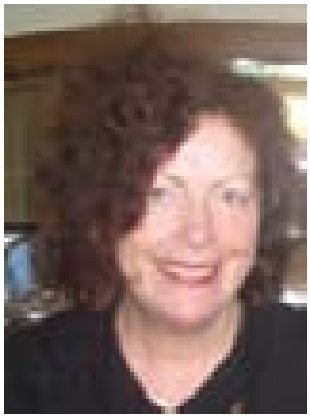
Goal setting and reality: maternal, perinatal and childhood malaria



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The protozoan, viral and bacterial infections of malaria, human immunodeficiency virus (HIV) and tuberculosis (TB) cause over 5.5 million deaths each year [1]. This burden of disease is largely concentrated in the same geographical regions, related to vector distribution, their association with poverty and the vulnerability of HIV infected people to both malaria and TB.

This paper is a review of the devastating effects of malaria in the most susceptible hosts – pregnant women and children. Importantly, a recent technical report from the WHO indicates that rapid coverage and sustained efforts with evidence-based interventions would have a major impact on reducing malarial mortality and morbidity in a relatively short time. Global eradication will require newly developed tools and research directed to prevention, diagnosis and treatment [2].

Epidemiology

Malaria in pregnancy is a major cause of maternal and perinatal infection, death and morbidity. In low income countries, most deaths in 2002 (>1 million) occurred in children less than 5 years and accounted for over 90% of all malarial deaths [1] and approximately 10% of the 10.6 million deaths in children of this age [3]. A recent systematic analysis of maternal deaths in a tertiary referral hospital in Maputo, Mozambique, challenges global estimates that most maternal deaths are attributable to direct, pregnancy-related causes. The authors conducted a prospective study (2002-2004) of 139 of the 179 maternal deaths and found that infectious diseases accounted for half of all deaths and included malaria, HIV and TB [4]. An estimated 50 million pregnancies and more than 40% of all births worldwide occur in endemic malarious areas of the tropics and subtropics, including most tropical regions of sub-Saharan Africa, south-east Asia and Latin America [5].

Parasites and transmission

Malaria is caused by an intracellular protozoan parasite of the genus *Plasmodium*. Five species infect humans – *P. falciparum, P. vivax, P. ovale, P. malariae* and the morphologically similar *P. knowlesi*. Infected female *Anopheles* mosquitoes transmit malaria parasites person-to-person and are more attracted to pregnant than non-pregnant women [6]. Increased recognition of vertical transmission from mother to fetus either during pregnancy or delivery has been documented in endemic areas with a prevalence rate of up to 32% [7]. Spread can also occur from transfusion of infected blood or via infected needles. Transmission of malaria by breast feeding does not occur.

P. falciparum is the most lethal malarial parasite with mortality and morbidity concentrated on pregnant mothers and young children, due to the severity of syndromes such as cerebral malaria, pulmonary oedema and profound anaemia [8, 9]. Secondary effects of maternal malaria include suppression of immune responses to vaccination, e.g. tetanus toxoid, and reduction in placental transfer of specific antibodies to the fetus, e.g. respiratory syncytial virus, measles, pneumococcus [8].

Maternal, perinatal and childhood morbidity and mortality

Pregnant women in endemic (stable or high transmission) areas are usually asymptomatic but develop anaemia and, if severe, both maternal morbidity and mortality may be increased. The risk of adverse maternal and perinatal outcome is greater during first pregnancies, younger age and for all gravida women who are HIV positive [10]. In epidemic (unstable or low transmission) areas, consequences of infection are more severe and the risk is similar across parity. Non-immune pregnant women are at high risk of cerebral malaria, hypoglycaemia, pulmonary oedema, severe haemolytic anaemia and perinatal death [11]. Risk of stillbirth may be increased seven-fold in unstable areas [12]. Symptoms and signs (fever, chills, headache, sweats, vomiting) are non-specific.

Adverse effects on pregnancy (anaemia) and pregnancy outcomes (stillbirth, abortion, low birth weight (LBW), prematurity, intrauterine growth reduction (IUGR), perinatal mortality, infant anaemia) are directly related to the extent of placental malaria and partly to the degree of maternal anaemia and fever [11, 13, 14]. Congenital malaria may present as fever, anaemia, jaundice, hepatosplenomegaly and early death [15].

The morbidity due to malaria is extensive, as LBW, IUGR and preterm infants are at increased risk of neonatal death and impaired cognitive development attributable to prenatal and

postnatal causes. Included in the latter are unrecognised and untreated hypoglycaemia in resource poor settings. Further, approximately 7% of children who survive cerebral malaria due to *P. falciparum* have permanent neurological impairment and others have learning difficulties which adversely affect school performance [16]. Similarly, recurrent fever and anaemia due to malaria are exacerbated by drug resistance so that children remain parasitaemic and anaemic, contributing to ill health and impaired school performance.

Placental malaria

In malaria-endemic areas, placental malaria, characterised by parasitised red cells in placental blood in the intervillous space, is a more common finding than parasites in the peripheral circulation of the mother, who is often asymptomatic due to acquired partial immunity. The only species shown to colonise the placenta is *P. falciparum.* A search for biomarkers to identify placental inflammation has so far established that maternal peripheral blood level of interleukin-10 at a cut off of 15pg/mL has 80% sensitivity and 84% specificity to detect placental malaria [17]. Severe maternal and neonatal mortality and sequelae are related to placental inflammation due to malaria [18]. The parasitised cells in the placenta express unique variant surface antigens and lack of immunity to these antigens, combined with acquired changes in cell mediated immunity in pregnancy, explain some of the susceptibility of pregnant women to malaria [19]. Placental malaria also increases the risk of mother-to-child HIV transmission, emphasising the role of malarial prevention for both malaria and HIV infection in improving perinatal and infant outcomes [20].

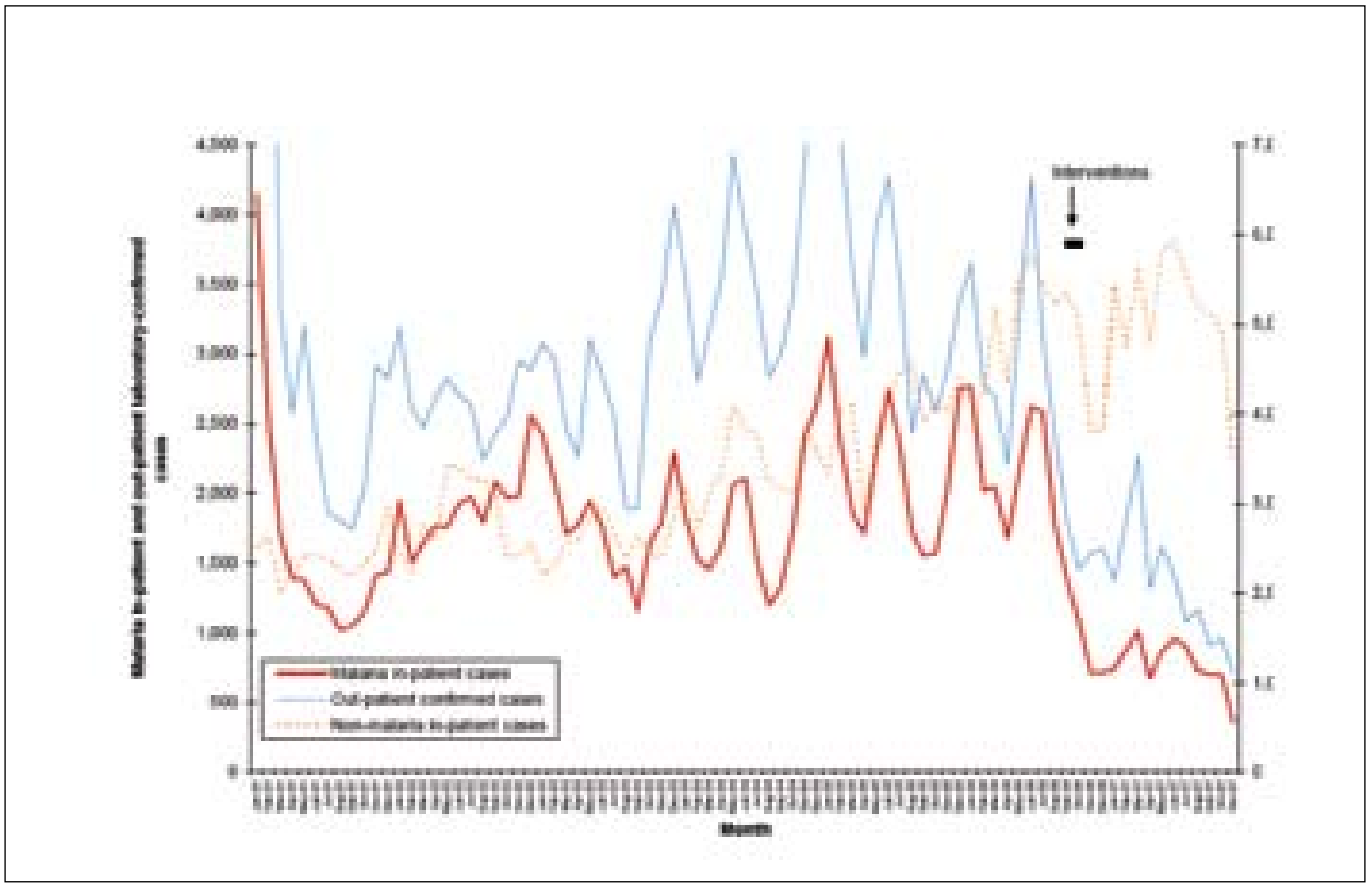
Diagnosis

Light microscopy of thick and thin Giemsa-stained blood smears is the gold standard for diagnosis. Further, rapid antigen detection provide rapid results in 2-10 minutes, with variable accuracy [21]. Additionally, several laboratory tests exist; most accurate and most expensive are tests using PCR to detect parasite nucleic acids. Finally, serology detects antibodies indicating past infection, either by indirect immunofluorescence (IFA) or ELISA.

Treatment

Prompt appropriate treatment of pregnant women with malaria requires early and effective case management in malarious areas together with screening and appropriate treatment of anaemia. Increasing resistance to efficacious drugs with a well established safety profile in pregnancy such as sulfadoxine-pyrimethamine has led to recommendations that artemisinin combination therapy (ACTs) are the most cost-effective strategy for control of malaria in sub-Saharan Africa [22]. Their effect is rapid and reliable,

Figure 1. In-patient malaria cases, out-patient laboratory-confirmed cases and in-patient non-malaria cases by month, all ages 2001-2007, Rwanda [33].



with >95% efficacy for artesunate-mefloquine, artemether-lumefantrine and dihydroartemisinin-piperaquine [23].

In pregnancy, when malaria is uncomplicated, WHO currently recommends ACTs as first choice for second and third trimesters (and if breast feeding) and oral quinine for 7 days in the first trimester [24, 25]. CDC updates treatment options, depending on location, for non-immune travellers [26].

Prevention

Non-immune pregnant women are advised to avoid malaria endemic areas. In general, chemoprophylaxis is not recommended in areas with <10 reported cases of *P. falciparum* malaria per 1000 inhabitants per year [27]. In endemic areas in Africa, WHO recommends a triple approach (the first three points below) for prevention and control in pregnant women [24].

Intermittent preventive treatment (IPT)

Intermittent preventive treatment (IPT) of at least two doses of antimalarial drugs should be given to all pregnant women at antenatal visits in areas of stable transmission. The relative risk (RR) of routine chemoprophylaxis (such as sulfadoxine-pyrimethamine) for pregnant women (low parity) in endemic malarial areas indicates significant reduction in severe anaemia (RR 0.62, 95% CI 0.50-0.78), LBW (RR 0.55, 95% CI 0.43-0.70) and perinatal death (RR 0.73, 95% CI 0.53-0.99) [28].

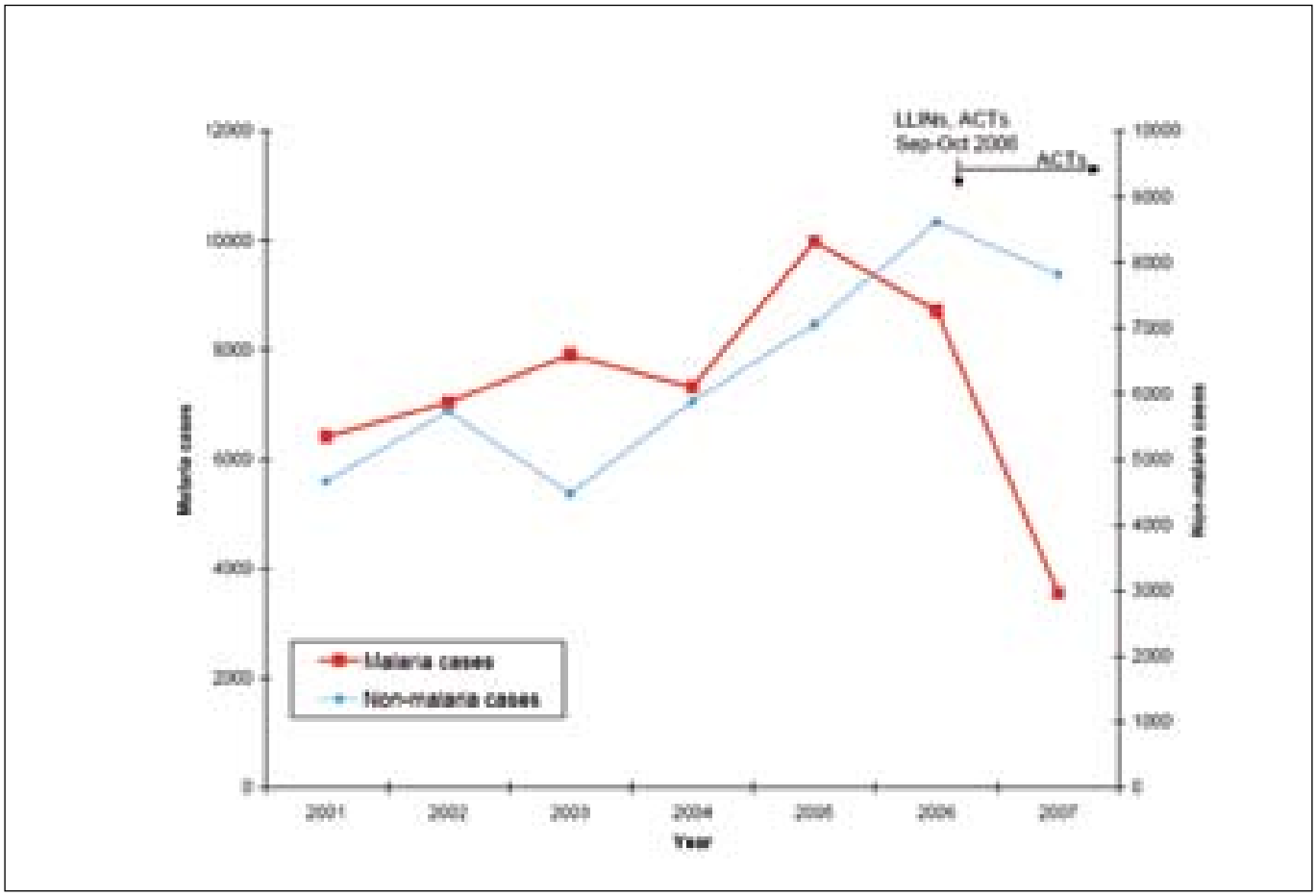
Recent research has similarly shown that treatment of infants at the time of routine immunisation at 2, 3 and 9 months reduced clinical malarial episodes by 60% and severe anaemia by 50% [29]. Current recommendations include use of sulfadoxine-pyrimethamine with close monitoring of safety for infants where the burden of disease is high and drug resistance low [30].

Insecticide-treated bed nets (ITNs)

Insecticide-treated bed nets (ITNs) are recommended as early in pregnancy as possible and postpartum [24]. In pregnant women in Africa, ITNs reduced placental malaria in all pregnancies (RR 0.79, 95% CI 0.63-0.98). They also reduced LBW (RR 0.77, 95% CI 0.61-0.98) and fetal loss in the first to fourth pregnancy (RR 0.67, 95% CI 0.47-0.97) [31]. ITNs are highly effective in reducing childhood morbidity and all cause mortality from malaria by 20% and halve episodes of malaria [32]. About 5.5 lives can be saved each year for every 1000 children protected with ITNs. This equates to 0.5 million child deaths prevented each year in sub Saharan Africa.

Recent review of investment in malaria control in four African countries found strong initial evidence that the combined effect of long-lasting insecticidal-treated bed nets (LLINs) and ACTs to

Figure 2. In-patient malaria and non-malaria cases in children <5 years old, January 2001 – November 2007, 19 in-patient facilities, Rwanda [33].



all children <5 and all households was associated with a >50% decline of inpatient malaria deaths in Rwanda (66% reduction children <5 years) and Ethiopia (51%) (Figures 1 & 2) [33].

Case management

Case management and appropriate treatment for febrile malaria and anaemia (see treatment).

Prevention/prophylaxis for pregnant travellers

The CDC also recommends prevention/prophylaxis for pregnant travellers [34] and lists drugs that are safe and those that are unsafe in pregnancy [35].

Vaccines

The difficulties associated with mosquito control and drug resistance to the parasite, together with the large burden of disease due to malaria, have provoked intense research for a suitable vaccine. Currently there is no effective, licensed vaccine, although phase III trials are underway [8, 36]. The pre-erythrocytic vaccine RTS,S has demonstrable protection against severe malaria in children for 18 months and clinical malaria episodes in adults [37].

Conclusion

The global public health need, attributable to the economic and social burden of malaria [38], the current situation and the research and development needs are outlined by Guerin *et al.* [36]. Research to address the disease burden, in children and pregnant women in particular, vector control, vaccine development, deployment of rapid tests adapted to field situations and effective combination drugs are essential priorities to reduce malaria and prevent escalation of the disease [36].

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