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Malaria in infants aged less than six months - is it an area of unmet medical need?

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Abstract

Despite the protection provided by several factors, including maternal antibodies, the burden of malaria in young infants may be higher than previously thought. Infants with congenital or neonatal malaria may have a different clinical presentation than older children, and diagnosis may be confused with other neonatal diseases due to an overlap of clinical manifestations. In addition, there is little information on the use of artemisinin-based combination therapy in young infants. There is the need for a more accurate estimate of the parasite prevalence and the incidence of clinical malaria in infants under 6 months old, as well as a better characterization of risk factors, pharmacokinetic profiles, safety and efficacy of currently available anti-malarial treatments, in order to develop evidence-based treatment guidelines for this population.

Keywords: Malaria, Neonate, Congenital, Prevalence, Parasitaemia, Artemisinin-based combination therapy

Background

Although the burden of *Plasmodium falciparum* malaria in children aged under five years is well documented [1], there is limited and contradictory information about the impact of the disease in infants under six months of age. Early studies concluded that malaria was uncommon in young infants and that clinical disease was of little importance [2-4], despite several early reports of a uniform rise in parasite prevalence during the first few months of life [5]. Young infants with malaria may have different clinical manifestations [6,7] and lower parasite densities [5] than older children. Nevertheless, even low-density infections (1–500 parasites/μL) in infants can result in anaemia if left untreated [8], and may rapidly progress to become life-threatening [9].

Neonatal malaria is considered a rare occurrence due to the protective effect of maternal immunity after birth. Maternal immunoglobulin G (IgG) antibodies are acquired by the fetus via the placenta *in utero* [10], although there is only limited evidence suggesting a protective role of these passively acquired antibodies against malaria parasites [11]. IgG levels are thought to decrease variably during the first year of life [12]. Neonates may also be protected through factors that inhibit parasite growth, such as lactoferrin (which binds iron) and secretory IgA, found in breast milk and in maternal and infant sera [13]. Parasite replication depends on the metabolic substrate para-aminobenzoic acid (pABA), which is present only in low levels in breast milk [10]. Haemoglobin F (HbF), present in high concentrations at birth [10], can inhibit parasite development [14] and can protect the infant in the first few months of life. The parasite antigen *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1) mediates cytoadherence of infected red blood cells to the endothelial cells lining the blood vessels. HbF and maternal IgG act cooperatively to impair the cytoadherence of parasitized erythrocytes in the first few months of life by altering PfEMP-1 display on HbF RBCs, and by binding PfEMP-1 and preventing sequestration of parasitized RBCs, respectively [15]. HbF levels decline after a peak at 6 weeks of age [10], and as both HbF and IgG disappear from circulation, infant susceptibility to *P. falciparum* malaria increases [15].

Iron-deficiency anaemia is common in sub-Saharan Africa and can cause impaired cognitive and motor development, growth impairment and anorexia. Consequently,

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in many areas, iron supplementation is recommended in children below two years of age. However, iron status has been shown to have an effect on the risk of malaria in young infants, with iron deficiency potentially causing a decrease in malaria morbidity and mortality [16].

In Mozambique and Benin, placental malaria has been associated with shorter time to first episode of infant malaria [17,18]. The mechanisms underlying this association are unclear but may relate to prenatal foetal priming [19]. Therefore, some reduction of malaria risk in infants can probably be achieved by improving malaria control in late pregnancy.

Burden of malaria in infants aged less than six months

Malaria in infants is classified according to the time of infection. Congenital malaria, defined as asexual parasites detected in the cord blood or in the peripheral blood during the first week of life [20], is due to transmission from the mother through the placenta just before or during delivery [21], while neonatal malaria, which can occur within the first 28 days of life, is due to an infective mosquito bite after birth [21]. Differentiating between congenital and acquired neonatal malaria can be difficult, especially in areas of intense malaria transmission [22]. Various studies across Africa have demonstrated that 7–10% of newborns may have malaria parasites in their cord blood [8], in some cases either without evidence of an active maternal infection or with parasite genotypes different to those found in the mother. This suggests transplacental passage of parasites followed by clearance from maternal and placental blood, with persistence in the foetus [8,23,24].

Recent reports suggest that malaria in infants under six months of age may not be uncommon, although data on prevalence and outcome are still contradictory [25]. Prevalence of infection can vary between 0% and 27% [9,25-33], while the percentage of deaths attributed to malaria (as determined by verbal autopsy) may be between 20.1% and 46.2% [34]. The occurrence of infection *in utero* is also reflected by the prevalence of splenomegaly at one month of age, which can be as high as 80%, indicating an early development of a splenic response to the infection [5,35].

In Mozambique, clinical malaria incidence in infants aged 1– < 6 months was substantial (320/1,000 child-years at risk in 2003–2004 and 146/1,000 child-years at risk in 2004–2005) [36]. Reports of congenital malaria have predominantly come from Nigeria; the prevalence of parasitaemia in infants in these studies as well as in those from other malaria-endemic regions varied widely – between 0.7% and 46.7% [20,33,37-51]. Parasite densities in neonatal blood were also varied, although most infections were of low density [20,40,42,48-50,52,53]. However, differences in transmission dynamics, small sample sizes and lack of details on quality control and sample selection procedures make the interpretation of these findings difficult [20,25].

Malaria infections (mean geometric parasite density = 533 parasites/μl of blood, as detected by PCR) were common in Ghanaian infants less than 6 months of age (13.6% in newborns; 1.5–9.7% in those aged from 2–26 weeks), although clinical malaria symptoms were rare or uncommon (fever, vomiting, diarrhoea and coughing occurred in 1.8%, 1.8%, 3.0% and 4.8% of infants aged 0–3 months, respectively, and in 4.5%, 3.0%, 8.0% and 10.6% of infants aged 3–6 months) [54]. In Mozambique, although malaria in infants aged under six months represented less than 20% of the total outpatient visits, infants with malaria were admitted in a significantly higher proportion than children aged 1–4 years [36]. The impact of malaria in this age group is also illustrated by a greater difference in mean haematocrit between malaria and non-malaria cases in infants aged from 2–12 months (4.9%) than in children aged 5 years or above (1.8%). Among infants aged under six months attending an urban hospital in Nigeria, 27.1% had a positive blood slide and a significantly lower haematocrit (33.0%) compared with those who were uninfected (35.1%)($p = 0.003$). Indeed, a haematocrit of less than 33% was the most common clinical finding among infected infants, while the occurrence of fever was 4% [9].

A systematic review of age-patterns of malaria revealed that as transmission increased, there was a shift of clinical malaria towards younger age groups, regardless of seasonality [55]. As transmission intensity increased and seasonality decreased, severe cases became more frequent in the younger ages. Nevertheless, wherever a comparison between age groups was possible, malaria mortality was higher in younger children, with the peak age shifting towards infants as transmission became more intense [55].

Clinical signs and symptoms and malaria diagnosis in infants aged under six months

Signs and symptoms of congenital malaria include fever, anaemia, splenomegaly, hepatomegaly, jaundice, vomiting, diarrhoea, poor feeding, restlessness, drowsiness, pallor, respiratory distress, cyanosis, and possibly convulsions [39,56].

Malaria in young infants may be asymptomatic [6,7], or it may be difficult to diagnose because the clinical presentation may mimic other diseases, such as sepsis [33]. Indeed, congenital malaria may be more common in newborns with suspected or confirmed sepsis (28.6%) [38,47]. It is unclear what influence infant HIV infection has on these risks.

In areas with limited resources, the capacity to diagnose malaria in young infants may be limited [57,58], and any issues with quality or accuracy of the diagnostic technique may result in the diagnosis of malaria being missed [59]. In many malaria-endemic countries, infants and children frequently die at home [60] and the cause of death remains undetermined and unrecorded [17,34,61]. Therefore, the overall malaria mortality in infants aged under six months is highly uncertain. As approximately 40% of all child deaths occur in the neonatal period, and many deliveries occur outside health facilities, the proportion of these deaths that is malaria-related is unclear [60].

Pharmacokinetics of anti-malarials in young infants

Due to the dynamic developmental changes experienced by infants aged under 6 months, the pharmacokinetic profiles of anti-malarials may be different than in older children, and age-dependent dose adjustments may be necessary [62]. For example, gastric emptying is slower in neonates and young infants, and is only comparable with adults after six months of age. Absorption of drugs is also affected by intestinal motor activity and villous formation, both of which mature by week 20 [62]. Drug metabolism may be altered as enzyme systems, such as the hepatic enzymes, are immature (anti-malarials are typically metabolized in the liver) [63], possibly resulting in an enhancement of bioavailability [62]. Activity of such metabolizing enzymes is typically low at birth and rapidly develops over the first 1–2 years of life [64].

Current national recommendations for treating infants aged under 6 months

As the burden of disease in infants under 6 months of age is not well defined, this age group has been excluded from previous clinical trials and national treatment guidelines on uncomplicated *P. falciparum* malaria. Thus, oral anti-malarials recommended as first- and second-line therapies are frequently used off-label, based on the recommended mg/kg dosing schedule for older children [28].

Issues with currently available anti-malarials

There is little information on the use of artemisinin-based combination therapy (ACT) in young infants, to the extent that many of them carry label restrictions for this age group [63]. Accurate dosing is particularly important, but this is difficult when paediatric formulations are unavailable. Nevertheless, young infants with malaria should receive appropriate treatment. Among the recommended ACT, excluding the combination containing sulphadoxine-pyrimethamine that is not recommended during the first 6 weeks of life [65], there is no evidence of specific serious toxicity [63]. However, additional efforts should be made to establish their safety profile, the correct dosage and formulation, so that young infants with malaria can be managed adequately.

With these issues in mind, it must be considered how ACT could be used to treat malaria in infants aged under six months. There are no official data on how to use ACT in this age group, despite the fact that malaria can occur at a very young age and that ACT offers greater efficacy and tolerability compared with quinine, which is often used in infants with clinical malaria. Furthermore, the use of a unified first-line therapy could offer benefits for healthcare providers with similar anti-malarial use for the whole population, as well as logistical benefits in terms of procurement and distribution. The safety profile of these combination therapies in young infants should be established.

Preventive treatment

Previous studies have shown that chemoprophylaxis in infants has the potential to reduce malaria-related morbidity and mortality [66]. In The Gambia, infants receiving weekly chloroquine from birth until the age of two years had fewer episodes of malaria, grew better, and had higher haemoglobin levels than the control group [67].

Some studies of intermittent preventive treatment (IPT) in infants (IPTi) have timed the doses of anti-malarial to coincide with routine vaccinations delivered by WHO's Expanded Programme on Immunization (EPI) at 2, 3 and 9 months. In a pooled analysis of six randomized, placebo-controlled trials of IPTi using sulphadoxine-pyrimethamine delivered at the same time as EPI immunizations, a protective efficacy against clinical malaria of 30.3% was reported [68].

Seasonal malaria chemoprevention (SMC), previously referred to as IPT in children (IPTc), involves the administration of full anti-malarial treatment courses during the malaria season to children aged 3–59 months [69]. The WHO recommends that SMC be used in areas of high seasonal malaria transmission across sub-Saharan Africa, and that treatment with amodiaquine plus sulphadoxine-pyrimethamine should be given at monthly intervals from the start of the transmission season, up to a maximum of four doses [69]. The main potential risks associated with SMC are safety and drug resistance [70]. However, SMC may provide a substantial protective effect against malaria [70], and is a potentially valuable tool that could contribute to reducing the malaria burden in infants aged over three months in areas with seasonal transmission.

The candidate malaria vaccine RTS,S/AS01 administered to infants aged 6–12 weeks at the time of the first vaccination provided modest protection against both

uncomplicated and severe malaria [71], casting doubts on whether this vaccine could be included in the routine panel of infants' immunization [72]. However, additional analyses are needed to understand the reasons of the observed lower efficacy in young infants as compared with older infants and children (aged 5–17 months) [73].

Future clinical studies

There are several ongoing or planned clinical studies aiming to obtain more accurate estimates of the malaria burden and parasite prevalence in infants aged less than 6 months living under different endemic conditions, as well as the safety and efficacy of currently available ACT in this population. Future longitudinal studies should also characterize infant iron status in relation to subsequent malaria risk, and relate findings to the occurrence of placental malaria.

A multicentre descriptive study is underway, aiming to assess malaria morbidity (prevalence and incidence) and corresponding risk factors in young infants, compared with their siblings, in areas of seasonal low (The Gambia) and high (Guinea) malaria transmission, and in an area with intense, perennial transmission (Benin).

A multicentre trial will evaluate the safety, pharmacokinetics and efficacy of dispersible artemether-lumefantrine tablets in infants weighing under 5 kg with uncomplicated *P. falciparum* malaria. This trial, sponsored by Novartis and in association with MMV, commenced in 2012 and involves sites in Benin, Burkina Faso, the Democratic Republic of the Congo, Nigeria and Togo.

Another study planned at the College of Medicine at the University of Malawi will assess the population pharmacokinetics and the safety and efficacy of ACT in infants weighing under 5 kg or aged less than 6 months.

Knowledge gained from such studies will assist in guiding the development of evidence-based treatment guidelines for this population.

Conclusions

The perception that malaria is uncommon in young infants has resulted in the paucity of information currently available and the lack of evidence-based treatment guidelines in this population. Many children are dying before malaria is diagnosed. In resource-constrained settings, diagnostic techniques may not be available, or malaria may not be recognized due to overlapping symptoms with other neonatal illnesses such as sepsis [33]. Malaria in infants aged under six months is not a rare occurrence in endemic areas and its burden may be underestimated. Therefore, it is necessary to collect reliable data on the malaria burden in this population. Awareness by health professionals should increase so that any infant aged under 6 months brought to a health facility in a malaria-endemic area with unexplained fever or suspected sepsis should be systematically screened for malaria. Current policy for malaria diagnosis dictates that all fevers in all age groups and settings should be tested for malaria before treatment is initiated.

ACT is being used off-label in this vulnerable patient group, with physicians using a pragmatic approach to guide dosing. At this time, a clear recommendation on the use of ACT could be difficult, due to a lack of data in infants with a body weight of less than 5 kg (less than 4.5 kg for artesunate plus amodiaquine). A more accurate estimate of the disease burden and parasite prevalence, risk factors for infection including iron status, as well as the pharmacokinetic profiles, safety and efficacy of currently available ACT in early infancy from data provided by clinical trials that are planned or underway will contribute to the development of evidence-based treatment guidelines for this population, as well as aid the research and development of new drugs. It is definitely worth providing malaria control strategies that are aimed directly at this vulnerable age group, in a bid to reduce infant mortality.

Abbreviations

ACT: Artemisinin-based combination therapy; EPI: Expanded Programme on Immunization; HbF: Haemoglobin F; HIV: Human Immunodeficiency Virus; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IPT: Intermittent preventive treatment; IPTc: Intermittent preventive treatment in children; IPTi: Intermittent preventive treatment in infants; MMV: Medicines for Malaria Venture; pABA: Para-aminobenzoic acid; PCR: Polymerase Chain Reaction; PfEMP-1: Plasmodium falciparum erythrocyte membrane protein-1; SMC: Seasonal malaria chemoprevention; WHO: World Health Organization.

Competing interests

UD has been invited as speaker at symposia organized by Sigma Tau and Novartis Pharma, and has received a research grant from Sigma Tau. KH is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. This declaration is made in the interest of full disclosure and not because the author considers this to be a competing interest. The other authors have no competing interest to declare.

Authors' contributions

All authors met International Committee of Medical Journal Editors criteria for authorship. All authors contributed to the development of the outline, revised the manuscript critically, and read and approved the final manuscript.

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