever be deployed as part of a strategy also deploying vector control and effective treatment.

3. Tools to control malaria

Treatment of Malaria

Artemisinin-based combination therapy is the recommended, widely implemented mainstay for the treatment of *P. falciparum* malaria. Artemisinin is extracted from the leaves of *Artemisia annua*, a plant which has been used as a traditional Chinese medicine for thousands of years and has high efficacy against malaria. Artemisinin can be chemically modified into artesunate, artemether and artether; referred to collectively as the artemisinins. ACTs are created by combining artemisinins with other antimalarials that have a different mode of action. Patients treated with ACTs benefit from a high efficacy, rapidly acting treatment and the drugs protect each other from the development of resistant parasites. However, only four ACTs are recommended by WHO: artesunate and mefloquine, artemether and lumefantrine, artesunate and amodiaquine, and dihydroartemisinin and piperazine.

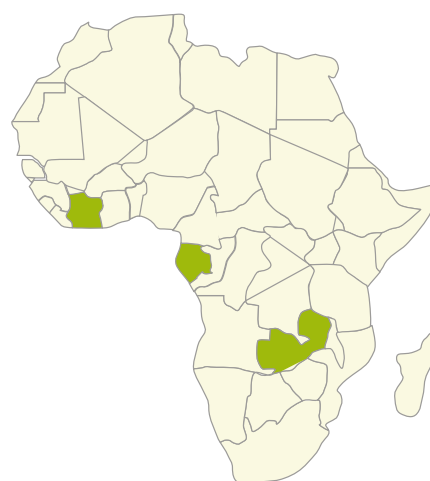
During the last 5 years increasing numbers of African countries have adopted ACTs as first line treatment (fig 3.5). However there are major challenges at almost every level of the production and utilisation of ACTs. In the sections that follow we consider issues surrounding the production of artemisinin, its appropriate formulation for treatment of children, assuring the quality of ACTs, challenges with the supply chain within endemic countries, the role of malaria diagnosis, making ACTs affordable, improving access to ACTs and, finally, the spectre of drug resistance.

Producing Artemisinin

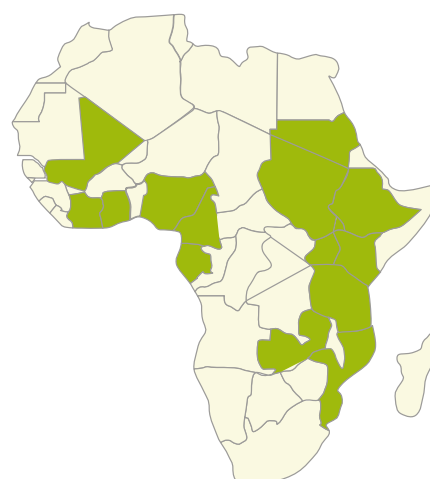
The Group heard how the lack of a consistent, affordable and high-quality supply of artemisinin, and the lack of systems to ensure matched supply and demand, threaten the ability to meet future demands for ACTs. The production of Coartem, by Novartis, for example, requires a very long lead time because the key ingredient, artemisinin, is extracted from a natural plant. Farmers need to have seeds, land and expertise to grow and harvest *Artemisia annua*. Factories need to extract, refine and combine the artemisinin derivatives with other drugs that need then to be co-formulated and delivered to clinics in Africa. The entire process takes about 14 months – 7 months for planting & harvesting, 3 months for extraction and chemical modification, 4 months for product manufacture and shipment.

There is a need to create a complementary source of non-seasonal, high-quality and affordable artemisinin to supplement the current plant-derived supplies and several approaches are being followed to achieve this: fast-track breeding of *Artemisia annua*, being developed by York University, the use of microbial fermentation and the development of novel artemisinin-like compounds.

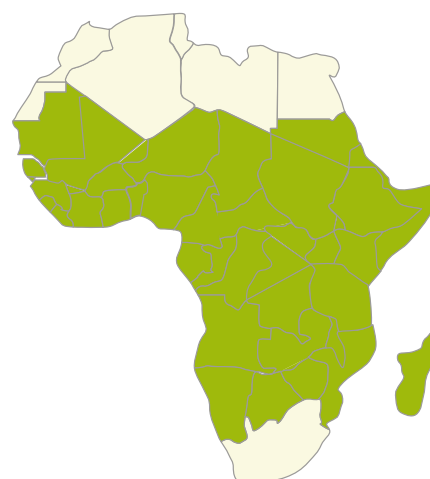
Fig 3.5. Speed of international public health policy change
Adoption of ACT as first line treatment for malaria



2003

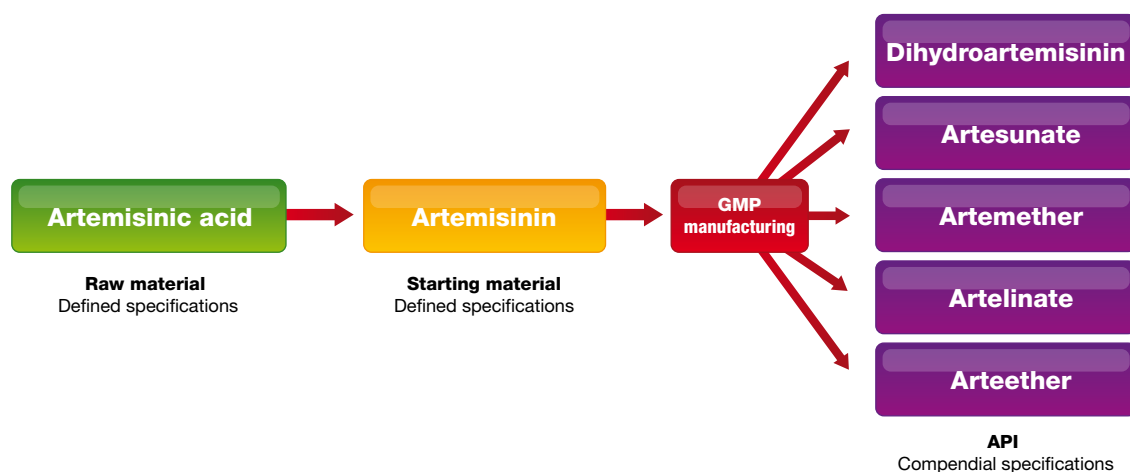


2004



2007

Fig 3.6.Artemisinin As A Starting Material



The development of synthetic approaches using yeast fermentation for artemisinin manufacture would enable production to be accelerated to days, instead of the months needed when using the standard approach.

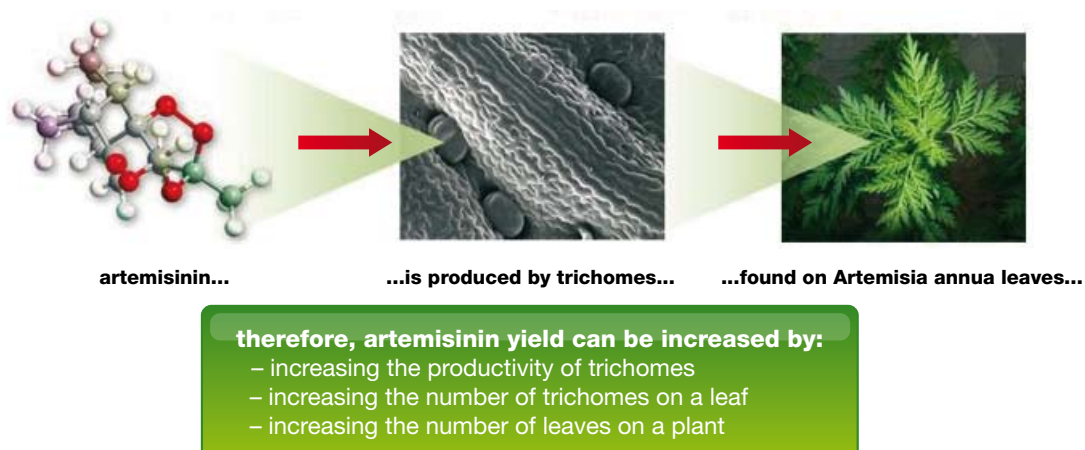
To be of maximum value, the regulatory status of artemisinin needs to be revised. The WHO monograph currently lists artemisinin as an Active Pharmaceutical Ingredient (API), which is at odds with current manufacturing practices. If designated a "starting material", with defined specifications, dihydroartemisinin, artesunate, artemether, artelinate and artether could then be derived using Good Manufacturing Practices to reach API compendia specifications (fig 3.6). This would facilitate the incorporation of synthetically manufactured artemisinin into ACTs.

The Group was informed of the activities of the Institute for OneWorld health, a non-profit pharmaceutical company aiming to develop an

approach to the synthetic production of artesunate. The cost of semi-synthetic artemisinin is anticipated to be comparable to the current cost of high quality field production. The intention is to make semi-synthetic artemisinin broadly available to those derivative and ACT manufacturers who apply a "no profit, no loss" principle.

The Centre for Novel Agricultural Products, at the University of York, is aiming to increase the yield of artemisinin from *artemisia annua* by producing robust plants with a stable, higher yield. High-yielding seed would then be delivered to the ACT supply chain. Higher yields could be achieved by increasing the productivity or number of trichomes, the artemisinin-producing 'organs' on the plant leaves, or by increasing the number of leaves on a plant (fig 3.7). The current two-fold increase in yield is encouraging and expected to be increased further in the near future. This work may benefit from the publication at the end of 2009 of the genetic code of *artemisia annua*.

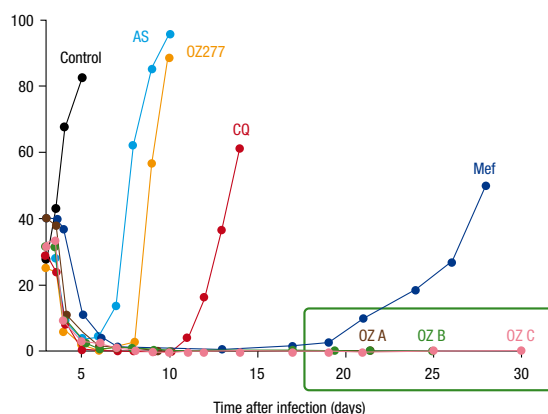
Fig 3.7.Artemisinin is produced by trichomes on *Artemisia annua* leaves



3. Tools to control malaria

Another approach to overcome deficiencies in the natural supply is the development of a new class of ozonide (OZ) compounds known as synthetic peroxides. These OZ compounds have been shown to be more potent than the currently available semi-synthetic artemisinin derivatives. The fully synthetic compounds are expected to cost less than \$1 USD per treatment when used in combination, as part of a three day treatment regimen. Next generation OZ compounds may form the basis of a single-dose oral cure for patients with uncomplicated *P. falciparum* malaria and have the potential to be used as a prophylactic or intermittent preventative treatment in pregnant women and infants (IPTp and IPTi). Currently, second generation ozonide compounds, such as OZ439, are still in early stages of clinical development but have proved better than current therapies when used in a single dose in a mouse model (fig 3.8).

Fig 3.8. OZ439 second generation ozonide: on the path to a single dose cure. OZ439 clearly better than current therapies in a single dose mouse model (100 mg/kg)



Appropriate formulation of ACTs

It is a strange fact that, although the worst effects of malaria are most frequently felt by children under 5 years of age, there have been very few appropriately formulated antimalarials to treat this vulnerable group of patients. As a result, small children have needed tablets to be cut into fractions before being crushed up and administered on a spoon. This results in only approximate dosing as it may be difficult to cut a tablet accurately into a half or a quarter; and difficulties with the actual administration of the tablet result in leakage of the medicine from the mouth or vomiting.

It is also important to have a co-formulated product, to make it impossible to administer each drug separately as a monotherapy, which carries with it an increased risk of selecting and spreading drug resistant parasites. Finally, the child-friendly, co-formulated ACTs, should be pre-qualified by WHO and available for procurement with finances from the Global Fund against AIDS, TB and malaria (GFATM).

The development by Novartis, in partnership with Medicines for Malaria Venture, of Coartem® Dispersible, a paediatric formulation of Coartem, is thus applauded. Coartem® is a combination of artemether and lumefantrine. Produced as a sweet-tasting, dispersible tablet designed to ease administration and improve compliance in children. In 2001, Novartis committed to make Coartem available, without profit, to public sector agencies and malaria-endemic countries under a unique private-public agreement with WHO. As part of the product launch, Novartis described its 'patient centric approach' which involves a training package for health professionals in appropriate languages, best practice workshops with National Malaria Control Programmes and educational materials for patients. Coartem Dispersible is currently the only fixed dose combination ACT recommended by WHO and on the Global Fund Approved List.

There is increasing evidence that poor antimalarial drug quality is a major impediment to malaria control, reducing the effectiveness of otherwise efficacious therapy and facilitating the spread of drug resistance. Despite counterfeit antimalarials having been a significant public health problem since the first trade in 'modern' antimalarials in the 17th century, the quality of the antimalarial drug supply has received remarkably little attention. Much effort and finance has been expended on trying to increase the efficacy of malaria treatment. Very little attention has been paid to the quality of antimalarials actually used by malaria patients or to improving the effectiveness of their delivery.

pyrimethamine, sulphalene-pyrimethamine, quinine, mefloquine, halofantrine, tetracycline, artesunate, artemether, dihydroartemisinin, dihydroartemisinin-piperaquine, artemether-lumefantrine and probably primaquine (fig 3.9).

Fig 3.9. Counterfeit and substandard artesunate have been found in many African countries



3. Tools to control malaria

What should be done to improve the quality of the antimalarial drug supply? First and foremost, sustained political will to improve the situation is desperately needed. The foundation of the International Medical Products Anti-counterfeiting Taskforce (IMPACT) and the recent Cotonou Appeal are important, but rare, statements of political will and action. Strengthening medicines regulatory authorities (MRAs), improving quality of production and facilitating the availability of relatively inexpensive, good quality anti-infectives are likely to be key factors in improving drug quality. There is an urgent need for data of sufficient sample size with representative sampling to estimate reliably the prevalence of poor quality medicines – to be able to decide appropriate interventions, assess their effectiveness, and follow changes through time. We also have little information on what proportion of patients or health workers are aware of the issues in different societies and what interventions may be the most effective. A major limitation is MRA capacity; WHO estimated that 30% of countries have either no drug regulation or a capacity that hardly functions. There are only two WHO pre-qualified Quality Control medicine analysis laboratories in malarious Africa. Support for MRAs, the development of regional laboratories and support for coordinated police, customs & MRA action would allow the regulation of the drug supply. The actions necessary to combat substandard drugs may be more straightforward, as criminal deception is not involved, however these interventions will involve costly improvements in Good Manufacturing Practice and periodic inspections. Increased provision of free or inexpensive medicines for key diseases would undercut the counterfeiters and reduce the criminal financial incentive. The available evidence suggests that poor quality essential medicines are having a very important, but avoidable, toll on health in the developing world and that this issue clearly needs to be taken much more seriously. We remain woefully ignorant and under-prepared as to how these problems can be addressed.

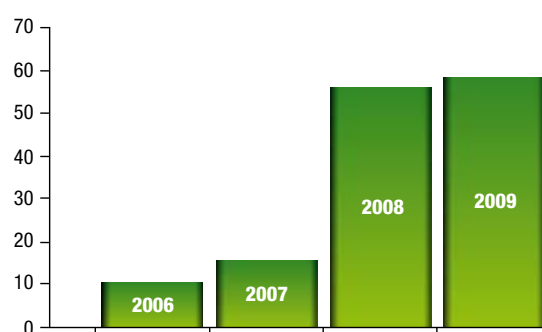
The very high demand for ACTs and their relatively high cost has created a strong incentive for criminal groups to produce counterfeit 'ACTs'. The committee heard how an initiative between academic researchers and forensic investigators identified, characterised and then located the source of counterfeit drugs. The advent of the AMFm should lower prices of good quality ACTs and remove the incentive for counterfeiters to introduce their murderous concoctions lower down the supply chain.

Supply Chain Issues

Adopting ACTs as a policy is one thing; implementing that policy can be quite another. Kenya, Uganda and Zambia are among the countries that have an ACT-based first line treatment policy but which have documented periods with no ACTs in health facilities, or "stock-outs". Clearly, if there are no ACTs in a health facility then even a policy recommending use of a highly efficacious ACT will have zero effectiveness in practice. The Group was informed how in Kenya the recommended ACT, artemether-lumefantrine, was not available in a quarter of facilities in a survey conducted in 2007 (fig 3.10). In contrast, chloroquine was abandoned when it failed to cure one in four patients, but was available everywhere. **Many of the efforts and gains of recent years are thus threatened by problems within the health system: there is a need to improve systems for the ordering, distribution and supply of ACTs. Importantly, the benefits of improvements are likely to be felt in the control of many other diseases.**

There are many potential contributory factors to stock-outs. Some stock outs appear to be due to an inability of some manufacturers to produce the needed supplies, as has been reported for Zambia and Kenya. In addition, stockouts highlight the need for better planning of a change in procurement strategy, and not doing this at a time when stocks are already very low in country. Better alignment between WHO, the Global Fund and the endemic country malaria programmes on the timing of the changed procurement practice could have avoided stock outs. Second, the procurement of millions of treatments from a manufacturer with no proven supply track record for such volumes carries risk; it would be prudent to contract smaller volumes and test the supplier reliability. As increasing numbers of suppliers of generic ACTs become available,

Fig 3.10. Percentage of Kenyan Health facilities without paediatric doses of ACT on day of survey



3/5 health facilities don't have drugs to treat malaria effectively in young children

countries need to implement a tendering process, with its attendant administrative and bureaucratic challenges. Relatively weak, under-resourced regulatory agencies within malaria endemic countries need to be strengthened to ensure robust quality control and management of supplies which make it to the national stores.

Problems with accountability of funds within ministries, including fraud, have also been documented. For example, the Ugandan Auditor General's office was unable to trace USD 150,000 worth of drugs in 2007. The resulting drug shortage led to some Ugandan health facilities not receiving any artemether-lumefantrine supplies from the government for 10 months. This led to increased deployment of sulphadoxine-pyrimethamine, a treatment abandoned in 2006 due to high failure rates, and the inappropriate use of quinine to treat uncomplicated malaria.

ACTs are more complicated to handle than some other drugs as they may be packaged in four different weight-specific categories. Practitioners are increasingly encouraged to confirm the diagnosis of malaria, using a rapid diagnostic test (RDT), before prescribing treatment, adding a fifth commodity that needs to be managed by the system. Each item needs to have its requirements forecast, to be procured and then distributed in a timely manner. Countries also need essential stocks which include a buffer supply.

Weak health information systems make it impossible to optimise the flow of drugs to peripheral health facilities within a country; if data is unavailable on the state of a facility's drug stocks and the number of patients being treated with those stocks, central forecasting of ACT requirements and dispatch of rational quantities, based on need, is impossible.

Stock-outs have also been shown to have negative influences on prescribers' practice even after supplies are replenished. Health workers in Kenya rationed ACT treatments because of a lack of confidence that the ACTs would be re-supplied in a reasonable timeframe.

Insufficient attention is being paid to these problems, but it is becoming abundantly clear that **effective malaria control requires more than efficacious interventions.**

The Group was called to a "third wave of activism". Having raised awareness about the discrepancy between the burden of malaria disease and the level of funding for malaria control - the first wave of activism - the malaria community then advocated for a shift away from poorly performing anti-malarial drugs to the highly efficacious ACTs - the second wave of activism. A third wave of activism, targeting stock-outs, would be timely. Activities could include publicising stock-outs when they occur; for example via Africa's Stop Stock-outs campaign (<http://stopstockouts.org>), advocacy to make the ACT supply chain less vulnerable, increased donor funding to fill gaps in research and deployment of approaches to strengthen the supply chain. It would also help to make technical assistance available from independent sources, especially the WHO and the Global Fund, to build national capacity for ACT procurement, stock management and health information systems. Investment into research on forecasting ACT requirements internationally, nationally, and in peripheral clinics, and on managing commodities, is badly needed and likely to be a very cost-effective activity. Many of the activities will have far-reaching effects for health service provision and commodity procurement and distribution, extending well beyond the single disease motivating the activities, malaria.

Diagnosis of malaria

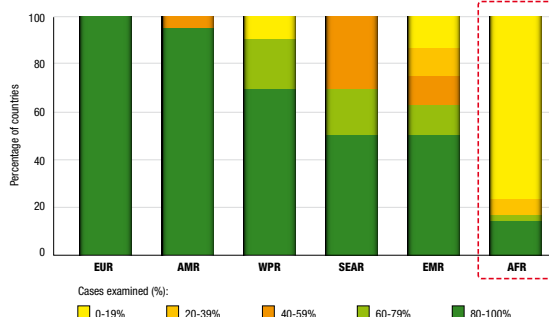
The WHO Global Malaria Programme published revised patient management guidelines in 2009 which recommend diagnosis before malaria treatment. This signals an end to the practise of presumptive malaria treatment for patients. The Group heard evidence from the Foundation for Innovative New Diagnostics on the rationale behind this recommendation. The significance of the change of policy should not be underestimated.

Prompt parasitological confirmation by microscopy or alternatively by rapid diagnostic tests (RDTs) is recommended in all patients suspected of having malaria, before treatment is started. Treatment solely on the basis of clinical suspicion should be considered only when a parasitological diagnosis is not accessible.

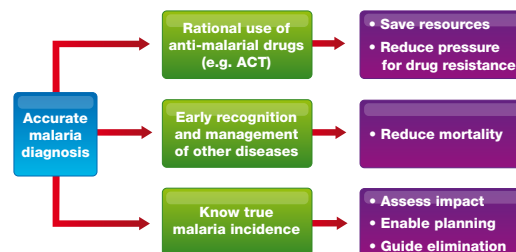
3. Tools to control malaria

Fig 3.11. Accurate diagnosis at community level: Effort and outcomes

Percentage of suspected malaria cases in public health facilities that were given a laboratory diagnostic test, by WHO region, 2006



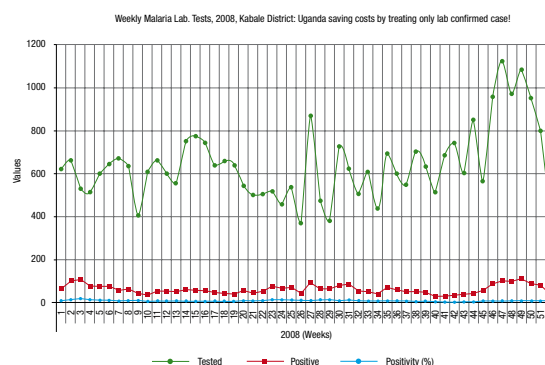
Is it good enough to guess in Africa, when this is not acceptable elsewhere?



This means the use of blood slide microscopy or RDT at all hospitals, Health Centres, private clinics, aid posts, private pharmacies and other health workers at a village or even household level. Such extensive use of diagnostics is common practice in all WHO regions except Africa (fig 3.11). The recommendation grows out of the observations that even in sub-Saharan Africa most malaria-like fevers are not due to malaria, with studies suggesting a frequency of parasitaemia of between 2% and 81%, and declining in recent years. Hence presumptive malaria treatment practices will result in about three quarters of antimalarials being given to patients who do not actually have the disease. This is unacceptable in terms of mis-diagnosis and the delayed treatment of other potentially fatal diseases, drug wastage, the risk of accelerating the spread of drug resistance, the cost of ACTs and the problems with global availability of artemisinin. A parallel consideration is that counting all episodes of fever as malaria inflates the estimated burden of disease and creates difficulties in the use of routine data to track progress with malaria control strategies, preventing evaluation of interventions and implementation of elimination strategies. Evidence from Zambia, Senegal and Uganda showed a dramatic reduction in reported malaria once RDTs were introduced (fig 3.12-3.13).

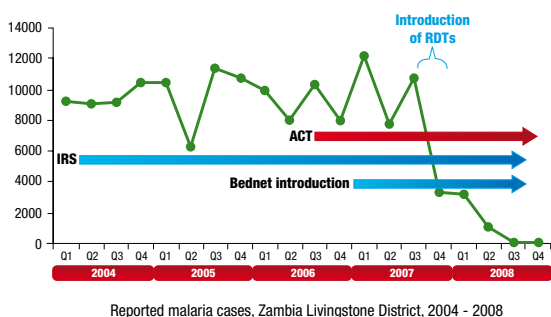
Introduction of diagnostic testing stands to improve the management of both malaria and non-malaria fevers, to reduce drug costs, improve availability of ACTs, limit the spread of artemisinin resistance and provide more reliable health information on the burden of malaria disease. Furthermore, the feasibility of deploying RDTs on a large scale has been demonstrated in a number of countries (fig 3.14).

Fig 3.13. Uganda, RDT implementation



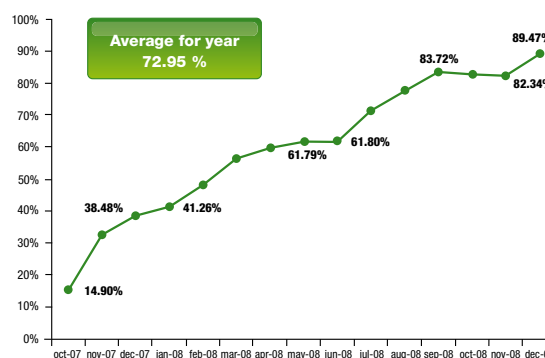
Sources: Courtesy Uganda MoH, Uganda WHO office

Fig 3.12. RDT impact, Zambia



Reported malaria cases, Zambia Livingstone District, 2004 - 2008

Fig 3.14. Senegal RDT implementation (% of RDT use by month in 2007 - 2008)



Sources: RBMME / PNLP dec-2008. Courtesy Babacar Faye and Senegal MoH

The performance of different types of RDTs has recently been evaluated by a joint WHO-FIND initiative, a valuable programme providing an independent, standardised assessment of the performance of a large number of RDTs. A total of over 200 products from over 60 manufacturers were considered, although initial screening quality criteria meant that formal performance testing was conducted on only 41 products from 21 manufacturers. A notable result was the relatively poor performance of many tests when the level of infection is low, an observation which has implications not only for the routine use of the tests but also for their use in the context of an elimination programme. This programme continues to evaluate further products.

Having identified the most appropriate tests to deploy as part of an integrated malaria control strategy, there is a pressing need to develop quality assurance strategies at the national level to ensure that product performance remains high. This is best done by re-testing products when they are purchased, before they are sent to the field, ensuring that they have not been damaged through poor handling during transport. This also provides evidence to users and regulatory authorities that tests are working, building confidence in the programme. A network of testing sites has been established in order to make this possible. Further, monitoring of quality when deployed in routine clinical practice is needed, along with adequate training materials and community education to enhance acceptance of the RDTs and their results. Many of these considerations can be developed in coordination with similar processes for laboratory services for other diseases, integrating supervision, training and reporting to strengthen more broadly community-level health systems. Such integrated, innovative approaches to planning, infrastructure and training for RDT programmes are being developed and include the use of programme management software, SMS (mobile telephone text messaging) to report disease and stock levels, standardised job aids, training manuals and logistics manuals.

Much attention has, in recent years, focussed on the performance of RDTs. There is a dawning realisation that, in order to have an impact with RDTs, it will be necessary to build programmes to support their proper use: to procure, transport and store RDTs; to train people to use the tests and how to manage those with non-malarial fever; to educate communities, supervise RDT users, monitor accuracy of RDTs in routine clinical use, establish lot-testing and laboratory monitoring, procure gloves, sharps disposal containers and related equipment. It is necessary not just to fund procurement of the RDTs, but to develop sustainable, in-country capacity to manage those programmes.

“ To realise the potential impact of RDTs, funding procurement is not enough: we need to build programmes and develop sustainable in-country capacity ”

Diagnostic challenges and developments in the pipeline

A major challenge to be resolved is **how best to manage patients who have a negative RDT result**. Health staff and patients alike have grown used to using anti-malarial treatment in almost all patients with fever. This makes sense if malaria is very common, the treatment readily available, safe, affordable and there are no concerns about drug resistance. However, this is no longer the situation. If a patient with fever has no malaria, how should poorly trained and equipped prescribers decide whether or not to refer the patient, to treat with antibiotics or reassure that the illness will be self-limiting? This is an important dilemma which cannot be ignored and warrants urgent investigation. Tests will frequently be done by people without comprehensive clinical training and without access to other diagnostic tests. In the absence of alternative therapeutic strategies evidence suggests that prescribers tend to follow the current and accepted norm of prescribing anti-malarial treatment, even in the face of a negative malaria test result. There is a clear need to explore options for guiding the management of patients with negative malaria test results. Extensive behaviour change communication programmes are likely to be necessary to educate communities and health workers that not all fevers are malaria and to enable them to accept negative results. Getting this message across may benefit from interactions with the educational sector, faith-based organisations and other relatively uncommon interactions. It will also be necessary to develop and test algorithms to guide the management of patients with negative malaria tests. It would also be very useful to develop additional diagnostic tests to indicate whether specific treatment (eg antibiotics), or referral of the patient, are warranted.

3. Tools to control malaria

Recommendations

- Support efforts to introduce competent systems for the diagnosis of malaria at all levels of the health system, remembering the need to go beyond procurement of RDTs and to build and implement sustainable in-country programmes providing all necessary logistic support and quality assurance.
- Explore the potential of RDTs in community-based management strategies and in the private sector.
- Support efforts to optimise the management of patients with a negative malaria test. In particular, identify patients who need referral, treatment with antibiotics or other interventions, and those with self-limiting illnesses for whom reassurance should suffice.
- Consider diverting some of the AMFm or alternative subsidy to supporting the implementation of routine diagnostics.

In the research pipeline

It is highly desirable to move control of **quality assurance** to national programmes and health workers in endemic countries. With this in mind recombinant antigen-based testing panels are being developed for RDTs. This also highlights the need to harmonise standards and RDT detection thresholds between developers, manufacturers and users.

As progress towards elimination continues it will be necessary to identify people, acting as potential transmission sources, who may frequently have low levels of parasitaemia. RDTs are more sensitive than routine field microscopy but still struggle to detect parasites when there are less than about 100 per µl of blood. A new approach being developed called LAMP (Loop-mediated isothermal DNA amplification) can detect 1-6 parasites/µl with minimal sample processing, requires no sophisticated equipment, can be read with the naked eye and could also be used as the basis for high throughput screening.

The need to make RDTs affordable

The Affordable Medicines Facility for malaria (AMFm – see page 20) introduces a complexity by reducing the cost of ACTs at a time when pre-treatment diagnosis is being encouraged. There is **little incentive to perform a diagnostic test if it costs more than the treatment**. For years it has been accepted that all fevers should be treated as malaria. There is now a need to educate communities, clinical professionals, politicians and administrators that malaria is a decreasingly common cause of fever in many places, and that it is possible to perform a test to see if ACTs are likely to help. If RDTs cost more than the ACTs then uptake of the diagnostics can be expected to be poor. There is therefore a case to consider diverting some of the AMFm subsidy to supporting diagnostics. Failure to do so will result in widespread but inappropriate use of ACTs, encouraging resistance, exacerbating ACT stock-outs and leaving other causes of illness inadequately recognised and treated.

If ACTs are widely available in the **private sector** it will be important to explore the feasibility of introducing **diagnostic capacity** into that setting. Failure to achieve this will result in all fever being treated as malaria at private drug shops while there will be pressure not to treat fever as malaria in the presence of a negative test result in public sector health facilities. Such mixed messages cause confusion and risk chaos.

Affordability of ACTs

The APPMG's 3rd Report, 2007, described the potential of the AMFm to save lives. The need to introduce ACTs was driven by the malaria parasite's development of resistance to affordable drugs, costing a fraction of a dollar (eg \$0.20) such as chloroquine and sulphadoxine-pyrimethamine. However, ACTs usually cost several dollars, and not infrequently up to \$10 -- prices which are beyond the majority of the vulnerable poor who most need the treatments. The AMFm concept requires a co-payment at the factory gate to allow first-line buyers to purchase ACTs at similar prices to the old but now ineffective drugs. The 2007 report endorsed the concept but recognised the need for more work to ensure a market mechanism to drive down prices and not to undermine local pharmaceutical enterprises in malaria endemic countries. **However, the need to improve access to ACTs and to reduce to a minimum the use of inappropriate drugs was, and remains, extremely urgent, so countries were asked to submit proposals to the AMFm in 2009.**

AMFm Pilot

The Group received evidence about a pilot implementation of an ACT subsidy run by the Clinton Foundation and launched in Tanzania in late 2007. Up to a 95% subsidy for the cost of ACTs was provided at the level of the national wholesaler. The wholesalers distributed subsidised ACTs to small private shops using their normal distribution networks and systems, in two intervention districts, a third district being maintained as a control. A package of interventions was involved, including marketing and training of shopkeepers within the districts. Collection of robust data enabled an assessment of impact. There was a rapid increase in people purchasing ACTs, particularly for children under 5 years, within 3 months of the launch in the intervention districts, with no change in the comparison district. At the same time, prices paid by patients for ACTs fell dramatically. For instance, ACTs which used to cost \$10 in Dar es Salaam became available to children under 5 years for \$0.35, comparing favourably with \$0.67 for sulphadoxine-pyrimethamine and \$0.85 for artemisinin monotherapy. Hence ACTs became more affordable than artemisinin monotherapies, which are considered an important driver of resistance to artemisinin. The Tanzania pilot treated ~100,000 patients in the first year and generated useful operational experience.

The launch of AMFm in 11 Phase I countries was announced at the end of 2009 and is expected to reach about 60 million patients per year. Independent evaluation is to be presented to the GFATM board

in 2012 which will then decide whether the AMFm should be extended and expanded. However, on the basis of current signs and the piloting experience, the APPMG recommends that the malaria donor and control communities plan for the success of AMFm Phase I and put in place a formal planning assumption which they commit to and work towards.

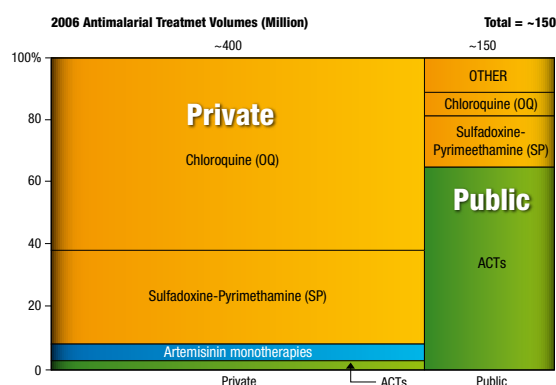
Access

The Group was informed that current evidence suggests that most of those who need ACTs do not get them and it is therefore necessary to invest not only in drug development but also in new ways of delivering drugs to those who need them.

Role of the private sector

Data presented to the Group showed that the majority of anti-malarial treatments, about 400 million of the total 550 million estimated treatments in 2006, were delivered through the private sector (fig 3.16). Furthermore, the types of antimalarials available from the private sector left much to be desired with artemisinin monotherapies and failed drugs such as SP and chloroquine making up the bulk of drugs dispensed. The AMFm should enhance the availability of affordable, quality ACTs through the private sector. There is a need to work with the private sector to explore the feasibility of introducing diagnostic testing to improve the targeting of ACTs (see page 16). A major challenge in the private sector is the difficulty of its regulation. There are a huge number of organisations of all sizes working in this field that need to be co-ordinated and regulated effectively.

Fig 3.15. Sources of anti-malarial therapy in 2006



Note: Other category includes Mefloquine, Amodiaquine and others. ACT data based on WHO estimates and manufacturer interviews.
Source: Biosynthetic Artemisinin Roll-Out strategy, BCG/Institute for OneWorld Health, WHO, Dalberg.

3. Tools to control malaria

Home Based Management of Fever

Home Based Management of Fever (HBMF) is an approach which aims to expand access to quality ACTs by having community health workers (CHW), who may be volunteers, deliver anti-malarials to families directly in the home. This should improve access to life-saving medicines for those who currently lack access.

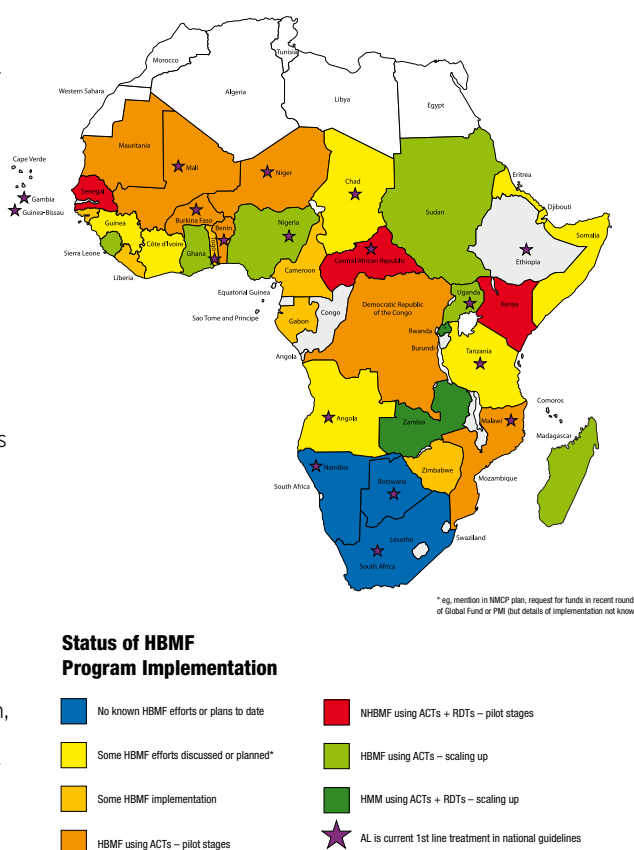
So far HBMF has focussed on children aged under five years living in highly endemic rural areas in Africa, where most fevers have been presumed to be *P. falciparum*. The expectation is that effective treatment delivered soon after symptoms appear will be a cost effective approach to reduce malaria morbidity and mortality. Work in the last decade has shown the importance of community participation and the acceptability of the approach, and generated operational experience about incentivising volunteers and the factors affecting attrition. Simple training materials and the availability of pre-packaged drugs are also important for the success of HBMF.

Work to evaluate the ability of community volunteers to use RDTs to diagnose malaria started in 2009. As in health facilities, the challenge of appropriate and acceptable management of those with a negative RDT has been recognised. In addition, the logistic and managerial challenges of establishing and supervising an adequate, community-based RDT programme are considerable.

There has been recent interest and support for Integrated Community Case Management (ICCM) which aims to broaden the remit of community workers to care also for those with pneumonia and diarrhoea, and ultimately to facilitate access to a range of treatments for all major childhood diseases. There are concerns about minimally trained individuals managing multiple therapies to which resistance can develop, including antimalarials and antibiotics, and the challenges of expanding CHW training and drug supply management.

The Group was told how MMV is tracking HBMF activities and compiling information on recent and ongoing CHW activities, thus generating a broad overview of the area (fig 3.16). Pilot studies have demonstrated that CHWs can deliver correct treatments and that adherence to treatments can be good. Despite the attractions of HBMF, efforts to scale up have been slow. Success in Zambia was associated with parallel investment and strengthening of malaria control in the formal health system. Work needs to be done to establish a reliable and adequate drug supply, develop mechanisms to train, manage and retain CHWs, and to develop information systems to assess quality of care and performance. Although the establishment of a new

Fig 3.16. Countries including HBMF in their national malaria control plans



cadre of health workers at the community level is an attractive idea, it must be recognised that they need to be managed and supported, something the formal health system struggles to do with those employed within the formal health system.

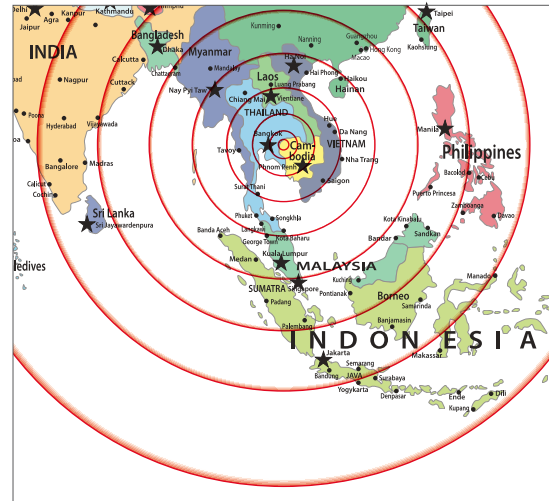
Critics of the approach warn that HBMF will be wasteful if diagnostics cannot effectively be introduced, and that the resulting overtreatment with ACTs would exacerbate supply challenges at the country level and stock outs in facilities at the same time as increasing concerns about drug resistance. HBMF has proved difficult to scale up, especially because of problems with retention of CHWs. It is important to note that HBMF is not applicable everywhere, for example in settings where there is relatively good access to health facilities. Despite these concerns, HBMF may be a useful stop gap while sustainable health infrastructure is built, if it is applied in a targeted manner. It is likely to be most useful in remote, rural villages without alternative means of access to care. Such community-based initiatives are still in the early stages of development in most countries and there is a lack of understanding or agreement about how best to approach the challenges.

The Threat of Resistance

In July 2009 the New England Journal of Medicine published a paper confirming the appearance of resistance to artesunate on the Thai-Cambodia border (fig 3.17). The senior author presented evidence to the Group and emphasised that this was a particularly worrying development as resistance to chloroquine was described in this area in the 1950s before appearing in Africa in 1978. Chloroquine resistance became a major operational problem, associated with increased child mortality, during the 1980's. Chloroquine was replaced in many African countries by SP, but rapidly rising resistance, also first described on the Thai-Cambodian border, necessitated a switch to ACTs in most countries during the early part of this millennium (fig 3.18). Hence the threat of resistance originating in south-east Asia to the first line treatment in many African countries is cause for grave concern.

Research over the last two years has confirmed an increased time for malaria parasites to be cleared from the blood – in other words, patients are taking longer to be cured of malaria. It is unclear how far the resistance has spread but a containment programme is underway in the areas known to have been affected.

Fig 3.18. The epicenter of anti-malarial drug resistance



During 2009-2010, several innovative packages of activities are being piloted and refined with the aim of containing artemisinin-resistant malaria. Evidence for key decisions is expected during 2010 so that, with support from WHO, the Bill and Melinda Gates Foundation, USAID and others, the chosen plan can be implemented. The primary focus will be on *P. falciparum* although activities will also target *P. vivax*. Three containment zones have been identified (fig 3.19). The aim is to eliminate malaria transmission from the relatively small Zone 1 and intensify malaria control in Zone 2. The target for 2015 is to have eliminated artemisinin-resistant malaria parasites from Thailand and Cambodia and to continue moving these countries towards pre-elimination status for *P. falciparum*.

Fig 3.17. Effect of artesunate on sensitive and resistant *P. falciparum* parasites

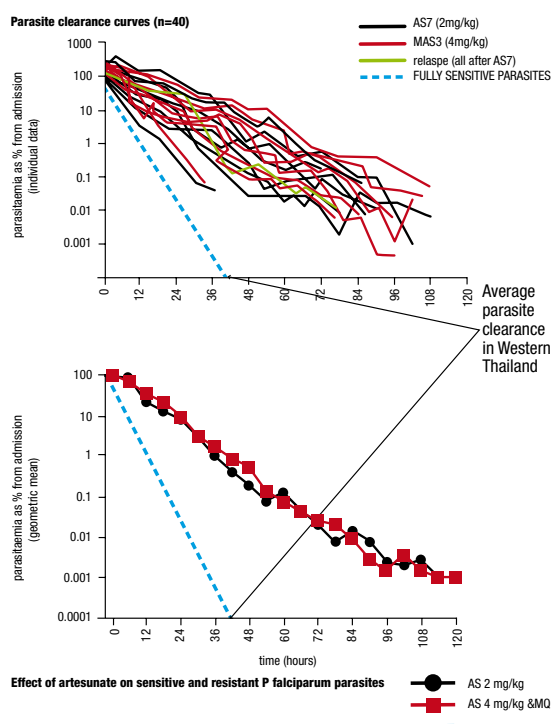
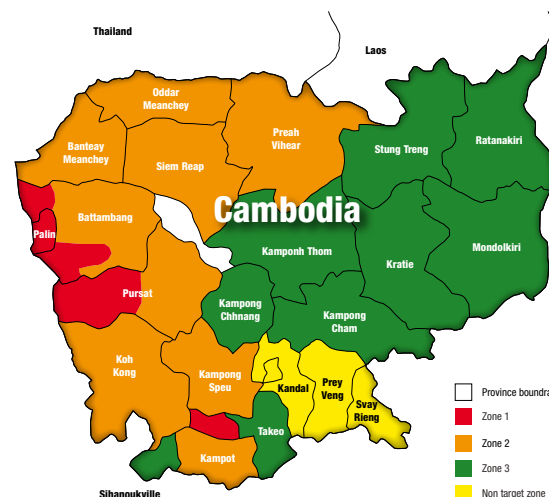


Fig 3.19. Map showing containment zones for efforts to contain resistance to artemisinin



3. Tools to control malaria

The intention is to detect all malaria cases, including those among the mobile and migrant populations, and ensure that they are effectively treated. Efforts to prevent the transmission of resistant parasites will be based on mosquito control and personal protection from mosquito bites, again with particular efforts to target mobile and migrant populations. A parallel strategy will decrease the amount of artemisinin available to select resistant parasites by preventing the use of monotherapy and substandard drugs in both the public and private sectors. These activities will be accompanied by comprehensive behaviour change communication (for example encouraging compliance with treatment courses and dissuading people from the use of monotherapies), community mobilisation, advocacy activities, and by efforts to provide effective co-ordination and management.

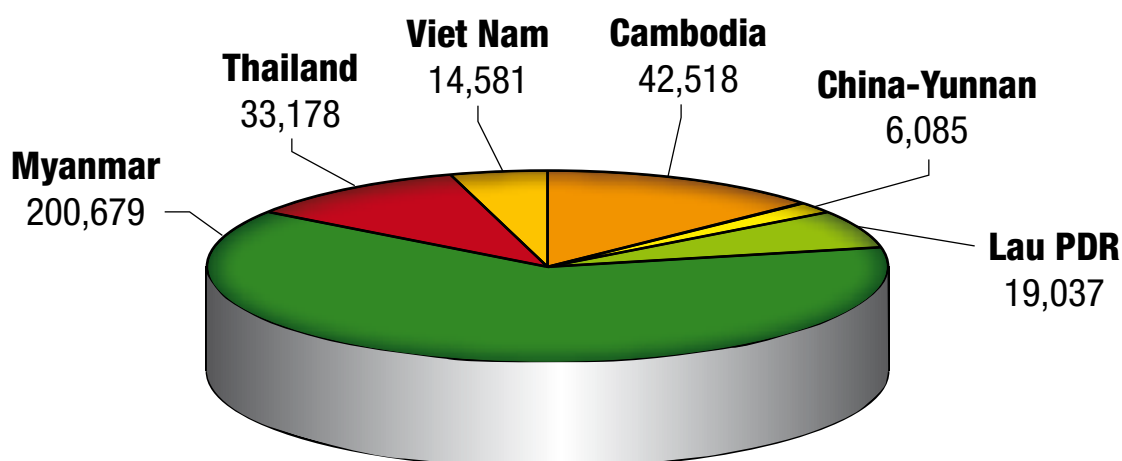
There are clearly many challenges; how best to access mobile and migrant populations; how to strengthen surveillance and information systems; how to suppress the use of monotherapies; how to engage with the private sector; issues surrounding patient behaviour and the need for joint action by Thailand and Cambodia. The countries are working to submit separate but co-ordinated proposals to the Global Fund for this work.

These activities are being planned with an eye to sustainability of the interventions in the longer term. An anticipated problem will be maintaining interest, understanding and commitment to this complex subject and ensuring adequate resources are made available quickly. It is important to appreciate that the issue of artemisinin resistance is not so much of a problem for the local people; the burden of malaria disease is not as high as in Africa and patients taking ACTs continue to see them work; they just take a little longer to recover from their illness. The main beneficiaries of effective resistance containment are likely to be outside the region. It is already proving hard to persuade people about the need to tackle the problem in south east Asia.

A major concern is that if action to prevent the spread of resistance is not successful and resistant parasites make it to Myanmar, it will become extremely difficult to contain the resistance. Myanmar has a considerably higher burden of disease than its neighbours (fig 3.20) and a difficult political situation. Nevertheless, there is a strong rationale to involve Myanmar in the containment efforts.

It is clear that there is no room for complacency and that we cannot rely on current tools lasting forever. We can retard the rate of loss of good tools by strengthening systems and taking regulation seriously. There remains an imperative to invest in the development of new malaria control tools.

Fig 3.20. Distribution of confirmed malaria cases in the Greater Mekong Subregion, 2007*



Source: National Malaria Control Programmes & WHO
*2006 data for Myanmar

4. Financing malaria control

Financing malaria control

The five years since the APPMG started have seen a sea change in funding for malaria control and research. Between 2004 and 2008 international donors increased available resources five-fold, from \$249 million to \$ 1.1 billion. Steady year on year growth in contributions from the GFATM were augmented by major additional contributions from the World Bank, the Bill and Melinda Gates Foundation and US President's Malaria Initiative (fig 4.1). The GFATM allocated over \$1.4 billion to malaria in its eight round of funding alone, with a further \$783 million awarded in round nine. **The increase in resources has been associated with reduced malaria cases and deaths, which should reassure the donor community that investing in malaria control works and the value of locking in the gain by sustaining the funding.** Malaria control is also expected to increase productivity of the workforce, thus helping endemic countries to pull themselves out of poverty.

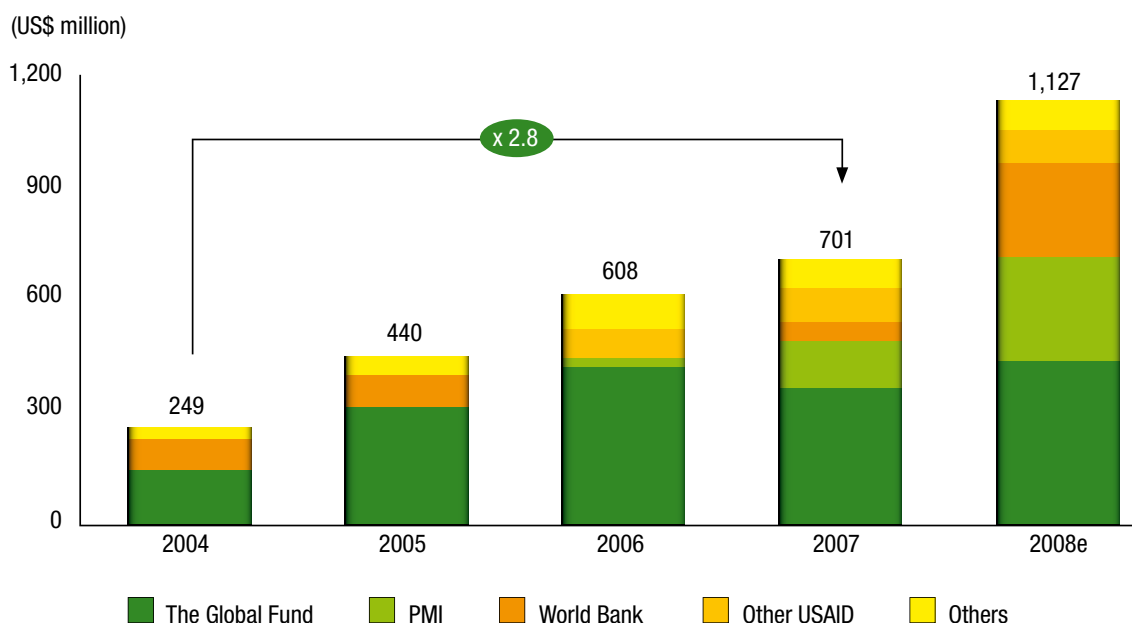
Nevertheless, progress to date falls far short of internationally recognised targets. The United Nations Millennium Declaration set a target to halt and begin to reverse the global incidence of malaria by 2015. However, effective interventions that reduce death and illness from malaria are still not widely accessible in most malaria endemic countries. The World Health Assembly in 2005 urged Member States to establish policies and operational plans to ensure that at least 80% of those at risk of malaria benefit from the major preventive and curative interventions by 2010, so as to ensure a reduction in the burden of malaria of at least 50% by 2010 and 75% by 2015, compared with

levels at 2000. These targets are echoed in the Roll Back Malaria Partnership's Global Strategic Plan (2005-2015) and the Global Malaria Action Plan (GMAP).

Despite the increased levels of funding, financial gaps remain and these targets have not been reached in most settings. Health systems are in dire need of strengthening to ensure that adequate human resources are available, even in remote health centres, and adequate surveillance, monitoring and evaluation is established. Supply chains need to be better managed to avoid stock outs of critical commodities. Diagnostics need to be introduced and managed, the cost of RDTs being maybe only half the cost of a proper RDT programme. The GMAP estimated a need for US\$ 5.3 billion in 2009 and US\$ 6.2 billion in 2010 in order to achieve malaria control and move towards the Millennium Development Goals. Hence a five-fold funding shortfall still exists and threatens the success of the GMAP.

Furthermore, the GFATM is facing a fiscal challenge and donors need to be held accountable to their pledges and additional resources will need to be identified if funding is to be made available at the required level and in order to be able to expand the AMFm after phase I. There is an important gap in funding for improved malaria control in the private sector and at the community level, although the PMI is investing in ICCM. Resolving these challenges will require an unprecedented level of coordination and collaboration but they must be tackled if the true power of available malaria control tools is to be unlocked.

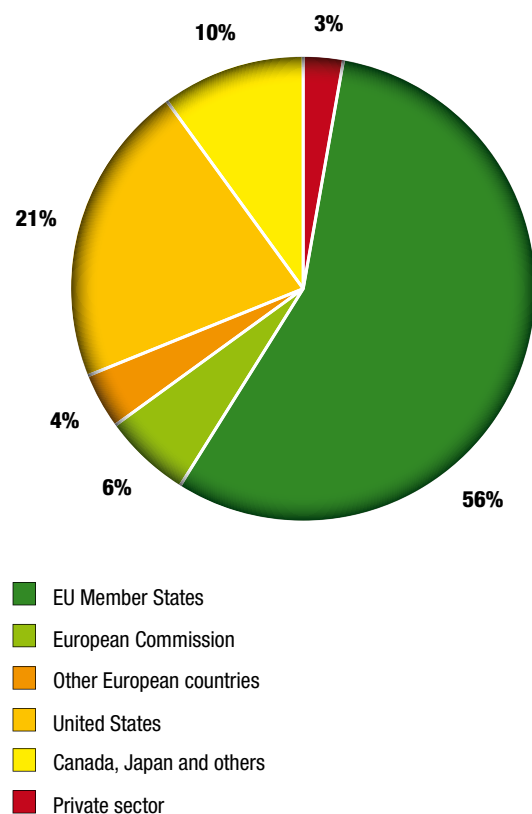
Fig 4.1. The contribution of international donors has grown dramatically and quickly



4. Financing malaria control

Fig 4.2. European ODA is a core funding source for the Global Fund

Pledges and contributions 2002-2010 and beyond: USD 20 billion



The role of Official Development Assistance (ODA) is important and the potential impact of governments increasing their contribution is enormous. In addition, new, long-term and predictable sources of financing need to be sought. Britain's involvement can help sustain European leadership at all levels. Improved European governance and aid harmonisation, and ensuring the additionality of innovative financing mechanisms with national decision-making processes, can make an enormous difference.

Europe played a crucial role in the creation of the Global Fund, an initiative which has profoundly changed the international landscape for the fight against AIDS, TB and malaria. Over 100 million mosquito nets, and a similar number of ACT malaria treatment courses, have been procured and delivered through the fund. European support continues to be vital for the fund's success, with 62% of total pledges and contributions between 2002-2010 originating from Europe (fig 4.2). France tops the list of European contributors (300 million Euros a year) with important contributions also from Germany, UK, Italy, the Netherlands and Spain, which pledged US\$ 213 million in 2009 alone. However, the existing pledges amount to about \$3 billion this year, far short of the \$15 billion likely to be needed in order to support competent proposals for improved AIDS, TB and malaria control from the 140 countries the GFATM supports. Particularly worrying is a fall in pledges for 2010 compared with 2009, the first time there has been no growth in annual pledges since the fund began. There is considerable variation (between 0.08-0.16%) in the proportion of Gross National Income (GNI) which European and north American countries donate to the GFATM. Agreeing a target proportional contribution could substantially increase the resources available to the GFATM and enhance the predictability of support. **Bold action now could consolidate the current fragile success in malaria control, a success that was hard fought but remains easy to lose.**

The past decade has seen several other innovative funding mechanisms developed, which have facilitated unprecedented collaboration and scale-up of control efforts. In addition to backing the GFATM, European countries have supported UNITAID, launched in 2006 by France, the UK, Brazil, Chile and Norway as an international drug purchase facility for treatments for AIDS, TB and malaria. France is the only country in Europe to have introduced an air ticket levy to ensure sustained funding to UNITAID, although the UK and Spain have allocated multi-year funding.

Another initiative, Debt2Health, was launched in 2007 as a debt relief mechanism which works by converting foreign debt owed by poor countries into investments for local prevention, treatment and care programmes, approved by the Global Fund. Germany was the first donor to support the Debt2Health Initiative by writing off more than 50 million euros of Indonesia's debt, in return Indonesia providing 25 million euros to fight these three diseases.

Finally, the Affordable Medicines Facility for malaria - AMFm - was launched in April 2009 in Norway (see page 20). This is an innovative mechanism to make the most effective medicine for malaria, the artemisinin-based combination therapies (ACTs), available and affordable. The initial costs for medicines, in the first two years, will be shared by UNITAID and the UK government.

Health benefits are likely to be visible and to remain visible for many years, as the number of malaria cases and deaths continue to decline with increasing investment. However, continued funding will also be required in settings where the benefits are not so obvious. Considerable resources will be required to maintain high coverage of preventive measures, case detection and other activities in settings where malaria has been effectively controlled. Only once elimination has been achieved might it be safe to start to ease off on investment for continued control. The main benefit of ongoing investment will be an absence of reintroduction and resurgence of malaria. Although success in elimination will produce endless ongoing health and economic benefits, high levels of investment in malaria control will continue to be needed when there are few and no cases. Maintaining political will at this point will be exceptionally challenging. The link between investment and burden of disease will be less clear: **It is thus essential to ensure that all governments and donors concerned with elimination in a setting understand the need for long-term funding and political commitment. Elimination activities should not be plagued by the commonplace, marked year on year variation in donor contributions to health. Concerned donors will need to make more than the customary 1-2 years time commitment and curb their appetite for demonstrable reductions in disease.**

A similar situation exists regarding containment of resistance to artemisinin, which has been reported from an area with only a modest burden of disease around the Thai – Cambodia border. Nevertheless, major investment will be required to stamp out the resistant parasites before they spread to other parts of the world. Should this not be achieved in south-east Asia and the resistant parasite spreads to Africa, vigorous efforts, on a sufficient scale and no doubt requiring substantial funding, will be required to avert losing the gains made in recent years.

5. Co-ordinating control

No single institution, government or company can alone achieve success in malaria control; strong partnerships are required at national, regional and global levels. The rapid expansion of resources and activities in malaria control and research has heightened the need for effective co-ordination and leadership. Malaria has to be fought from multiple sides and with the involvement of several sectors: research and product development, programme implementation and evaluation, education, communication & advocacy. There is a vital need for collaboration between donor governments, developing country governments, private sector firms, communities, and NGOs, at the national level in endemic countries, and also across countries and continents.

Leadership & Co-ordination

Ministries of Health and National Malaria Control Programmes look to **WHO for technical expertise and leadership.** The Global Malaria Programme (GMP) has been through a period of turmoil giving some the impression that it is in competition with rival, wealthier institutions, and struggles to take a clear lead. Yet it has achieved a surprising amount given the very limited resources available to it. There is a strong case for increased support to the only UN agency whose mandate relates solely to health, to enable it to re-build its credibility and leadership role. The GMP should be resourced to take full advantage of its power to convene technical and public health experts, programme managers and policy makers, in order to develop robust, evidence-based recommendations and strategies for malaria control and elimination. At the same time, the GMP needs clear signs of support from within WHO to demonstrate to Member States and to the international donor community the high priority it places on rolling back malaria.

Strong leadership is undermined unless supported by powerful, co-ordinated efforts to effect progress on the ground. The RBM partnership achieves impressive feats of co-ordination (fig 5.1) and advocacy by engaging with the entire malaria community – governments, Parliaments, civil society, aid and UN agencies, business leaders and philanthropic ventures. The launch in 2008 of the Global Malaria Action Plan was an important milestone. The GMAP is the comprehensive consensus strategy on malaria, produced through an inclusive process and aiming to reduce malaria rapidly, incrementally eliminate from countries, and eventually eradicate, malaria worldwide. The GMAP provides a roadmap for reaching key malaria targets - universal coverage by 2010, reducing deaths to near zero by 2015 and sustaining gains and working towards elimination beyond 2015. The plan details the required actions in distinct geographic regions and on a year by year basis. Furthermore, by calculating the cost of reaching the targets - roughly \$ 5 billion annually for control and \$1 billion for research and development – it clearly sets the funding targets.

Fig 5.1. A Partnership forged to fight malaria



GMAP Targets:

- Achieve universal coverage by 2010 and sustain universal coverage indefinitely;
- Reduce global malaria cases from 2000 levels by 50% in 2010 & by 75% in 2015;
- Reduce global malaria deaths from 2000 levels by 50% in 2010 & to near zero in 2015;
- Eliminate malaria in at least 8 countries by 2015 and afterwards in all countries in the pre-elimination stage today; and
- In the long term, eradicate malaria world-wide through progressive elimination in countries

Achieving these targets is expected to expand access to core interventions and help save 4.2 million people's lives in the 20 highest burden African countries by 2015. The GMAP recognises that, in some high-transmission countries, control measures may need to be maintained for many years until new tools are developed to enable elimination. However, by documenting the impact of investment in control in high burden settings it will be possible to demonstrate the return on the financial investment.

RBM continues to raise awareness and encourage collaboration between governments, international organisations, researchers, Civil Society Organisations and business leaders. The group heard evidence from several major corporations on their approach not only to product development but sustainable development and corporate and social responsibility.

Novel initiatives from industry

The Group was presented evidence of an African manufacturing success story involving a novel private sector model for development. Sumitomo Chemical, founded in 1913, comprises over 100 companies and had total sales in 2006 of around \$15bn. Sumitomo manufacture the Olyset net, the first long-lasting insecticidal mosquito net to receive a full WHOPE recommendation. Guaranteed for five years, these nets use controlled release technology to kill mosquitoes and reduce malaria transmission. The nets, which are ready

to use and never need treatment, can be washed at least 20 times and still retain their insecticidal properties. The company worked with partners (Acumen Fund, ExxonMobil, PSI, UNICEF, RBM Partnership and WHO) to transfer, royalty-free, the net manufacturing technology to a company in northern Tanzania, A to Z Textiles. A state-of-the-art factory was built and in full production in 2007, it produced over 19 million LLINs in 2009. The material so produced is exported to a further 14 countries where it is stitched into mosquito nets. The company has created 4,500 jobs, 90% filled by women, to produce a life-saving intervention and in parallel creating local and macro level economic development. This approach has fostered African ownership of an African issue resulting in more secure supplies and quicker regional supply times.

BASF, with sales of Euro 62 billion in 2008, uses its innovative capacity to contribute to a better future for the poorest in the world. For malaria, the company co-operates with the Innovative Vector Control Consortium and others to develop insecticides. It also works on "product stewardship", with the Grameen Health Care Trust in Bangladesh. The idea is to empower people to take part in business life through investments into entrepreneurial skills and through Microcredits. Supply of LLIN, by Vestergaard Frandsen, Sumitomo and BASF, sometimes with other interventions such as the BASF-manufactured dietary supplement sachets, and also education on the use of products, is expected to result in higher utilisation and increase impact.

These two examples illustrate how industry can innovate when linked with the bigger picture through an effective co-ordination and advocacy mechanism.

The Artemesia Enterprise is another initiative, linking researchers, growers of Artemesia, policy makers, donors, regulatory experts and industry. This facilitates exchanges on the progress of three major projects, assessment of various impacts on the artemesia supply chain and works towards the deployment of technologies to help meet projected ACT demand. The enterprise has developed a joined-up communications strategy across the three projects and established a regular stakeholder forum, increasing the likelihood that the projects' outputs will benefit the manufacturers of high quality ACTs.

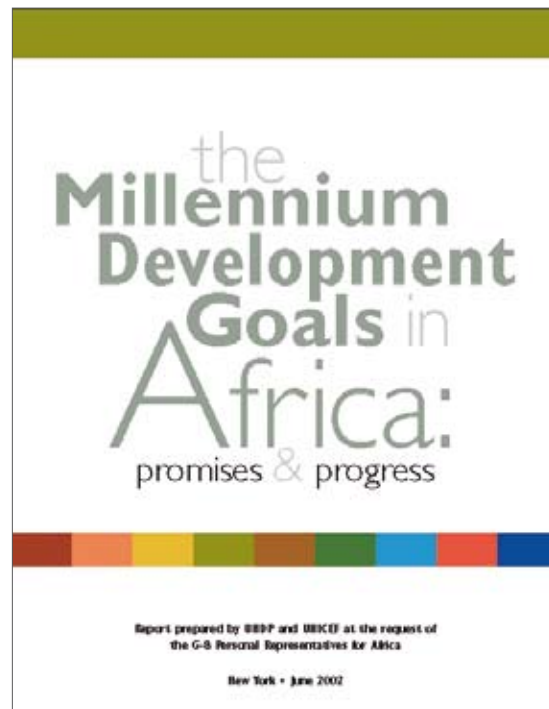
5. Co-ordinating control

Co-operation

The UK plays an important role in shaping European aid programmes and, as the European Union provides nearly 70% of the US\$ 117 billion global Official Development Assistance (ODA), has a crucial leadership-role in the fight against poverty and communicable diseases.

The value of specific commitments from individual countries and economic groupings (such as the European Union (EU)) has been enhanced by assertions such as the Paris Declaration on aid effectiveness (2005) and the Accra Agenda for Action on Aid Effectiveness (2008), which strive to improve ownership, alignment, harmonisation, mutual accountability and management for results in development programmes while adopting the principles of ethics, equity, transparency and evaluation. It is clearly essential that new and innovative financing mechanisms represent real, additional support. That there is coherence and coordination between national, European and international decision-making processes and policies. That partnerships are fostered between the north and south, donors and recipients, between government, civil society organisations, the private sector and communities - and that respect towards local strategies is maintained.

Priorities on the international development agenda compete with each other; with the global economic and financial crisis, food security issues, climate change and other pressing concerns, causing uncertainty in Overseas Development Assistance (ODA) increases. Nevertheless, a strong commitment from some key donors (US, UK, France, Germany), with their high level of accountability, and the potential to quantify the results of investing in malaria tools, should continue to make malaria an attractive target for development assistance.



The UN General High-Level Event on MDGs (2008), G8 Hokkaido Summit (2008) and EU MDG Action Plan (2008) included renewed declarations of political commitment towards international development and global health at UN, G8 and EU levels. The G8 commitment, for example, reaffirmed US\$ 60 billion aid to Africa to fight infectious diseases, strengthen health systems and work towards the goal of universal access to control tools for AIDS, tuberculosis and malaria by 2010. The EU MDG Action Plan called for speeding up achievement of the MDGs and delivering on pledges for increased ODA by the European Union.

Parliamentarians are encouraged to help meet MDG commitments and related global health goals by engaging in policy debate, facilitating north - south cooperation and exchanges, advocating for innovative additional financing mechanisms to mobilise additional resources and supporting the UK's role as a Board Member of the RBM Partnership. Continued UK Support for the International Health Partnership, established in 2007 by a group of donors, will help the response to the MDG challenge, in conjunction with the European Commission, Finland, France, Germany, Italy, Portugal, Sweden and the Netherlands. Supporting and consolidating the role of the UK, and Europe, in initiatives such as the European and Developing Country Clinical Trial Platform (EDCTP) and the Multilateral Initiative on Malaria (MIM) can help to strengthen and sustain research capacity in malaria endemic countries.

The role of Civil Society Organisations needs strengthening to advocate more effectively for malaria control. The European Alliance against Malaria (EAAM) is a dedicated advocacy network in Europe, working since 2006 to connect and coordinate advocacy efforts across Europe. The EAAM involves organisations from Brussels, France, Germany, Spain and the United Kingdom and has the advocacy objective of increasing funding and improving malaria programmes, based on the Global Malaria Action Plan. The aim is to strengthen and expand European action in a global context, in coherence with the European Community and Member States strategies and strengths, preventing fragmentation, improving coherence and promoting a cross-sectoral approach.

Finally, the value of the APPMG should also be recognised. This non-partisan mechanism brings together the many faces of the malaria community, facilitating exchange of ideas and a better appreciation of priorities. In addition to the Parliamentarians, those working in malaria policy, financing, control and research are exposed to the breadth of issues and the variety of interests. This creates an opportunity for informed and balanced opinion, the ability to agree common denominators which can then be communicated with a loud and clear voice. The APPMG model is one which could be extended to other Parliaments, opening up the potential for interactions between different APPMGs and opportunities for enhanced co-operation.

Advocacy

National malaria advocacy networks have emerged in several countries and are starting to play an important role. National coalitions against malaria exist in the UK, France and Germany, working in partnership with coalitions in the South in Cameroon, Ethiopia and Mozambique. These coalitions provide a useful source of expertise, good practice and advocacy for the fight against malaria. The Group was presented with evidence from the Cameroon Coalition Against Malaria (CCAM) which is an advocacy organisation affiliated to the Malaria Consortium, UK. Based in Yaounde, it seeks to improve education, prevention and treatment for malaria by working with civil society and partners to mobilise political support and increase resource allocation for malaria. It seeks to enhance the capacity of Civil Society Organisations (CSOs) engaged in the fight against malaria in Cameroon by strengthening links for coordinated advocacy and resource mobilisation. Their advocacy activities aim to increase media coverage and policy debates on malaria, gradually moving towards concerted action by CSOs/NGOs at country level, based on effective technical approaches. The CCAM works with 65 organisations and has trained grassroots & faith based organisations on malaria programming (integrating malaria into existing programmes, promotion of LLINs use, etc), mobilising schools and churches/mosques to engage in the fight against malaria (children in some 500 schools engaged in malaria songs/sketch competition, raising malaria awareness among them), interacting with the Cameroon Association of School Administrators, with InterNap, a network of faith based organisations, training religious leaders and supporting them to raise awareness of malaria. CCAM produces a biannual magazine "About Malaria" and works with parliamentarians to engage them in the fight against malaria. CCAM also seeks to monitor malaria indicators to strengthen advocacy and help mobilise resources for malaria, although this activity is so far unfunded. Such organisations have the potential to empower communities to influence the quality and scope of services provided through the strengthening of civil society and can help to improve educational materials about malaria in schools and health facilities.

Much more could be done in schools, through faith-based communities and through charity, where the potential to make a genuine contribution – a LLIN for \$5 – is an affordable opportunity to make a genuine difference.

6. Elimination

Definitions

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

Malaria elimination: the interruption of local mosquito-borne malaria transmission; reduction to zero of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts; continued measures to prevent reestablishment of transmission are required.

Certification of malaria elimination: granted by WHO once the chain of local human malaria transmission has been interrupted in an entire country for at least 3 consecutive years.

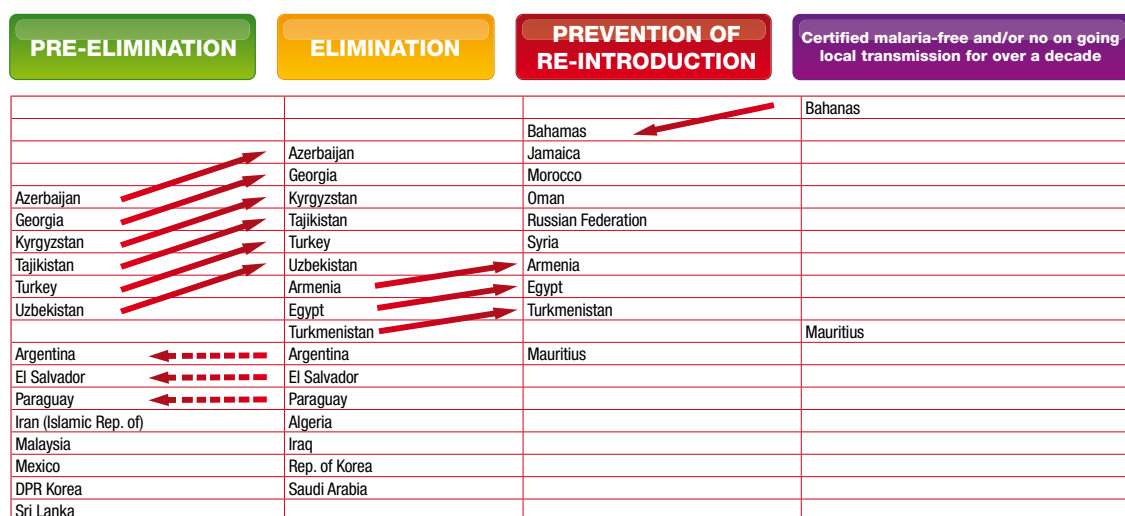
Malaria eradication: permanent reduction to zero of the worldwide incidence of infection caused by a particular malaria parasite species. Intervention measures are no longer needed once eradication has been achieved.

to increased coverage of anti-malaria interventions and has been associated with a decrease in malaria disease and death, even in tropical Africa. There is growing interest in the prospect of malaria elimination, with the Global Malaria Action Plan targeting 8-10 countries, currently in the elimination phase, achieving zero incidence of locally transmitted malaria by 2015, and countries currently in pre-elimination moving to elimination thereafter (fig 6.1). Current elimination efforts are driven by ministries of health, with the technical support of WHO and partners, and national governments are providing most of the funds, although some receive support from the GFATM. The WHO's GMP is considering approaches to enhance elimination activities and the Malaria Elimination Group (MEG) has initiated several demonstration projects.

Encouraging though this is, current tools are not likely to be sufficient to eliminate malaria in all settings. The steps to elimination proceed from malaria control, using nationally scaled-up implementation of integrated malaria control strategies, through pre-elimination and elimination phases before finally working to prevent reintroduction. Initial scale-up of interventions is followed by a period of consolidation, where control is maintained, health services adapt to the new patterns of malaria and surveillance systems are strengthened to allow rapid identification of, and response to, malaria cases. Quality assurance of diagnostic procedures, clinical practice and health information becomes even more important in the pre-elimination period before the critical push for elimination. Major investments are required to ensure adequate case management, and

It is clear that malaria can be eliminated, from some settings, with the tools available today. Indeed, malaria was eliminated from various temperate countries in the 19th century, from a further 24 countries between the start of the Global Malaria Eradication Programme in 1955 and 1987, and an additional nine, previously endemic countries have reported zero annual malaria cases, at least for some years, since then. An increasing number of reports show how the recent surge in investment in malaria control has led

Fig 6.1. Movement of countries between types of programme between 2008 and 2009. (Source: World Malaria Report, 2009)



NB: Names in bold type are of countries in the programme phase as of 2009; names in light type are of countries that were in the programme phase in 2008 but moved a category forwards or backwards as indicated by the associated arrows. Countries that have no arrows associated with their names are those which were in the same category in 2008 as in 2009. The three backwards arrows for Argentina, El Salvador and Paraguay are to correct for a previous error in classification and do not reflect a deterioration of the programme status of these countries.

for identifying and managing remaining transmission foci, for preventing onward transmission from existing cases, and for ensuring adequate control of imported cases. WHO has suggested criteria to move from one phase to the next, for example on the basis of parasite prevalence or the total number of malaria cases reported. It is clear that to move through the phases towards elimination will take a country many years, masses of resources and enormous political resolve. Nevertheless, the prospect of a malaria-free future, with endless ongoing health benefits, is the prize of a political and philanthropic generation worth fighting for.

In south east Asia, 1.6 billion people are at risk of *P. falciparum* infection, 57% at very low risk (less than 1 case per 10,000 population per year) and 38% subject to stable transmission but at levels that satisfy the WHO transmission criterion to move to pre-elimination. If individual or groups of countries decide to proceed to elimination, they should be supported only if they are adequately prepared and committed. Maintaining adequate financial support will be difficult even when a future without malaria represents an infinite return on the investment, but prevention of re-emergence will require sustained relatively high levels of funding which will be difficult to gain credit for politically in democratic countries.

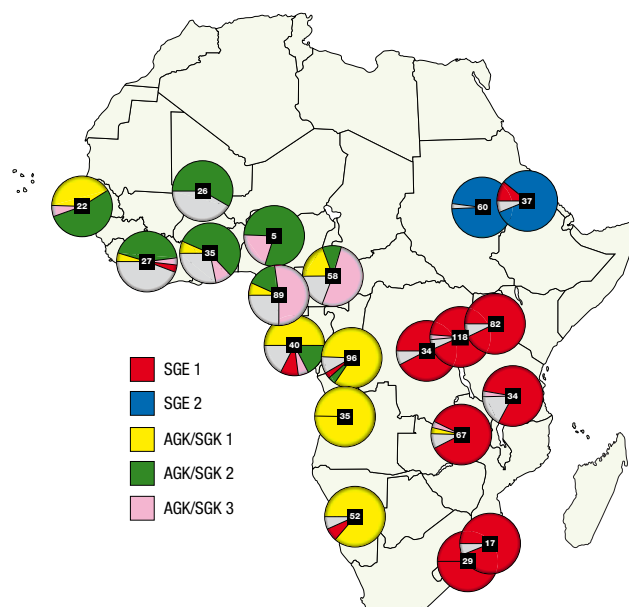
Early in 2010 will see the culmination of a consultative process, known as MalERA, which aims to identify the research agenda surrounding malaria elimination. The conclusions of this group will be important in identifying the key issues to be addressed in order to increase the speed at which countries are able to eliminate malaria. Eliminating and eradicating malaria will require research

and development of new tools, the generation of knowledge to inform policy, and improving the use and effectiveness of current and new interventions.

The group was informed of a novel molecular study which has documented the geographic range of parasite populations in Africa. This suggests that malaria parasites tend to circulate in areas the size of economic blocks (fig 6.2), a finding of considerable potential operational importance when deciding the scale on which to launch a programme to contain a focus of artesunate resistance or determining the area to be included in an elimination programme. It may well make more sense to operate across an economic block than to stay within national boundaries.

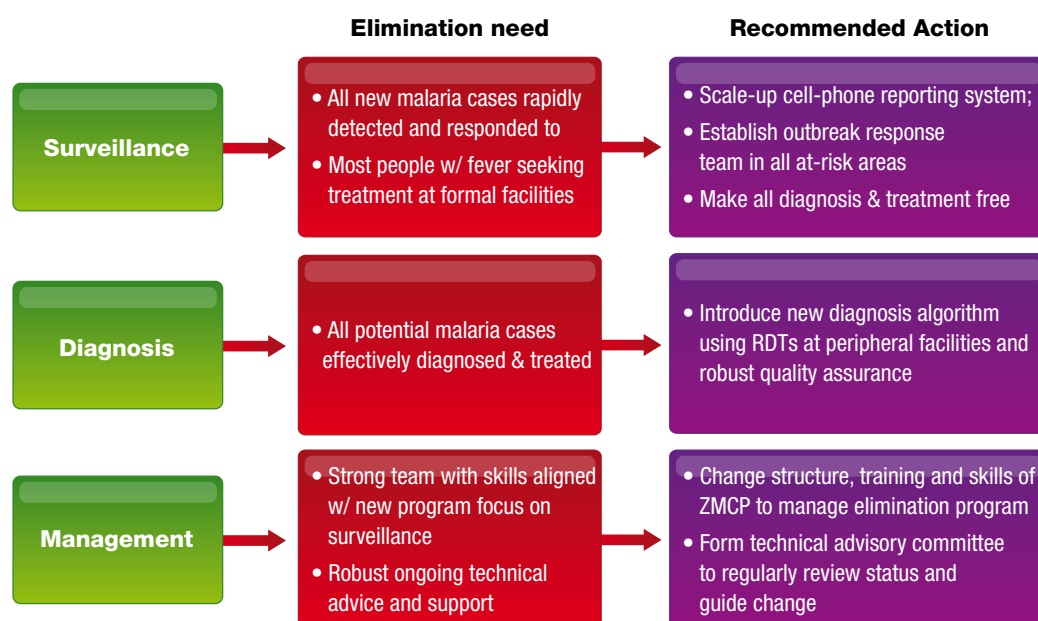
Researchers and product development agencies informed the Group how increasing interest in elimination is affecting their research portfolios. For example, the Malaria Vaccine Initiative is paying more attention to molecules which might interrupt the malaria parasites lifecycle and reduce transmission. This may be by blocking the sexual form of the parasite's lifecycle, which is transmitted to the mosquito, but could also be through a vaccine that is highly effective at preventing blood stage infection. Possible targets include oocyst formation in the mosquito's gut, which would prevent onward transmission of the disease. Such "Transmission Blocking Vaccines" (TBV) may have no direct, immediate benefit to the vaccinee; infections would be reduced as a result of reduced transmission through a mass, or herd, effect. Testing of TBVs is facilitated by the availability of membrane feeding experiments in the laboratory, and some promising results are already being generated.

Figure 6.2: Molecular analysis reveals three broad populations of parasites in eastern, southern and central-west Africa. This provides a rationale for co-ordination at the economic block level of control and elimination efforts in Africa.



6. Elimination

Fig 6.3. The health system does not need to be “perfect,” but significant, targeted improvements will be needed



Although global eradication is unlikely with available tools it is probably possible to eliminate malaria from some countries. The feasibility of elimination with current tools is, however, difficult to assess. Four countries currently in the pre-elimination phase were previously close to elimination some time between 1963 and 1982. This demonstrates the ease with which malaria control can slip backwards and also demonstrates that control can be hard to re-gain. The APPMG was presented the results of a feasibility study of eliminating malaria from the island of Zanzibar. Three areas of feasibility were assessed: technical – whether malaria transmission could be interrupted and maintained with available tools; operational – what’s required to achieve adequate coverage of anti-malaria interventions; and financial – what would elimination cost in comparison to sustained control, and how could this be achieved. The conclusions were stark. It would be technically feasible to eliminate malaria from Zanzibar some time between 2015 and 2030. Continued intervention coverage and surveillance would be required to sustain elimination, unless importation of malaria carriers could be prevented. Operationally, the health system would need specific improvements in terms of surveillance, diagnostic and programme management, with a strong emphasis on surveillance (fig 6.3). However, in financial terms, elimination would not be cost-reducing, compared to continued control, even with importation rates reduced to 0.4/1000/year. It is pertinent to note that malaria has been controlled on Zanzibar, to a very large extent, on two previous occasions. However, when control activities were relaxed malaria re-emerged, as it will again if key interventions are not sustained.

Not all commentators are supportive of the attention paid to malaria elimination. There is a real risk that expectations will be raised too high and that support and interest will then wane when targets are missed. Subsequent reduced interest and commitments to malaria could result in overall deterioration in malaria control. In those settings where control improves and malaria transmission decreases, it is inevitable that populations will become less immune to malaria. Any lapse in commitment to full scale control in such settings may lead to devastating epidemics. Yet elimination will never be achieved if this phase is not passed through.

Huge public health gains are possible within the next 20 years in all areas with stable transmission, even if a target of elimination is not set. Maximal control is a prerequisite to elimination with currently available tools and something to be strived for in every malaria-endemic setting. As malaria control tightens, health systems will be strengthened, and these improvements – in staff supervision, diagnostic capacity, strengthened supply chains, consolidated health information systems, and so on - will benefit the control of other illnesses. Early indications suggest that improved malaria control has dramatic benefits on health and survival. Those areas of the world where elimination is likely to be feasible will need to ensure adequate and sustained political and financial commitment to go for the ultimate, audacious goal.

7. Recommendations

Financing, Leadership & co-ordination

- Hold donors accountable to the pledges they make to the GFATM.
- Increase support for the GFATM. There is considerable variation (between 0.08-0.16%) in the proportion of GNI which European and north American countries donate to the GFATM. Agreeing a target for the proportional contribution to the GFATM could substantially increase available funds and improve the predictability of support.
- Continue support for the AMFm and maximise opportunities for learning in the first phase, including through targeted operational research.
- Commit to a formal planning assumption that the AMFm Phase 1 will be a success and initiate the steps required to support AMFm roll out to phase 2.
- Lead the development of additional solutions to sustain malaria financing in line with existing leadership on innovative financing and long-term commitments
- Increase support for WHO's technical leadership role to guide evolving, evidence-based malaria strategies. The GMP should be resourced to take full advantage of its power to convene technical and public health experts, programme managers and policy makers, in order to develop robust, evidence-based recommendations and strategies for malaria control and elimination.
- Continue support and engagement with the RBM partnership and its central co-ordinating role.
- Invest in research centres and field sites in endemic countries.
- Support networks to enable the co-ordinated monitoring of resistance to insecticides and drugs, and for evaluating the performance of potential new products.

Human resources

- Ensure an adequate number of well trained staff capable of managing integrated malaria control programmes at national level.
- Enable and empower district health teams to manage malaria control at the district level as malaria transmission falls. This will involve improving the availability, quality, completeness and utility of district-wide data to support rational local decision making.
- Support moves to give communities ownership over defeating malaria. Community engagement is a pre-requisite to maximised community control.

LLINs

- Where LLIN coverage is low, catch-up campaigns should be supported to increase coverage rapidly of this key intervention.
- In all malaria endemic settings, approaches to maintain LLIN coverage – 'keep up' – should be developed and maintained.
- Support operational work to close the gap between net ownership and usage, and support the development of robust systems to ensure the continued availability of LLINs.

Insecticide Resistance

- Hold vector control implementation agencies responsible for the monitoring of insecticide resistance and regard such monitoring as mandatory.
- Support mechanisms to enable sub-regional coordination of insecticide resistance monitoring.
- Prioritise work to reduce the rate of development and spread of resistance to insecticides in order to maximise the utility and longevity of available products.
- Accelerate research and development of new classes of compound by investing in the development of new insecticides for public health use. Failure to be prepared for a rapid spread of resistance to currently available insecticides will lead to a public health catastrophe.

7. Recommendations

Health information

- Strengthen routine surveillance data so that it becomes a reliable principal source of information in endemic countries at all levels. This will enable monitoring of the burden and trends of malaria, thus enabling evaluation of intervention impact, responses to changes in transmission and tracking of availability and use of malaria commodities.

Artesunate production

- Achieve consensus on whether artemisinin should be considered a starting material by regulatory bodies.
- Support pathways to assure the sustainable and appropriate local production of ACTs

Quality Assurance

- Strengthen national regulatory authorities to enable effective monitoring and management of drug quality.
- Procure WHO prequalified products and work to support pre-qualification of drugs produced in endemic countries.
- Support efforts to assure the quality and performance of rapid diagnostic tests
- Strengthen National Regulatory Authorities to enable robust monitoring of the quality of anti-malarial and other drugs, the appropriate licensing of products and policing of outlets.

Supply Chain

- Strengthen systems for forecasting commodity needs, managing supply chains, training and supervising health staff in order to reduce the risk of drug stock outs in front line healthy facilities.
- Work to agree the approach to, including timing of, changes in procurement strategy, applying risk mitigation strategies when sourcing from manufacturers without a proven track record.

Diagnosis and treatment

- Support efforts to introduce competent systems for the diagnosis of malaria at all levels of the health system, remembering the need to go beyond procurement of RDTs and to build and implement sustainable in-country programmes providing all necessary logistic support and quality assurance.
- Explore the potential of RDTs in community-based management strategies and in the private sector.
- Support efforts to optimise the management of patients with a negative malaria test. In particular, identify patients who need referral, treatment with antibiotics or other interventions, and those with self-limiting illnesses for whom reassurance should suffice.
- Consider diverting some of the AMFm or alternative subsidy to supporting the implementation of routine diagnostics.
- Contain the spread of drug resistance by cessation of oral artemisinin monotherapies manufacture and improved targeting of ACTs.
- Work towards elimination of malaria from areas with resistant parasites and engage with malaria control efforts in Myanmar in order to increase the likelihood of containing artemisinin resistance in south east Asia.
- Monitor drug efficacy through routine surveillance, ensuring resistance is detected early and acted upon.
- Continue to support the development of new medicines, including non-artemisinin based combination treatments, to treat malaria

Care in the Community

- Work to co-ordinate disease-specific community-based initiatives (eg HBMF) with efforts to establish integrated community-based disease control programmes (eg ICCM).
- Support efforts to understand how CHWs can be appropriately motivated and rewarded for their work.

Elimination

- Catalyse and support new efforts to investigate the financial implications and challenges of sustained control and elimination

**The principle is proven:
adequate, appropriate
investment in malaria control
saves lives,
improves health and
enhances life chances
of the poor**