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TACKLING MALARIA IN DEVELOPING COUNTRIES

Malaria is a parasitic disease responsible for the deaths of at least a million people every year, 90% of whom live in sub-Saharan Africa. The greatest death toll occurs in children under five. Despite effective prevention and treatment methods, the burden of malaria remains high. The UK has agreed to the UN Millennium Development Goal of halting the spread of malaria by 2015. This note examines progress towards this target and considers the remaining UK and international priorities.

Background

The scope of the problem

Malaria is spread by mosquitoes carrying parasites of the *Plasmodium* type. Four species of *Plasmodium* are responsible for the majority of human infections (Box 1) of which by far the most devastating is *Plasmodium falciparum*. 40% of the world's population lives in malarious areas and an estimated one million people die each year from *P. falciparum* malaria. The worst affected are young children (who have yet to develop immunity to the parasite) and pregnant women (who are more susceptible to the disease). Almost one fifth of all deaths of children under 5 in sub-Saharan Africa are thought to be due to malaria. HIV/AIDS and emergencies such as war or famine exacerbate the malaria problem. Many of the world's poorest countries are severely affected and there is a strong link between malaria and lack of economic growth. Since the global eradication effort ceased in 1969, malaria has resurged in many areas and has only recently returned to the international agenda[1].

While almost all deaths attributable to malaria are due to infection with *P. falciparum*, the burden of *P. vivax* malaria is also significant. Although rarely fatal, *P. vivax* infection is acute and debilitating and approximately 70 – 80 million cases are thought to occur annually, particularly in Asia. The low transmission rates of this parasite mean that people are not likely to have immune protection against it. Its detrimental impact upon men of working age is particularly significant.

Box 1. Major species of human malaria

- *Plasmodium falciparum* causes the most dangerous form of malaria and is found worldwide in tropical and subtropical areas. Infection may lead to anaemia and blockage of small blood vessels and can result in serious consequences such as cerebral malaria.
- *Plasmodium vivax* is found in Asia, Latin America and some parts of Africa. It rarely causes death but often results in relapses and contributes significantly to disease burden (morbidity).
- *Plasmodium ovale* is very similar to *P. vivax*. It produces mild disease.
- *Plasmodium malariae* produces infections which can last a life-time but do not relapse. It is found worldwide.

The disease

Human infection begins when malaria parasites enter a person's body via a mosquito bite. Parasites multiply in the liver and are then released into the bloodstream. The blood-stage parasites invade and multiply within red blood cells, the destruction of which produces clinical disease. The resulting symptoms include high fever, sickness and chills, but infection can be complicated by organ failure and coma (severe malaria). As discussed below, the complexity of the parasite's life cycle means there are numerous preventative and curative measures.

Tools available to tackle malaria

Prevention

Methods to prevent malaria involve targeting mosquitoes or using pre-emptive treatment. Approaches include:

- Insecticide treated nets (ITNs) which are highly effective at reducing malaria-related and other causes of death in children under 5. Long-lasting ITNs which do not need re-treatment are a recent development.

- Indoor residual spraying (IRS) of houses with approved insecticides. The World Health Organisation (WHO) has recently recommended greater use of IRS in certain areas and endorsed DDT for this purpose[2]. Some groups are concerned about its persistence in the body and in the environment, however.
- Destruction of mosquito larvae and draining swamps to inhibit mosquito breeding – strategies that are effective in certain specific areas related to breeding preferences of the predominant mosquito species.
- Intermittent preventive treatment (IPT) for pregnant women. This involves administering a full course of an anti-malarial drug or drugs at regular intervals, regardless of whether the woman is infected. There is also significant interest in IPT for infants and studies are currently examining its effectiveness.

Treatment

Resistance to many anti-malarials, such as chloroquine (CQ) and sulfadoxine-pyrimethamine (SP), is widespread. This has mainly arisen due to the large-scale deployment of single anti-malarial drugs as the sole therapy (monotherapy). As a result, many anti-malarials have been rendered virtually useless against *P. falciparum* malaria. The artemisinin group of compounds (derived from the sweet wormwood plant) have been highly successful in areas of failing drug treatment. Artemisinin combination therapy (ACT) (Box 2) has replaced CQ and SP as first-line malaria treatment policy in 41 African countries to date. However, in many countries, changes to policy do not reflect ACT availability on the ground.

Box 2. Artemisinin combination therapy (ACT)

- ACT is the simultaneous use of two or more drugs with independent modes of action and different biochemical targets, of which one component must be artemisinin or a derivative. It can be co-formulated (single tablet) or co-administered (separate tablets).
- The rationale is to improve treatment and to reduce or delay the development of anti-malarial resistance. The probability of resistance mutations arising to two drugs with different modes of action is very low.
- The benefit of using artemisinin (or a derivative) in the combination is that it works quickly to clear infection. As yet there is no reported resistance to the artemisinin component.

It is widely agreed that to have a significant effect on the burden of malaria it is necessary to implement strategies for treatment and prevention in combination. An example of the success of this type of approach has been in KwaZulu Natal in South Africa (Box 3). Unfortunately, this story has not been reproduced across much of sub-Saharan Africa where the need is greatest.

Box 3. Case Study: KwaZulu Natal province

In KwaZulu Natal province in South Africa there are 600,000 people living in malaria-risk areas. Between 1995 and 2000 there was a marked increase in *P. falciparum* malaria fuelled by escalating mosquito resistance to insecticides and parasite resistance to anti-malarial drugs.

In March 2000, DDT was introduced to replace failing insecticides for indoor residual spraying and in 2001 the South African Ministry of Health implemented ACT in place of failing drugs.

Between 2000 and 2003 there was a 97% reduction in malaria-related deaths and a 99% decrease in malaria-related hospital admissions.

The success of the malaria control strategies in this province was a result of both the therapeutic effect of ACT coupled with effective mosquito control. In addition, KwaZulu Natal is an area of low transmission, with good healthcare infrastructure, and 81% of people in the province live within 10 km of a public clinic.

Source: Barnes et al., *PLOS Medicine*, 2 (11), 2005.

The International Response

Policy

The Roll Back Malaria Partnership (RBM) (an alliance of WHO, UNICEF, World Bank, UN Development Programme, malaria endemic countries, donors, NGOs, private sector and academia) was established in 1998 to provide a global approach to combating malaria. The UK Department for International Development (DFID) has been a board member of RBM and has contributed £49 million since its inception. The RBM aims, set out in 2001[3], are to halve the burden of malaria by 2010. As part of these aims, countries in the African Union committed to contributing 15% of their national budgets to health. Furthermore over 190 countries (including the UK) have signed up to the UN Millennium Development Goals[4] (MDGs), a set of shared targets aimed at meeting the needs of the world's poorest people. Goal 6 specifies that by 2015 we will have "halted and begun to reverse the incidence of malaria". Malaria also has an impact on several of the other goals including those which focus on improving maternal and child health.

Finance

With all development aid there is a need for sustainable and predictable financing so that countries can forecast the amount of money they will receive. Funding for malaria has been extremely unpredictable over recent years. There has been a wide gap in terms of the amount of money needed to make an impact on malaria (estimated at $3 billion per year[5]) and the sum contributed by donors (estimated at $600 million in 2004[6], although this figure has since increased).

Most multilateral funding for malaria now goes through the Global Fund to fight AIDS TB and Malaria (the Global Fund) – a financial instrument created to increase funds for preventing and treating these diseases. The UK has pledged over $600 million to the Global Fund to date. Between 2001 and 2006, the Global Fund approved grants with a total value of $2.6 billion to programmes in 85 countries to support anti-malarial interventions. However, the Global Fund has been criticised for its lack of transparency and failure to renew grants to some countries to which it awarded first-round grants. Withholding of grants is largely due to poor performance or governance issues, but can leave anti-malarial programmes unfunded. Other mechanisms to increase the volume of aid include Advanced Market

Commitments, the International Finance Facility (detailed in POSTnote 241) and the international drug purchase facility UNITAID. Substantial new support for malaria control has also been secured from the Bill and Melinda Gates Foundation, the US President's Malaria Initiative and the World Bank Booster Programme.

Despite international collaboration, there is still a large deficit in aid directed towards malaria. Even with the array of tools available, the global burden of malaria remains very high. In addition to funding issues, there are other barriers towards achieving reductions in malaria-related illness and death, which are discussed below.

Barriers to progress

Diagnosis and monitoring

Diagnosis of malaria is complex but is increasingly important in view of both the high cost of ACT (see below) and of the need to limit selection of drug resistant parasites by reducing unnecessary treatment. It requires equipment such as microscopes or rapid diagnostic tests which are often unavailable or inadequate. Even when these tools do exist, there is frequent over-diagnosis of malaria in developing world hospitals, partly due to a historical tendency to treat all fevers with anti-malarials. In addition, there is large-scale under-diagnosis of malaria especially in rural areas because many people with malaria do not seek (or are unable to reach) healthcare. Attributing the cause of illness or death is compounded by the fact that symptoms of malaria are non-specific and many people with malaria also have other illnesses.

The MDGs set out clear targets for reducing the burden of malaria but data on the true extent of the problem are incomplete. Estimates of the annual number of deaths due to malaria vary between 1 and 3 million, and those for malaria illness vary between 350 and 600 million. The RBM monitoring and evaluation reference group was set up in 2003 and has established a set of indicators to examine progress made towards the MDGs, which are assessed using household surveys carried out every few years. Due to the difficulties set out above, the most recent data do not contain accurate figures of malaria-related illness and death. Overall, estimates suggest that deaths from all causes among African children under 5 have reduced by only 9% between 1990 and 2004[7].

Staff shortages and healthcare infrastructure

A functioning healthcare system and infrastructure are essential for successful delivery of basic aid. A key problem with healthcare in poor countries is the loss of trained medical staff for more stable and better paid jobs elsewhere. One criticism of the MDGs is that they may further weaken health systems by encouraging medical staff away from government institutions into donor funded programmes. In response to the lack of health workers, the UK Prime Minister commissioned a report[8] which recognised the need to retain staff and increase healthcare training in developing countries. The UK has announced £1 million for the Global Health Workforce Alliance – a WHO task-force set up to address this need. A Department of Health code of practice[9] requires that the NHS no longer recruits medical professionals from any of the poorest countries and encourages private sector employers to follow suit. DFID and the Global Fund have established a partnership with the Malawian government to scale up the number of doctors and nurses in training. The UK Tropical Health and Education Trust (THET) has established links between African and UK institutions to address needs identified by specific countries. While staff shortages are important, many people are unable even to access healthcare due to a lack of facilities, inadequate roads and their inability to pay the costs incurred. In order to address these issues, DFID provides both direct budget support and support for the health sector and has also funded THET. DFID plans to increase its spending in the coming years.

Access to insecticide treated nets

Between 1999 and 2003, it is estimated that there was a ten-fold increase in net distribution in Africa[5] and in countries such as Kenya as many as 50% of children under 5 sleep under a net. Progress in some countries has been slower, however, and figures published in 2005 (although outdated at the time) suggested that only 3% of nets used in Africa were treated with insecticides[10]. Nets are supplied through a combination of mechanisms including free distribution, social marketing schemes with subsidised vouchers for the poorest people and via the commercial sector. The new long-lasting nets do not require re-treatment, but are more expensive and manufactured by few companies. The Global Fund and DFID have supported net distribution schemes in several countries. Ensuring the nets reach the poorest people and that their availability is sustained even if funding is not are key issues. Insecticide resistance is a also a matter of concern, and new insecticides are urgently needed.

Access to medicines

Introduction of ACT

In the face of increasing drug resistance, WHO guidelines for treatment of malaria now stipulate use of ACT as first-line treatment in all countries with *P. falciparum* malaria. A high profile campaign by Médecins sans Frontières and a series of letters published in *The Lancet* accelerated the adoption of the new policy. However, a major drawback in procuring and implementing ACT has been the higher cost in comparison to chloroquine (CQ). This cost arises because currently the only method of obtaining artemisinins is by extracting them from plants – a long and low-yielding process. Attempts to reduce the cost of ACT include sale of drugs at not-for-profit prices and diversification of the supply. For instance research is looking at synthetic artemisinins and higher yielding plants, but the technology is still several years away.

Global ACT buyer subsidy

Global Fund grants have been key in enabling the switch to ACT policy in most countries. However, grant money is usually used for public sector procurement whereas most people in the developing world obtain their anti-malarials from the private sector. Here, ACT is still unaffordable for many people, resulting in two major problems:

- Use of monotherapy – either artemisinin (a potential resistance problem) or CQ (often ineffective);
- Widespread production and distribution of counterfeits which have no public health benefit.

To address these problems and increase access to ACT a global ACT buyer subsidy has been proposed[11]. This would act at the very top of the purchasing chain – permitting ACT uptake into both private and public sectors and reducing the cost to undercut monotherapy and counterfeits. While some have questioned whether it will be possible to keep the cost low throughout the supply chain, the subsidy idea has gained ground and a draft proposal has been prepared. If sufficient support is forthcoming it could be launched in late 2007.

Progress in drug, insecticide and vaccine development

The need for anti-malarial drugs and insecticides

Even if ACT is deployed correctly it is expected that resistance to the artemisinin component will eventually emerge and rapidly spread. New drugs are urgently needed to pre-empt this potential public health disaster. There is an equal need to develop or test new drugs for pregnant women (for whom ACT is not recommended in the first trimester) and for patients with *P. vivax* malaria (since ACT does not prevent relapses of latent infection). The development of new insecticides has been neglected, but the Bill and Melinda Gates Foundation has recently funded the Innovative Vector Control Consortium to address this research area.

The UK Medical Research Council and Wellcome Trust fund numerous research projects into malaria in the UK, Africa and Asia. In the absence of a developed world market, it is difficult to get drugs into and beyond clinical trials. In response to this need, public-private partnerships (PPPs) such as Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi) have been established. Both the Wellcome Trust and DFID have provided financial support for PPPs. MMV currently has 5 drugs in late stage clinical trials which are expected to be licensed in the next 1-2 years, including a drug combination for infants. However, these trials are costly and MMV is likely to run into a funding shortfall as a result. DNDi and Sanofi-Aventis recently launched a new off-patent anti-malarial drug (ASAQ). Although this new anti-malarial drug combination has been widely welcomed, there has been some criticism of the decision to fast-track the drug by gaining regulatory approval outside Europe[12]. All of the drugs likely to be licensed in the near future contain artemisinin or derivatives – it is essential that new drugs with a different mode of action are developed so that alternatives are available should resistance emerge.

The development of a malaria vaccine

An effective malaria vaccine would be a huge step forward in preventing malaria cases worldwide. However, due to the difficulty of identifying appropriate vaccine targets and a lack of understanding about the types of immune response involved in protection, only one vaccine (developed by GlaxoSmithKline) has made significant progress to date. This vaccine (RTS,S/AS02A) is currently in mid-late stage clinical trials. It reduces the risk of clinical disease by 35% and has 50% efficacy against severe malaria in children under 4. However it would not be a substitute for other control methods and would need to be deployed in combination with other preventative measures. Even if results of current trials are promising it will be several years before the vaccine launch. A financial commitment to subsidise the future purchase of a malaria vaccine (Advanced Market Commitment) may be put in place to encourage research and to scale up production of future vaccines. Another area of ongoing research involves genetically modifying mosquitoes so that they are unable to transmit malaria[13]. Recent results show promise but further trials are needed. Releasing the mosquitoes into the wild will be subject to government and local community approval.

Overview

- The tools to prevent and cure malaria exist, but accurate knowledge of the malaria burden is limited.
- International collaboration has resulted in an increased awareness of the need to reduce the impact of malaria in the developing world.
- Funding is currently falling well short of the amount that is required to combat malaria.
- New financing mechanisms may increase available aid, but political will is necessary to ensure that sufficient money is invested and put to best use.
- Key priorities are to ensure that people have access to essential drugs and vector control and that there is also investment in infrastructure and health services.
- Continued research and development will be essential in ensuring that effective drugs, insecticides and vaccines will be available in the future.

Endnotes

1 *Tackle Malaria Today - Give Tomorrow a Chance*, APPMG, 2005.
2 www.who.int/en/
3 www.rbm.who.int/docs/abuja_declaration.pdf
4 www.un.org/millenniumgoals/
5 *World Malaria Report*, WHO, RBM and UNICEF, 2005.
6 *Financing Mechanisms for Malaria*, APPMG, 2007.
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9 *Code of practice for the international recruitment of healthcare professionals*, DH, 2004.
10 *Report on Progress towards MDG 6,* UN Statistics Division, (1990-2005).
11 *Saving Lives, Buying Time*, Institute of Medicine, 2004.
12 www.dndi.org/pdf_files/Position_Paper_FT_response_ASAQ.pdf
13 Proceedings of the National Academy of Sciences U S A. 2007 Mar 27;104(13):5580-3

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