Congenital malaria: an overview

CHIGOZIE J. UNEKE
Department of Medical Microbiology/Parasitology, Faculty of Clinical Medicine, Ebonyi State University, PMB 053 Abakaliki, Nigeria
E-mail: unekecj@yahoo.com

Abstract: Congenital malaria is a public health concern globally. This report reviews publications on congenital malaria in the last two decades (1990-2010) with the view to establishing the current global epidemiological trends and the public health implications. A Medline Entrez-PubMed search was performed and published studies on congenital malaria in the last two decades (1990–2010) were identified. A combination of key words *"congenital malaria"* were used for the search which yielded 180 publications as of December 2010. Of the 180 publications, 93 were within the period 1990 to 2010. Bibliographies of all publications selected were checked for additional relevant references and were obtained and included in the review. The critical issues identified and discussed include the (i) current global trends of congenital malaria; (ii) controversies associated with the frequency of occurrence of congenital malaria; (iii) mechanism and clinical features; (iv) role of maternal HIV infection (v) effects of congenital malaria on infants; (vi) diagnostic challenges; and (vii) treatment considerations. Operational research into various aspects of congenital malaria is essentially lacking as many unresolved issues requiring urgent scientific investigation abound. Public health policy on malaria control should integrate guidelines on congenital malaria management and control.

Keywords: Plasmodium; malaria, congenital; diagnosis, treatment, pregnancy

Introduction

Malaria continues to remain the most severe and complex health challenge facing the vast majority of the countries in tropical and sub-tropical regions of the world. It is one of the most predominant infectious diseases associated with underdevelopment, poverty and ignorance (Worral *et al.*, 2005). Malaria is still a major contributor to high rate of the global infectious disease–related mortality and morbidity particularly in Africa, South-East Asia, Eastern Mediterranean Regions and parts of South America (WHO 2008). In the World Malaria Report (WMR) of 2009 the World Health Organization (WHO) estimated that 243 million cases of malaria occurred worldwide in 2008, and majority of the cases (85%) occurred in the African Region, followed by the South-East Asia (10%) and Eastern Mediterranean Regions (4%) (WHO 2009). According to the WMR, malaria accounted for an estimated 863,000 deaths in 2008, of which 89% were in the African Region, followed by the Eastern Mediterranean (6%) and the South-East Asia Regions (5%) (WHO, 2009).

Plasmodium falciparum is considered as more dangerous than the other three species (*P. vivax, P. malariae* and *P. ovale*) of the human malaria parasites because it is responsible for virtually all the severe malaria cases and deaths (WHO, 1997; 2000a). The sub-Saharan Africa remains the region with the highest burden of malaria accounting for nearly 90% of global malaria deaths because *P. falciparum* is the predominant species and the most effective malaria vector - the mosquito *Anopheles gambiae* - is the most widespread in the region and the most

difficult to control (WHO, 1992). However, increasing number of reports has indicated that *P. vivax* is also associated with significant malaria disease especially in parts of Asia and South America (Nimir *et al.,* 2006; Guerra *et al.,* 2010).

In areas of high malaria endemicity most of the malaria-associated morbidity and mortality are recorded in young children (Uneke, 2009a; Snow *et al.,* 2004). Available evidence indicates that pregnant women are also highly vulnerable to malaria in these endemic areas (Uneke, 2007a; Tagbor *et al.,* 2008; Schantz-Dunn & Nour, 2009; Davis *et al.,* 2010). However, the impact of the malaria burden is much more devastating among children particularly in sub-Saharan African region. Almost all of the malaria deaths in sub-Saharan Africa occur in children below five years of age and this translates to the child mortality of nearly 1 million each year (DFID, 2004; Hopkins *et al.,* 2007; WHO, 2008). Indeed, a child dies of malaria every 30 seconds, a death toll of about 3000 children every day in the sub region alone (WHO, 2003, 2008). Reports from studies and reviews within the last few years are of the consensus that malaria causes at least 20% of all deaths in children under 5 years of age in sub-Saharan Africa (Rowe *et al.,* 2006; Gyapong & Garshong, 2007; Hopkins *et al.,* 2007; Sharp *et al.,* 2007). However, it is pertinent to state that many of the reports presenting data on the burden of malaria among young children appear not to focus on infant specifically (Larru *et al.,* 2009). This is presumably because it is thought that infants under the age of six months are relatively protected against clinical malaria as a result of maternal antibodies transfer and the presence of foetal haemoglobin (Snow *et al.,* 1998; Klein Klouwenberg *et al.,* 2005; Duah *et al.,* 2010). However, findings from a number of hospital-and community-based studies within sub-Saharan Africa suggest that the burden of malaria during the six first months of life may be substantial (Afolabi *et al.,* 2001; Nweneka & Eneh 2004; Larru *et al.,* 2009). Thus the burden of malaria among young children might be higher than what is generally estimated.

The high burden of childhood malaria in endemic regions of the world has been associated with malaria during pregnancy (Murphy & Breman 2001). In sub-Saharan Africa for instance, malaria affects an estimated 24 million pregnant women (Steketee *et al.,* 2001) and each year between 75,000 and 200,000 infant deaths are attributed to malaria infection in pregnancy globally (Steketee *et al.,* 2001; WHO, 2003). Pregnant women residing in malaria endemic areas often experience a high frequency and density of parasitemia, resulting to high rates of maternal morbidity including fever and severe anaemia, with abortion and stillbirth, and with high rates of placental parasitisation (Brabin 1983; Steketee *et al.,* 2001). Severe parasitization of the placenta by malaria parasites particularly *P. falciparum* and *P. vivax* which is known as placental malaria can result in transplacental transmission of the parasite to the foetus and consequently to congenital malaria (Brabin, 1983; Menendez & Mayor 2007; Uneke, 2007b).

Congenital malaria resulting from the transplacental transmission of malaria parasites particularly *P. falciparum* from mother to foetus, is well described by some early reports (Schwetz & Peel 1934; Covell, 1950; Reinhrdt *et al.,* 1978). However the precise definition of congenital malaria is still a subject that is not devoid of controversy debatable, but symptoms usually occur 10 to 30 days postpartum (Behrman *et al.,* 2004). The disease can be observed in a day-old baby or be delayed for weeks or months (Hashemzadeh & Heydarian, 2005). In 80% of the cases of congenital malaria, the most common clinical features include fever, anaemia, and

splenomegaly (Remington & Klein, 1995). Some reports indicate that other signs and symptoms which could manifest are hepatomegaly, jaundice, regurgitation, loose stools, and poor feeding, and occasionally, drowsiness, restlessness, and cyanosis (Remington & Klein 1995; Hashemzadeh & Heydarian 2005).

In recent times there has been renewed public health concern about the increase in the burden of congenitally acquired infectious diseases including malaria (McGovern *et al.,* 2007). The global drive towards making motherhood safer, improving perinatal outcome and enhancing neonatal health has made congenital malaria an important public health issue (Halin, 2002; van Geertruyden *et al.,* 2004; Bhutta *et al.,* 2005). The purpose of this paper was to review some current epidemiological developments in congenital malaria and to highlight the public health implications with respect to the management of congenital malaria, public health policy guidelines and operational research needs. In this review, congenital malaria was defined as the presence of asexual stages of malaria parasites in cord blood smear at delivery or peripheral blood smear of the baby in the first 7 days of life, irrespective of clinical symptoms.

To achieve the objective of this paper, a Medline Entrez-PubMed search was performed and reported studies on congenital malaria in the last two decades (1990–2010) were identified. A combination of key words *"congenital malaria"* were used for the search which yielded 180 publications as of December 2010. Of the 180 publications, 93 where within the period 1990 to 2010. The 93 publications were then selected for the review. Bibliographies of all publications selected were checked for additional relevant references and were obtained and included in the review. Particular attention was paid to articles providing information on the prevalence of congenital malaria, the clinical significance, role of maternal HIV infection, diagnosis and treatment considerations, and policies on prevention and control.

Congenital malaria: rare or frequent event

For a long time the frequency of the occurrence of congenital malaria remained a subject of controversy with many reports before the 1970s describing it as an extremely rare event (Covell, 1950; Bruce-Chwatt, 1952; Logic & McGregor, 1970). Some other reports in the 1980s however noted that the low reported incidence of congenital malaria particularly in Africa was surprising since malaria occurs more commonly in pregnancy (McGregor, 1983; Lehner & Andrews, 1988). More recently, findings from a number of studies from sub-Saharan Africa have described congenital malaria as a rare event largely because the prevalence of malaria parasite in cord blood or neonatal blood was very low and few newborns developed clinical disease during the first few weeks of life (Lamikanra 1993; Djibo & Cenac, 2000; Adachi *et al.,* 2000; Sule-Odu *et al.,* 2002). These studies had speculated that the effectiveness of the placenta to restrain the malaria parasite passage to the foetus and the remarkable capacity of the foetus to resist infection as demonstrated by Miller & Telford (1997) was responsible for the rarity of congenital malaria. It was further argued that the resistance to congenital malaria is enhanced by physical barrier of the placenta to infected red cells, the passive transfer of maternal antibodies, and the poor environment afforded by foetal erythrocytes for plasmodial replication, due to their foetal haemoglobin composition and low free-oxygen tension (Miller &

Telford, 1996). Moreover, because neonates in Africa rarely present with clinical disease, congenital malaria was assumed to be of little clinical importance in areas of high malaria endemicity (Steketee *et al.*, 1996a).

Interestingly however, evidence from most of the cross-sectional studies conducted in parts of sub-Saharan Africa on congenital malaria within the last two decades (1990-2010) clearly indicates that congenital malaria is not as uncommon as previously thought. In fact, congenital malaria prevalence in majority of the cross-sectional studies within the last five years (2005-2010) ranged from 10.8% to as high as 54.2% (Table 1). In most of these recent reports there was a strong association between placental malaria and umbilical cord parasitaemia which was suggested to be responsible for the congenital malaria (Uneke, 2007a, b, c). Until recently, it was unclear if the presence of malaria parasites in umbilical cord blood was an indication of infection acquired antenatally or a result of contamination with infected maternal blood at delivery. In a 2006 report however, Malhotra *et al*. (2006*)* demonstrated from their study in Kenya that malaria parasites identified in cord blood were acquired antenatally by transplacental transmission of infected erythrocytes and that primigravid and secundigravid women with placental malaria were at increased risk for congenital infection. This finding therefore confirmed earlier reports which had noted that the rate of transplacental transmission of malaria in endemic region was high and suggested that the placental barrier is not very effective when infected with malaria parasites (Redd *et al.*, 1996; Brabin *et al*., 2004).

Table 1: Prevalence of congenital malaria as reported by various studies in malaria endemic areas of sub-Saharan Africa from 1990-2010.

Type of study	Study location	Prevalence of congenital malaria (%)	Year of publication	Study authors/reference
Cross-sectional	Lagos, Nigeria	13.6	2010	Lesi et al.
Cross-sectional	Western Kenya	10.8	2009	Perrault et al.
Cross-sectional	Muheza, Tanzania	19.1	2008	Mwangoka et al.
Cross-sectional	Calabar, Nigeria	13	2008	Ekanem et al.
Cross-sectional	Sagamu, Nigeria	10.9	2008	Sotimehin et al.
Cross-sectional	Ibadan, Nigeria	5.1	2007	Falade et al.
Cross-sectional	Enugu, Nigeria	32.48	2006	Okafor et al 2006.
Retrospective	Sagamu, Nigeria	17.4	2006	Runsewe-Abiodun et al.
Cross-sectional	Lagos, Nigeria	15.3	2006	Mukhtar et al.
Cross-sectional	Ile-Ife, Nigeria	54.2	2005	Obiajunwa et al.
Cross-sectional	Southern Cameroon	7.8	2005	Akum et al.
Cross-sectional	Sagamu, Nigeria	0.7	2002	Sule-Odu et al.
Prospective survey	Niamey, Niger	13.3	2000	Djibo & Cenac
Cross-sectional	Dar-es Salaam, Tanzania	0.33	2000	Adachi et al.
Cross-sectional	Ibadan, Nigeria	15.0	2000	Olowu et al.
Cross-sectional	Ibadan, Nigeria	2.6	1997	Achidi & Salimonu
Cross-sectional	Jos, Nigeria	2.82	1997	Egwunyenga et al.
Cross-sectional	Various sites in SSA	23.0	1997	Fischer

Cross-sectional	Central, Nigeria	10.5	1996	Egwunyenga et al.
Cross-sectional	Southern Malawi	6.7	1996	Redd et al.
Case series	Benin, Nigeria	8.0	1995	Ibhanesebhor
Case series	Ibadan, Nigeria	23.7	1993	Akindele et al.
Cross-sectional	Lagos, Nigeria	0	1993	Lamikanra
Cross-sectional	Maputo, Mozambique	1.5	1993	Bergstrom et al.
Cross-sectional	Southern Zambia	36.0	1991	Larkin &Thuma
Cross-sectional	Kinsasha, DRC	4.0	1990	Omanga &Kapepela

SSA= sub Saharan Africa; DRC= Democratic Republic of Congo

It is thus not very unlikely that early reports which indicated that congenital malaria was a rare event in endemic areas may have underestimated the prevalence of the disease since transplacental transmission of malaria parasites was not an uncommon event even in semi-immune women who usually have high levels of anti-malaria acquired immunity (Menendez & Mayor, 2007). It is pertinent to add that there exist a number of factors which to a large extent influence the estimation of congenital malaria. Menendez and Mayor (2007) described these factors as (i) differences in the definition of congenital malaria; (ii) levels of maternal immunity; (iii) the type of blood sample examined (peripheral blood of neonates or cord blood); (iv) the expertise in blood-smear examinations; (v) the method of parasite detection (Giemsa staining or polymerase chain reaction (PCR); or even (vi) a reflection of true environmental differences. The lack of consideration of these factors could give rise to congenital malaria underestimation. For instance Perrault *et al*. (2009) found 0% of cord blood infection by microscopy and 10.8% of cord blood infection by PCR in the same population. These differences are the major limitations in the comparison of studies on congenital malaria and so the interpretation should be done cautiously. Despite finding that 13.3% of neonates examined had malaria parasite Djibo & Cenac (2000) indicated they found no cases of congenital malaria with clinical signs in their study. Furthermore four studies from various parts of Nigeria which examined both umbilical cord blood and neonatal blood for malaria parasites observed that the frequency and density of parasitaemia were consistently higher in cord blood than the neonatal blood (Lamikanra, 1993; Egwunyenga *et al.,* 1995; Obiajunwa *et al.,* 2005; Mukhtar *et al.,* 2006). Therefore a proper estimation of congenital malaria must take these influencing factors into consideration to avoid underestimation of the prevalence of the disease. The stark reality however, is that congenital malaria is no longer a rare event.

Mechanisms and clinical features of congenital malaria

In spite of the increase in the number of recent reports indicating that congenital malaria frequently occurs, the mechanism of transplacental passage of the malaria parasite from mother to foetus is still obscure. It has been postulated that the possible mechanisms include direct penetration through chorionic villi, premature separation of the placenta, and the possible physiologic transfusion of maternal red blood cells to the foetal circulation *in utero* or at the time of delivery (De Silva *et al.,* 1982; Menendez & Mayor, 2007; Reynolds *et al.,* 2007). A number of previous studies have identified many other factors that directly influence the occurrence of

congenital malaria. These factors include: (i) pre-existing level of malaria immunity in the pregnant woman (Hviid, 2004; Bir *et al*., 2006; Rogerson *et al*., 2007); (ii) occurrence of severe malaria during pregnancy (Lagerberg, 2008; Coll *et al*., 2008); (iii) absence of immunity especially pregnant women travelling to endemic areas (Coll *et al*., 2008); (iv) placental malaria especially among primigravid and secundigravid women (Uneke, 2007c; 2008); and (v) maternal human immunodeficiency virus (HIV) infection (Uneke, 2007c; Perrault *et al*., 2009).

The onset of symptoms in congenital malaria typically occurs at 10-30 days postpartum (Behrman *et al*., 2004), which is the estimated half-life of maternal immunoglobulin G in the infant (Reynolds *et al*., 2007). The most common clinical features in 80% of cases are fever, anaemia, and splenomegaly (Remington & Klein, 1995) and these features can be observed in a day-old baby or in some cases be delayed for several weeks or even months (Hashemzadeh & Heydarian, 2005). Other signs and symptoms include hepatomegaly, jaundice, regurgitation, loose stools, and poor feeding, and occasionally, drowsiness, restlessness, and cyanosis can also be seen (Hashemzadeh & Heydarian 2005; Remington & Klein 1995; Ibhanesebhor, 1995). The delay in the onset of the disease has been attributed to factors that may protect the infant initially, particularly infants born to mothers residing in endemic areas. These factors include foetal haemoglobin, abnormal haemoglobins that are resistant to malarial infection, the secretion of lymphocytes or macrophage-derived toxic substances across the placenta to foetal circulation, and partial malaria chemotherapy during pregnancy (Reynolds *et al*., 2007).

Effect of maternal HIV infection on congenital malaria

The human immunodeficiency virus (HIV) infection has been described as a major factor that is contributing to worsen the burden of malaria in most endemic areas particularly in sub-Saharan Africa (Abu-Raddad *et al*., 2006). Evidence abound indicating that HIV infection interacts negatively with malaria, with each disease driving the progression and transmission of the other (Whitworth *et al*., 2000; French *et al*., 2001; Patnaik *et al*., 2005). Some studies have demonstrated that HIV increases the risk of clinical and severe malaria, while malaria increases HIV replication *in vitro* and *in vivo* (Xiao *et al*., 1998; Whitworth *et al*., 2000; French *et al*., 2001; Patnaik *et al*., 2005; Kamya *et al*., 2006). Both HIV infection and malaria are known to critically intersect in pregnancy and have serious consequences in pregnant women, their foetuses and their infants (Ticconi *et al*., 2003; ter Kuile *et al*., 2004). It is estimated that approximately 1 million pregnancies per year are complicated by co-infection with malaria and HIV in sub-Saharan Africa (WHO, 2004). However, whether the dual infection with malaria and HIV in pregnancy increases the risk of congenital malaria is yet to be unequivocally established, as studies examining these relationships are few and have inconsistent findings and a wide range of unanswered questions (ter Kuile *et al*., 2004; Perrault *et al*., 2009; Uneke, 2009b).

Nevertheless, in a recent report from Western Kenya, Perrault *et al.* (2009) demonstrated that malaria and HIV co-infection in pregnancy increased placental parasite density and the rate of antenatal malaria transmission. The authors found that HIV serostatus was strongly correlated with cord blood infection, suggesting that HIV may impact congenital malaria primarily by allowing for higher parasite densities in the placenta (Perrault *et al*., 2009). This

finding was consistent with an earlier report by Steketee *et al.* (1996b) who showed via a multivariate analysis that HIV infection was an important determinant of umbilical cord parasitaemia and added that HIV potentiates malaria infection in the umbilical blood of newborns especially in multigravidas. In addition, findings from another early study noted that HIV infection was associated with umbilical cord parasitaemia in univariate analysis and was probably acting as surrogate marker for maternal malaria infection (Reed *et al.,* 1996). Reports from the 12th World AIDS Conference in Geneva also provided additional information from various researchers indicating that the presence of HIV may reduce a pregnant woman's ability to control the perinatal transmission of malaria (Anderson, 1998).

On the contrary, reports from Kisumu, Kenya (van Eijk *et al.,* 2002) and rural Malawi (Verhoeff *et al.,* 1998), did not observe any consistent effect of maternal HIV on congenital malaria. Although it has been demonstrated that maternal HIV infection induces pathological changes in the placenta that potentially could interfere with the materno-fetal transfer of antibodies, the mechanism of this process and whether a decreased transfer of antibodies to some malaria antigens has an impact on increased susceptibility to congenital malaria is not known (WHO, 2005). Clearly more research is required to properly elucidate this interaction between malaria and HIV with respect to congenital malaria.

Effects congenital malaria on infants

There is a dearth of studies on the effects of congenital malaria on infants. The few available studies providing information on the burden of malaria in early infancy, especially the neonatal period reported a wide range of results that were inconclusive and contradictory (Runsewe-Abiodun *et al.,* 2006; Ekanem *et al.,* 2008; Mwaniki *et al.,* 2010) . The direct burden of neonatal malaria infection in terms of prevalence and outcome is therefore not well described in malaria endemic areas. Available evidence however indicates that some newborns in endemic areas who are parasitaemic at birth, the parasites spontaneously clear without the newborn ever becoming ill (Lesko *et al.,* 2007). The protective effect of the maternal antibodies passed to the newborn and also the protective role of the foetal haemoglobin in slowing the rate of parasite development are thought to be responsible for the parasite clearance (Sutherland *et al.,* 2007; Moormann, 2009). In malaria endemic areas parasite clearance rates ranging from 87% to 100% have been documented (Obiajunwa *et al.,* 2005; Mukhtar *et al.,* 2006).

Congenital malaria in some newborns particularly those whose mothers are non-residents of malarious areas, could be life threatening. The presence of malaria parasites in cord blood or in the asymptomatic newborn may be related to an increased risk of anaemia in infancy (Remington & Klein, 1995; Ndyomugyenyi & Magnussen, 2000; Hashemzadeh & Heydarian, 2005). There is sufficient evidence indicating that malaria causes anaemia through haemolysis and increased splenic clearance of infected and uninfected red blood cells and cytokine-induced dyserythropoeisis (Menendez *et al.*, 2000; Nagel, 2002; Ekvall, 2003). If untreated this could result in life-threatening anaemia, metabolic acidosis and, death (Ekvall *et al.*, 2001; Crawley, 2004). In a comprehensive review on congenital malaria, Menendez & Mayor (2007) noted that newborn exposure to blood-stage malaria antigens may have profound long-

term effects during infancy and childhood by priming the immune responses of the foetus, by inducing immune tolerance, which could result in a reduced (priming) or increased (immune tolerance) susceptibility to malaria in the infant and child. This is however subject to further investigation and confirmation.

Diagnosis of congenital malaria and the challenges

The diagnosis of malaria in most developing countries particularly in sub-Saharan Africa has been described as very challenging (Uneke 2008b). Early and accurate diagnosis and appropriate case management are essential to addressing congenital malaria, and have been advocated consistently by the World Health Organization as one of the main interventions of the Global Malaria Control Strategy (WHO, 2000). Hence prompt and accurate diagnosis cannot be overstated because the congenital malaria caused by *P. falciparum* that is not diagnosed and promptly treated is potentially rapidly lethal, especially in babies born to non-immune women (Menendez & Mayor, 2007).

A lot of diagnostic challenges are however, encountered when performing the diagnosis of malaria among the vulnerable groups like pregnant women and neonates in endemic areas such as sub-Saharan Africa (Uneke, 2008b). It is pertinent to state that most cases of congenital malaria are misdiagnosed initially because of the lack of specific symptoms and a general lack of awareness of this uncommon disease (Reynolds *et al.,* 2008). Because malaria is endemic in this region, it is often difficult to diagnose, and thus report, "classic" congenital malaria (Uneke, 2007b). One of the major factors constituting diagnostic problems is that it is much more difficult to differentiate congenital malaria from those acquired from mosquitoes following delivery (Balatbat *et al.,* 1995). Thus, the proponents of the rarity of congenital malaria have argued that the majority of the cases of malaria noticed in newborn infants in Africa were probably transmitted by mosquitoes (Uneke, 2007b). In fact, it was suggested that several diagnostic problems may also have been responsible for the increasing incidence of congenital malaria (Romand *et al.,* 1994), in addition to the fact that the frequency of congenital malaria also depends on factors such as perinatal clearance of occult parasitemia, maternal immunity, and coexisting infections (Miller & Telford, 1997).

The diagnosis of malaria is established by the microscopic identification of organisms on Giemsa-stained smears of peripheral thick or thin blood smears. The Giemsa-stained smears diagnostic technique is widely used in most malarious areas for the diagnosis of congenital malaria. This technique is considered fraught by many pitfalls including: artifacts often mistaken for parasites; Maurer's clefts often confused with Schuffner's dots, causing *P. falciparum* to be diagnosed as *Plasmodium vivax*; *Babesia* and *Bartonella* infections often mistaken for malaria; young gametocytes of *P. falciparum* often mistaken for *P. vivax* (WHO, 2000). In addition to this, there is a high chance of not finding the parasite by the microscopic method in babies that are having congenital malaria. Stauffer & Fischer (2003), had reported that a single smear without parasites is not sufficient to rule out malaria.

In Gaziantep, Turkey for instance, researchers studying congenital malaria were able to find malaria parasites only in repeat blood smears (Baþpýnar *et al.,* 2006), and in India,

congenital malaria was detected accidentally in cases investigated because they were essentially asymptomatic (Kothare *et al.,* 1987). Findings from a recent study in Western Kenya indicated that the prevalence of placental and cord blood infections were 17.2% and 0% by microscopy, and 33.1% and 10.8% by polymerase chain reaction (Perrault *et al.,* 2009). These findings suggest that the diagnosis of malaria in neonates using the microscopic technique is frequently missed and previous estimates of congenital malaria prevalence may be under-representative because of the limited sensitivity of light microscopy used in the majority of studies (Perrault *et al.,* 2009). There is evidence proving that congenital malaria is usually mistaken for sepsis or infections in the TORCHS syndrome (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis) (Hulbert, 1992*)*. Therefore for the purpose of performing accurate diagnosis of congenital malaria, a good index of suspicion, a careful physical examination and repeated peripheral blood smears are therefore needed (Perrault *et al.,* 2009). Sometimes, parasitemia cannot be shown on blood smear, and plasmodial antigen detection or polymerase chain reaction of the blood may be necessary (Perrault *et al.,* 2009).

Treatment of congenital malaria

There are very few recent studies that have provided information and data on appropriate and effective treatment of congenital malaria. However, there are no clearly established protocols for the clinical management of congenital or neonatal malaria. Menendez & Mayor (2007) noted in their review that in order to establish treatment recommendations it would be useful to distinguish between babies born to non-immune women, in which case congenital falciparum malaria, whether symptomatic or not, should be treated with quinine (10 mg/kg orally every 8 h, or same dosage in intravenous infusion until oral administration is possible). However there have been reports of high level of chloroquine resistance in the treatment of malaria by a number of studies. In Pakistan, chloroquine resistance of 26.66% was recorded among babies born with congenital malaria and this resulted in a mortality rate of 16.66% (Khichi *et al.,* 2005).

In Nigeria a cure rate of 89.1% was recorded in the treatment of babies with symptomatic congenital malaria with oral chloroquine but the treatment failures subsequently received oral sulfadoxine-pyrimethamine with good outcome (Orogade *et al.,* 2008). In another recent study by Harrington & Duffy (2008), quinine plus clindamycin was reported as being effective in the treatment of *P. falciparum* congenital malaria, and chloroquine for the treatment of other malaria parasites, such as *P. vivax*. The authors added that severe cases of congenital malaria should be managed with intravenous quinine or with intravenous artesunate, which has recently been approved for investigational use in some countries including the United States. The same authors have advised that primaquine is not required for infants with congenital *P. vivax* or *P. ovale*, but should be offered to their mothers after excluding G6PD deficiency (Harrington & Duffy, 2008). In a very recent study in India, it was reported that a baby with congenital malaria failed to respond to chloroquine treatment but responded well when oral artesunate was used (Avabratha *et al*., 2010).

The rising incidence of resistance to chloroquine which has been the drug of choice in malaria treatment necessitates investigation on the efficacy of other antimalarials for the

treatment of congenital malaria. There are very few studies reporting the use of drugs such as quinine, artesunate and mefloquine in neonates and the studies with use of oral artesunate is even scanty (Patel & Belsare, 2002; Ming, 2008). These drugs have been used effectively in older children and could be hence adapted for neonates to treat congenital malaria. In China, a study comparing the efficacy of artesunate versus quinine in the treatment of congenital malaria observed that the total effective rates of the artesunate treatment group and the quinine group were 92.31% and 83.33% and the clearance rates of plasmodium were 92.31% and 78.57%, respectively (Patel & Belsare, 2002). The study therefore demonstrated that efficacy of artesunate over quinine and noted that it can be used as drug of first choice for treatment of congenital malaria. More studies are however required to further elucidate the potency of artesunate in the treatment of congenital malaria.

Conclusion

A very vital lesson derived from this review of the reports on congenital malaria is that the disease is no longer an uncommon occurrence. Congenital malaria has now assumed a public health concern both in malaria endemic and semi-endemic areas. As countries all over the world and international aid agencies such as WHO intensify efforts towards the control of malaria it is important that such efforts do not neglect congenital malaria control. There is clearly a lack well established guidelines for the definition, diagnosis and treatment of congenital malaria. Operational research into various aspects of congenital malaria is also essentially lacking as many unresolved issues requiring urgent scientific investigation abound. Public health policy on malaria control should also take into cognizance the importance of integrating guidelines on congenital malaria management and control.

References

Abu-Raddad, L.J., Patnaik, P. & Kublin, J.G. (2006) Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. *Science* 314, 1603–1606.

Achidi, E.A. & Salimonu, L.S. (1997) Malaria parasitaemia and immunoglobulin levels in paired maternal-cord sera from south western Nigeria. *African Journal of Medicine and Medical Sciences* 26, 167-170.

Adachi, M., Manji, K., Ichimi, R., Nishimori, H., Shindo, K., Matsubayashi, N., Mbise, R.L., Massawe, A., Liu, Q., Kawamoto, F., Chinzei, Y., Sakurai, M. (2000) Detection of congenital malaria by polymerase-chain-reaction methodology in Dar es Salaam, Tanzania. *Parasitology Research* 86, 615-618.

Afolabi, B.M., Salako, L.A., Mafe, A.G., Ovwigho, U.B., Rabiu, K.A., Sanyaolu, N.O. & Ibrahim, M.M. (2001) Malaria in the first 6 months of life in urban African infants with anemia. *American Journal of Tropical Medicine and Hygiene* 65, 822–827.

Akindele, J.A., Sowunmi, A. & Abohweyere, A.E. (1993) Congenital malaria in a hyperendemic area: a preliminary study. *Annals of Tropical Paediatrics* 13, 273-276.

Akum, A.E., Kuoh, A.J., Minang, J.T., Achimbom, B.M., Ahmadou, M.J. & Troye-Blomberg, M. (2005) The effect of maternal, umbilical cord and placental malaria parasitaemia on the birthweight of newborns from South-western Cameroon. *Acta Paediatrica* 94, 917-923.

Anderson, J.R. (1998) Report from Geneva: women and HIV. *Hopkins HIV Report* 10, 12-13.

Avabratha, K.S., Chettiyar, L.A. & John, N.P. (2010) Oral artesunate for neonatal malaria. *Journal of Tropical Pediatrics* 56, 452-453.

Balatbat, A.B.N., Jordan, G.W. & Halsted, C. (1995) Congenital malaria in a nonidentical twin. *Western Journal of Medicine* 162, 458-459.

Baþpýnar, O., Bayraktarðlu, Z., Karslýgil, T. & Bayram, A. (2006) A rare cause of anemia and thrombocytopenia in a newborn: malaria. *Turkish Journal of Pediatrics* 48, 63-65.

Behrman, R.E., Keligman, R. & Jenson, H.B. (2004) *Nelson Textbook of Pediatrics,* 17th edn. WB Saunders, Philadelphia. 2004.

Bergstrom, S., Fernandes, A., Schwalbach, J., Perez, O. & Miyar, R. (1993) Materno-fetal transmission of pregnancy malaria: an immunoparasitological study on 202 parturients in Maputo. *Gynecologic and Obstetric Investigation* 35, 103-107.

Bhutta, Z.A., Darmstadt, G.L., Hasan, B.S. & Haws, R.A. (2005) Community-based interventions for improving perinatal and neonatal health outcomes in developing countries: a review of the evidence. *Pediatrics* 115, 519-617.

Bir, N., Yazdani, S.S., Avril, M., Layez, C., Gysin, J. & Chitnis, C.E. (2006) Immunogenicity of Duffy binding-like domains that bind chondroitin sulfate A and protection against pregnancy-associated malaria. *Infection Immunology* 74, 5955-5963.

Brabin, B.J. (1983) An analysis of malaria in pregnancy in Africa. *Bulletin of World Health Organization* 61, 1005-1016.

Brabin, B.J., Romagosa, C., Abdelgalil, S., Menéndez, C., Verhoeff, F.H., McGready, R., Fletcher, K.A., Owens, S., D'Alessandro, U., Nosten, F., Fischer, P.R. & Ordi, J. (2004) The sick placenta-the role of malaria. *Placenta* 25, 359-378.

Bruce-Chwatt, L.J.(1952) Malaria in African infants and children in southern Nigeria. *Annals of Tropical Medicine and Parasitology* 46, 173-200.

Coll, O., Menendez, C., Botet, F., Dayal, R., World Association of Perinatal Medicine Perinatal Infections Working Group., Carbonell-Estrany, X., Weisman, L.E., Anceschi, M.M., Greenough, A., Gibss, R.S. & Ville Y. (2008) Treatment and prevention of malaria in pregnancy and newborn. *Journal of Perinatal Medicine* 36, 15-29.

Covell, G. (1950) Congenital malaria. *Tropical Disease Bulletin* 47, 1147-1165.

Crawley, J. (2004) Reducing the burden of anemia in infants and young children in malaria-endemic countries of Africa: from evidence to action. *American Journal of Tropical Medicine and Hygiene* 71, 25-34.

Davis, T.M., Mueller, I. & Rogerson, S.J. (2010) Prevention and treatment of malaria in pregnancy. *Future Microbiology* 5, 1599-1613.

De Silva, D.H.G., Mendis, K.N., Premaratne, U.N., Jayatilleke, S.M.D. & Soyza, P.E. (1982) Congenital malaria due to *Plasmodium vivax*: A case report from Sri Lanka. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 75, 33-35.

DFID (2004). Department for International Development DFID. Fact Sheet-Malaria. 2004. Available at: http://www.dfid.gov.uk/pubs/files/malaria-factsheet.pdf Accessed January 10, 2011.

Djibo, A. & Cenac, A. (2000) Congenital malaria. Parasitological and serological studies in Niamey (Niger). *Sante* 10, 183-187.

Duah, N.O., Miles, D.J., Whittle, H.C. & Conway, D.J. (2010) Acquisition of antibody isotypes against *Plasmodium falciparum* blood stage antigens in a birth cohort. *Parasite Immunology* 32, 125-134.

Egwunyenga, O.A., Ajayi, J.A. & Duhlinska-Popova, D.D. (1995) Transplacental passage of *Plasmodium falciparum* and seroevaluation of newborns in northern Nigeria. *Journal of Communicable Diseases* 27, 77-83.

Egwunyenga, O.A., Ajayi, J.A., Popova-Duhlinska, D.D. & Nmorsi, O.P. (1996) Malaria infection of the cord and birthweights in Nigerians. *Central African Journal of Medicine* 42, 265-268.

Ekanem, A.D., Anah, M.U. & Udo, J.J. (2008) The prevalence of congenital malaria among neonates with suspected sepsis in Calabar, Nigeria. *Tropical Doctor* 38, 73-76.

Ekvall, H. (2003) Malaria and anemia. *Current Opinion in Hematology* 10, 108–114.

Ekvall, H., Arese, P., Turrini, F., Ayi, K., Mannu, F., Premji, Z. & Bjorkman A. (2001). Acute haemolysis in childhood falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 95, 611–617.

Falade, C., Mokuolu, O., Okafor, H., Orogade, A., Falade, A., Adedoyin, O., Oguonu, T., Aisha, M., Hamer, D.H., Callahan, M.V. (2007) Epidemiology of congenital malaria in Nigeria: a multi-centre study. *Tropical Medicine and International Health* 12, 1279-1287.

Fischer, P.R. (1997) Congenital malaria: an African survey. *Clinical Pediatrics* 36, 411-413.

French, N., Nakiyingi, J., Lugada, E., Watera, C., Whitworth, J.A. & Gilks, C.F. (2001) Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. *AIDS* 15, 899–906.

Guerra, C.A., Howes, R.E., Patil, A.P., Gething, P.W., Van Boeckel, T.P., Temperley, W.H., Kabaria, C.W., Tatem, A.J., Manh, B.H., Elyazar, I.R., Baird, J.K., Snow, R.W. & Hay, S.I. (2010) The international limits and population at risk of Plasmodium vivax transmission in 2009. *PLoS Neglected Tropical Diseases* 4, e774.

Gyapong, M. & Garshong, B. (2007) Lessons learned in Home Management of Malaria: Implementation research in four African countries. Geneva, World Health Organization.

Hanlin, R.B. (2002) Congenital infections and preconception counseling. *Journal of South Carolina Medical Association* 98, 277-280.

Harrington, W.E. & Duffy, P.E. (2008) Congenital malaria: rare but potentially fatal. *Pediatric Health* 2, 235-248.

Hashemzadeh, A. & Heydarian, F. (2005) Congenital malaria in a neonate. *Archives of Iranian Medicine* 8, 226-228.

Hopkins, H., Talisuna, A., Whitty, C.J.M. & Staedke, S.G. (2007) Impact of homebased management of malaria on health outcomes in Africa: a systematic review of the evidence. *Malaria Journal* 6, 134.

Hulbert, T.V. (1992) Congenital malaria in the United States: report of a case and review. *Clinical Infectious Diseases* 14, 922-926.

Hviid, L. (2004) The immuno-epidemiology of pregnancy-associated *Plasmodium falciparum* malaria: a variant surface antigen-specific perspective. *Parasite Immunology* 26, 477-486.

Ibhanesebhor, S.E. (1995) Clinical characteristics of neonatal malaria. *Journal of Tropical Pediatrics* 41, 330-333.

Kamya, M.R., Gasasira, A.F., Yeka, A., Bakyaita, N., Nsobya, S.L., Francis, D., Rosenthal, P.J., Dorsey, G., Havlir, D. (2006) Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: a population-based study. *Journal of Infectious Diseases* 193, 9–15.

Khichi, Q.H., Channar, M.S., Wairraich, M.I. & Butt, A. (2005) Chloroquine resistant malaria in neonates. *Journal of the College of Physicians and Surgeons Pakistan* 151, 34-36.

Klein Klouwenberg, P.M., Oyakhirome, S., Schwarz, N.G., Glaser, B., Issifou, S., Kiessling, G., Klopfer, A., Kremsner, P.G., Langin, M., Lassmann, B., Necek, M., Pötschke, M., Ritz, A., Grobusch, M.P. (2005) Malaria and asymptomatic parasitaemia in Gabonese infants under the age of 3 months. *Acta Tropica* 95, 81-85.

Kothare, S.V., Kallapur, S.G., Irani, S.F., Prabhu, S.B., Gangal, P.S. & Agarwal, G.J. (1987) Congenital malaria (a report of 2 cases). *Journal of Postgraduate Medicine* 33, 158-161.

Lagerberg, R.E. (2008) Malaria in pregnancy: a literature review. *Journal of Midwifery and Women's Health* 53, 209-215.

Lamikanra, O.T. (1993) A study of malaria parasitaemia in pregnant women, placentae, cord blood and newborn babies in Lagos, Nigeria. *West African Journal of Medicine* 12, 213-217.

Larkin, G.L. & Thuma, P.E. (1991) Congenital malaria in a hyperendemic area. *American Journal of Tropical Medicine and Hygiene* 45, 587-592.

Larru, B., Molyneux, E, Ter Kuile F.O., Taylor, T., Molyneux, M. & Terlouw, D.J. (2009) Malaria in infants below six months of age: retrospective surveillance of hospital admission records in Blantyre, Malawi. *Malaria Journal* 8, 310.

Lehner, P.J. & Andrews, C.J.A. (1988) Congenital malaria in Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2, 822-826.

Lesi, F.E., Mukhtar, M.Y., Iroha, E.U. & Egri-Okwaji, M.T. (2010) Clinical presentation of congenital malaria at the Lagos University Teaching Hospital. *Nigeria Journal of Clinical Practice* 13, 134-138.

Lesko, C.R., Arguin, P.M. & Newman, R.D. (2007) Congenital malaria in the United States: a review of cases from 1966 to 2005. *Archives of Pediatrics and Adolescent Medicine* 161, 1062-1067.

Logic, D.E. & McGregor, I.A. (1970) Acute malaria in newborn infants. *British Medical Journal* ii, 404-405.

Malhotra, I., Mungai, P., Muchiri, E., Kwiek, J.J., Meshnick, S.R. & King, C.L. (2006) Umbilical cord-blood infections with *Plasmodium falciparum* malaria are acquired antenatally in Kenya. *Journal of Infectious Diseases* 194, 176-183.

McGovern, L.M., Boyce, T.G. & Fischer, P.R. (2007) Congenital infections associated with international travel during pregnancy. *Journal of Travel Medicine* 14, 117-128.

McGregor, I.A., Wilson, M.E. & St Billewicz, W.Z. (1983) Malaria infection of the placenta in the Gambia, West Africa; its incidence and relationship to stillbirth, birthweight and placental weight. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 77, 232-244.

Menendez, C. & Mayor, A. (2007) Congenital malaria: the least known consequence of malaria in pregnancy. *Seminars in Fetal and Neonatal Medicine* 12, 207-213.

Menendez, C., Fleming, A.F. & Alonso, P.L. (2000) Malaria-related anaemia. *Parasitology Today* 16, *469*–476.

Miller, I.J. & Telford, S.R. III. (1997) Congenital malaria. *New England Journal of Medicine* 336, 71-72.

Ming, H.K. (2008) Treatment of 39 congenital malaria with artesunate. *China Tropical Medicine* 8, 223-224.

Moormann, A.M. (2009) How might infant and paediatric immune responses influence malaria vaccine efficacy? *Malaria Journal* 31, 547-559.

Mukhtar, M.Y., Lesi, F.E., Iroha, E.U., Egri-Okwaji, M.T. & Mafe, A.G. (2006) Congenital malaria among inborn babies at a tertiary centre in Lagos, Nigeria. *Journal of Tropical Pediatrics* 52, 19-23.

Murphy, S.C. & Breman, J.G. (2001) Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. *American Journal of Tropical Medicine Hygiene* 64, 57-67.

Mwangoka, G.W., Kimera, S.I. & Mboera, L.E.G. (2008). Congenital *Plasmodium falciparum* infection in neonates in Muheza District, Tanzania. *Malaria Journal* 7, 117.

Mwaniki, M.K., Talbert, A.W., Mturi, F.N., Berkley, J.A., Kager, P., Marsh, K. & Newton, C.R. (2010) Congenital and neonatal malaria in a rural Kenyan district hospital: an eight-year analysis. *Malaria Journal* 9, 313.

Nagel, R.L. (2002) Malarial anemia. *Hemoglobin* 26, 329–343.

Ndyomugyenyi, R. & Magnussen, P. (2000) Chloroquine prophylaxis, iron/folic-acid supplementation or case management of malaria attacks in primigravidae in western Uganda: effects on congenital malaria and infant haemoglobin concentrations. *Annals of Tropical Medicine and Parasitology* 94, 759-770.

Nimir, A.R., Isa, N.H., Eugene, C.B., Ghauth, I.M., Salleh, F.M., & Rahman, R.A. (2006) Severity of Malaria cases reported in urban and rural hospitals in Malaysia. *Southeast Asian Journal of Tropical Medicine and Public Health* 37, 831-837.

Nweneka, C.V. & Eneh, A.U. (2004) Malaria parasitaemia in neonates in Port Harcourt, Nigeria. *Journal of Tropical Pediatrics* 50, 114–116.

Obiajunwa, P.O., Owa, J.A. & Adeodu, O.O. (2005) Prevalence of congenital malaria in Ile-Ife, Nigeria. *Journal of Tropical Pediatrics* 51, 219-222.

Okafor, U.H., Oguonu, T. & Onah, H.E. (2006) Risk factors associated with congenital malaria in Enugu, South Eastern Nigeria. *Journal of Obstetrics and Gynaecology* 26, 612-616.

Olowu, J.A., Sowunmi, A. & Abohweyere, A.E. (2000) Congenital malaria in a hyperendemic area: a revisit. *African Journal of Medicine and Medical Sciences* 29, 211-213.

Omanga, U. & Kapepela, K. (1990) Epidemiology of congenital malaria in the urban milieu of Kinshasa (Zaire). *Annales de Pediatrie* 37, 195-197.

Orogade, A.A., Falade, C.O., Okafor, H.U., Mokuolu, O.A. & Mamman, A.I. (2008) Clinical and laboratory features of congenital malaria in Nigeria. *Journal of Pediatric Infectious Diseases* 3, 181-187.

Patel, A.B. & Belsare, H.S. (2002) Resistant malaria in a neonate. *Indian Pediatrics* 39, 585- 588.

Patnaik, P., Jere, C.S., Miller, W.C., Hoffman, I.F., Wirima, J., Pendame, R., Meshnick, S.R., Taylor, T.E., Molyneux, M.E., Kublin, J.G. (2005) Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. *Journal of Infectious Diseases* 192, 984–991.

Perrault, S.D., Hajek, J., Zhong, K., Owino, S.O., Sichangi, M., Smith, G., Shi, Y.P., Moore, J.M., Kain, K.C. (2009) Human immunodeficiency virus co-infection increases placental parasite density and transplacental malaria transmission in Western Kenya. *American Journal of Tropical Medicine and Hygiene* 80, 119-125.

Redd, S.C., Wirima, J.J., Steketee, R.W., Breman, J.G. & Heynann, D.L. (1996) Transplacental transmission of *Plasmodium falciparum* in rural Malawi. *American Journal of Tropical Medicine and Hygiene* 55, 57-60.

Reinhrdt, M.C., Ambroise-Thomas, P., Cavallo-Serra, R., Meylan, C. & Gautier R. (1978) Malaria at delivery in Abidjan. *Helvetica Paediatrica Acta* 33, 65-84.

Remington, J.S. & Klein, J.O. (1995) *Infectious Diseases of the Fetus and Newborn Infant*. 3rd edn. WB Saunders, Philadelphia.

Reynolds, S., Bollinger, R. & Quinn, T.C. (2008) Parasitic Diseases During Pregnancy. Global Library of women's medicine (ISSN: 1756-2228); DOI 10.3843/GLOWM.10188. Available at: http://www.glowm.com/? Accessed January 10, 2011.

Rogerson, S.J, Mwapasa, V. & Meshnick, S.R. (2007) Malaria in pregnancy: linking immunity and pathogenesis to prevention. *American Journal of Tropical Medicine and Hygiene* 77, 14-22.

Romand, S., Bouree, P., Gelez, J., Bader-Meunier, B., Bisaro, F. & Dommergues, J.P. (1994) Congenital malaria. A case observed in twins born to an asymptomatic mother. *Presse Medicale* 23, 797-800.

Rowe, A.K., Rowe, S.Y., Snow, R.W., Korenromp, E.L., Armstrong Schellenberg, J.R.M., Stein, C., Nahlen, B., Bryce, J., Black, R.E. & Steketee, R.W. (2006) The burden of malaria mortality among African children in the year 2000. *International Journal of Epidemiology* 35, 691–704.

Runsewe-Abiodun, I.T., Ogunfowora, O.B. & Fetuga, B.M. (2006) Neonatal malaria in Nigeria-a 2 year review. *BMC Pediatrics* 6, 19.

Schantz-Dunn, J. & Nour, N.M. (2009) Malaria and pregnancy: a global health perspective. *Reviews in Obstetrics and Gynecology* 2, 186-192.

Schwetz, J. & Peel, M. (1934) Congenital malaria and placental infections amongst the negroes of Central Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 28, 167-174.

Sharp, B., Kleinschmidt, I., Streat, E., Maharaj, R., Barnes, K., Durrheim, D.N., Ridl, F.C., Morris, N., Seocharan, I., Kunene, S., La Grange, J.J.P., Mthembu, J.D., Maartens, F., Martin, C.L. & Barreto, A. (2007) Seven years of regional malaria control collaboration-Mozambique, South Africa and Swaziland. *American Journal of Tropical Medicine and Hygiene* 76, 42-47.

Snow, R.W., Korenromp, E.L. & Gouws, E. (2004) Pediatric mortality in Africa: *Plasmodium falciparum* malaria as a cause or risk? *American Journal of Tropical Medicine & Hygiene* 71, 16–24.

Snow, R.W., Nahlen, B., Palmer, A., Donnelly, C.A., Gupta, S. & Marsh, K. (1998) Risk of severe malaria among African infants: direct evidence of clinical protection during early infancy. *Journal of Infectious Diseases* 177, 819–822.

Sotimehin, S.A., Runsewe-Abiodun, T.I., Oladapo, O.T., Njokanma, O.F. & Olanrewaju, D.M. (2008) Possible risk factors for congenital malaria at a tertiary care hospital in Sagamu, Ogun State, South-West Nigeria. *Journal of Tropical Pediatrics* 54, 313-320.

Stauffer, W. & Fischer, P.R. (2003) Diagnosis and treatment of malaria in children. *Clinical Infectious Diseases* 37, 1340-1348.

Steketee, R.W., Nahlen, B.L., Parise, M.E. & Menendez, C. (2001) The burden of malaria in pregnancy in malaria-endemic areas. *American Journal of Tropical Medicine Hygiene* 64, 28-35.

Steketee, R.W., Wirima, J.J., Slutsker, L., Heymann, D.L. & Breman, J.G. (1996a) The problem of malaria and malaria control in pregnancy in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene* 5, 2-7.

Steketee, R.W., Wirima, J.J., Slutsker, L., Roberts, J.M., Khoromana, C.O., Heymann, D.L. & Breman, J.G. (1996b) Malaria parasite infection during pregnancy and at delivery in mother, placenta, and newborn: efficacy of chloroquine and mefloquine in rural Malawi. *American Journal of Tropical Medicine and Hygiene* 55, 24-32.

Sule-Odu, A.O., Ogunledun, A. & Olatunji, A.O. (2002) Impact of asymptomatic maternal malaria parasitaemia at parturition on perinatal outcome. *Journal of Obstetrics and Gynaecology* 22, 25-28.

Sutherland, C.J., Drakeley, C.J. & Schellenberg, D. (2007) How is childhood development of immunity to *Plasmodium falciparum* enhanced by certain antimalarial interventions? *Malaria Journal* 6, 161.

Tagbor, H., Bruce, J., Browne, E., Greenwood, B. & Chandramohan, D. (2008) Malaria in pregnancy in an area of stable and intense transmission: is it asymptomatic? *Tropical Medicine and International Health* 13, 1016-1021.

ter Kuile, F.O., Parise, M.E., Verhoeff ,F.H., Udhayakumar, V, Newman, R.D., van Eijk, A.M., Rogerson, S.J. & Steketee, R.W. (2004) The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene* 71, 41—54.

Ticconi, C., Mapfumo, M., Dorrucci, M., Naha, N., Tarira, E., Pietropolli, A., Rezza, G. (2003) Effect of maternal HIV and malaria infection on pregnancy and perinatal outcome in Zimbnabwe. *Journal of Acquired Immune Deficiency Syndrome* 34, 289—294.

Uneke, C.J. (2007a) Impact of placental *Plasmodium falciparum* malaria on pregnancy and perinatal outcome in sub-Saharan Africa: I: Introduction to Placental Malaria. *Yale Journal of Medicine and Biology* 80, 39-50.

Uneke, C.J. (2007b) Congenital *Plasmodium falciparum* malaria in sub-Saharan Africa: a rarity or frequent occurrence? *Parasitology Research* 101, 835-842.

Uneke, C.J. (2007c) Impact of placental *Plasmodium falciparum* malaria on pregnancy and perinatal outcome in sub-Saharan Africa. II: Effects of Placental Malaria on Perinatal Outcome; Malaria and HIV. *Yale Journal of Medicine and Biology* 80, 95-103.

Uneke, C.J. (2008a) Impact of placental *Plasmodium falciparum* malaria on pregnancy and perinatal outcome in sub-Saharan Africa. III: Placental malaria, maternal health and public health. *Yale Journal of Medicine and Biology* 8, 1-7.

Uneke, C.J. (2008b) Diagnosis of *Plasmodium falciparum* malaria in pregnancy in sub-Saharan Africa: the challenges and public health implications. *Parasitology Research* 101, 835-842.

Uneke, C.J. (2009a) Impact of home management of *Plasmodium falciparum* malaria on childhood malaria control in sub-Saharan Africa. *Tropical Biomedicine* 26, 182–199.

Uneke, C.J. (2009b) Impact of placental malaria and HIV co-infection on congenital malaria and perinatal HIV transmission in sub-Saharan Africa: an overview. *Parassitologia* 51, 35-41.

van Eijk, A.M., Ayisi, J.G., ter Kuile, F.O., Misore, A.O., Otieno, J.A., Kolczak, M.S., Kager, P.A., Steketee, R.W. & Nahlen, B.L. (2002) Placental malaria and HIV infection as risk factors for post-neonatal infant mortality in Kisumu, Kenya. The XIV International AIDS Conference. Barcelona, Spain.

van Geertruyden, J.P., Thomas, F., Erhart, A. & D'Alessandro, U. (2004) The contribution of malaria in pregnancy to perinatal mortality. *American Journal of Tropical Medicine and Hygiene* 71, 35-40.

Verhoeff, F.H., Brabin, B.J., Chimsuku, L., Kazembe, P., Russell, W.B. & Broadhead, R.L. (1998) An evaluation of the effects of intermittent sulfadoxine-pyrimethamine treatment in pregnancy on parasite clearance and risk of low birthweight in rural Malawi. *Annals of Tropical Medicine and Parasitology* 92, 141-150.

Whitworth, J., Morgan, D., Quigley, M., Smith, A., Mayanja, B., Eotu, H., Omoding, N., Okongo, M., Malamba, S., Ojwiya, A. (2000) Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet* 356, 1051–1056.

WHO (1992) World malaria situation, 1990. *WHO Weekly Epidemiological Record* 67, 161-167.

WHO (1997) World malaria situation in 1994. *Weekly Epidemiological Record* 72, 285-290.

WHO (2000) Expert Committee on Malaria. WHO technical report series 892, i-v. Geneva World Health Organization.

WHO (2000) Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 94, S1-S90.

WHO (2003) *The African Malaria Report 2003*. WHO, 17-23. Geneva, World Health Organization.

WHO (2004) Malaria and HIV/AIDS interactions and implications: conclusions of a technical consultation convened by WHO, 23—25 June 2004. Geneva: World Health Organization.

Available at: http://www.who.int/malaria/malaria HIV/malaria hiv flyer.pdf Accessed January 10, 2011

WHO (2005) *Malaria and HIV Interactions and their Implications for Public Health Policy*. Report of a Technical Consultation on Malaria and HIV Interactions and Public Health Policy Implications 2004. World Health Organization, 20 Avenue Appia, Geneva, Switzerland.

WHO (2008) *World Malaria Report 2008*. Geneva, Switzerland. World Health Organization.

WHO (2009) *World Malaria Report 2009*. Geneva, Switzerland. World Health Organization.

Worral, E., Basu, S. & Hanson, K. (2005) Is malaria a disease of poverty? A review of literature. *Tropical Medicine and International Health* 10, 1047-1059.

Xiao, L.H., Owen, S.M., Rudolph, D.L., Lal, R.B. & Lal, A.A. (1998) *Plasmodium falciparum* antigen-induced human immunodeficiency virus type 1 replication is mediated through induction of tumor necrosis factor-alpha. *Journal of Infectious Diseases* 177, 437–445.