

Review

***Plasmodium falciparum* malaria and antimalarial interventions in sub-Saharan Africa: Challenges and Opportunities**

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Accepted 20 October, 2005

***Plasmodium falciparum* malaria is one of the most important parasitic diseases affecting sub-Saharan Africa, despite the availability of interventions. It exerts tremendous socio-economic and medical burden on the continent, particularly in under five children and pregnant women. In this review, we have attempted to highlight the problems, constraints and the opportunities that are available for effective prevention and control within the region.**

Key words: Burden, challenges, interventions, *Plasmodium falciparum* malaria.

INTRODUCTION

Malaria is a febrile illness characterized by fever and related symptoms. It has been one of the most prevalent human diseases affecting particularly the populations of tropical regions and in the past those of temperate climates (Bruce-Chwatt, 1986). Malaria is a complex disease that varies in epidemiology and clinical manifestation in different parts of the world. This variability occurs as a result of several factors such as: the species of malaria parasites that are found in a given area, the distribution and efficiency of mosquito vectors, climate and other environmental conditions, the susceptibility of malarial parasites to commonly used or available antimalarial drugs and the level of acquired immunity by the exposed human population (Bloland, 2001). Of the four common species of *Plasmodium* responsible for malaria in endemic regions of the world, *Plasmodium falciparum* is the most virulent (Bruce-Chwatt, 1986). It is responsible for over 90% of all causes of malaria in sub-Saharan Africa (WHO, 2000).

In Africa, as in other parts of the world, the malaria situation is not homogenous. In spite of its wide distribution in the continent, it is actually a focal disease. It varies from country to country and in the same country,

it may vary from one part to another (FMoH, 2000). Therefore, the distribution of malaria in Africa may be classified broadly into four epidemiological areas - the hypo-, meso- holo- and hyper-endemic. The epidemiological profile is usually determined in any given location by several factors including the ecosystem, climate, state of the environment, human behaviour, and vector and parasite bionomics (FMoH, 2000).

The recent increases in malaria mortality rates in Africa are probably due to increasing resistance to insecticides and antimalarial drugs, breakdown in public-health infrastructure, and land-use changes-such as dam-building, irrigation, and deforestation (Sachs and Malaney, 2002; WHO/UNICEF, 2003). In this review article, we briefly discuss the burden of falciparum malaria in sub-Saharan Africa and the challenges and opportunities for the implementation of antimalarial interventions within the region.

BURDEN OF MALARIA DISEASE IN SUB-SAHARAN AFRICA

Despite considerable progress in malarial control over the past decade, malaria remains one of the most important potentially fatal parasitic diseases in the world. It is a major public health problem and a negative factor in the socio-economic development in sub-Saharan

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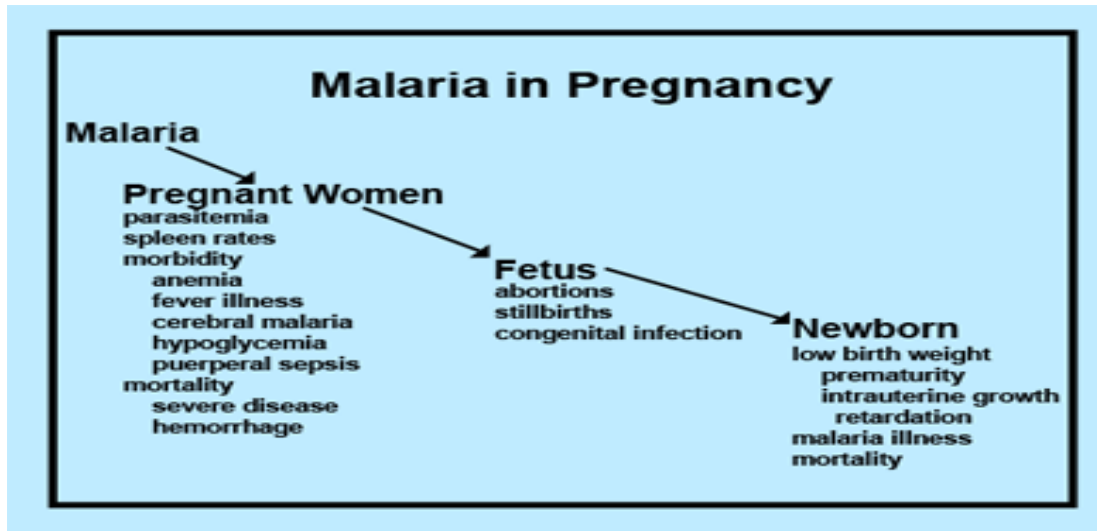


Figure 1. Consequences of malaria in pregnancy (Source: WHO Regional Office for Africa, 2004).

Africa. It is one of the top three killers among communicable diseases, particularly in tropical Africa.

Economic impact of malaria: In a World Health Organization (WHO) report, half of over 2400 million of the world's population at risk of malaria are in Africa (WHO, 2000). Malaria affects the health and wealth of nations and individuals alike. In Africa today, malaria is understood to be both a disease of poverty and a cause of poverty (Greenwood and Mutabingwa, 2002; Sachs and Malaney, 2002). Malaria has significant measurable direct and indirect costs, and has been shown to be a major constraint to economic development (Sacks and Malaney, 2002). What this means is that the gap in prosperity between countries with malaria and countries without malaria has become wider every single year. Gallup and Sachs (2003) show that where malaria has been eliminated economic growth has increased substantially over the following five years, compared to growth in neighbouring countries. Countries with intensive malaria lagged behind in growth by 1.3% per person per year compared to neighbouring countries; a 10% decrease in malaria incidence was associated with a 0.3% increase in annual economic growth (Breman et al., 2001).

Morbidity and mortality associated with malaria in children: About 300 to 500 million clinical cases of malaria occur each year with 90% of these occurring in tropical Africa - mostly caused by *P. falciparum* (WHO, 1999; Sachs and Malaney, 2002). In Africa, a visit to the paediatric ward or to the general outpatient department of most hospitals is all that is needed to convince a visitor that malaria remains a major cause of mortality and morbidity in African children. Malaria accounts for 10

to 30% of all hospital admissions and is responsible for 15 to 25% of all deaths of children under the age of five (WHO, 1999). Between the 1980s and the 1990s, malaria-related deaths in children doubled in many parts of Africa, and malaria now accounts for about a fifth of childhood mortality (WHO, 2003).

Burden of malaria during pregnancy: Pregnant women are also at high risk from malaria, and malaria is responsible for a substantial number of maternal morbidity, and perinatal morbidity and mortality (WHO, 2001). In pregnancy, the consequences of malaria are severe both to the mother and her unborn child. Malaria in pregnancy can result in a number of maternal, fetal and infant complications (Figure 1). Important examples are: severe maternal illness, hypoglycaemia, acute pulmonary oedema and anaemia; fetal distress, premature labour, intrauterine growth retardation (IUGR), prematurity, low birth weight infants and stillbirths (Bouvier et al., 1997; Brabin, 1983; Menendez, 2000; Philips-Howard, 1999; Schultz et al., 1995, Shulman, 2001, and Steketee, 2001). Malaria during pregnancy contributes to approximately 2 to 15% of maternal anaemia and 8 to 14% of low birth weight in areas with stable malaria transmission, where prevalence during pregnancy ranges from 10 to 65% (Steketee et al., 2001). Malaria contributes to an estimated 8 to 36% of prematurity and to an additional 13 to 70% of intrauterine growth retardation, depending on level of malaria risk and 3 to 85 of all infant deaths (Steketee et al., 1996b). Steketee et al (1996b) have shown that maternal malaria infection accounts for almost 30% of all the causes of low birth weight that can be prevented during pregnancy through antenatal interventions. Maternal parasitized red blood cells and perivil-

lous fibrin deposition were found to be associated independently with increased risk of premature delivery. Massive mononuclear intervillous inflammatory infiltration is an important mechanism in the pathogenesis of IUGR in malaria-infected placentas. Placenta malaria was associated with prematurity even in high transmission areas (Menendez et al., 2003).

Malaria and HIV during pregnancy: Placenta malaria is more common in HIV-positive than HIV-negative women (Brahmbhatt, 2003). HIV infection alters patterns of malaria in pregnant women (van Eijk, 2003). Interventions to reduce malaria during pregnancy could potentially reduce mother-to-child transmission (MCTC) of HIV (Brahmbhatt, 2003). Therefore, in areas with both infections (malaria and HIV), all pregnant women should use malaria prevention (van Eijk et al., 2003).

MALARIA INTERVENTION IN SUB-SAHARAN AFRICA

The Global Malaria Control Strategy is a concerted effort meant to bring about changes in the way malaria problem is addressed. As a result, this strategy stresses the selective use of preventive measures wherever they can lead to sustainable results (WHO, 1993). The measures are aimed at halting the deteriorating effects of the malaria situation, minimizing the wasteful use of resources and contributing appropriately to the development of health services, intersectoral cooperation and community participation. The ultimate goal of malaria control will be to prevent mortality and reduce morbidity and social and economic loss through the progressive improvement and strengthening of local and national capacities (WHO, 1993; FMOH, 2000).

Several interventions have been recommended to curb the rising burden of the disease in endemic regions. These interventions form the pillar of the global campaign for effective malaria intervention, particularly in sub-Saharan Africa. In April 25, 2000, African Heads of State and Government at the Abuja, Nigeria summit on Roll Back Malaria expressed their political will to vigorously pursue the interventions. The target set at the Summit was that by 2005 at least 60% of those at risk of malaria particularly pregnant women and children under five years of age will benefit from the most suitable combination of personal and community protective measures such as insecticide-treated mosquito nets and other interventions which are accessible and affordable to prevent infection and suffering (FMOH, 2000).

Insecticide-treated bed net (ITNs): ITN is one of the measures recommended to curb the rising burden of the disease (Figure 2). It reduces human-vector contact by acting as a barrier to prevent vector mosquitoes bite or repelling them, thereby driving them from the vicinity of

sleepers, but also killing or shortening their lifespan if they land on ITNs (WHO, 2001; WHO, 2000). High levels of ITN coverage provide protection both to the individuals sleeping under them and to other community members (WHO 2001). Several controlled studies mainly from Africa have demonstrated the preventive effects of ITNs. Bed net use was found to have a marginal impact in reducing maternal malaria-associated anemia (Dolan et al., 1993). The incidence of anaemia at all study sites was significantly lower at delivery in the permethrin-impregnated bed net (27%) and non-impregnated bed net (41%) than those using no net (56%). In another study, the effectiveness of ITN in Kilifi district, Kenya, ITN had little impact on the morbidity associated with malaria infection in primigravidae, despite its documented evidence on paediatric severe malaria and mortality (Shulman, 1998). However, in a recent study ITN was found to substantially reduce childhood mortality at peripheral health facilities in western Kenya (Philips-Howards, 2003).

Intermittent preventive treatment (IPT): This involves the administration of two or three full, curative treatment doses of an efficacious, preferably single-dose, antimalarial drug (e.g. sulfadoxine/pyrimethamine) at predefined intervals during pregnancy, beginning in the second trimester after quickening. IPT can significantly reduce maternal anemia and low birth weight (van Eijk et al., 2004). Women should receive at least two doses of IPT, each at least one month apart, and this has been found to be highly effective in decreasing the proportion of women with placental malaria infection at delivery (Schultz et al., 1994; Schultz et al., 1995). A study in Malawi showed that with the use of sulphadoxine/pyrimethamine (S/P)-based IPT, led to a decrease placenta malaria prevalence from 31.9 to 22% and a decrease in prevalence of low birthweight from 23% in women not receiving S/P to 10.3% in women given > or = 2 doses. There were also higher maternal haemoglobin concentrations (Rogerson, 2000). IPT can be administered under direct observation in the clinic or be given in the community. WHO recommends a schedule of four antenatal care visits, with three visits after quickening. The delivery of IPT with each scheduled visit after quickening will help ensure that a high proportion of women receive at least two doses (Figure 3).

Intermittent preventive treatment for infants (IPTi) is currently been tried in some malaria research areas in Africa. Reports have shown that sulphadoxine/pyrimethamine-based IPTi given during immunization was effective in protecting children against malaria. The resultant effects will be reduced malaria morbidity and mortality among this patient population (Schellenberg et al., 2001; Verhoef et al., 2002).

Case management of malaria: Early diagnosis, prompt and effective treatment is one of the strategies

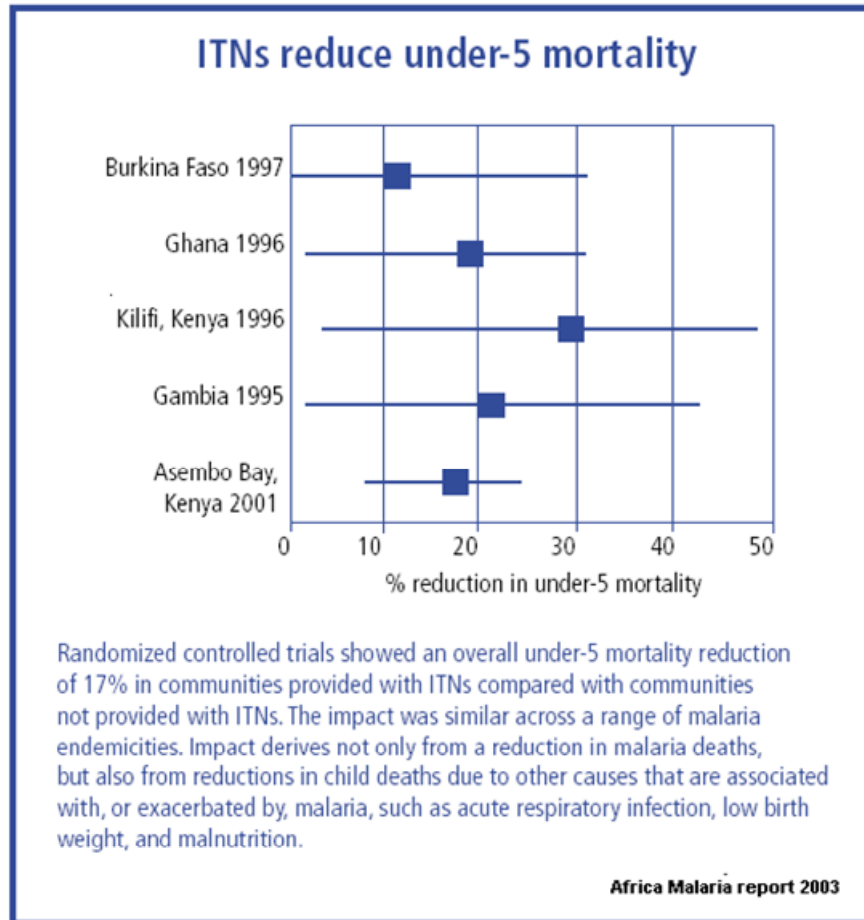


Figure 2. The impact of ITNS on under five mortality in some African countries.

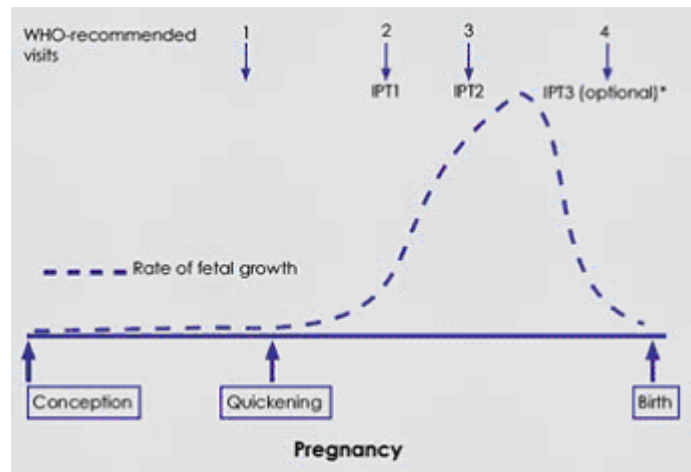


Figure 3. WHO recommended IPT administration schedule (Source: WHO Regional Office for Africa, 2004).

*HIV infection diminishes a pregnant woman’s ability to control *Plasmodium falciparum* infections. Women with HIV infection are thus more likely to have symptomatic infections and to have an increase risk for malaria-associated adverse birth outcomes. At least three doses of IPT are required to obtain maximum protection. In areas where HIV prevalence among pregnant women is > 10%, a third dose of IPT should be administered at the last scheduled antenatal care visit.

developed by the World Health Organization to combat malaria disease, and it remains the main pillar of global malaria control programme (WHO, 2000). Prompt and adequate clinical case management of malaria results in early resolution of the clinical symptoms and hence decrease in morbidity and mortality. It also decreases school and work absenteeism, resulting in improved productivity and economic growth (Were, 2004). This intervention is in-line with the Abuja summit on malaria that stated that by year 2005, 60% of malaria episodes should be appropriately treated within 24 hours of onset of symptoms (FMoH, 2000).

CHALLENGES

Many malaria endemic countries have guidelines for malaria preventive measures, particularly among the high risk groups (under five children and pregnant women). However, the effectiveness of these interventions is being challenged by a number of factors. In a study by Enato and Okhamafe (2005) in two Nigerian rural communities, low coverage of antimalarial intervention during pregnancy was found, possibly due to poor delivery system. It has been noted that the success of any programme depends not only on the efficacy of the intervention provided under ideal and controlled conditions, but also on achieving optimal use by the target population (Fosu, 1994). The challenges faced by the malaria control programmes in sub-Saharan Africa can be classified into: delivery systems for ITNs and IPT for malaria prevention, malaria drug resistance and poor accessibility of health care facilities.

Delivery system for ITNs and IPT: This is the development of effective means to ensure a wider coverage in the delivery of these interventions. The delivery of ITNs services is expected to ensure a wider net ownership and insecticide-treatment of nets on time, and to provide relevant information to encourage proper use (WHO, 2001b). The specific issues to address include:

- Quality assurance of products delivered.
- Gaining access to other formal and non-formal public and the private sector and community-based structures and processes in support of INT delivery.
- Access to populations at higher risk of contracting malaria (e.g. under five children and pregnant primigravidae), focusing on those who may live in less accessible areas, and/or cannot afford the services.

In a study of the impact ITNs on malaria and anaemia in pregnancy in Kassena-Nankara district Ghana, it was found that effective use varied from 42% in primigravidae to 63% in multigravidae in spite of free nets and

insecticide impregnation (Brown, 2001).

The control of malaria in pregnant African women applied through antenatal care has been particularly challenging (Steketee et al., 1996; Philips-Howard, 1999). Antenatal care (ANC) services are traditionally delivered from health facilities along with other health promotive and preventive programmes such as vaccination and under five clinics. However, often the services suffer from problems of accessibility, affordability and client satisfaction. In such circumstances, pregnant women, when seeking health care during pregnancy often opt for alternative services provided at the community level where female relatives and traditional birth attendants can play a major role (Magnussen, 2003). For example, only 42% of pregnant women in Uganda attend the required four ANC visits and less than 40% deliver at health units (Ndyomuggenyi, 1998).

The preventive and control recommendations for typical area of high *P. falciparum* transmission have promoted the use of antimalarial chemoprophylaxis using chloroquine (Steketee et al., 1996b), and use of sulphadoxine/pyrimethamine (S/P) as intermittent preventive therapy (IPT). However, the concept of using antimalarial drugs to prevent malaria is not wide spread and this leads to low compliance with usual chemoprophylaxis regimens (weekly chloroquine). Most pregnant women in high transmission areas are asymptomatic and are more aware and worried about side-effects of antimalarial drugs than about the deleterious effects of malaria infection on them and their babies (Magnussen, 2003; Enato et al., 2005). Even with the introduction of S/P-based IPT, a logistically simpler intervention than weekly chemoprophylaxis, low coverage and compliance remain a problem. In Malawi, for example, 75% of pregnant women get one dose of S/P but only 30% get the recommended two doses (Rogerson et al., 2001).

Resistance to antimalarial drugs: This has been defined "as the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the subject." Later modification of this definition required accessibility of the drug in question to the parasite or the infected red blood cell for the time duration required for its normal action (Bruce-Chwatt et al., 1986).

Antimalarial drug resistance weakens the impact of chemotherapy malaria control in Africa thereby creating a difficult situation for policy makers on their choice of drugs for implementing the early treatment strategy as recommended by the WHO. Antimalarial drug resistance is heightened in individuals e.g. children less than 5 years, pregnant women, non-immune immigrants to malarious areas, malnourished individuals and in patients with human immunodeficiency virus, who have

National scaling up for ITNs: a strategic framework for partners

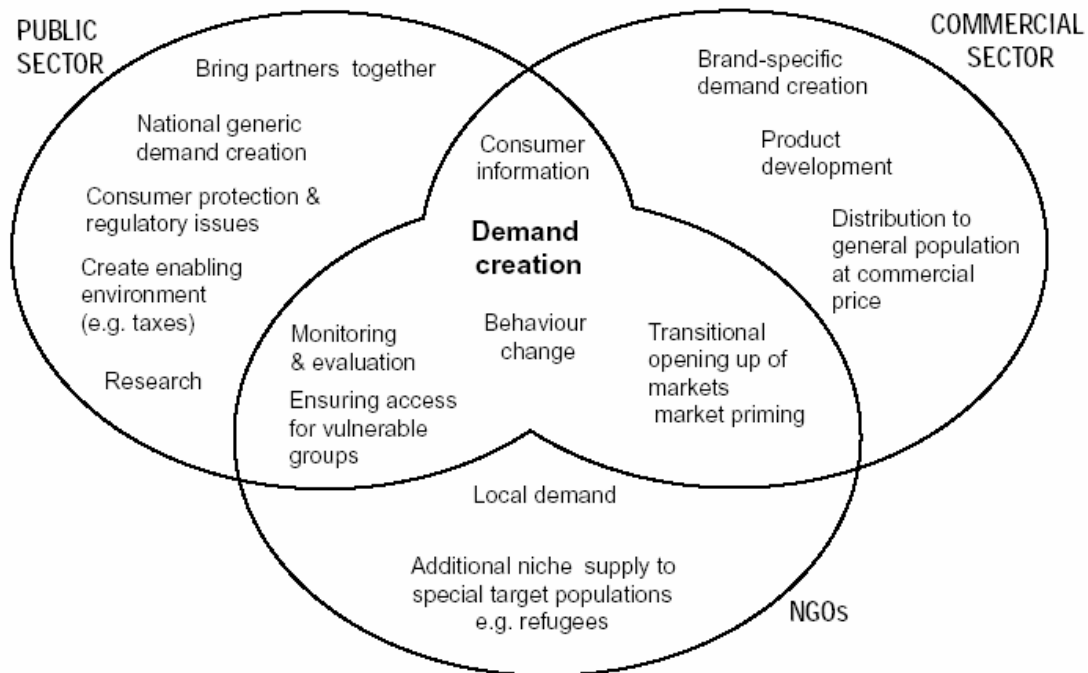


Figure 4. National scaling up for ITNs: a strategic framework.

reduced immunity (Bloland, 2001). Reduced immunity allows the survival of a residuum of parasites that are able to survive treatment, and as such this may further increase the development, intensification and spread of resistant strains. Verdrager (1986, 1995) in his studies proposed this mechanism as a significant contributor to resistance in South-East Asia.

For a very long time chloroquine was the most cost-effective antimalarial drug in most endemic regions. However, following reports of its resistance to *P. falciparum* in 1960 from Colombia and subsequent report from south-East Asia, the spread has been tremendous with resistant strains appearing in most parts of the world. Virtually all antimalarial drugs in common use, with the exception of the newer agents (e.g. artemisinins), have shown resistance to malaria parasites. Antimalarial drug resistance has emerged as one of the greatest challenges facing malaria control today, and the pace of the spread is greater than the pace at which new antimalarial drugs are being developed for clinical use. The geographical distribution of resistant strains of *P. falciparum* and *P. vivax* to any single agent varies from country to country, and within a particular country from region to region. Thairthong (1983) has shown a single Plasmodium isolates to consist of heterogeneous populations of parasite whose sensitivity range from highly resistant to completely sensitive strains. Also,

epidemiological evidences exist for varying parasite sensitivity to the different antimalarials drugs in any geographical area. Several factors can lead to the development, intensification and distribution of antimalarials drug resistance. These factors can broadly be classified as: factors leading to treatment failure (incorrect dosing regimen, non-compliance with medications, substandard drugs and misdiagnosis), human behaviour, parasite and vector biology, and drug pharmacokinetics (Bloland, 2001).

Poor access to diagnostic and curative care: A strong health care delivery system would ideally provide early diagnosis prompt and effective treatment. However, access to curative and diagnostic services is limited in malaria-endemic countries, resulting in inappropriate antimalarial utilization with the resultant development and spread of *P. falciparum* strains (Bloland, 2001; Enato et al., 2003; Hamel et al., 2001).

OPPORTUNITIES

Within the African region, opportunities abound for quick and adequate intervention of malaria situation in the continent. Such interventions will include appropriate application of old malaria preventive tools adapted to



Figure 5. Countries that include artemisinin-based combination therapy in antimalarial treatment policy, as of 2004 (RBM, World report 2005).

local needs and the development and application of new methods (e.g. vaccines and drugs). The success in the development and implementation of these new tools will depend on a connection with scientists from endemic countries of Africa who have a better understanding of local customs and are experienced in communicating with the poorest people in villages of Africa (Miller et al., 2002).

Figure 4 shows the market mix that is involved in the demand supply chain for insecticide-treated bed nets. One approach to achieve equity while not undermining the long-term commercial viability will be the use of vouchers and coupons enabling a reduced price through the commercial distribution network (WHO, 2000). Also, some researchers working in parts of Africa in collaboration with their overseas partners are developing methods which will involve the use of community-based approaches in the delivery of S/P-based IPT (Magnussen, 2003). When successful, this approach can also be applied to ITNs.

Home management of uncomplicated malaria in children is currently being promoted to enhance accessibility to good, efficacious antimalarial chemotherapy within the shortest possible time after development of fever. This current effort will depend on the applicability of artemisinin-based combination therapy (ACTs), which are safe and efficacious in most malaria endemic regions. Most countries in sub-Saharan Africa have changed their antimalarial treatment policies to ACTs (Figure 5). What is required right now is to ensure accessibility and affordability. The growing of the

plant, *Artemisia annua*, is currently being undertaken in some east African countries. The prohibitive price of ACTs is as a result of the high cost of the artemisinin, obtained from the plant. Other means to ensure affordability will be through deliberated international subsidy by donor bodies. This approach has been successfully used to enhance the affordability of antiretroviral drugs to most poor countries of the world, majority of who are in Africa (Mrazek, 2002).

Combination therapy: Combination therapy (CT) with antimalarial drugs is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets in the parasite. The concept of combination therapy is based on the synergistic or additive potential of two or more drugs, to improve therapeutic efficacy and also delay the development of resistance to the individual components of the combination (WHO, 2001a). Current combination therapy can be classified into nonartemisinin-based and artemisinin-based combination therapies. Artemisinin-based combination therapies (ACTs) have been shown to improve treatment efficacy and also curtail drug resistance in South-East Asia (White, 1999; White and Olliaro, 1996). The rationale for the use of ACTs is based on the combination of the rapid schizontocidal effects of artemisinin with the long half life of the partner drug (WHO, 2001). However, major challenges of deployment and use of antimalarial drug combination therapies, particularly in Africa should be addressed.

REFERENCES

- A Strategic Framework for Malaria Prevention and Control during Pregnancy in the African Region (2004). World Health Organization Regional Office for Africa, Brazzaville – AFR/MAL/04.01.
- African Malaria Report (2003). Africa malaria report 2003. Geneva. WHO/UNICEF: http://www.rbm.who.int/amd2003/amr_toc.htm.
- African Summit on Roll Back Malaria, Abuja – Working document (2000). Federal Ministry of Health, Abuja, Nigeria.
- Bioland PB (2001). Drug resistance in malaria. World Health Organization. WHO/CDS/CRS/DRS/2001.4.
- Bouvier P, Doumba O, Breslow N (1997). Seasonality, malaria, and impact of prophylaxis in a West African village 1. Effect on anemia in pregnancy. *Am J Trop Med Hyg.* 56(4): 378-383.
- Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Sewankambo N, Lutolo T, Waver MJ, Abramowsky C, Sullivan D, Gray R (2003). The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. *AIDS.* 17 (17): 2539 – 2541.
- Breman JG, Egan A, Keusch G (2001). The intolerable burden of malaria: a new look at the numbers. *Am. J. Trop. Med. Hyg.* 64: (1,2 Suppl): iv-vii
- Dolan G, ter Kuile FO, Jacoutot V et al (1993). Bed nets for the prevention of malaria and anaemia in pregnancy. *Trans. Roy. Soc. Trop. Med. Hyg.* 87(6): 620-626.
- Enato EFO, Okhamafe AO (2005). A survey of antimalarial activity during pregnancy, and child's malaria care-seeking behaviour in two Nigerian rural communities. *Scand. J. Infect. Dis.* 2005 (in press).
- Enato EFO, Aghomo OE, Oparah CA, Odili UV, Etaghene BE (2003). Drug utilization in a Nigerian rural community. *JMBR* 2003; 2(2): 15 – 22.
- Enato EFO, Okhamafe AO, Okpere EE (2005). A survey of knowledge, attitude and practice of malaria management among pregnant women from two health care facilities in Nigeria. *Acta Obstetrica et Gynecologica Scandinavica* 2005 (in press).
- Gallup JL, Sachs JD (2001). The economic burden of malaria. *Am. J. Trop. Med. Hyg.* 64(1 suppl): 85-96.
- Greenwood B, Mutabingwa T (2002). Malaria in 2002. *Nature.* 415: 670-672.
- Hamel MJ, Odhacha A, Roberts JM, Deming M (2001). Malaria control in Bungoma district, Kenya: a survey of home treatment of children with fever, bed nets use and attendance at antenatal clinics. *Bull. World Health Org.* 79: 1014-1023.
- Menendez C, Ordi J, Ismail R (2000). The impact of placental malaria in gestational age and birthweight *J Inf Dis.* 181 (5): 1740-1745.
- Mrazek M (2002). Pharmaceutical pricing in the developing world: issues of access to medicines. *Expert Rev Pharmacoeconomics Outcomes Res.* 2 (1): 43-50.
- Ndyomugenyi R, Neema S, Magnussen P (1998). The use of formal and informal services for antenatal care and malaria treatment in rural Uganda. *Health Pol Plan.* 13: 94-102.
- Miller LH, Baruch DI, Marsh K, Doumbo OK (2002). The pathogenic basis of malaria. *Nature.* 415: 673-677.
- Phillips-Howard PA (1999). Epidemiology and control issues related to malaria in pregnancy. *Ann Trop. Med. Hyg.* 93 (1 Suppl): S 11-7).
- Phillips-Howard PA, Nahlen BL, Wannemuehler KA et al (2003). Impact of permethrin-treated bed nets on the incidence of sick child visits to peripheral health facilities. *Am J Trop Med Hyg.* 68 (suppl 4): 38 - 43.
- Rogerson SJ, Chaluluka E, Kanjala (2001). Intermittent sulphadoxine-pyrimethamine in pregnancy: effectiveness against malaria morbidity in Blantyre, Malawi, in 1997 – 99. *Trans R Soc. Trop. Med. Hyg.* 94 (5): 549- 553.
- Sachs J, Malaney P (2002). The economic and social burden of malaria. *Nature* 415: 680 – 685.
- Schellenberg D, Menendez C, Kahingwa E (2001). Intermittent treatment for malaria and anaemia control at time of routine vaccinations in
- Schultz LJ, Steketee RW (1994). The efficacy of antimalarial regimens containing sulphadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental *Plasmodium falciparum* infection among pregnant women in Malawi. *Am. J. Trop. Med. Hyg.* 51 (5): 515-522.
- Schultz LJ, Steketee RW, Chitsulo L, Macheso A, Kazembe P, Wirima JJ (1996). Evaluation of maternal practices, efficacy, and cost-effectiveness of alternative antimalarial regimens for use in pregnancy: chloroquine and sulphadoxine-pyrimethamine. *Am. J. Trop. Med. Hygiene.* 55 (1 Suppl): 87-94.
- Schultz LJ, Steketee RW, Chitsulo L, Wirima JJ (1995). Antimalarials during pregnancy: a cost-effective analysis. *Bull World Health Org.* 73 (2): 207-214.
- Steketee RW (1996). Impairment of a pregnant woman's acquired ability to limit *Plasmodium falciparum* by infection with human immunodeficiency virus type-1. *Am. J. Trop. Med. Hyg.* 5 (1 Suppl): 42-49.
- Steketee RW, Nahlen BL, Parise M, Menendez C (2001). The burden of malaria in pregnancy in malaria endemic areas. *Am J Trop Med and Hygiene.* 64 (1-2 Suppl): 28-35.
- Steketee RW, Slutsker L (1996). The problem of malaria control in pregnancy in sub-Saharan Africa. *Am J Trop Med and Hygiene.* 5 (1 Suppl): 2-7.
- Steketee RW, Wirima JJ, Campbell CC (1996). Developing effective strategies for malaria prevention program for pregnant African women. *Am J Trop Med and Hygiene.* 55 (1 Suppl): 95-100.
- Tanzanian infants: a randomized, place-controlled trial. *Lancet.* 357: 1471-1477.
- Van Eijk AM, Ayisi JG, ter Kuile FO (2004). Effectiveness of intermittent preventive treatment with sulphadoxine-pyrimethamine for control of malaria in pregnancy in western Kenya: a hospital-based study. *Trop. Med. Int. Health* 9 (3): 351-360.
- Verdrager J (1986). Epidemiology of the emergence and spread of drug-resistance *falciparum* malaria in South-East Asia and Australia. *Journal of Tropical Medicine and Hygiene.* 89: 277-289
- Verdrager J (1995). Localized permanent epidemics: the genesis of chloroquine resistance in *Plasmodium faciparum*. *South East Asian J. Trop. Med. Hyg.* 2623-2628.
- Verhoef H, West CE, Nzyuko SM (2002). Intermittent preventive treatment of iron and sulphadoxine-pyrimethamine to control anaemia in Kenyan children: a randomized controlled trial. *Lancet* 360 (9337): 908-914.
- Were W (2004). Bringing malaria management closer to the home. Supporting Agency-Roll Back Malaria, WHO. pp.???
- White NJ (1999). Delaying antimalarial drug resistance with combination therapy. *Parasitologica.* 41: 301-308.
- White NJ, Olliaro PL (19??). Strategies for prevention of antimalarial drug resistance: rationale for combination therapy for malaria. *Parasitology Today* 1996; 12: 399-401.
- Wolfe EB, Parise ME, Haddix AC (2001). Cost-effectiveness of sulphadoxine - pyrimethamine for the prevention of malaria-associated low birth weight. *Am. J. Trop. Med. Hyg.* 64 (3-4): 178-186.
- World Health Organization (1993). Implementation of the global malaria control strategy. Reports of the World Health Organization Study Group on The Implementation of the Global Plan of Action for malaria control 1993 – 20002. WHO Technical Report Series Number 839.
- World Health Organization (1999). The who Report 1999. Making a difference. Geneva.
- World Health Organization (2001). Guidelines on the use of insecticide-treated mosquito nets for the prevention and control of malaria in Africa. CTD/MAL/AFRO/97.4
- World Health Organization Expert Committee on Malaria (2000b). WHO Technical Report Series 892, 12th Report: 3 – 6.