Targeting Zero: sustaining success in malaria control

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

Cover photograph: Ronald Kalyango

Targeting Zero: Sustaining Success in Malaria Control

All-Parliamentary Group on Malaria and Neglected Tropical Diseases Report

2010 – 2011

Chairman: Jeremy Lefroy MP

Vice Chairman: Lord Rea, Eleanor Laing MP, Kevin Barron MP
Treasurer: Andrew George MP **Secretary:** Pauline Latham MP
Coordinator: Susan Dykes e-mail susanmdykes@gmail.com

www.appmg-malaria-org.uk

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Chairman's Foreword

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

Chairing the All Party Parliamentary Group on Malaria and Neglected Tropical Disease Group has been a highlight of my first year in Parliament. The aim of the Group remains as it was under the inspirational leadership of Stephen O'Brien MP, now the Under Secretary of State for International Development – to provide a forum at the heart of the UK for discussing malaria and NTDs and to be a strong advocate in and out of Parliament for all those who are committed to tackling these diseases.

This report brings together much of the work about which we have heard this year. We have heard from the Minister himself on DFID's strategy to accelerate progress to meet the Millennium Development Goals and the particular importance this Government attaches to making progress on malaria. The British Government's leadership role in the fight against malaria is unprecedented and we have been delighted to welcome the results of a series of reviews and the Malaria Framework for Results paper that has been published. More recently we have been very pleased to welcome DFID's initiative in publishing detailed plans for each of the countries in which it works, that sets out for the first time what work will be done on malaria and where, with a budget attached.

We have received regular updates of progress in the drug and vaccines pipeline, the state of funding for malaria programmes and the extent of mosquito net coverage; and we have learned about projects involving the private sector to reduce malaria drug stockouts through SMS technology and to deliver mosquito nets using empty trucks which travel to pick up produce from farmers.

What I have found so refreshing in the community of those who are taking on malaria is the desire to work together for the common good. Partnership is the norm. People are willing to exchange ideas and help each other.

The results are evident. Deaths from malaria have fallen, mosquito net coverage is increasing and the best drugs are more widely available and cheaper.

Nowhere was the progress brought home to me and my colleague Pauline Latham OBE MP more clearly than when we visited Hoima District in Uganda with the Malaria Consortium. Almost every home had a mosquito net and each village had trained health workers whose job was to test and treat young children presenting with fever.

The kits with which they were supplied enabled them to test the children for malaria using rapid diagnostic tests. If the child had malaria, paediatric Coartem was given. If there was no malaria, the child could also be tested and treated for pneumonia. Oral rehydration therapy was available for those with diarrhoea.

When we visited the local hospital, we found that the number of children admitted with malaria had fallen sharply, beginning shortly after the

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programme had begun. Dealing with children in their village meant that they were treated earlier and avoided the expense and danger of a long journey to the hospital.

A recent visit to Rwanda with the International Development Committee also showed us the effect of a well-run campaign to tackle malaria through the universal distribution of mosquito nets and an improving health system.

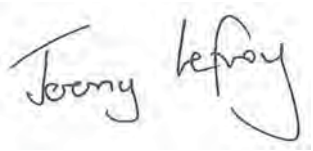
At a time when the value of aid is often questioned, it is vital to broadcast such progress. One of my aims for the coming year is to see how we can do so more effectively.

But we cannot be complacent. We will not be satisfied until every home at risk from malaria has sufficient mosquito nets. We cannot let up on the research to develop vaccines and discover new insecticides and medicines. Even though the tools we have today work well, it will only be a matter of time before the versatile malaria parasite develops some resistance - we must continue to develop new tools today to maintain our effectiveness tomorrow.

This all requires money. Governments and private foundations have been extremely generous in recent years and our own Government's commitment is a tremendous asset to the malaria community's quest to accelerate progress over the coming years. I believe that their faith in the malaria community to bring results has been rewarded.

But we must go on making the case that beating malaria is an excellent use of money: not only in the hundreds of thousands of lives saved but also in enabling millions of people to stay healthy, free from malaria and its devastating impact on productivity, education and household income.

I would like to thank all those who have supported the group so faithfully over the past year – RBM, the Malaria Consortium, Malaria No More UK, Medicines for Malaria Venture, Vestergaard Fransen. I am grateful to Professor David Schellenberg for giving up so much time to produce this report. Without the support of Parliamentary colleagues, it would not be possible to run the group – and I mention Pauline Latham OBE MP and Lord Nick Rea in particular for chairing meetings in my place. Finally, I wish to thank Susan Dykes, our administrator, who is unfailingly cheerful, committed and efficient. Grateful thanks to Owen Meredith for all his support and work for the Group.



Jeremy Lefroy

Chairman of the All-Party Parliamentary Group
on Malaria and Neglected Tropical Diseases
July 2011

Abbreviations

ACT	Artemisinin-based Combination Treatment
AMFm	Affordable Medicines Facility-malaria
ALMA	African Leaders Malaria Alliance
ANC	Ante Natal Care
APPG	All Party Parliamentary Group
APPMG	All Party Parliamentary Group on Malaria and Neglected Tropical Diseases
BCC	Behaviour Change Communication
CDC	Centre for Disease Control
CDD	Community Drug Distributors
CHW	Community Health Worker
COD	Cash on Delivery
DFID	UK Department For International Development
DNDi	Drugs for Neglected Diseases initiative
DSM	Drug Supply Management
DTU	Diagnostics and Treatment Unit
FIND	Foundation for Innovative New Diagnostics
GFATM	Global Fund for AIDS, Tuberculosis and Malaria
GMAP	Global Malaria Action Plan
GPARC	Global Plan for Artemisinin Resistance Containment
HMIS	Health Management Information Systems
ICCM	Integrated Community Case Management
IEC	Information Education Communications
IPT	Intermittent Preventive Treatment
IPTc	Intermittent Preventive Treatment in children
IPTi	Intermittent Preventive Treatment in infants
IPTp	Intermittent Preventive Treatment in pregnancy
IRS	Indoor Residual Spraying
ITN	Insecticide Treated mosquito Nets
IVCC	Innovative Vector Control Consortium
IVM	Integrated Vector Management
LLIHN	Long-lasting insecticide treated hammock nets
LLIN	Long Lasting ITNs
M&E	Monitoring and Evaluation
MMV	Medicines for Malaria Venture
MVI	Malaria Vaccine Initiative
NGO	Non Governmental Organisation
NMCP	National Malaria Control Programmes
NTDs	Neglected Tropical Diseases
PDP	Product Development Partnerships
PMI	President's Malaria Initiative
R&D	Research and Development
RBM	Roll Back Malaria Partnership
RDT	Rapid Diagnostic Test
SMS	Short Message Service
PPP	Public Private Partnerships
SP	Sulphadoxine-Pyrimethamine
UNICEF	United Nations Children's Fund
VHT	Village Health Team
VMW	Village Malaria Workers
WHO	World Health Organisation

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Nicko Debenham	Director of Tracability and Sustainability, Amajaro
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Dr Sue Kinn	Head of Research at the Department of International Development
Sarah Kline	Executive Director, Malaria No More UK
Dr Jo Lines	Co-coordinator of Vector Control and Prevention at the Global Malaria Programme, World Health Organisation
Dr Christian Loucq	Director, PATH Malaria Vaccine Initiative
Dr Godfrey Magumba and his staff	Malaria Consortium Uganda
Dr Sylvia Meek	Technical Director Malaria Consortium
Bruno Moonen	Director of Malaria Control, the Clinton Health Access Initiative
The New Vic Youth Theatre	Staffordshire
Dr Robert Newman	Head of the Global Malaria Programme at the World Health Organisation
Dr Paul Newton	Director, Wellcome Trust-Mahosot Hospital Laos an Oxford University Tropical Medicine Research Collaboration (Microbiology Laboratory)
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Executive Summary

The 2010 APPMG Report presented clear evidence of some early successes in malaria control. Increased funding had driven up the coverage of key malaria control tools, especially mosquito nets, and made more effective malaria treatment available. This had been associated with a decrease in the number of malaria cases, admissions to hospital and deaths. The initial findings were documented by research groups working in a small number of African settings.

The encouraging early findings have now been complemented by data from routine health information systems. Continued investment has further increased the coverage of life-saving malaria control tools. Eleven African countries have now reported a decrease of at least 50% in malaria cases between 2000 and 2009. Last year, the annual number of malaria deaths fell by 20% in comparison with the beginning of the millennium. International financial commitments are translating into increased coverage of malaria control tools and reducing illness, improving survival, enhancing businesses and stimulating economies. The success remains fragile, and further investment is needed to consolidate and expand the early gains. Nevertheless, the growing body of evidence shows that investing in malaria control pays off. However, gains made in the past could be lost if continuous efforts are not maintained. A business as usual approach won't get us to win the fight against the parasite.

During the last year, the All Party Parliamentary Group on Malaria and Neglected Tropical Diseases heard how investment in malaria control by private companies has generated financial returns. Also how countries, funders and industry are beginning to co-ordinate actions around Roll Back Malaria's Global Malaria Action Plan (GMAP).

The APPMG has also hosted Stephen O'Brien, Under Secretary of State for International Development, and examined the historic commitment of this Government to tackling malaria. It has followed each step of DFID's work to consult, develop and publish its new Framework for Results for Malaria and the accompanying Bilateral and Multilateral Aid Reviews that set out the overall vision for DFID's future work. Most of those who have addressed the APPMG have also fed into these documents.

The British Government's key commitments to accelerating progress on malaria have been unprecedented: to help halve the number of people dying of malaria in ten of the most highly burdened countries; and to spend up to £500 million per annum on tackling malaria by 2014/15. At country level, DFID has now published its plans for measuring progress towards achieving these goals – both in terms of outcomes and funds spent. The APPMG has welcomed these documents and in particular DFID's commitment to Nigeria and the Democratic Republic of the Congo which have such high malaria burdens at present. The next step is to put the plans into action – something on which DfID is now working.

While the APPMG has been heartened by these successes, and the historic commitments of the British Government in particular, the Group has also been informed of a number of challenges, and new threats emerging on the horizon.

Challenge 1: Delivering the goods

The first challenge is to ensure the continued flow of resources to support the purchase of commodities, their delivery and use in the settings that suffer the most from malaria. Global funding for malaria control appeared to plateau last year, before the UK Government's announcement of its increased commitment. Even with this, a substantial gap still remains, and malaria continues to kill hundreds of thousands of people every year.

There is also an urgent, ongoing need to remedy the problems of access, which constrain the effectiveness of malaria control programmes. All too frequently the recommended malaria treatment is not available in front line health facilities, even though supplies are present in the central medical stores. Investment is needed in the systems required to ensure that commodities are delivered through efficient supply chains down to the end-users, and that information - on malaria case numbers, drug use and other key parameters – flows back up the chain to enable proper forecasting and targeting of

resources. Systems to monitor insecticide and drug resistance need to be consolidated and expanded.

Staff and patients need better education to consolidate case management messages, including the correct use of - and compliance with – Rapid Diagnostic Test (RDT) results. This in turn should result in more rational use of Artemisinin-based Combination Treatments (ACTs) and improved management of patients with malaria. Furthermore, a negative RDT should prompt the search for alternative causes of illness which might otherwise have been missed. Finally, wider use of RDTs and strengthening information systems will provide more reliable information on the impact of control programmes. This is essential in order better to track the impact of investments in malaria control.

Challenge 2: Containing resistance

A growing threat to progress is the emerging resistance to drugs and insecticides. Resistance is an almost inevitable consequence of use of these products and redoubled efforts are required to retard its emergence and spread. Early signs of resistance to the leading malaria treatments have been documented in South East Asia. The threat of this spreading to Africa, which carries the brunt of malaria disease and death, is considerable cause for concern and should prompt sustained investment in activities to contain the threat. Resistance in mosquitoes to the insecticides which are commonly used for vector control has also been documented. As yet, neither drug or insecticide resistance has led to the failure of malaria control programmes. However, this is likely to be only a matter of time and, when that time comes, we need to be prepared. Investing now in the research and development (R&D) of new tools is imperative.

Challenge 3: Developing new tools

Investments over the last 16 years have seen a four-fold increase in malaria R&D spending. As a result, the malaria commodity development pipeline is stronger now than at any time previously. Several new drugs and a vaccine are in the final stages of development. Recent years have seen more intensive work on the development of insecticides and a number of potential products are now in the early stages of development. More needs to be done on this, and also in the development of new diagnostic capacities. Nevertheless, for the first time, the malaria community is on the verge of being able to assail the parasite with a succession of new weapons, as they are needed. It is imperative to maintain R&D funding at this stage in order to maximise the benefit of earlier investments.

Challenge 4: Sustaining financing

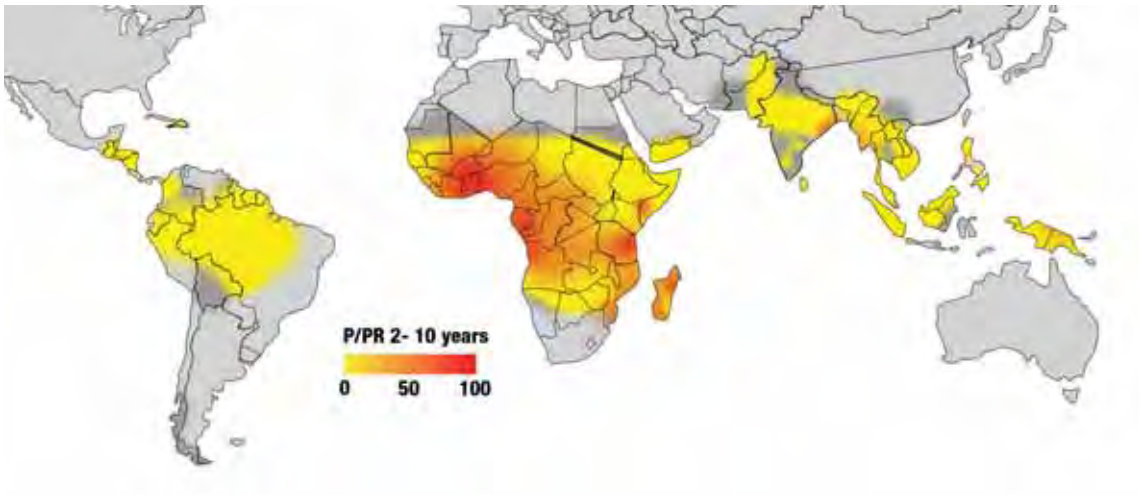
It will become increasingly important to be able to sustain the gains made in countries which successfully control malaria. The risk is that they become a victim of their own success; as the burden of disease falls away, political resolve weakens and financial commitments diminish. Yet premature relaxation of control efforts can be disastrous: history has shown how malaria can bounce back with a vengeance from a situation of tight control. The threat of malaria will remain until the parasite is eradicated from the planet, and novel approaches will be required to generate and sustain funds in order to maintain success.

This report sets out in more detail each of these issues in turn. A final conclusion sets out some recommendations for each of the key groups working to tackle malaria and from whom we have heard updates during the year. For MPs both in the UK and abroad, we hope these recommendations will draw attention to some of the areas that need further discussion in the coming year.

By maintaining and building commitment to malaria control in the UK and abroad, substantial improvements can be expected in individuals' health and the survival of vulnerable communities. Investing in delivery systems will not only enable the full potential of existing malaria control tools to be realised but, by preventing millions of episodes of illness every year, will help vulnerable people in endemic countries to reach their full potential.

Malaria: Burden of the disease

Figure 1: The spatial distribution of P. falciparum malaria endemicity. PfPR – P falciparum parasite prevalence. (Source: Hay S et al. PLoS Medicine 2009: 6 (3).e1000048)



Approximately half of the world's population remains at risk of malaria (Fig. 1). Malaria was the third most important single infectious cause of death in the last decade, killing an estimated 781,000 people in 2009 and causing around 225 million episodes of illness. Malaria is responsible for millions of lost days of work and education. Yet malaria infection is preventable and the disease can be treated.

Five species of *Plasmodia* cause disease in people. *P falciparum* causes the vast majority of severe malaria disease and death, with 78% of cases and 91% of deaths occurring in Africa. *P vivax* also causes large numbers of malaria episodes, especially in South America and Southeast Asia. This relapsing form of malaria is considered relatively benign, although recent evidence suggests that the burden of disease and even death attributable to *P vivax* may have been under-estimated.

Despite the challenges of malaria control, major improvements have been documented (Figs 2 & 3). Indeed, malaria elimination has been certified in both Morocco and Turkmenistan since the 2010 APPMG malaria report, providing further evidence that elimination in some settings is possible with available control measures. Further, not a single case of *P. falciparum* malaria was reported in the WHO European Region during 2009 – the first year this has been documented.

Trends in malaria are monitored by WHO's Global Malaria Programme, which generates a picture of the global malaria situation by complementing data from National Malaria Control Programs with that from household surveys. Table 1 shows a 7% decrease in malaria illness in 2009 compared with 2005 – a reduction of about 19 million episodes.

Figure 2: Reported malaria cases, Livingstone District, Zambia, 2004 – 2008. (Source: Zambia NMCP, WHO, FIND, URC, Malaria Consortium)

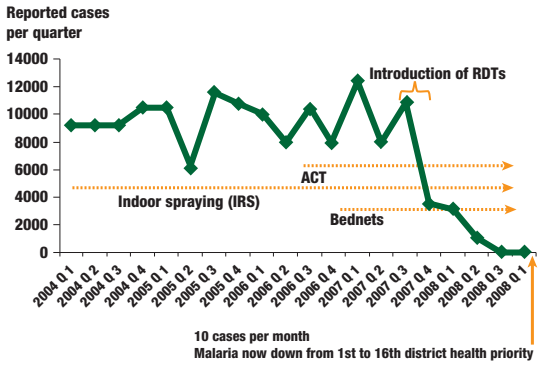
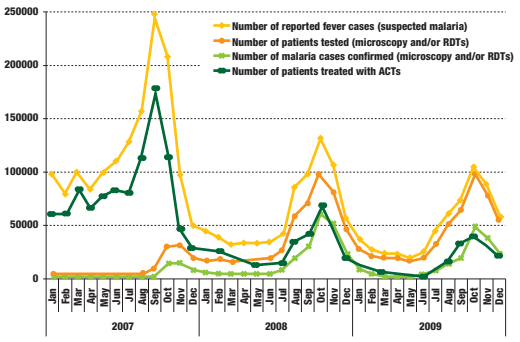


Figure 3: Reported malaria cases and ACT treatment courses, Senegal, 2007 – 2009. (Source: National Malaria Control Program, Senegal)



This relatively modest average change masks important country to country variations: 11 African countries reported a decrease of at least 50% in malaria cases between 2000 and 2009. More impressive progress has been made with malaria deaths, with a 20% reduction in deaths over the last decade. The picture from the routine data is

Table 1. Source: World Malaria Report, WHO 2010.

ESTIMATES OF MALARIA CASES AND DEATHS BY WHO REGION, 2000-2009

CASES (in thousands)	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Uncertainty bounds	
											lower	*upper*
African	173,000	178,000	181,000	185,000	187,000	188,000	187,000	186,000	181,000	176,000	117,000	241,000
Americas	2,800	2,300	2,200	2,100	1,900	1,900	1,700	1,500	1,100	1,100	1,000	1,300
Eastern Mediterranean	15,000	15,000	17,000	16,000	15,000	12,000	12,000	12,000	13,000	12,000	14,000	16,000
European	47	34	27	22	13	7	4	2	1	1	1	1
South-East Asia	38,000	37,000	35,000	34,000	37,000	39,000	34,000	33,000	34,000	34,000	28,000	41,000
Western Pacific	2,800	2,400	2,200	2,500	2,800	2,300	2,500	2,100	1,900	2,300	2,000	2,500
World	233,000	235,000	237,000	240,000	243,000	244,000	238,000	234,000	231,000	225,000		
lower bound	181,000	181,000	182,000	184,000	185,000	185,000	179,000	175,000	171,000	169,000		
upper bound	302,000	304,000	308,000	313,000	314,000	317,000	310,000	304,000	298,000	294,000		

DEATHS	000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Uncertainty bounds	
											lower	*upper*
African	900,000	893,000	885,000	880,000	870,000	853,000	832,000	802,000	756,000	709,000	554,000	892,000
Americas	2,400	2,300	1,400	1,400	1,500	1,600	1,600	1,400	1,100	1,300	900	1,700
Eastern Mediterranean	18,000	18,000	21,000	19,000	17,000	17,000	16,000	15,000	16,000	16,000	12,000	892,000
European	0	0	0	0	0	0	0	0	0	0	0	1
South-East Asia	58,000	55,000	51,000	50,000	52,000	50,000	48,000	43,000	48,000	49,000	37,000	892,000
Western Pacific	6,800	5,800	5,200	5,900	6,500	4,900	5,400	4,700	4,200	5,300	3,400	7,300
World	985,000	974,000	963,000	957,000	947,000	927,000	904,000	867,000	826,000	781,000		
lower bound	797,000	785,000	775,000	769,000	765,000	744,000	725,000	694,000	662,000	628,000		
upper bound	1,228,000	1,212,000	1,199,000	1,191,000	1,174,000	1,152,000	1,120,000	1,075,000	1,024,000	968,000		

supported by a range of more robust research evaluations providing solid evidence of progress, but it is patchy.

Some caution is needed when considering malaria disease burden estimates. WHO uses comparable methodology to present information over multiple years and is probably the best source to identify trends. However, relying on country reports is imprecise due to weaknesses in diagnostics and information systems at country level. It is possible that the burden of malaria has been under-estimated in some parts of the world (for example India) and under-appreciated as a cause of death in adults. As control improves it will become increasingly important to strengthen diagnostics and information systems to enable progress to be better measured and to ensure appropriate treatment is given.

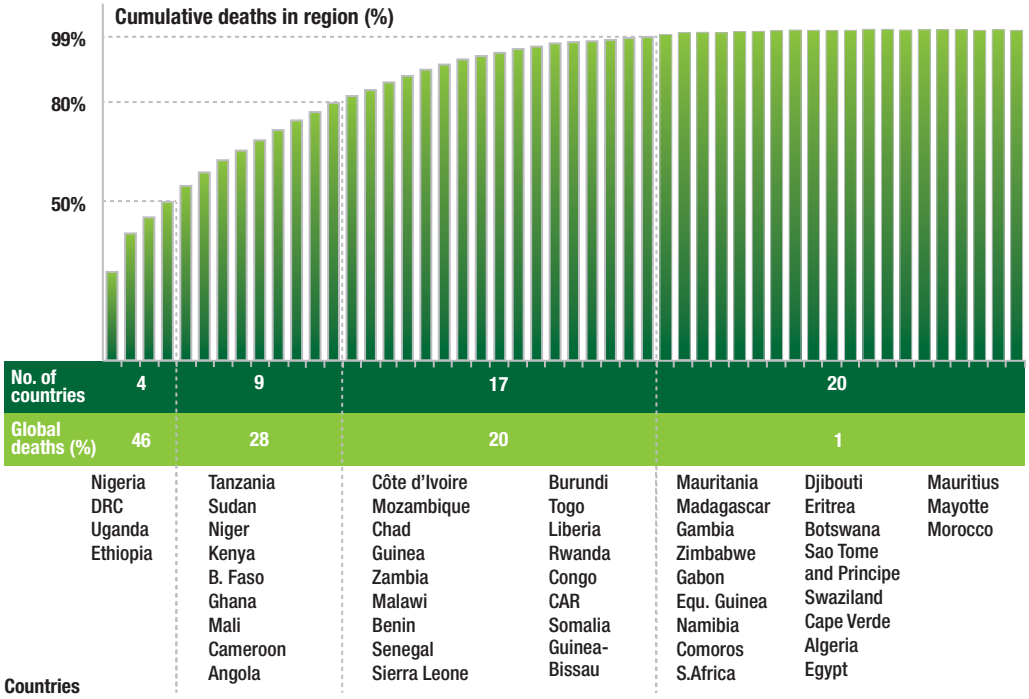
Even where we can be confident that progress has been made, there is no room for complacency as gains can quickly be lost. In 2009, several countries reported a deterioration in their situation following previous good progress. In Sao Tome and Principe, modest increases in disease (from 1,647 to 3,893) and death (from 16 to 23) followed a year in which Indoor Residual Spraying (IRS) was not deployed. Malaria also increased in five of Zambia's nine provinces, dramatically so in two where Insecticide Treated mosquito Nets (ITNs) were last delivered on a large scale 2-3 years previously. Whilst the exact reasons for these and other malaria resurgences are not known, these observations raise important questions about when it might be safe to relax malaria control efforts, and for how long protection from an individual ITN can be expected. Several countries have experienced resurgent malaria after periods of tight control. The fact is that the availability of the mosquito vector ensures that transmission can dramatically increase if control measures are not sustained. We now have a unique opportunity to make a difference – new technologies, new funding and new political will can make a real difference, if sustained for long enough.

For now, it is clear that the greatest gains for health and survival will be generated by increasing malaria control efforts on those countries with the highest burden of malaria disease and death. Fig. 4 shows that just four countries account for 50% of malaria deaths in Africa. Furthermore, those with the highest disease burden tend to have the lowest coverage of key control tools.

Malaria Control

Effective malaria control depends on the prevention of infection and the treatment of clinical cases. The cornerstone of prevention is vector control, which aims to limit the ability of female Anopheles mosquitoes to transmit the malaria parasite. Drugs can also be used to prevent malaria in some situations. Malaria treatment depends heavily on Artemisinin-based Combination Therapy (ACT), recommended by WHO as the first line malaria treatment in Africa since the early 2000's. The tools currently available to prevent, diagnose and treat malaria work well if they are delivered to those

Figure 4. Distribution of malaria deaths in Africa. (Source: GMAP. Based on data from WMR 2008.)



who need them. However, getting control tools to the people who need them, when they need them, is the greatest immediate challenge for malaria control in Africa and beyond.

Malaria Prevention

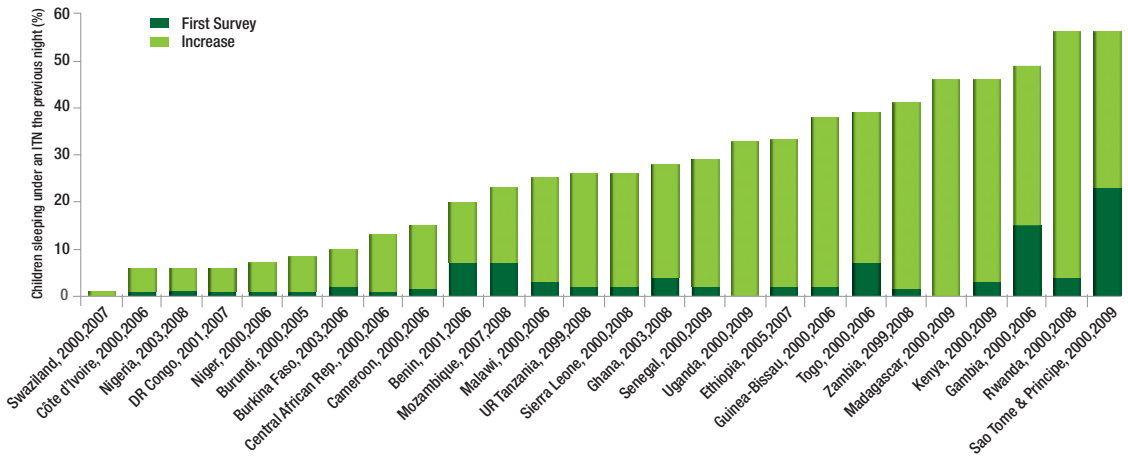
By reducing mosquitoes biting at night using a protective mosquito net. Research dating back to the 1980's has shown that **Insecticide Treated mosquito Nets (ITNs)** can reduce malaria episodes in children by 50% and deaths from all causes by 23%. This is equivalent to 5.5 lives saved for every 1,000 children using an ITN. Originally ITNs were created by dipping standard mosquito nets into insecticide, but the need for retreatment presented a challenge. New technology has enabled the production of **Long Lasting ITNs (LLIN)** which last longer and survive washing by incorporating insecticide into the fabric of the net.

The coverage of ITNs and LLINs has increased dramatically in recent years, from an estimated 5.1% in 2003 to 32% in 2008. This required a 15-fold increase in the annual number of nets delivered to sub-Saharan Africa, from 5.6 million to 88.5 million, between 2004-2009. **Between 2008 and 2010 a total of about 254 million nets were supplied and delivered to sub-Saharan Africa – sufficient to protect about two thirds of the 765 million people at risk.** However, Fig 5 shows that the largest increase in coverage has tended to happen in smaller countries. This is worrying, especially as two very large countries – the Democratic Republic of Congo and Nigeria – accounted for approximately one third of all reported malaria cases in 2006. This draws attention to the need for geographic targeting of LLIN programmes and has led to concerted action. For example, in Nigeria, plans to distribute 62 million LLINs have been drawn up, and implementation is well underway. With support from the DFID-funded SuNMaP partnership (Box 1), over half the nets have been delivered at the time of writing. Similar geographic targeting has seen over half the ITNs delivered between 2008 and 2010 delivered to countries comprising 56% of the population at risk of malaria in sub-Saharan Africa (Nigeria, Democratic Republic of the Congo, Ethiopia, Sudan, United Republic of Tanzania, Kenya, and Uganda) (Fig 6).

In 2008 the coverage goal was raised to move beyond the 80% target for high risk groups to universal coverage – every person, every sleeping place, every night.

By the use of Indoor Residual Spraying (IRS) of insecticide onto walls where mosquitoes like to rest. Whilst solid data has not been collected, it appears that IRS can play a useful role in areas with localised and less stable transmission. Hence, IRS

Figure 5: Trends in percentage of children sleeping under an ITN for countries with more than one survey 2000-2009 (Source: World Malaria Report 2010)



Box 1. The SuNMaP project – Supporting the Nigerian National Malaria Programme

According to preliminary Malaria Indicator Survey (MIS) 2010 results, 41 percent of households in Nigeria have at least one ITN / LLIN; however its entire population - which stands at over 150 million people - is at high risk of contracting the disease. A huge injection of resources and support to the public and commercial sector is required if the country is to meet its Malaria Control Strategic Plan Targets of at least 80 percent of households having two or more LLINs by 2010 and maintained until 2013, as well as access to proper diagnosis and treatment .

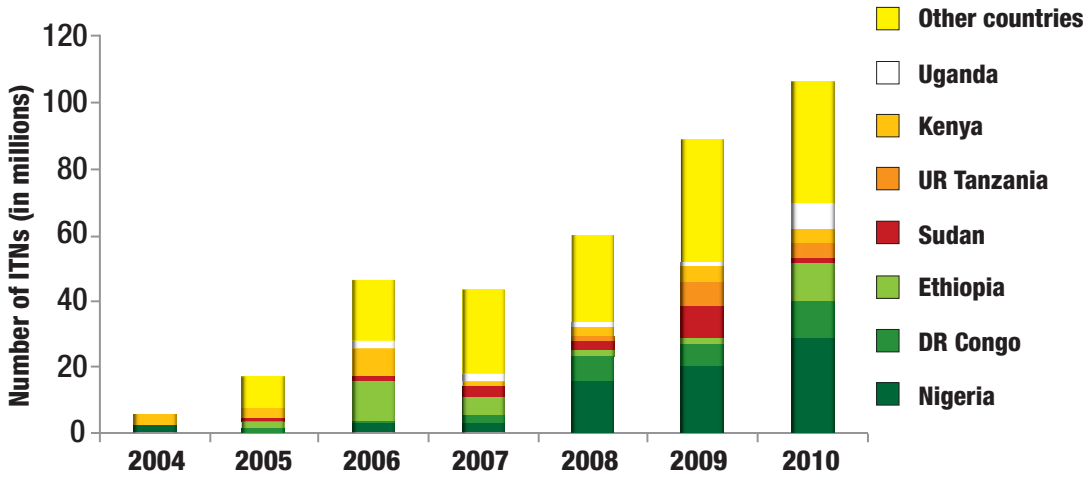
The SuNMaP project (Support to the National Malaria Programme) is leading the national response to the malaria burden. It is assisting in the coordination of malaria control interventions at national, district and local levels and harnessing the advantages of public, private and commercial sector engagement in scaling up malaria control activities across the country. This project, funded by the UK Department for International Development (DFID), is managed by Malaria Consortium with support from Health Partners International, GRID Consulting Nigeria and other local partners. The project was designed around a multi-sector approach to malaria control, with the commercial sector playing a critical role in the development of the LLIN retail market in response to increasing demand and the gradual return of 'net culture' in Nigeria as a result of the ongoing universal bednet campaign.

As the LLIN market grows, pricing is likely to decrease with more competition and access therefore increases. SuNMaP's support to the commercial net sector is to analyse and identify constraints in the market using the Making Markets work for the Poor (M4P) approach and work in partnership with key market players to address them. This allows the market to flow unhindered and ensures that nets are available both in local markets and as part of routine distributions to rural areas.

"Working with the commercial sector has been both exciting and challenging, with a record 600,000 plus LLINs sold with SUNMAP support through retail markets in one year." said Project Director, Dr. Kolawole Maxwell. "New partners and brands have entered into the net business; and new products, such as insecticide treated net curtains for doors and windows, have been launched."

In the very near future there will be potential for a huge boom in the LLIN retail market in Nigeria and the commercial sector supported players are well positioned to take the full advantage of this. Malaria Consortium believes that long term commercial development should utilise local businesses in order to achieve viability and sustainability in the marketplace.

Figure 6: Number of ITNs delivered by manufacturers to countries in sub-Saharan Africa. (Source: World Malaria Report 2010)



is often, but not exclusively, targeted at urban and semi urban settings and may be particularly useful for controlling areas with persistent transmission as part of intensive control efforts. IRS is deployed by 32 African countries and 39 others. About 10% of Africans at risk of malaria were protected by IRS in 2009 and, though coverage was deliberately patchy, four countries achieved coverage greater than 50%. DDT is used for malaria control in 13 African countries and four in other regions. Other forms of vector control include larval control and house screening, though these are currently practiced on a limited basis as evidence of impact is less convincing than for ITNs.

The choice of vector control measure requires knowledge of the identity and behaviour of the vector in each area – where do the mosquitoes prefer to breed? To which insecticides are they sensitive? When and where do they tend to feed - indoors or outdoors? Such basic entomological information is not always available despite its importance in tailoring control strategies to individual settings and signals the need for investment in entomological capacity strengthening.

Malaria can also be prevented by drugs. Intermittent Preventive Treatment (IPT) is the administration of a treatment dose of an antimalarial drug at pre-defined times, regardless of the presence of *Plasmodium* parasites. The aim of IPT is to avert the worst manifestations of malaria – severe disease and death. IPT in pregnancy (IPTp) is delivered when women attend routine antenatal clinic, and consists of the administration of a treatment dose of sulphadoxine pyrimethamine (SP). IPTp has been recommended since 2001 in places where transmission is moderate or intense.

The 2010 World Malaria Report shows that 33 of 43 endemic countries in Africa have adopted IPTp. However the emergence of resistance to SP, especially in East and Southern Africa, has become a cause for concern and work is ongoing to find alternative drugs for IPTp. A related approach, IPT in infants (IPTi), delivers treatment doses of SP to children less than one year of age when receiving some of their routine vaccinations. This new strategy was recommended by WHO in 2010 but as yet no country has adopted it. IPT has also been evaluated in children (IPTc) up to five years of age living in intensely seasonal transmission settings; the evidence is good that monthly treatments can reduce the incidence of malaria episodes by over 80% but systems to deliver IPTc need to be established.

Malaria Treatment and Diagnosis

Artemisinin-based Combination Treatments (ACTs) are the recommended first line treatment for uncomplicated malaria caused by *P falciparum*. Artemisinin is a fast acting and highly effective drug capable of rapidly reducing the number of viable malaria parasites in a patient. Artemisinin is used in combination with a second drug with a different mechanism of action, to enhance efficacy and mitigate against resistance, giving rise to the concept of ACTs. Artemisinin monotherapy has been banned by the WHO since 2007, however, 25 countries were still allowing the use of artemisinin monotherapy in 2010. Urgent measures to implement effective bans on this single treatment therapy are needed.

ACTs have been recommended by WHO for about a decade, following recognition of the growing resistance to older antimalarials such as chloroquine and sulphadoxine-pyrimethamine (SP). Countries rapidly adopted ACTs as first line treatment -- 77 of the 86 P falciparum endemic countries had ACTs as their first line treatment by 2009. This change in policy brought various challenges. The new ACTs were relatively expensive, a treatment course costing about $7 compared with $0.20 for a course of chloroquine or SP, when procured in a private sector outlet or facility. The costs of the drugs have started to come down in recent years, partly due to economies of scale in their manufacture and also because of improvements in tests of the purity of the raw material, Artemisinin. This is derived from the plant *Artemesia annua* (Fig 7) but difficulties forecasting demand and the unpredictability of cultivation have created challenges at the top of the supply chain for artemisinin.

The introduction of ACTs coincided with early reports of falling transmission in some settings.

Figure 7: Artmesia annua – the source of artemisinin for ACTs. (Source: MMV)

Previously, a high proportion of fever cases had been due to malaria and safe, effective and inexpensive treatments were widely available. Now the falling intensity of malaria transmission and the introduction of a relatively expensive treatment provided a strong rationale to improve malaria testing and the targeting of antimalarial treatments to only those who are known to have malaria. Testing increases the likelihood that patients are correctly treated, whether for malaria (if confirmed) or for another disease if the test is negative. In 2010, WHO's Global Malaria Programme recommended that prompt parasitological confirmation by microscopy or rapid diagnostic tests (RDTs) be

Box 2. The Treatment of severe malaria with Artesunates

Quinine has been the first choice for the treatment of severe malaria for hundreds of years. However, two large clinical trials have recently shown that artesunate is more effective in saving lives and that it is safer and easier to use than quinine. A study in Asia showed that artesunate reduced mortality in adults with severe malaria by 39% compared with quinine, and a study in children in nine African countries showed that artesunate reduced deaths by 24%*. The studies provide convincing evidence that artesunate is superior to quinine and, if it were possible to treat all cases of severe malaria with artesunate instead of quinine, approximately 195,000 lives would be saved every year. IV Artesunate, manufactured by Guilin Pharmaceutical Co. Ltd in China, was added to WHO's prequalified list. MMV partnered on this project with Guilin, to improve to GMP standards its manufacturing processes for this product. As a prequalified drug, this important medicine for the treatment of severe, life-threatening malaria will now be accessible to all countries using donor funds to procure antimalarials, for example from the Global Fund.

Following the publication of these studies, WHO's Global Malaria Program swiftly revised its treatment guidelines and now recommends intravenous/intramuscular artesunate as first-line treatment for children and adults with severe malaria everywhere. These guidelines need to be adopted by endemic-country control programmes and translated into practice. Healthworkers need to be trained and communities made aware of the new treatment. There is a need to increase production of artesunate and ease off production of quinine. Although the unit cost of artesunate is greater than that of quinine ($3.30 compared with $1.30), cost effectiveness analyses suggest that the total costs (including those of administration, duration of hospital stay and management of adverse effects) are similar and that artesunate is overall more cost effective.

** Artesunate vs. quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label randomized trial. Lancet 2010; 376: 1647–57*

Figure 8: A Rapid Diagnostic Test for malaria. A single line confirms the test has worked; a second line shows the patient has malaria. (Source: Malaria Consortium)

obtained in all patients with suspected malaria before initiating treatment.

The traditional approach to **parasitological diagnosis** depends on microscopy. A drop of blood is carefully smeared onto a glass slide and left to dry before being stained and examined by a skilled microscopist. Proper blood slide examination is painstaking work and requires dedicated and well-supported staff. In most malarious settings this support is often lacking and the quality of routine slide microscopy has been, and remains, lamentable. Recent years have seen the development and introduction of Rapid Diagnostic Tests (RDTs) (Fig 8]) With just a few hours training it is possible for a relatively untrained person, working without electricity or a sophisticated laboratory, to determine whether a patient has malaria. For the first time it has become possible to take the guess work out of malaria diagnosis and get a proper test.

The roll out of diagnostic testing should also take the guess work out of tracking progress with malaria control and help to identify areas with persistent malaria transmission. A further potential benefit is that, having excluded malaria as a cause of a patient's illness, a negative malaria test can prompt the search for an alternative cause of illness. Hence the introduction of malaria diagnostics has the potential to improve the identification and therefore management of non-malaria febrile illness.

In the early 2000's less than 5% of suspected malaria cases reported in Africa were confirmed with a diagnostic test. In 2008, WHO in conjunction with the Foundation for Innovative New Diagnostics (FIND) and CDC produced a systematic assessment of the quality of RDTs. By 2009 the number of suspected malaria cases confirmed with a diagnostic test in Africa had risen to more than a third. The Global Fund for AIDS, TB and Malaria (GFATM) supported the procurement of 105 million RDTs in 2010 and supplies have been further boosted by PMI and others. A small number of African countries have been able to scale up malaria diagnostic testing to the national level. Not only has this resulted in the saving of hundreds of thousands of courses of ACTs annually, but it has also allowed the implementation of timely and accurate malaria surveillance.

Nevertheless, the MMV/RBM report on tracking progress in scaling-up diagnosis and treatment of malaria, which monitors countries' stated need for ACTs and RDTs, indicates that there is still some way to go for countries to achieve full coverage of RDT use, and thus support correct case management of malaria. In 2010, Africa's 45 malaria endemic countries identified their need for ACTs at 300 million courses of treatment, while only identifying a need for 138 million RDTs. The 2011 report, currently under preparation, provides a better balance indicating that countries are scaling up the use of RDTs, but that significantly more support is required in this area. In particular, countries require support in identifying the correct balance between RDTs and ACTs, support for RDT implementation, and analysis of the benefits in improving case management (eg improved health outcomes, cost savings on ACTs, protection against resistance for the medicines).

Box 3. The importance of education and behaviour change communication

It is hard to over emphasise the importance of education to change behaviour and maximise the impact of malaria control tools. Healthworkers and communities alike need to understand why it is important to use prevention tools like mosquito nets, along with diagnostic tests and malaria treatment appropriately. Ownership of an LLIN does not equate with use and extensive efforts to encourage use all year round have been and continue to be needed. An important current challenge is to make people aware that NOT all fever is due to malaria and that malaria treatment will only work for those with a positive malaria diagnostic test. After generations of presumptive treatment – where all fever was treated as malaria – this requires a major change in understanding and practice. Without such understanding and assured access to the affordable treatment of non-malarial febrile illnesses, it is unlikely that people will accept withholding of malaria treatment when a malaria test is negative.

Challenge I - Delivering the Goods

In order to realise the full potential of the different malaria control tools it is necessary to deliver them to the people who need them, when they need them. Major challenges surround the delivery of control tools. The poorest people are often the most difficult to reach, and yet also tend to have the highest risk of malaria infection, disease and death. The immature infrastructure of the highest burdened malaria endemic countries compounds the challenge of access. Many of the delivery challenges apply to all commodities (Box 4), though each has its own unique set of issues and potential novel solutions (Box 5).

Box 4. Some common challenges in the delivery of malaria control tools

- Where to target efforts? Requires reliable local information on disease burden – who has malaria, where and when?
- How to forecast needs – how many LLINs, ACTs, RDTs?
- Efficient procurement of commodities
- Transportation to destination country, and within country to delivery hubs, and appropriate, secure storage solutions
- Importation – excise and duty, timing
- Supply chain – how to ensure uniterrupted availability to the end user
- Stock control at transit depots and point of dispensing
- Quality control in the field
- Reliable information from good, appropriately used diagnostics
- Effective information management - relevant summaries of complete data available to decision makers at key levels
- Physical access of end users to point of delivery (e.g. health facilities, shop keepers, village health workers)
- Cost to end user in health facilities, shops and in the communities
- Incentivisation of private sector staff and patients to use RDTs and ACTs appropriately
- Availability of appropriately trained health workers, shop keepers and community medicine distributors
- Control tools accepted by informed end-users who understand and are compliant

Box 5. Getting Mosquito Nets to hard-to-reach Cocoa Farmers: *Innovation for Delivery*

Malaria No More UK and Source Trust presented to the APPMG how they formed a novel partnership to deliver LLINs to hard-to-reach Ghanaian cocoa farmers. Source Trust is a collaborative, not-for-profit organisation established by Armajaro Trading Limited that works in partnership with NGOs, farming communities and chocolate makers to develop sustainable farming businesses in the developing world. Chocolate makers pay a premium for traceable Source Trust cocoa. The premiums are donated to Source Trust which, at the suggestion of Malaria No More UK, has been using some of these funds to pay for LLINs. Armajaro Trading Limited uses its traceable supply chain in reverse, enlisting otherwise empty trucks returning from delivering cocoa to the ports to deliver nets back to farming communities. Source Trust has also enlisted local malaria partners in Ghana to train its own staff to help deliver malaria education. So far over 75,000 nets have been distributed to this hard to reach group in Ghana and the communities have reported they are using them. (Fig 9)

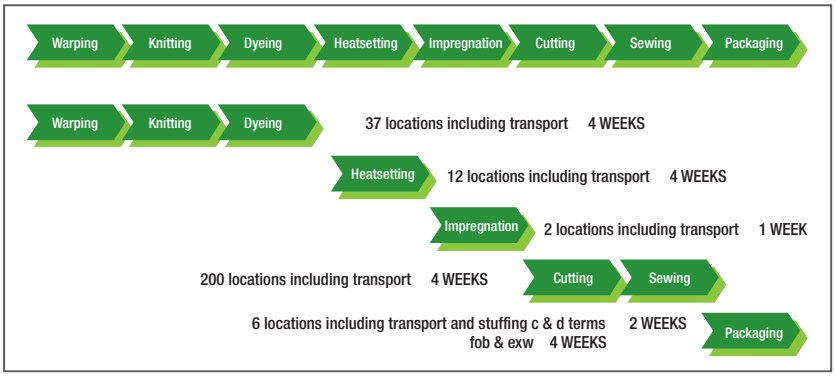
Figure 9: LLINs delivered to a target group (Source Malaria No More UK – Armajaro presentation to APPMG)

It is important to recognise that investments in this neglected area can be expected to produce benefits beyond improved malaria control. Reducing stock outs of malaria drugs is likely to go hand in hand with an improved supply of other drugs.

An LLIN Manufacturer's Perspective

The Vestergaard Frandsen Group showed how various challenges create difficulties in the provision of LLINs to a programme. LLIN manufacture takes about four months (Fig 10). Lack of forecasting is a hindrance as shifts in demand lead to bottlenecks in production. The number of nets needed has

Figure 10: Timeline for LLIN manufacture (Source: Presentation to APPMG from Vestergaard Frandsen)



previously been based on two people sharing each net. The forecasting of LLIN needs is starting to get more complex as the average life span of a net is about three years and hence some nets distributed in earlier programmes need replacing. Now we're moving into a period where forecasting of needs has to consider the existing coverage gap that new nets need to plug, and add to this the anticipated number of nets needing replacement. This has significant implications for planning manufacturing capacity, and thus the sustainability of manufacturing in the long term. Similar issues are faced by the ACT and diagnostics manufacturers, emphasising the need for strong national data, good demand forecasts and reliable financing flows.

Lack of communication at the country level causes uncertainty, especially during the bid evaluation process, which can be very lengthy. The process of opening Letters of Credit is often slow and unpredictable with unforeseen requests – such as certificates of financial capabilities, the provision of CV's, a five year order overview – slowing down the process. The limited number of Inspection Companies leads to further delays. The transfer of approved in-country funding can elongate the procurement and contract award process. Suppliers often over promise on delivery times and, while there are no penalties for delays in awarding, contracting, or delivery, the expectation is that manufacturers will start production before contract finalisation – leaving the manufacturer at risk. Countries have a limited understanding of the requirements of the process (bid security, performance bonds, payment terms, etc.) and there are no obligations for procurement agencies to maintain timeframes.

Despite these challenges, huge quantities of nets have been supplied requiring major mobilisation of resources and massive logistic operations (Box 6).

Box 6. Logistic considerations in Large-scale LLIN distribution

After production, LLINs nets are packed into containers and shipped to distribution points.

1,000,000 nets require approximately twenty-five 40ft shipping containers

The scale of large net campaigns create logistic challenges, as the final distribution hubs are often in rural locations – rarely conveniently located near major transportation hubs. Challenges include:

- Sourcing containers within the tight deadlines of contractual obligations
- Sourcing interim storage for re-packing of nets from containers to trucks
- Ensuring the timely delivery to multiple final end-destinations
- Managing regulatory/customs/inspection-related issues as they arise

Delivering Drugs

Availability of ACTs

Many malaria endemic countries have adopted ACTs as the first line treatment for uncomplicated malaria. Despite this, patients in most settings have difficulty accessing the recommended malaria treatment (Box 7), a reflection of the long process in production and distribution of ACTs (Fig 11). An important consideration is that the predominant source of malaria treatment varies between settings. For example, about 90% of malaria treatments are sourced through the private sector in Nigeria and DRC, compared with less than 10% for children in Uganda. It is therefore important to recognise the role of the private sector in delivering malaria treatments. The private sector comprises pharmacies, general grocery shops and itinerant

Box 7. ACT Access: problems of stockouts

The APPMG visited the Nile Breweries programme in Jinja, Uganda to learn more about their health programme. Nile Breweries Ltd is a beer brewing company that has been in operation in Uganda since 1951. The company engages with its supply chain at every level, including small and medium-sized enterprises, farmers, truck drivers and even bar goers to raise awareness and carry out health prevention education for HIV/AIDS, TB and malaria. The Nile Breweries programme has trained over 300 peer educators to promote health awareness within sorghum farming communities, reaching over 4,000 farmers.

APPMG Chairman, Jeremy Lefroy MP commented that the Nile Breweries had developed an exemplary programme using peer educators to educate colleagues about HIV/AIDS, encourage them to be tested, especially with spouses, and to counsel them. Unfortunately, the hospital had been without ACTs for malaria for several weeks at the time of the visit. 'Given that there was no shortage of ACTs in the country – and indeed a nearby factory making them which was looking for a market - this seemed to us to be unacceptable', commented the APPMG Chairman.

While effective antimalarials are recommended policy in countries, they are often not available on the ground where patients need them. Failure to get the necessary drugs to front-line health facilities remains a major hurdle.

'There is no doubt that the work done by Nile Breweries, together with the local health centres is making a significant difference for the people in the Community, and those we visited said so openly,' said Jeremy Lefroy MP. 'It is clear that when a large company decides to take on responsibility both for the health of its staff and employees and for those in its supply chain, it can make a great difference provided it works together with the existing health system'.

drug pedlars. The regulated and unregulated private sector should therefore be considered when assessing access to malaria treatment. However, data is not routinely available from the private sector, an omission that needs correction.

There are also important differences in the availability of ACTs in different types of outlet. The examples shown in (Fig 12) indicate the importance of malaria control plans that are tailored to the needs and reality of individual countries, using outlets in the public and private sectors.

ACTwatch is a project working to generate comparable information on the availability of ACTs and treatment-seeking behaviour in seven countries (Benin, DRC, Nigeria, Madagascar, Uganda, Zambia, Cambodia). The systematically collected information will help to build a picture of the availability of quality ACTs in the private sector and consumer treatment-seeking behaviour, amongst other things. This will inform the development of country-specific advocacy plans and should also form a useful basis for the development of systems to collect similar information in other countries.

Affordability of ACTs

Cost is a critical consideration in the many counties in which malaria treatments are largely sourced in the private sector. ACTs are considerably more expensive than older, less effective drugs, making ACTs relatively unaffordable and incentivising ACT counterfeiters. AMFM hosted by the Global Fund and supported by DFID, UNITAID and Bill & Meilinda Gates Foundation is working to counter these problems. A high-level subsidy for ACTs is introduced at the manufacturer level so that first line buyers at country level receive quality ACTs at affordable prices. The subsidy should then be passed down the supply chain so that end users benefit from affordable, quality ACTs. It works through the public and private sectors.

AMFm implementation has started in seven phase I countries and, by end June 2011, had approved payments for 150 million packs of ACTs, of which 75% were to private sector buyers. A consultation

Figure 11: Artemesia: from plant to patient (Source: J Barrington presentation to APPMG)

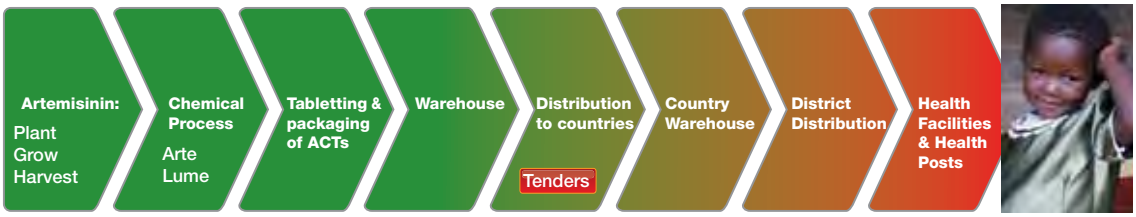
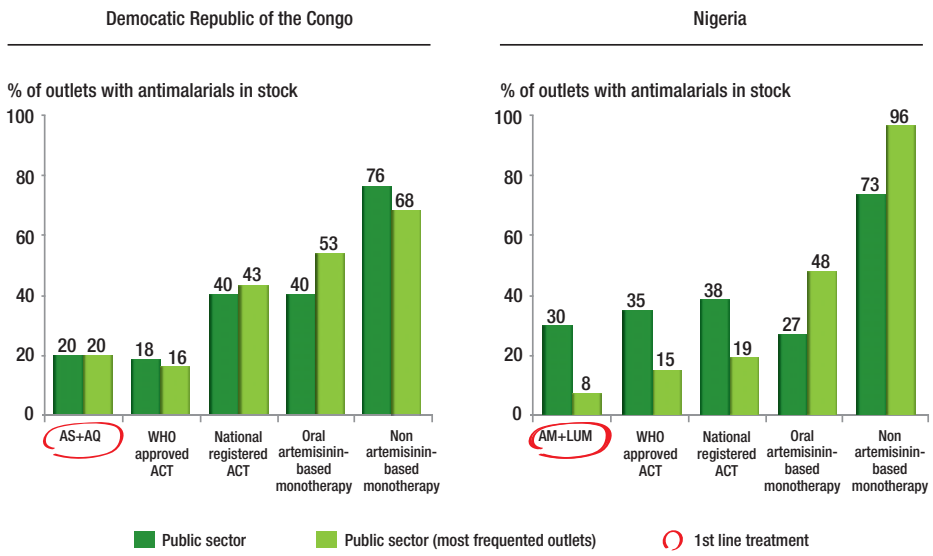


Figure 12: Availability of ACTs in the Democratic Republic of the Congo and Nigeria. (Source: GPARC, 2011)



AS+AQ, artesunate plus amodiaquine; AM+LUM, artemether plus lumefantrine
Source: ACTwatch Outlet Survey Rports (baseline as of 2008),Population Services International

in June 2011 (Dar es Salaam) revealed some encouraging initial findings. In Ghana, for example, 6.5 million doses of ACT had been delivered to the country by April 2011. Launches at national and three regional levels had taken place, including adverts on 31 radio and six television stations, and in four newspapers. Distribution of the drugs through the normal drug distribution network had been complemented by the training of over 1,400 pharmacists and 6,000 licensed chemical sellers. Co-paid ACTs were available in 56% of 808 outlets surveyed across the country at a modal price of GHC 1.50 (about £0.60). Similarly encouraging early results were presented by the Kenyan NMCP (Fig 13). The indications are that the AMFm can produce a rapid fall in retail prices as co-paid ACTs enter the market and enhance the availability of quality ACTs within private sector facilities. The early experience suggests that, in addition to government clinics, the commercial private sector is a viable channel for delivering donor-financed ACTs at country level.

An Independent Evaluation is ongoing and expected to provide information for a GFATM Board decision on the future of the AMFm at the end of 2012. Information on availability, price, market share and use of quality-assured co-paid ACTs will feed into this decision.

As in so many other aspects of malaria control, patient awareness and information are likely to be key to the success of the AMFm.

The importance of information

Timely and complete data, and the ability to respond to it, are required at all levels to improve the availability of malaria control commodities for the end user. For example, manufacturers need to decide whether to invest in capacity to meet ACT demand if the AMFm is expanded, at the same time recognising the increasing coverage of vector control and other factors will decrease malaria transmission and that the roll out of diagnostic testing will further reduce the quantities of ACTs needed. These complex considerations are compounded by uncertainty over the availability of donor funding and the questionable availability of raw materials, especially the plant-derived Artemisia.

Reliable data on case numbers is a key requirement for efficient malaria control planning. The absence of better trend data is causing ongoing problems with forecasting and breaks in supply of malaria

Figure 13: Affordable Medicines for Malaria (AMFm) poster.

treatment and related commodities. New technologies are being developed, tested and deployed which have the potential to ameliorate the situation (Box 8)

Importantly, lessons learnt through strengthening the information system for malaria are likely to benefit the supply of commodities for other, non-malaria goods. The use of new technology such as mobile phones is also being piloted to help track cases of malaria. Such approaches will be important for the future improvement of malaria control and to help in the mapping of disease incidence in countries working towards elimination. This is an issue the APPMG may wish to examine further in the coming year.

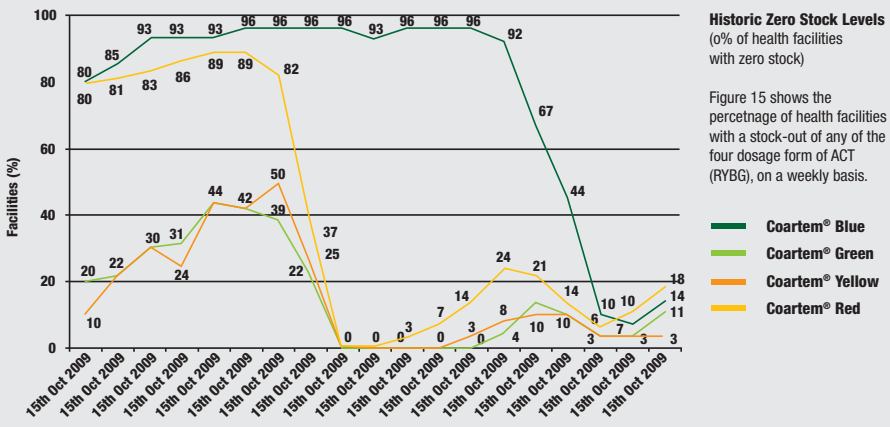
Box 8. SMS for Life

SMS for life was developed by Novartis, Google, Vodafone, IBM and RBM in collaboration with the Tanzanian Ministry of Health and Social Welfare. The project assessed the potential of mobile-phone Short Messaging Services (SMS) to improve data on stock levels in order to reduce the frequency of ACT stock outs (Fig 14]) Each week, health care providers in 129 peripheral health facilities receive an SMS requesting information on stock levels of Coartem, Tanzania's first line treatment for malaria, and quinine. Prescribers count stock levels of the four different dosage packages and text the information to a central server. They are rewarded with credit to their phone account while the information is automatically summarised and presented to key decision-makers in an appropriate format. Evaluation showed a 95% response rate from health workers and 94% accuracy compared to a physical count. The availability of ACT (all dosages) increased from 23% to 74% of facilities during the pilot study (Fig 15). Stock levels can be checked online and District Medical Officers are automatically notified, via mobile phone, when stock outs arise and where nearby facilities have surplus stock. The annual running costs of the system are about $100 per facility per year. The pilot was so successful that the system is being rolled out nationwide with support from SDC and MMV.

Figure 14: SMS for life. (Source: J Barrington presentation to APPMG)

Mobile phone technology is an easy and accessible way to gather important health data quickly. In addition to helping to assure the timely availability of commodities where they are needed, this technology may also play a useful role in the containment of drug resistance and in the context of malaria elimination, helping to pinpoint and respond to clusters of malaria cases or transmission "hotspots".

Figure 15: Stock outs in 30 rural health facilities in Ulanga district, Tanzania fell from 87% to 30% following introduction of SMS for life (Source: J Barrington presentation to APPMG)



Challenge 2 – Containing Resistance

In malaria treatment and control, the development of drug or insecticide resistance is an almost inevitable consequence of their use as the parasite evolves to evade the threat. Strategies to delay the onset and spread of resistance must be employed to maximise a compound's lifespan. Such strategies include targeting the treatment where it's needed, ensuring complete treatment is administered and combining more than one compound – as with ACTs. It is useful to combine treatments, each working through a different mechanism, as it is much more difficult for the parasite or mosquito to develop resistance to two separate treatments used together than to each used individually. However, once resistance to ACTs starts to develop it must be detected and the extent to which it has spread, monitored. Ultimately, new medicines and insecticides will continue to be needed, and hence adequate investment in their development now as well as learning how best to use them, is important.

Insecticide Resistance

Several mechanisms of insecticide resistance have been described. Molecular biology techniques have shown evidence of widespread pyrethroid resistance in sub-Saharan Africa. Pyrethroid insecticides target the same site in mosquitoes as DDT, encoded by a mosquito gene called kdr. Molecular and mosquito-based evidence of resistance to pyrethroids and DDT has been documented in some countries. However, so far, this has not translated into a failure of these insecticides to control malaria. Other types of insecticides – the carbamates and organophosphates – show little signs of resistance to date.

Good pesticide management is important to reduce unnecessary exposure of mosquitoes to insecticide. This implies efforts to minimise waste and to target spraying where it's needed. Rotations of insecticide, combinations and mixtures of insecticides all make it harder for mosquitoes to develop resistance. Mixtures of insecticides from different classes may be the best way to ensure that insects developing resistance to one insecticide are killed by another. However, although a few mixtures are used in agriculture, none is available for public health use where mixtures face regulatory and formulation challenges.

Only pyrethroids are currently licensed for use on mosquito nets, but insecticides from several different classes can be used for IRS. The spread of resistance will be impeded by selecting insecticides from different classes in successive years for IRS.

The use of a carbamate for IRS in conjunction with a pyrethroid on an LLIN presents a greater challenge for the mosquito than if a permethrin was used also for the IRS. Preliminary studies of such combinations have generated promising results but further investigation, in both small-scale studies and operational trials, is urgently needed.

Effective resistance monitoring is an integral part of resistance control – it's important to know when and where resistance has developed. Monitoring needs to extend beyond national borders and implies the need for co-ordination at the regional level. This will only be possible if there is effective in-country coordination, by National Malaria Control Programmes, ensuring that resistance monitoring is cohesive and collaborative amongst all partners. Funders should check that such monitoring is taking place and that information flows efficiently to co-ordination points.

The development pipeline for new insecticides is the poor relation amongst malaria control tools. Its relative neglect is particularly worrying given the importance of vector-based strategies for malaria control. Although some products are under development for IRS, the prospects for new insecticides for LLINs are less promising. This is partly because the insecticide on LLINs represents only a small proportion of its total value, but a much larger proportion of other vector control products. Novel incentives may be needed to stimulate the development of new insecticides for LLINs.

The development of a new class of insecticides takes about ten years, but manufacturers are only likely to invest in this if clear prospects exist for a market that will last for more than a decade. Only major chemical manufacturers have the resources to search for new molecules but they are cautious about the apparent instability of the public health market. There is a need to produce realistic estimates of future needs, show that donors remain committed and project the market size in the medium to long term (15 years or so). This is a market failure similar to that seen in the vaccines, treatment and diagnosis fields and addressed to some extent by PDPs.

Development of new insecticides and the use of newer agents imply greater costs in the short term. However, investment now - especially in developments that prolong the utility of pyrethroids for LLINs - will almost certainly be cost saving in the long run.

Drug Resistance

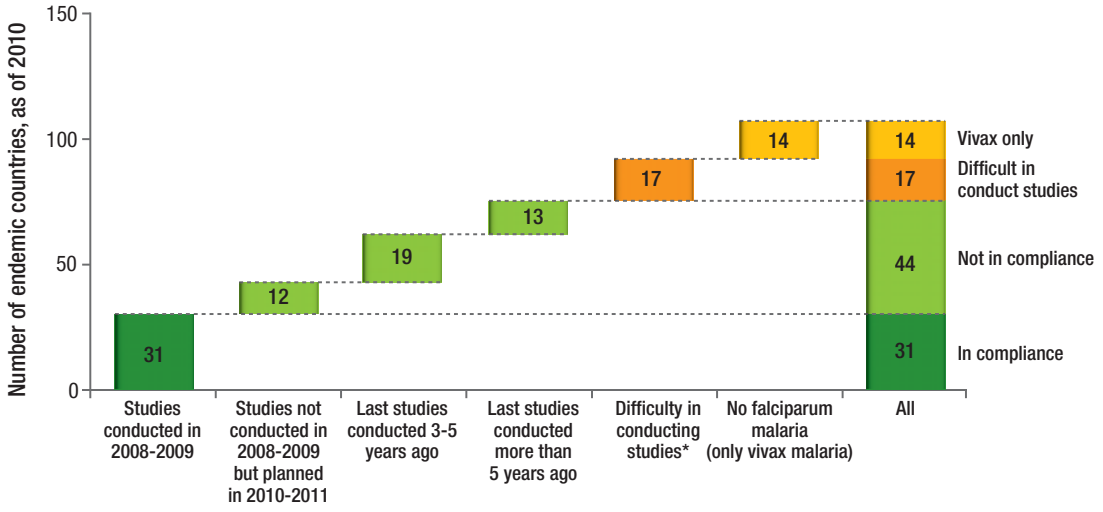
The first reports of resistance to antimalarial drugs have successively come from Southeast Asia. Specifically, resistance to chloroquine, sulphadoxine-pyrimethamine (SP) and mefloquine was reported first from the Thai-Cambodia border. The reason for this area being a hotbed for anti-malarial drug resistance is not clear. However, the first reports of artemisinin resistance in 2009, emerging from the same epicentre, raise the spectre that history might repeat itself and resistance to artemisinin, the mainstay of current first-line treatment, might also become widespread. There is a limited window of opportunity to contain or eliminate the resistant parasites before they spread to areas of higher transmission. The urgency to contain artemisinin resistance is increased by the fact that no other class of antimalarial medicine is available that offers the same level of efficacy and tolerability as ACTs. To address that gap, the malaria community has set the goal of developing a new combination therapy every five years. This is an ambitious challenge since we need to develop combination therapies (two drugs combined in a single pill), which significantly increases the chance of failure (see box below). Significant efforts and investments, notably by MMV, in early research over the last five years is, however, starting to pay off. Indeed there is now a sustained flow of distinct new compounds progressing into preclinical development each year. For the first time, the malaria community is in a position to be able to successively assail the parasite with new weapons should they be needed. Dropping funding at this stage would seriously jeopardize the benefit of this earlier effort.

WHO published a Global Plan for Artemisinin Resistance Containment (GPARC) in 2011. This is a call to action and high-level plan of attack that defines the priorities for containment and prevention of artemisinin resistance. The GPARC recognises that one of the most important components of successful artemisinin resistance containment and prevention is intensified, sustained malaria control or elimination in all endemic regions. Countries and areas are allocated to one of three tiers. Tier 1 settings have credible evidence of resistance and require an immediate, multifaceted response. Tier 2 settings have significant inflows of mobile populations from Tier 1 areas, or shared borders, and need to launch and maintain intensive and accelerated malaria control activities, including a focus on migrant populations. Tier 3 areas have no evidence of artemisinin resistance and limited contact with Tier 1 settings, should continue malaria control and to ensure monotherapy and poor quality drugs are not available.

Information from the monitoring of drug efficacy is extremely important to inform the development of effective resistance containment activities. Unfortunately this is frequently not undertaken (Fig 16) – a situation which should be remedied.

Activities were launched in 2009 to contain artemisinin-tolerant *Plasmodium falciparum* parasites around the Thai-Cambodian border. Initial support from the Bill and Melinda Gates Foundation (2009-2010) was followed by GFATM grants for Cambodia (2009) and Thailand (2010), a grant from DFID and ongoing commitment from the Thai and Cambodian Ministries of Health. The strategy aims to (i) eliminate resistant parasites by detecting

Figure 16: Status of therapeutic efficacy monitoring in 106 countries endemic for malaria. (Source: GMAP, 2011)



* Very small number of cases makes it difficult to conduct studies in these countries

all malaria cases in target areas and ensuring effective treatment and gametocyte clearance. (ii) decrease drug pressure for selection of artemisinin-resistant malaria parasites. (iii) prevent transmission of resistant parasites by mosquito control and personal protection, and (iv) limit the spread of resistant parasites by mobile/migrant populations. These objectives are supported by a behaviour change communication (BCC) programme and other strategies designed to target migrant and mobile people (Box 9), a particular challenge to the programme.

Most Cambodians get antimalarials from the private sector, where there have been concerns about drug quality, completeness of dosing regimens and treatment with artemisinin monotherapy. The current strategy aims to reduce this by providing free high quality diagnosis and treatment in the public sector and by strengthening regulation. To this end over 200 'Justice Police' have been appointed to inspect drug outlets for artemisinin monotherapy and fake or substandard drugs.

Strengthened surveillance is an important component of the containment activities. A village-level malaria database has been created that includes over 14,000 villages with their geospatial co-ordinates. Information on malaria cases detected by VMW's, MMW's and health facilities is forwarded to the database using SMS texting services. Follow-up information on day 3 from Zone 1 villages enables village-level investigation and a containment response. The system allows up to date malaria risk stratification on the basis of village incidence data and makes use of Google earth to map cases. Cross-border surveillance systems are being developed to enable information sharing and co-ordinated responses.

The next steps are to extend containment efforts to Myanmar, where the government is working with donors, including DFID, to set up 24 sites for monitoring resistance. This is important because Myanmar's malaria burden is considerably higher than other countries in Southeast Asia. Its large population at risk, extensive migration, civil conflict along some border areas and inadequate investment in malaria control over decades makes this a particular challenge. The Ministry of Health, with support from various partners, has developed the Myanmar Artemisinin Resistance Containment Framework (MARC), in line with the WHO Global Plan for Artemisinin Resistance Containment. The UK Government used World Malaria Day 2011 to highlight the issue of resistance in the region and to publicise its work to help tackle the problem.

Valuable lessons are being learnt in south-east Asia; the challenge now is to make use of them to intensify drug efficacy monitoring throughout Africa.

Box 9. Behaviour change communication (BCC) for migrant and mobile people.

Providing information to migrants and mobile people can be challenging. The BCC strategy to support the containment of artemisinin resistance on the Thai-Cambodia border uses a variety of approaches. Bill boards at forest entry points encourage people to seek care if they become unwell and to carry with them an insecticide treated hammock. Mobile Malaria Workers (MMW) target newly settled villages, while role models are used to catalyse behaviour change in other communities. In Thailand, private farm owners and long-term workers are employed to screen and treat workers. Long-lasting insecticide treated hammock nets (LLIHN) are distributed to migrants who work and live in forested areas and work is ongoing with farmers to provide LLINs and LLIHNs to migrant workers. The potential of taxi drivers for outreach services is also being piloted. Surveys have been done to track and understand the behaviour of migrants, though more work is needed. Cross-border malaria check points have been established with voluntary screening of the mobile population. Regular meetings are held at district level, including private owners, public health authorities, security forces and others, to maintain awareness and co-ordinate malaria-related activities.

Challenge 3 – Developing New Tools

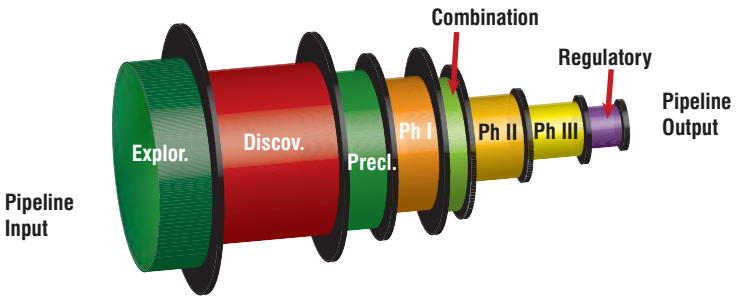
The antimalarial product development pipeline is stronger now than it has ever been before. This is a result of a wave of investment which started in the 1990s. Five new ACTs are either registered or submitted for registration. The first child-friendly formulation of a malaria drug is now available – though it is astonishing that it has taken until now for this to happen given the massive toll malaria exacts on young children. A reasonably efficacious first-generation malaria vaccine is likely to become available by the end of 2015. A plethora of RDTs and an international quality control system have been developed. The malaria research and development scene is stronger than it has

Box 10. Developing new anti-malarial medicinal products

When developing new drugs or vaccines, pre-clinical studies are conducted before the 'first in man' – or Phase I – clinical trial starts to gather safety data in people. Phase I studies are small, involving a few 10's of subjects. Phase II studies are conducted next, still small scale - perhaps involving 100's of participants - and aim to get the dosing quantity and timing right and to generate further safety information. Phase III studies generate evidence that the product really works and consolidates its safety profile when used in the target population. Such studies need to be large enough, usually involving 1000's of people, to provide the confidence that the product works as expected and is safe. Such trials are expensive [Fig 17] but required before regulatory authorities can consider granting a license for the product. Post-registration (Phase IV) studies are also needed, to monitor the safety and effects of the intervention when used in routine practice. Phase III and sometimes Phase IV data are considered by WHO when making a recommendation about a new tool or approach for malaria control. When developing a new combination drug, or vaccine, phase II studies are conducted on the individual components before the new combination is tested. This increases the cost, risk of failure and time taken to develop new, combination products.

Figure 17: The drug development pipeline. POS: Probability of Success. (Source: MMV)

A heavy emphasis is placed on Portfolio Management to mitigate attrition



	Exploration	Discovery.	Preclinical	Phase I	Phase IIa	Phase IIb	Phase III	Regulatory
POS	30%	40%	55%	70%	90%	50%	65%	95%
Cum POS	30%	12%	7%	5%	4%	2%	1.5%	1.3%
Phase length (quarters)	8	20	3	2	3	4	9	4
Phase cost (k USD)	250-500	1.00	1.5-2.00	0.5-2.00	2.00	6.00	15.00/ pivotal study	0.5-2.00

Cumulative probability of completing pipeline is 1.3%

Preclin, Phase I and Phase IIa studies have to be done for each compound and repeated for the combination (for a full drug combination development, these costs are multiplied by 3)

ever been before, but much remains to be done, multiple tools need to be developed and deployed in parallel if malaria is to be defeated. There is no room for complacency.

Vector Control

Current vector control strategies are very highly dependent on the pyrethroid class of insecticides, the only one licensed for use on ITNs and LLINs. As a result, vector control is in an exquisitely vulnerable state and the development of new classes of insecticide is a high priority. However, funding in this area is relatively poor: the GMAP estimates a 2.5 fold increase, to about $90m per year in 2015-2016, is needed to remedy the situation. Although 14 candidate products ranging from new active ingredients to reformulations of known agricultural insecticides are in development with support from the Innovative Vector Control Consortium, most (11) of these are in the early stages. Clearly there is a need for further investment and activity in this area.

The WHO Pesticide Evaluation Scheme (WHOPES) was set up in 1960 and consists of a four stage evaluation and testing programme, studying the safety, efficacy and operational acceptability of public health pesticides and developing specifications for quality control and international trade. Two long-lasting IRS products, whose development was supported by IVCC, are currently being considered by WHOPES (from Bayer and Syngenta) and Vestergaard's LLIN is in the registration phase.

Drugs

Efforts and investments in early research over the last five years are starting to pay off. There is now a sustained flow of distinct new compounds progressing into preclinical development each year, with 47 candidates in the development pipeline - 27 in preclinical and clinical stages of development. For the first time, the malaria community is getting prepared to assail the parasite with a succession of new weapons.

Recent years have seen several new products registered with the support of either DNDi or MMV, both of which receive funding from DFID. DNDi supported the development and registration by Sanofi Aventis of artesunate/amodiaquine (Coarsucam) in 2007. This is being used in 25 African countries and in India -- over 50 million treatments have been distributed. DNDi also supported the development of artesunate/mefloquine by the Brazilian public pharmaceutical company Fiocruz in 2008. MMV in partnership with Novartis developed Coartem® Dispersible in 2009, the first pediatric high-quality ACT currently on the market. As of March 2011, 64 million treatments of this life-saving medicine have been delivered to 35 countries. In addition, MMV worked with the Italian company Sigma-tau Industrie Farmaceutiche Riunite S.p.A to develop dihydroartemisinin (DHA-) piperaquine phosphate (Eurartesim) which was submitted for registration in 2009 and pryonaridine-artesunate (Pyramax®), in partnership with Korean based Shin Poong Pharmaceutical submitted for registration in 2010. The European Medicines Agency has now in June 2011 recommended the approval of Eurartesim a fixed combination product intended for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants aged 6 months or over and weighing 5 kg or more. Drug development does not always work out: compounds sometimes fail to meet safety or efficacy requirements. The development of isoquine was terminated in 2008 and chlorproguanil-dapsone-artesunate in 2009 due to failure to meet go/no go criteria.

Having brought new drugs and formulations through expensive Phase III trials to registration, the priority for funding has now shifted towards a larger number of less expensive pre-clinical and early clinical studies to accelerate the development of new compounds. The intention is to simplify dosing, counter artemisinin resistance, block transmission and cater to the needs of vulnerable groups such as children and pregnant women.

Increased funding is required to assure the development of paediatric formulations – safe and appropriate for use in children. For the other particularly vulnerable group, pregnant women, treatment is constrained by the paucity of effective antimalarials that have been proven safe for use during pregnancy. MMV in partnership with Pfizer are working on an azithromycin-chloroquine combination currently in Phase IIb/III trials to be used intermittently during pregnancy to provide protection against malaria and potentially other infections.

Some of the more advanced compounds in the global portfolio focus on artemisinin derivatives to develop improved therapies. Others, such as

tafenoquine, entering Phase II/III, aim to provide a radical cure of *P. vivax*. This relapsing form of malaria is the most prevalent species in Southeast Asia and South America. It has the ability to become dormant in the liver, and may reactivate after several months leading to an attack of malaria in the absence of a mosquito bite. Current therapy is with primaquine, which is associated with a number of side effects and must be taken over 14 days. In addition to tafenoquine, MMV is actively seeking to discover further new molecules that will provide a radical cure for vivax malaria and will therefore put an end to relapses.

Novel compounds are needed to meet the challenge of drug resistance. The next-generation combination treatments based on synthetic peroxides, such as arterolane piperaquine phosphate and OZ 439, are now in clinical development. OZ 439 is being developed by MMV as a single dose cure for both *P.vivax* and *P.falciparum*. The challenge is to identify three partner drugs to be combined with OZ 439. In order to mitigate the risk of failure of each individual compound, and ultimately reduce the overall time to registration, the development of the three fixed, different combinations will be conducted in parallel. These intensified scenarios will require sustained funding efforts over the next five years.

Over the next several years, the global malaria community will need new tools as existing medicines are deployed in ever-greater numbers. The paradox is that the more successful the community is in using the current treatments, the higher the likelihood of resistance emerging and intensifying. As we enter the period where many new medicines will be launched, it is all the more important to accelerate the discovery and development of new antimalarial drugs. This will require an increase in funding and a greater focus on the early-stage pipeline, from which innovation will emerge.

Vaccines

Vaccine development is more difficult to predict than drug development. Development of a malaria vaccine presents a unique challenge as there has never before been a vaccine effective against a parasite. There are currently 63 vaccine candidates, 41 in preclinical and clinical stages of development. Vaccines are being designed to target either the forms of parasite inoculated by the mosquito and developing in the liver (pre-erythrocytic stages), the most common form appearing in the blood (erythrocytic stage), the sexual stages taken up by a feeding mosquito, or multiple stages. Most (14/25) of the vaccines undergoing clinical trials are erythrocytic vaccines, with 8 targeting pre-erythrocytic stages and three containing a combination of targets. All but two vaccines in pre-clinical and clinical development target P falciparum.

The most advanced candidate is the pre-erthrocytic vaccine RTSs, being developed by GSK, the PATH Malaria Vaccine Initiative (MVI) and investigators from 11 research centres in seven African countries. Experience to date has shown that RTSs can reduce malaria incidence by about half in young children. The ongoing Phase III trial will produce several sets of results over the coming years, with data being available for review by Regulatory Authorities and WHO by 2015. All being well, WHO has indicated that it could make a policy recommendation as early as 2015, paving the way for deployment of the world's first malaria vaccine at the country level.

Work has begun on the development of more efficacious second generation vaccines, one of which is expected to enter large scale clinical trials in 2016. In addition to building on the success-to-date of RTSs, other approaches being explored include those that target the parasite during its journey through the mosquito.

Diagnostics

There is an urgent need to improve the quality and stability in field conditions of currently available RDTs. Diagnosis of non-*falciparum* parasites has been relatively neglected and warrants urgent attention. As malaria control improves and populations are less exposed to infection, people are likely to become unwell with relatively low density infections. As a result, more sensitive RDTs will be needed. Some drugs, including primaquine, cannot be given to people with a deficiency of the G6PD enzyme. Primaquine is the only drug currently available that kills the dormant liver form of the P vivax parasite. Rapid tests to screen for G6PD deficiency could be used to identify patients who can safely receive primaquine and be cured of a relapsing *P vivax* infection.

A number of additional diagnostic avenues are being explored, such as automated microscopy and non-invasive sampling (using saliva, urine or scanning technology). Loop-mediated isothermal amplification (LAMP) of DNA is able to detect very low levels of parasitaemia. New serology-based tools for population screening are being evaluated, and digital microscopy, polarised light microscopy, haemozoin detection systems and spectrometry may be useful in case management. Low cost quality control tools are needed to ensure diagnostic tests work as expected in the field.

In addition to new diagnostic technologies, it will be increasingly important to develop strategies to screen large numbers of people to identify persistent 'hotspots' of transmission and to screen people travelling into areas suitable for transmission but where malaria has been eliminated.

Tests are needed to diagnose non-malarial febrile illness. The appropriate management of patients who do not have malaria is a major current challenge. Having excluded malaria as a cause of a patient's illness, their management would be enhanced by the identification of specific causes of disease, or by identifying people who warrant antibiotic treatment or referral to better-equipped facilities.

Operational research

Operational research helps to maximise the impact of available malaria control tools, but has been relatively neglected. Until this is remedied we can expect the challenges in the delivery and use of tools (Box 4) to continue. Many of the issues relate to the supply chain and in-country distribution, to the collection and use of health information, to improving knowledge and behaviour, optimising the roles of available human resources, developing appropriate financing mechanisms and functional approaches to quality assurance. Innovations in these areas will be required to maximise the impact of malaria control. At the same time, tackling these issues will improve the provision of services for other, non-malarial, diseases. As malaria control moves towards elimination it will become necessary to enhance the responsiveness of the health system. Unusual patterns of infection and disease will need to be recognised and to trigger co-ordinated and concerted responses. The development of such capacities will also require operational research.

Inclusion of operational research in future estimates of malaria R&D costs would help to ensure that the malaria control tools so painstakingly developed are deployed to maximum effect.

Challenge 4 – Sustaining Financing

The Economics of malaria control

Malaria costs up to 1.3% of an endemic country's gross domestic product per year. In addition to the costs of treatment, illness and premature death, malaria erodes the productivity of people, prevents school attendance and impairs the ability to learn.

Adequate malaria control requires investment into control activities and into the research and development (R&D) of new malaria control tools. RBM's 2008 GMAP estimates that the total cost of the global strategy (including both country implementation and R&D costs) is US$ 5.9 billion per year from 2011 to 2020. R&D costs come in at US$ 750 - 900 million per year up to 2018. The Global Strategy needs long-term commitment - continued funding is essential in both country implementation and R&D to prevent a re-emergence of malaria following successful control. Malaria control is one of the most cost-effective ways to invest in health. By investing in R&D today, new and improved interventions will help countries eliminate malaria faster and reduce the need for longer-term R&D costs. To decrease investments now could jeopardise the gains made through past investments.

Financing malaria control

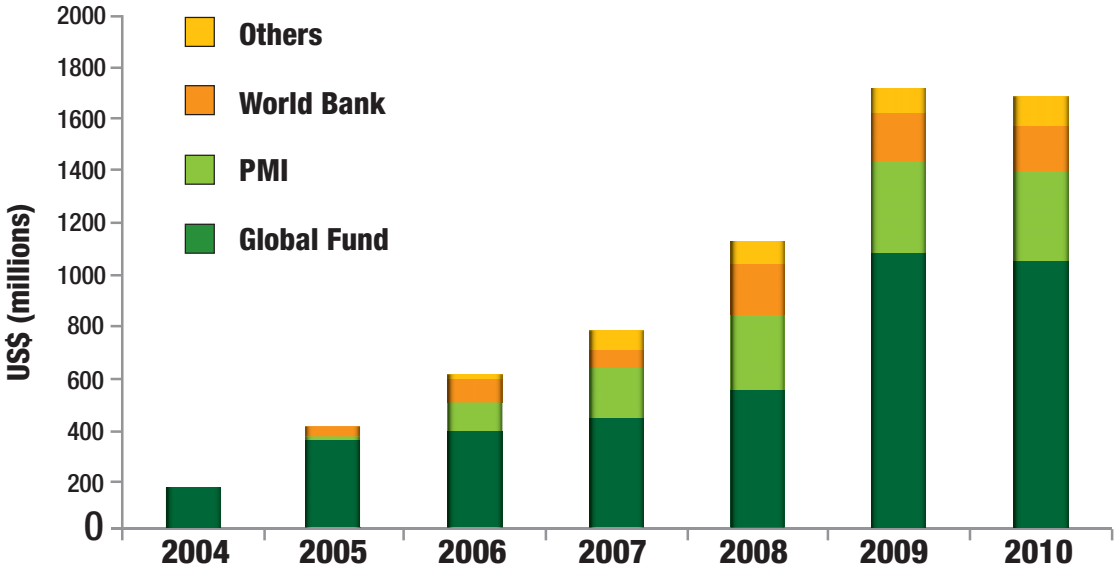
Funds for malaria control have increased considerably over the last decade, but appear to have levelled off in 2010 at US$ 1.8 billion (Fig 18) This still falls far short of the GMAP's estimate of $5.1 billion annual funding requirement for effective malaria control between 2011-2020. The Global Fund is the single largest donor for malaria control. In DFID's Multilateral Aid Review the Global Fund was assessed as providing very good value for money, although future UK funding will be conditional on reforms to improve the way it operates. The money allocated reflects the quality of proposals received, and there remains a need to invest in supporting countries to develop sound proposals.

The American President's Malaria Initiative (PMI) has increased commitments over the last 5 years, increasing from $30 million in 2006 to $300 million in each of 2008 and 2009, and expected to reach $500 million in the 2010 fiscal year. Table 2 shows the contributions of the various bilateral and multilateral agencies to malaria control between 2005-2009. DFID's commitment last year of up to £500M per year by 2014/15 represents a very important contribution to international malaria control over the coming years.

	Malaria Control	Infectious disease control (exc TB and STDs)	Total
Total	**3718**	**5969**	**9688**
Bilateral Contributions	***855***	***4285***	***5140***
United States	560	1744	2304
United Kingdom	124	773	897
Canada	43	458	501
Japan	70	249	319
Germany	1	251	252
Norway	1	145	146
Australia	10	127	137
France	1	102	103
Spain	14	83	96
Netherlands	12	73	85
Belgium	5	77	82
Sweden	0	69	69
Ireland	8	57	65
Luxembourg	1	22	23
Finland	1	15	15
Italy	2	10	12
Korea	1	9	9
New Zealand	0	8	8
Denmark	0	6	6
Austria	1	5	6
Greece	0	2	2
Switzerland	1	1	1
Portugal	0	1	1
Multilateral contributions	**2863**	**1684**	**4547**
Global Fund	2601	0	2601
GAVI	0	623	623
EU Institutions	1	516	526
IDA	202	304	506
UNICEF	50	127	177
WHO	0	92	92
Other multilaterals	0	0	22

Table 2: Official development assistance - expenditure on control of malaria and infectious diseases other than TB and STDs, $m, 2005-09 Source OECD CRD Database

Figure 18: Commitments to malaria endemic countries 2004 – 2010. (Source: World Malaria Report 2010)



Box 11. Case Study:
Quality Chemicals Industries, Uganda

The APPMG visited Quality Chemicals Industries in Uganda where drugs produced locally are unable to compete in the international marketplace.

Quality Chemicals Industries (QCIL) is a Ugandan pharmaceutical plant that manufactures antiretroviral drugs (ARVs) and antimalarials (ACTs). The plant was the first in Uganda to produce these life saving drugs locally in high quality facilities that are compliant with WHO Good Manufacturing Practices. The plant has the potential to produce 6 million doses each day, and to employ 600 people. However output is currently only 2 million doses per day and employment is at 280 people.

The January 2011 APPMG visit to the Kampala plant found that the biggest obstacle to raising output was access to the market. Companies like QCIL are being priced out of the market by foreign manufacturers and multinationals which have the ability to produce low cost drugs. The foreign competitors receive the bulk of orders for medicines financed by donors.

Following successful negotiations, in mid-2010 QCIL became the first Africa-based manufacturer to sign a Master Supply Agreement with the Global Fund, enabling them to participate as suppliers of WHO-prequalified ACTs in the AMFm. This should make it more feasible for QCIL to produce ACTs in larger quantities, access the global market and therefore achieve greater economies of scale.

QCIL point out that other factors need to be taken into consideration by donors looking to invest in manufacturing. QCIL has the potential to create several hundred skilled jobs, pay taxes locally and to reduce the dependency on foreign products.

Lessons from the Private Sector

In May 2011, the Roll Back Malaria partnership published a report documenting the experience of several private entities which had invested in malaria control. The premise for their investment was that malaria is bad for business. About three quarters of companies operating in the African region had reported negative effects of malaria on their business in 2005. Direct economic costs from malaria included absenteeism through illness or care duties for sick relatives, reduced worker productivity due to illness and increased health care spending. Indirect economic consequences included effects on the local economy, deterioration of human capital, loss in savings, investments and tax revenues and reduction in public health budgets. In the Zambian case study, two mining companies and a sugar company invested an average of $34 per employee per year between 2001 and 2009. About 70% of this was spent on indoor residual spraying, complimenting the government's distribution of ITNs in the areas concerned. Between 2000 and 2009, there was a 94% reduction in recorded malaria cases (from 27,925 to 1,631); a 94% reduction in malaria-related absenteeism (from 19, 392 to 1,133); spending

Box 12. The Cost of Price: a case study of the Sumitomo Chemical Company (SCC) A to Z Textile Mills, Tanzania

Sumitomo Chemical Company (SCC) show that manufacturing mosquito nets in Africa provides direct economic benefits to African communities that are long-term and sustainable, but that donor procurement policies that focus only on price threaten the success of such initiatives.

SCC produces WHO-recommended long-lasting insecticidal nets (LLINs)—Olyset Net. In 2003, they partnered with A to Z Textile Mills in Tanzania to pioneer African-based manufacturing of nets. The A to Z facilities are now the largest employers in the area with over 7,000 local employees. An evaluation conducted by The School of Oriental and African Studies (SOAS), to assess the economic impact of the partnership, showed that employees were mostly young women who were previously unskilled and had not had regular employment. In turn, employee's wages supported over 25,000 people in the local community.

The impact assessment showed that:

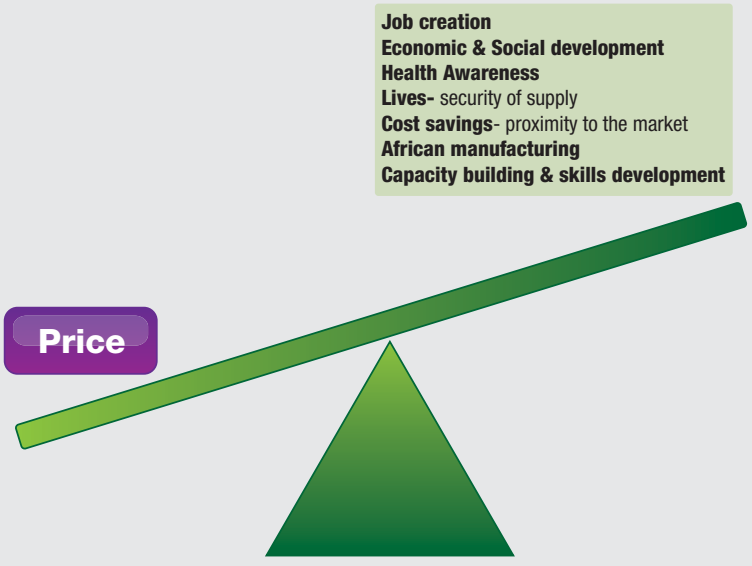
- 75% of employees were able to save money from their wages
- 72% believed they could meet the costs of schooling or hospital fees from their wages
- 64% said that they could now plan for the future

The A-Z facilities have had other knock-on effects in the wider community: 13 new businesses have opened in the area as a result of the A-Z factory, 90% of which said they rely on the factory for their business.

Unfortunately, the success of partnerships like this is under threat. Like most domestic companies in sub-Saharan Africa, they struggle to compete with foreign manufacturers on price. Donor agencies are the largest buyers of nets and their procurement policies place a premium on price. Although the cost of nets produced locally is slightly higher than that of some foreign companies, their presence in Arusha provides cost savings in terms of proximity to the market. In addition, the factory provides employment and creates new skills, awareness of health issues and fosters long term economic & social development.

By the end of 2010, 30 million nets per annum were being manufactured in the plant - enough to supply the needs for Kenya and Tanzania. However Sumitomo was not able to match the price of LLINs produced in Asia and had to make 850 people redundant in January 2011. This was discussed by the APPMG and the general consensus was that procurement decisions should take into consideration the positive benefits of locally produced nets, in terms of local employment opportunities and related benefits. In this context the use by DFID of LLIN price - excluding insurance and transit costs – as a result indicator in their framework for results is a cause for concern.

Figure 19: The cost of price for local LLIN manufacture.



on malaria-related activities at company clinics dropped by 26% (from US$ 1.02 million to US$ 241,000). The cost effectiveness analysis suggested a net **benefit** per employee of about $9 equivalent to an internal rate of return of 28%. Together with the other studies it is clear that private companies working in partnership with the public sector can produce major health improvements and generate a good return on their investment.

Another way in which private sector investment can help control malaria relates to the production of malaria control commodities. Boxes 11 and 12 summarise two examples which were presented to the APPMG.

Financing Research & Development for malaria control

The nature of product development means that well-defined goals exist, and it is therefore possible to sketch out timelines for product development and attach estimates of the costs involved at different stages. As products are either registered or their development is terminated, funding needs decrease because expensive late-stage trials are concluded. As phase IV studies get under way the focus of tool development shifts once again to the less expensive discovery and preclinical projects which fuel the drug development pipeline. Depending on the maturity of the portfolios for drug, vaccine, vector control and diagnostic products (Fig 20), it is possible to anticipate needs for funding and to predict when funders may be able to reduce their investments in malaria R&D.

RBM launched a report in June 2011 which

Box 13. Costs of product development

New anti-malarial drug	$ 300-500 million over 10-15 years
Malaria vaccine	$ 600 – 800 million over 10-15 years
Vector control product	$ 60-65 million over 10-12 years
New diagnostic	$ 2-5 million over 3-5 years

Note that expenditure is not split evenly over the years of product development; the clinical trials required immediately before a new drug or vaccine is launched are particularly expensive. In contrast, mid-development toxicological testing is the most expensive phase of insecticide development.

Figure 20: Anti-malaria product development portfolios (Source: Staying the course? Malaria research and development in a time of economic uncertainty. Seattle: PATH; 2011)

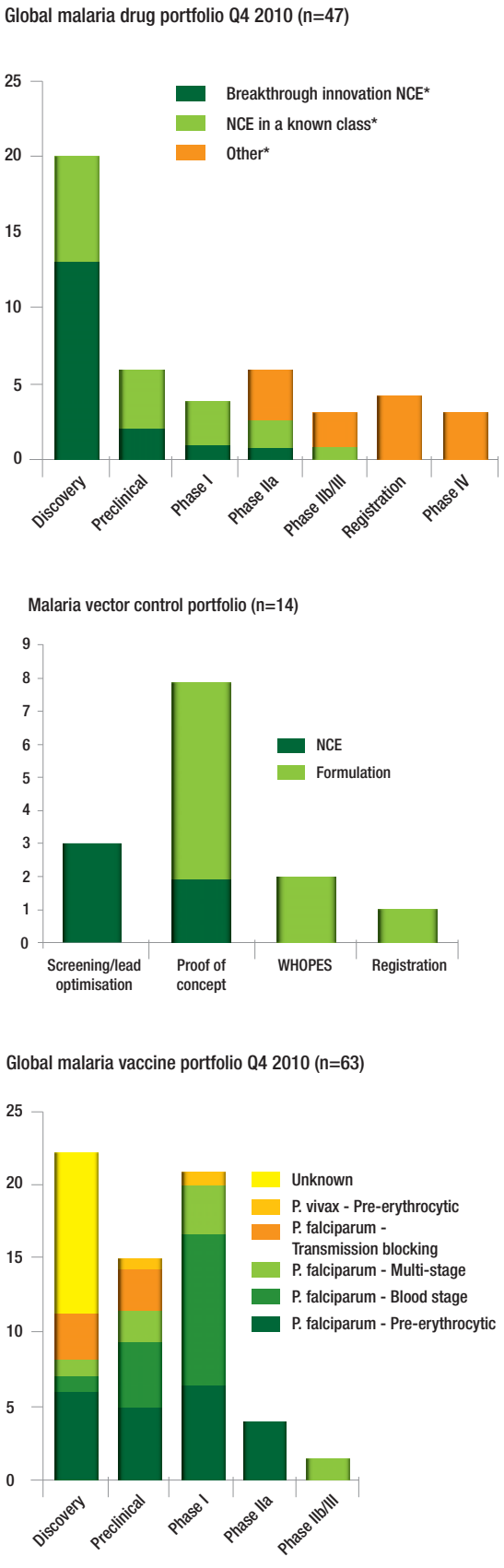
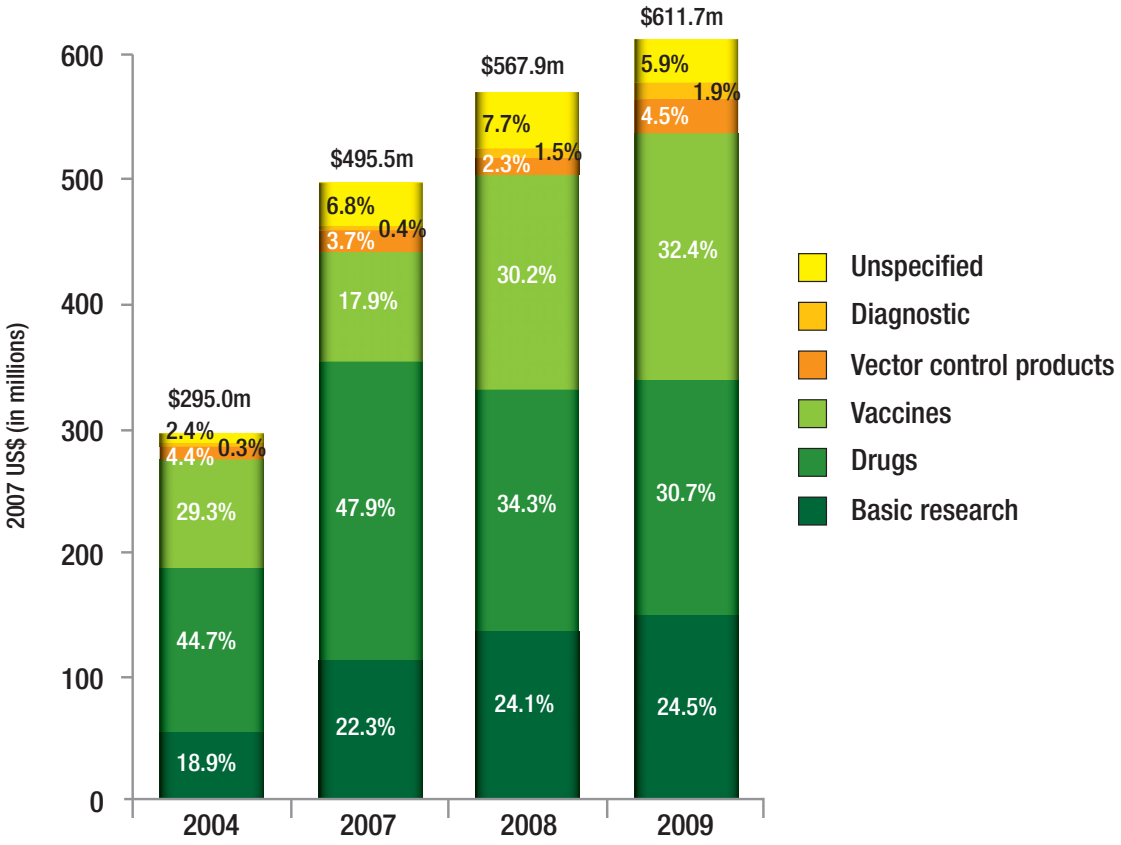


Figure 21: Malaria R&D funding by product, 2004 – 2009. (Source: Staying the course? Malaria research and development in a time of economic uncertainty. Seattle: PATH; 2011)



presents analyses of funding flows for malaria R&D between 2004-2009 and sets these alongside the anticipated needs up to 2020. The report documents a more than four-fold increase in malaria R&D funding since the mid-1990s, reaching $612 million in 2009 (Fig 21). Between 2004 and 2009 just over a third (38% - $752m) of funds were invested in drug development, about a quarter each in vaccine development (28% - $544) and basic research (23%), with only 4% ($72m) going to the development of vector control products and just 1% ($23m) on diagnostics. Recognition of the benefits of diagnostics, and the massive dependence of malaria control on vector-targeted interventions, requires an urgent increase in investment in diagnostics and vector control. However, the absolute amounts required to achieve this are relatively modest and can be accommodated within a small additional investment to enable global R&D needs to be met. This is because of the relatively low costs of developing vector control and diagnostic tools (Box 13)

The methodology to anticipate future funding needs took into consideration when the different products will reach different stages of development, and therefore the level of funding needed on a year to year basis. This approach is limited to some selected data and indicates that a minimum 2% increased level of investment per year up to 2015 will ONLY cover basic needs without taking into account projections made on higher cost for e.g. new generation of medicines tackling resistance or blocking transmission. Discussion of the R&D financing report has drawn attention to the need for new classes of drugs, and especially those tackling resistance which are urgently needed and will require funding above and beyond this limited timeline. Drugs will be required until malaria is eradicated. In addition, substantial funding needs exist for the diagnostic and vector control portfolio - diagnostic funding needs to quadruple immediately.

A surprisingly small number of funders are involved in funding malaria R&D, with 90% of funds coming from only 12 funders each year. Just two funders – the Bill and Melinda Gates Foundation and NIH - provided half of the total R&D malaria funding for 2007-2009 and account for 85% of the increase in funding in the same period. Ten governments contributed 90% of the public sector funding, including the UK (ranked second), India (ranked six) and Brazil (ranked seventh). The Gates Foundation alone provides 75% of PDP funding,

the UK Government being the second largest PDP funder, contributing 5.4%. The limited number of donors renders the R&D portfolio susceptible to changes in funders' priorities and diversification is required to ameliorate this threat. The observation that support for PDPs reduced in recent years is also cause for concern as about half the products in the development pipeline – and almost all new products delivered in the last 5 years - were produced as part of PDPs.

A limitation of the R&D report is that it does not include the costs of operational research. Such activities are essential to unlock the full potential of the tools being developed. By planning such operational research activities at the same time as investment into new products we can be confident that this critical final stage in product development and deployment will not be neglected. At the launch of the R&D report, DFID confirmed its intention to invest in this important but neglected area and we look forward to publication of this work at the earliest possible opportunity.

Investment in malaria R&D in the short term is expected to produce new tools which could rapidly decrease the burden of malaria and decrease not only future malaria control needs but also the need for further investment in malaria R&D to create new tools. This is because the rate at which resistance develops is likely to decline as the burden of disease falls. Hence, **front loading of R&D budgets stands to maximise benefits to people at the same time as saving money in the long term.**

Investment in R&D will be required as long as malaria has not been eradicated. In particular, new compounds will be required to guard against the inevitable risk of resistance to drugs and insecticides. Front-loading the development of effective tools and understanding how best to deploy them will reduce the rate at which new tools are needed and save millions of lives.

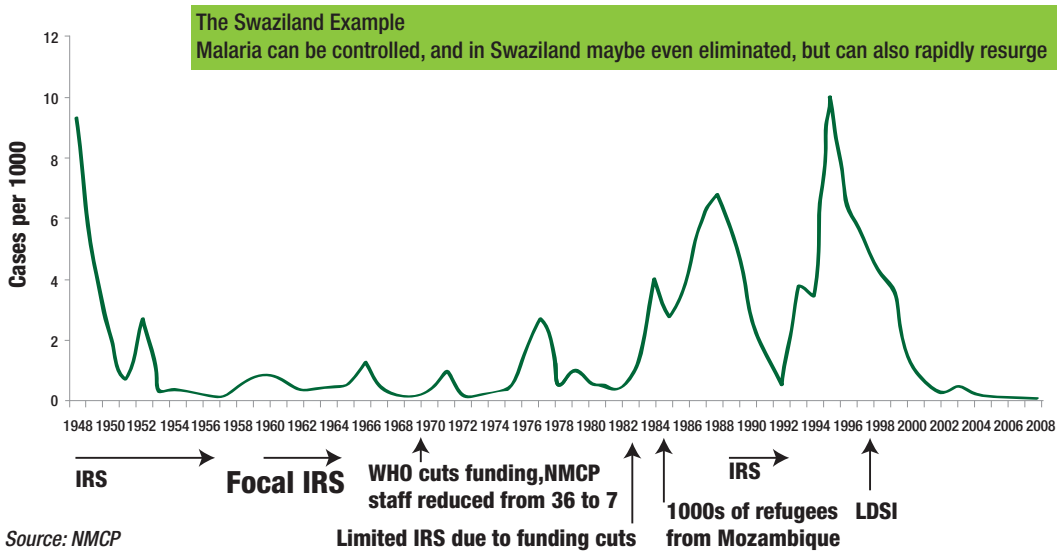
Sustaining the gains

Much is being invested in malaria control on the ground and in the research and development of new malaria control tools. As a result, countries are reporting substantial declines in the number of malaria cases and/or deaths. The drug pipeline is looking strong, with a number of drugs in the late stages of development. The ongoing Phase III trial of the RTS,s vaccine and prospect of its deployment as part of an integrated malaria control package gives further cause for optimism. We are approaching a critical point in the concerted global attempt to control malaria. At this stage it is imperative that our resolve and commitment do not weaken. Where malaria has been effectively controlled it will come bouncing back if control measures are relaxed prematurely (Fig 22). Investment in new screening and diagnostic tools and strategies is needed to prevent this, enabling health systems to manage malaria as a low-burden disease where transmission has successfully been reduced.

Financing Strategies for Ongoing Malaria Control.

Financing ongoing malaria control may become particularly challenging once a country has controlled malaria. No longer can progress simply be measured in terms of numbers of nets delivered

Figure 22: The need for sustained investment in control (Source: B Moonen presentation to APPMG)



or decreases in malaria cases; everyone should have a net and the best programmes will have no deaths and few cases. How then can progress be measured? How can sustaining the gains be incentivised? Donor investments in countries that have been successful in controlling malaria may appear to be less effective than those in high burden countries because the numbers of annual cases and deaths are small. It will be important to find a way to prevent countries becoming a victim of their own success in malaria control. Changing the focus to the number of cases and deaths that have been averted and ensuring integrated management of other causes of fever, together with malaria, may be one way to incentivise funders and programme staff alike.

One possible approach would consider historical information on the burden of disease and use this to estimate the number of cases and deaths which are avoided because of effective malaria control. In Zambia, for example, continuing effective control could prevent 40 million episodes and 300,000 deaths between 2010 – 2015.

Novel mechanisms can be developed to ensure long-term predictable funding and, at the same time, new funding sources – including domestic sources - should be identified. A Sustainable Financing Project is working to find and implement context adapted solutions for sustainable financing. The African Leaders Malaria Alliance (ALMA) has started to catalyse interactions between ministries of health and finance in endemic countries with the support of various partners, including WHO and RBM (Fig 23). A number of country-tailored potential solutions are starting to emerge.

(i) Cash on delivery. Jointly define a target (for example the prevalence of infection) with national government and, if they stay below this target, steady bulk funding is made available.

(ii) A tax code for private companies to support the malaria programme.

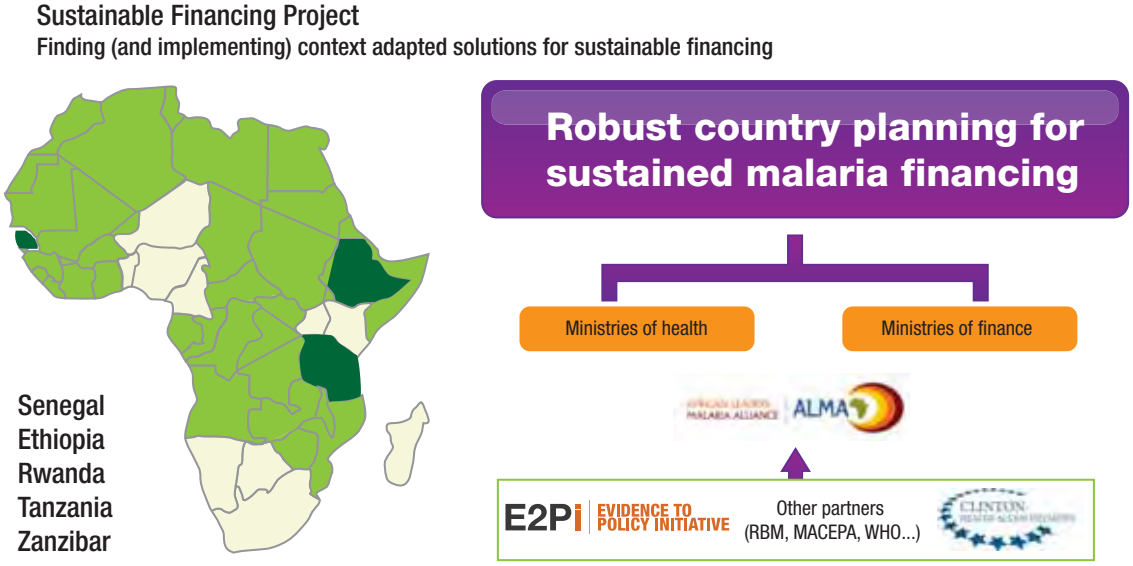
(iii) Pooled funds within a country for the purchase of anti-malarial drugs that allow contributions from a variety of sources, including the private sector

(iv) Contributions from national or community-based health insurance schemes to support the malaria programme.

Cash on Delivery (COD) may be attractive as it focuses attention on outcomes rather than inputs, emphasising the need for sustained control. Transparent processes can reduce transaction costs and allow a hands-off approach from donors, increasing recipient responsibility and country ownership. As long as parasite prevalence, or some other routinely monitored malaria - relevant parameter, is maintained below an agreed level, COD payments are made to the Ministry. If a target is not met then COD payments are replaced by more strictly controlled input financing. Once prevalence falls below the agreed targets, COD payments can start again.

The feasibility and practicalities associated with COD financing warrant operational research to fine tune the design and evaluate the benefits. The APPMG understands DFID is currently examining COD in some detail and looks forward to hearing more on this in the coming year.

Figure 23: Financing sustained malaria control (Source: B Moonen presentation to APPMG)



Recommendations

Over the course of the past year the APPMG has heard evidence from a wide variety of groups and has reflected on some of the key issues for the malaria community. These recommendations are based on the evidence presented to the Group and on additional conversations with key stakeholders in the fight against malaria. Given the APPMG's position as a group of British Members of Parliament, many of the recommendations are focussed on the UK Government. However this report is designed to contribute to the discussion on accelerating progress on malaria internationally and many of the recommendations are potentially appropriate for parliamentary colleagues elsewhere.

For DFID

- **Malaria Commitment and UK leadership:** We are very aware of the key role that the UK is playing in leading the fight against malaria. We welcome the commitment of the UK government to this fight as evidenced by statements by the Prime Minister, Deputy Prime Minister, Chancellor and others around last Septembers UN General Assembly; the Malaria Framework for Results and the Multilateral and Bilateral Aid Reviews. We welcome DFID's enhanced malaria commitment, making malaria one of the top UKAid priorities and aiming to help halve malaria deaths in at least 10 high burden countries by 2015. We encourage the UK to continue to use all available opportunities (UNGA, Davos, G8, G20 etc.) to strengthen international leadership on malaria, champion the issue and press for further progress by all stakeholders.
- **Malaria Research and Development Strategy:** Following on from the hugely informative and thoughtful Malaria Framework for Results, Multilateral and Bilateral Aid Reviews, and the set of country plans that have been published, we encourage DFID to publish a further strategy document outlining its plans for investment in malaria research and and development, including Operational Research, over coming years. This document should set out the funding priorities and levels from now until at least 2015, indicating how effectiveness will be measured and how this work will complement DFID's other malaria control interventions.
- **Malaria Funding:** We were pleased to see the announcement of DFID's country plans rapidly following the Bilateral Aid Review, and the inclusion of specific malaria targets for many countries. Examining these documents alongside what is already known of the UK Government's current commitments to the Global Fund and World Bank, it is apparent that the current public UK Government funding commitments fall significantly short of the malaria spending target of up to £500 million per year by 2014/15, pledged through UKAid last year. We understand DFID will review its spending again in 2013 or before, and urge DFID to make public all aspects of its funding and strategy for tackling malaria, and to increase funding available for malaria control rapidly over the parliamentary term to help maintain and build on the success to date and avoid the danger of backsliding on gains made – costing lives.
- **Delivering Country Plans:** We were delighted DFID has now published its set of country plans and at the information set out on both the key development indicators by which success will be measured and the funding levels for each year to 2014/15. We were particularly pleased to note the future commitments made to both Nigeria and the DRC, two of the countries with the highest malaria burdens. We urge DFID to work now with partners to operationalise these plans in short order, accompanied by the necessary research to ensure effective implementation on the ground.
- **Bilateral support for India:** Given the UK's strong bilateral aid commitments to India, and evidence suggesting that India's malaria burden is likely to have been underestimated, we urge DFID to consider multi-state malaria interventions within its health support to India, particularly in the five most affected states of Orissa, Madhya Pradesh, West Bengal, Chhattisgarh and Jharkhand.

- **Global Fund to Fight AIDS TB and Malaria:** We were encouraged to see DFID evaluate the Global Fund as "very good value for money" in the recent Multilateral Aid Review. We are keen to see a quick follow up announcement of DFID's increased contributions to the Fund (this is critical for malaria as the Global Fund accounts for approximately 70% of global funding for malaria control) following the outcome of the current Global Fund review. We also look forward to the report of the independent evaluation of AMFm Phase 1, which is managed by the Global Fund and will inform decisions about future commitments. Finally, we hope that DFID will use its influence to encourage the Global Fund to renew its commitment to drug and insecticide resistance monitoring and quality assurance of malaria diagnostics.
- **World Bank:** As one of IDA's largest shareholders, DFID should ensure the World Bank delivers in full its commitments to tackle malaria under Booster II and responds positively and quickly to the financing and technical assistance requests of countries as they move forward in their effort to reach the UN malaria goals s (one of) IDA's largest shareholders, DFID should ensure the World Bank delivers in full its commitments to tackle malaria under Booster II and responds positively and quickly to the financing and technical assistance requests of countries as they move forward in their effort to reach the UN malaria goals.
- **Global Alliance for Vaccine Initiative (GAVI):** We welcomed UK leadership at the recent GAVI replenishment meeting, helping to secure remarkable pledges exceeding the fund's original target by USD $600M. We are hopeful that the first malaria vaccine will be approved for use within the next five years. We encourage DFID to clarify the role it is asking GAVI to play in preparing for the advent of a malaria vaccine.
- **Work in Partnership:** We encourage countries to work with multiple partners on malaria control, including exploring private sector opportunities, which, as we have seen through this report, can offer significant mutual benefits in fighting malaria.

For all donors

- **Investing in Health:** Major progress has been made in malaria control over the last five years. Increased international focus and investment is yielding results and malaria interventions (including prevention, diagnosis and treatment) represent some of the best and most cost effective humanitarian investments in the world today. We urge donors to recognise the significant contribution that effective malaria control can make to achieving progress on global heath and poverty reduction under MDG's 1, 4, 5 and 6.
- **Investing in Tackling Malaria:** Whilst there has been significant success in the fight against malaria, these gains are fragile and could be lost without sustained investment. Current 2011 funding commitments to tackle malaria amount to just one third of the estimated annual resources needed. We urge donors to renew their commitment to this fight - one we can win - through bilateral and multilateral support both to organisations investing in malaria control today, and those investing in research to prepare for tomorrow, including (but not limited to): the Global Fund to Fight AIDS, TB and Malaria; WHO; World Bank IDA; UNICEF; Roll Back Malaria Partnership; Foundation for Innovative Diagnostics; Innovative Vector Control Consortium; Malaria Vaccine Initiative and the Medicines for Malaria Venture.

Private sector

- **Investing in Tackling Malaria:** Investing in malaria control is not just a CSR opportunity; it can offer real benefits to your business in terms of increased productivity and a healthy workforce. We encourage all businesses operating in malaria endemic countries to consider how they can contribute to local and national malaria control plans.
- **Investing in New Tools:** Public/Private Product Development Partnerships around prevention, diagnostics, medicines and vaccines have significantly enhanced the research and development pipeline and new tools available to fight malaria. We urge companies involved in this work to continue to invest in new tools to help maintain momentum in tackling malaria and to stay one step ahead of the spectre of resistance.
- **Investing in Service Delivery:** Public/Private Partnerships can extend beyond private sector contributions to public delivery of services. We encourage the private sector to intensify its involvement in service delivery while continuing to contribute to the development of public sector capacities for delivery.

NGOs and Faith Groups

- **Protecting the Vulnerable:** NGOs can and do play a key role in the fight against malaria particularly in efforts to reach the most vulnerable and those living furthest from public health facilities. NGOs are also supporting work to research and improve methods for malaria control on the ground and to champion new approaches to tackling malaria. We encourage NGOs to continue this work and to look for ways to work in partnership with other stakeholders and to work closely with national governments to ensure maximum impact for their efforts.
- **Supporting Service Delivery:** Faith groups play a key role in countries affected by malaria by identifying those most in need of malaria prevention and treatment and ensuring delivery of those services. They have also worked in partnership with NGOs and governments to help educate vulnerable populations. We encourage them to continue this work and to use their unique abilities to reach large numbers of people in countries with high malaria burdens to help accelerate progress on malaria control.

Useful Links

ACT Watch
http://www.actwatch.info/home/home.asp

AMFm

http://www.theglobalfund.org/en/amfm/?lang=en

ALMA
www.alma2015.org

Bill & Melinda Gates Foundation
www.gatesfoundation.org

DFID
www.dfid.gov.uk

Foundation for Innovative New Diagnostics
www.finddiagnostics.org/

GFATM
www.theglobalfund.org

GSK
www.gsk.com

Innovative Vector Control Consortium
www.ivcc.com/

Malaria Consortium
www.malariaconsortium.org

Malaria No More UK
www.malarianomore.org.uk

Malaria Vaccine Initiative
www.malariavaccine.org

Medicines for Malaria Venture
www.mmv.org

Novartis
www.novartis.co.uk

Quality Chemicals
www.qcil.co.ug

Nets for Life
www.netsforlifeafrica.org

Roll Back Malaria Partnership
http://www.rollbackmalaria.org/

Sumitomo
www.sumitomocorp.co.jp

UNICEF
www.unicef.org

Vestergaard Frandsen
www.vestergaard-frandsen.com

WHO
http://www.who.int/malaria/en/