The epidemiology and treatment of childhood anemia in western Kenya
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Chapter I

General introduction
Anemia, the most common health disorder worldwide, predominantly afflicts young children and women of childbearing age, the former being the focus of this dissertation. While the absolute number of deaths associated with childhood anemia is not well documented, severe anemia is indisputably associated with increased risk of child morbidity and mortality in sub-Saharan Africa (Brabin et al. 2001).

The World Health Organization (WHO) recommends the use of hemoglobin below 11 g/dL as a practical definition of anemia in children between 6 and 60 months of age (WHO 1997a). Although various definitions for the different grades of anemia have been reported in the literature, in this dissertation severe anemia among children less than 5 years of age is predominantly defined as a hemoglobin level below 5.0 g/dL, moderate anemia as a hemoglobin level of 5.0-7.9 g/dL, and mild anemia as 8.0-10.9 g/dL (MOH 1994).

In 1980, WHO estimated that about 1300 million people, or 30% of the world’s population, were anemic (DeMaeyer and Adiels-Tegman 1985). It is estimated that this number has since increased to 2 billion people, or 40% of the world’s population (ACC/SCN 2000; INACG/WHO/UNICEF 2000). The burden of anemia is grossly disproportionate, with 42% of pre schoolers in non-industrialized countries being anemic compared to 17% in industrialized countries (ACC/SCN 2000). In sub-Saharan Africa, one to two-thirds of children less than five years of age are estimated to be anemic (DeMaeyer and Adiels-Tegman 1985; ACC/SCN 2000) and childhood anemia accounts for more than half of hospital pediatric mortality in some areas with intense malaria transmission (Lackritz et al. 1992; Schellenberg et al. 1999).

**Determinants of childhood anemia**

Pediatric anemia in the tropics has a complex and multifactorial etiology, that includes infectious diseases (e.g. malaria, intestinal helminths, HIV), various nutritional deficiencies (e.g. iron, folic acid, other micronutrients, and protein-calorie malnutrition), and genetic factors (e.g. hemoglobinopathies, thalassemias, and glucose-6-phosphate dehydrogenase (G6PD) deficiency)(Fleming 1994). The relative significance of each varies with geographic location, season and age.

Below is a brief review of malaria and iron deficiency as causes of childhood anemia.

**Malaria:** In 1992, global estimates of the burden of malaria indicated that between 300-500 million clinical cases occurred annually, of which 90% were in sub-Saharan Africa. In addition, 1.5-2.7 million deaths are estimated to be caused by malaria each year, with Africa baring the
largest proportion (WHO 1997b; WHO 1997c; WHO 1997d; WHO 2003). In 2001, malaria was ranked the 8th highest contributor to the global Disability Adjusted Life Year (DALY) and 2nd in Africa (WHO 2002).

Malaria is a major contributor to severe morbidity (WHO 2000) and may cause death through direct and indirect pathways. Direct malaria mortality may result from two major overlapping syndromes, severe anemia and cerebral malaria. The relative contribution of these two syndromes is age dependent (Greenwood 1997; Marsh and Snow 1997; Snow and Marsh 1998); severe anemia is the main manifestation of severe malaria in children < 3 years, whereas in older children and adults the two syndromes can overlap (WHO 2000). Severe metabolic acidosis is also a common manifestation in both children and adults with severe malaria.

Indirect mortality due to malaria may result from the implications of recurrent episodes of low-grade malaria parasitemia, that in some remain asymptomatic and therefore undetected and untreated, resulting in chronic and eventually in severe anemia, immuno-suppression, and increased susceptibility to other infectious diseases (Molineaux 1997). Furthermore, malaria in pregnancy may result in low birth weight (Brabin 1991; Garner and Gulmezoglu 2003), and possibly infant anemia (le Cessie et al. 2002), both of which are associated with early infant morbidity and mortality (Luxemburger et al. 2001; Steketee et al. 2001). The relative contributions of direct and particularly indirect mortality are difficult to measure and not well described, but likely vary with the level of transmission intensity with a greater contribution of indirect mortality in areas with intense malaria transmission (Molineaux 1997).

In areas with high malaria endemicity, clinical immunity is developed early in life and the burden of malaria in these areas is in pregnant women and young pre-school children, and predominantly associated with severe anemia (Greenwood 1997; Ekvall 2003). In areas with less intense and more seasonal malaria transmission, children are less frequently exposed to malaria and protective immunity against severe malaria takes longer to develop. As a consequence the burden of disease is spread over a wider age range and death due to severe malaria in older children (>2-3 years) and adults also occurs (Snow and Marsh 1995; Greenwood 1997; Menendez et al. 2000; Ekvall 2003).

Malaria-associated anemia can result from a combination of increased red blood cell (RBC) destruction and decreased RBC production (Weatherall and Abdalla 1982; Menendez et al. 2000; Ekvall 2003). The extent to which RBC destruction contributes to anemia compared to the effect of suppression of erythropoietin synthesis or bone marrow dysfunction likely depends on age, immune status, malarial endemicity, and duration of infection, among other factors.
Severe anemia could be the result of an acute falciparum malaria infection that often presents itself with a short duration of illness and higher-density parasitemia; or chronic or repeated infections where patients present with lower parasite densities, a longer history of febrile illness, or no symptoms; or a combination of an acute episode superseding on chronic mild malaria-associated anemia (Abdalla et al. 1980; Menendez et al. 2000).

**Iron deficiency:** In a recent Comparative Risk Assessment project of the WHO, undernutrition in pregnancy and childhood was the largest contributor to the DALY in Africa (Ezzati et al. 2002). Specific micronutrient deficiencies and malnutrition cover a broad spectrum of illness, including deficiencies of iron, vitamin A, zinc, vitamin B₁₂, and folate. These are the result of inadequate dietary intake of animal products, fruits, and vegetables, but can also be the consequence of intestinal parasites causing mal-absorption of iron, retinol, folic acid, and vitamin B₁₂, or blood loss due to helminth infections, particularly hookworm (Lindsay and Casterline-Sabel 2000). Due to common etiology and underlying mechanisms, many micronutrient deficiencies overlap and interact (Dijkhuizen et al. 2001). Worldwide, approximately 20% of pre-school children are estimated to have multiple micronutrient deficiencies and half of the children with any micronutrient deficiency could have multiple deficiencies (Mason et al. 2001).

Iron is the most important hematopoietic nutrient that lacks in either dietary availability or quantity (Lindsay and Casterline-Sabel 2000). WHO estimates indicate that there are four billion iron deficient individuals in the world (ACC/SCN 2000). Young children in less developed countries are particularly vulnerable to iron deficiency anemia (IDA) due to inadequate intake of total iron or otherwise absorbable (bio-available) iron, low stores of iron at birth, high physiological demands for iron related to growth and development, and high losses of iron to parasitic infections (Yip and Dallman 1995; Lindsay and Casterline-Sabel 2000).

The body has three major iron-containing compartments classified as storage iron (e.g. ferritin), transport iron (e.g. transferrin), and functional iron. In healthy individuals, functional iron constitutes over two-thirds of total body iron; eighty-five percent of functional iron is in the form of hemoglobin, and the remaining 15% is incorporated into myoglobin and iron-containing enzymes (Fairbanks and Beutler 2001). In terms of total iron content, the transport compartment of plasma is the smallest but the most active of the iron compartments; its iron turns over approximately 10 times each day.

Iron deficiency comprises several stages. Iron depletion is the earliest stage of iron deficiency in which ferritin is decreased (or absent) but serum iron concentration and blood hemoglobin levels remain normal. Iron deficiency without anemia, the next stage, is characterized by
decreased ferritin levels, low serum iron concentration and transferrin saturation, without anemia. IDA, the most advanced stage, comprises of low ferritin, low serum iron, low transferrin saturation, and low hemoglobin or hematocrit (Fairbanks and Beutler 2001). IDA is often diagnosed by subnormal hemoglobin concentration in addition to abnormal values of one of the biochemical markers of iron status (e.g. free erythrocyte protoporphyrin, serum ferritin, mean cell volume, transferrin saturation, serum transferrin receptors) or an increase in hemoglobin levels in response to iron supplementation.

**Consequences**
Decreased oxygen delivery to the central nervous system is associated with light-headedness, headache, lethargy, and lack of attention, although a gradual onset of anemia can be asymptomatic due to physiologic adjustment by the body (Tefferi 2001). IDA has been associated with decreased physical activity and work capacity (Haas and Brownlie 2001), decreased appetite, decreased resistance to infections and increased risk of HIV infection when blood transfusions are needed (UNICEF/UNU/WHO/MI 1999). There is some evidence that iron deficiency may impair brain development and long-term cognitive function in children > 2 years of age, although this has not been well characterized by randomised placebo-controlled trials involving children < 2 years old, the age at which brain growth is at a maximum (Grantham-McGregor and Ani 2001; Gordon 2003). Furthermore, there appears to be some evidence for the impact of iron supplementation on weight gain, but mixed results have been reported on its effect on linear growth (Allen 1994). Causal evidence linking IDA in young children to mortality is weak (Brabin et al. 2001).

**Measles Immunization**
Mild viral infections, such as those following immunization with the attenuated measles virus have been associated with transient decrease in hemoglobin concentrations and cellular immunity that may persist for several weeks and mimic iron deficiency (Olivares et al. 1989). The pathophysiology is not completely understood but may include a shift in iron distribution from functional towards storage compartments and possibly decreased iron absorption or intake during the febrile phase, with adequate erythropoietin levels (Scrimshaw and SanGiovanni 1997). While these changes are not clinically consequential in healthy children, it is unknown if children who are already hematologically compromised may experience a greater fall in hemoglobin following immunization. In rural western Kenya, for example, one third of children 7-12 months of age have hemoglobin concentrations less than 8 g/dL, and 50% have hemoglobin concentrations between 8.0 and 10.9 g/dL (mild anemia) (McElroy et al. 1999). Thus a substantial
proportion of older infants are in a precarious hematological state placing them at risk of developing subsequent severe anemia with further insult. Furthermore, cell-mediated immunity provides partial protection against malaria in persons living in malaria-endemic areas, which raises the question as to whether measles vaccination may increase the severity of latent infections or increase the susceptibility to new infections with *Plasmodium falciparum* and further the risk of childhood anemia.

**Treatment and control of anemia**

**Iron supplementation:** For documented IDA, iron supplementation is the treatment of choice; for the prevention of IDA, combined iron supplementation and food based approaches are recommended in developing countries (Yip and Ramakrishnan 2002). New international guidelines recommend the use of iron supplementation in all areas with a high prevalence of iron deficiency anemia (INACG/WHO/UNICEF 2000). Despite the well-recognized public health burden of anemia, implementation of these guidelines continues to be hindered due to inadequate iron supplies, low coverage, and poor adherence to daily dosing (Schultink 1996; Schultink and Gross 1999). Dose related gastrointestinal side effects and the lengthy duration of required daily intake contribute towards poor adherence (Charoenlarp et al. 1988; Galloway and McGuire 1994; Cook and Reddy 1995).

**Intermittent iron:** In search of strategies to reduce costs and improve compliance and effectiveness, a series of studies was conducted in the early 1990s that opened up new avenues towards the design of iron regimens, which may be more likely to be adhered to.

Animal models have shown that iron when given intermittently (e.g. weekly or twice-weekly) is more efficiently absorbed resulting in significantly lower iron loss, and avoidance of the temporary iron overload associated with daily iron supplementation. The reduced iron absorption and transport with daily exposure to high doses is explained in part by an apparent inhibitory mucosal block, which can be overcome when iron is given intermittently at intervals of more than 3 days (Viteri et al. 1995). Based on these results, a series of studies was conducted in humans of all ages that concluded that weekly or twice-weekly iron supplementation is as effective, or almost as effective in the prevention (Angeles-Agdeppa et al. 1997; Thu et al. 1999; Muslimatun et al. 2001; Sungthong et al. 2002) or treatment (Gross et al. 1994; Schultink et al. 1995; Liu and Liu 1996; Nwanyanwu et al. 1996; Ridwan et al. 1996; Berger et al. 1997; Kruske et al. 1999; Kianfar et al. 2000) of mild and moderate anemia as the conventional daily iron supplementation, despite a 3- to 7-fold reduction in the cumulative dose. Such regimens are potentially better tolerated, with less gastrointestinal side effects, and may therefore improve compliance compared
with daily dosing.

A subsequent review of experimental studies in humans using radio-labeled iron, however, failed to confirm the existence of such a mucosal block (Cook and Reddy 1995; Hallberg 1998). It was suggested that the lack of empirical difference between daily and intermittent iron in hemoglobin response observed in these earlier clinical studies in humans could be explained by the experimental design of some of these trials which evaluated the differential efficacy of high dose regimens after relatively long intervention periods (≥ 8 weeks) in subjects with predominantly mild iron deficiency and low grade anemia (Hallberg 1998). This challenged the earlier conclusion that intermittent iron is as effective as daily iron supplementation (Mumtaz et al. 2000; Sharma et al. 2000; Zavaleta et al. 2000; Ekstrom et al. 2002), and resulted in much debate (Beard 1998; Schultink and Gross 1999).

A recent meta-analysis of 14 clinical trials involving pregnant women, adolescents, and pre-school children (N= 5,100) demonstrated that both daily and intermittent iron were effective, but the beneficial effect of daily dosing was consistently greater. This was particularly evident in pregnant women. In adolescents and pre-school children, however, there was large inter-study variation and the differences were inconclusive (Beaton and McCabe 1999). Further studies are required to provide a definitive answer to whether daily iron is indeed more efficacious than intermittent iron in pre-school children and adolescents.

It is critical to address how ‘natural’ patterns of compliance with iron regimens affect the efficacy under ‘real life’ conditions (Solomons 1997). The natural tendency for mothers to ‘skip’ doses when iron is prescribed for daily use, or to share the daily dose with siblings may raise the possibility that mothers unknowingly already enhance the relative efficacy of iron uptake by spacing the dose, or by reducing the daily dose (Solomons 1997). Beaton et al. in their meta-analysis of completed studies also indicated that the degree of supervision was an important predictor of post-intervention anemia prevalence, and more so in the intermittent than in the daily group. As a result, it was suggested that intermittent supplementation should only be recommended when adherence is expected to be high. A more recent study demonstrated that six weeks of twice-weekly iron when given as directly observed therapy for anemia in children is superior to unsupervised daily iron supplementation in improving hemoglobin concentrations (Kruske et al. 1999). Further studies are needed that simultaneously assess the efficacy and effectiveness of daily versus intermittent iron supplementation in pre-school children.

**Malaria and iron:** Successful implementation of iron supplementation programs has also been limited due to the long standing controversy surrounding the use of iron supplementation in
malaria-endemic areas (INACG/WHO/UNICEF 1999; Oppenheimer 2001). Whereas iron deficiency causes a number of biochemical abnormalities and impaired cell mediated immunity with increased susceptibility to infections (Dallman 1986; Farthing 1989; Hercberg and Galan 1989), concerns have been raised that iron therapy even at the recommended treatment (3 mg/kg/day) or preventive (1-2 mg/kg/day) dosage may exacerbate infections, in particular malaria, as many infectious agents depend on iron for growth (Rosenthal and Meshnick 1996; Egan et al. 2002).

A recent meta-analysis of 13 clinical trials addressing this concern (INACG/WHO/UNICEF 1999), as well as another review of 28 randomized controlled trials (Gera and Sachdev 2002) suggested that the hematological benefits from iron supplementation outweigh the clinically non-significant increase in the risk of malaria infection and symptomatic malaria (INACG/WHO/UNICEF 1999). Conversely, another review by Oppenheimer of eight studies suggested up to a 50% increased risk of symptomatic malaria when iron was given in doses greater than 2 mg/kg/day (Oppenheimer 2001). Oppenheimer suggested that iron supplementation should only be administered in the presence of adequate protection from malaria. The rationale for this recommendation has yet to be confirmed through controlled clinical trials.

**Iron and sickle cell trait**: Oppenheimer also suggested that in populations with a high prevalence of hemoglobinopathies, depending on type and zygosity, a potential deleterious effect of iron on malaria might be either masked due to the protective effect in carriers, or aggravated due to carriers losing their pre-existing protective effect, and thus being predisposed to malaria (Oppenheimer et al. 1987). In studying the effect of the sickle cell trait on the response to iron supplementation, a study among pregnant Gambian women reported lower hemoglobin levels and birthweights in response to iron in HbAS than HbAA women. HbAS women assigned to the iron group were also at an increased risk of placental malaria, compared to the HbAA women (Menendez et al. 1995). The need for further evidence to identify subgroups in whom risk of adverse effects of iron supplementation are higher or lower compared to the general population has been highlighted in an INACG consensus statement (INACG/WHO/UNICEF 1999).

**Malaria control**: The strategy in the control of malaria in endemic regions constitutes three important components: insecticide treated bednets (ITNs), early detection and prompt treatment, and prophylaxis, including intermittent preventive treatment (IPT) (RBM 2003).

**ITNs**: Bed nets have been in use since the early 1930s, although ITNs were not introduced until the 1970s. A recent review of 18 randomized trials on ITNs suggests a protective efficacy of 17% against all-cause mortality (Lengeler 2000). Ten of these trials were conducted in sub-Saharan Africa, of which six reported an impact on anemia. The mean hematocrit was 1.4%
higher among children sleeping under ITNs compared to those without ITNs. Despite an extensive database on the effect of treated bed nets and curtains on malaria infection and morbidity, little information was available from randomized controlled trials in settings with intense perennial malaria transmission. Since the Cochrane review, however, further data from randomized trials as well as social-marketing studies conducted in areas with intense malaria transmission in western Kenya and Tanzania have shown ITNs to reduce all-cause morbidity, including anemia (D'Alessandro et al. 1995; Premji et al. 1995; Fraser-Hurt et al. 1999; Abdulla et al. 2001; Holtz et al. 2002; Maxwell et al. 2002; ter Kuile et al. 2003a). In the trial conducted in western Kenya, ITNs reduced the incidence of clinical malaria and severe to moderate anemia (Hb <7 g/dL) by 60% (ter Kuile et al. 2003a) and the mean Hb was 0.5 g/dL higher in children living in ITN compared to those in non-ITN villages (ter Kuile et al. 2003b). These studies also helped to define pregnant women and young preschool children as the main target groups for malaria control in areas with intense malaria transmission.

*Early detection and prompt treatment:* in sub-Saharan Africa where most malaria is due to *Plasmodium falciparum*, prompt and effective treatment of malaria is critical to saving lives of young children. Untreated falciparum infection can result in death, sometimes within hours of the onset of symptoms (Greenwood et al. 1987). Furthermore, diagnosis is complicated by the lack of a specific clinical presentation, simultaneous presence of several other diseases, and - in areas with intense malaria transmission - asymptomatic malaria infections (WHO 2003). In most malaria-endemic areas, diagnostic facilities within the peripheral health system are also sub-optimal.

Thus, the WHO is implementing new strategies for the integrated management of the sick child in the primary care setting, which includes algorithms based on clinical signs detected by trained professional health care workers (WHO 1995). As part of this algorithm, palmer pallor is used to evaluate the presence of severe anemia in the absence of routine hemoglobin measurement (Kalter et al. 1997; Weber et al. 1997a; Weber et al. 1997b; Zucker et al. 1997). The initial focus of the WHO and UNICEF has been on the use of the algorithm by health care workers in health facilities. However, early recognition of moderate to severe anemia by the primary caregiver is essential to ensure that these children are brought to the formal health care system. Information is limited on the ability of primary caregivers to recognize signs of pallor in their children.

*Intermittent preventive treatment (IPT):* In the early 1950s, the role of malaria chemoprophylaxis was studied as part of the malaria eradication effort. Chemoprophylaxis was later integrated into national malaria control programs of many African countries (WHO 2001), but this strategy lost support due to concerns regarding development of drug resistance, sustainability, cost-effectiveness, and appropriate delivery systems (WHO 1993). A recent review of several studies
conducted over the last 50 years shows a beneficial role for malaria chemoprophylaxis on hematological outcomes in children, although rebound effects may occur when such strategies are implemented in infancy (Geerligs et al. 2003).

The term 'chemoprophylaxis' implies that a drug is used to prevent infection of the tissue or blood and the resulting clinical manifestations at dosages lower than required for treatment (Geerligs et al. 2003). In most African settings, however, children are already parasitemic and the frequent therapeutic use of antimalarials is a form of regular intermittent chemotherapy. Most short acting drugs require frequent administration to achieve treatment or prophylactic effects. On the other hand, drugs that provide long-term suppression due to slow elimination (e.g. sulfadoxine-pyrimethamine [SP]), provide effective treatment of existing infections (i.e. clearance of parasitemia) as well as a period of protection against new febrile or asymptomatic infections of up to 3 to 4 weeks. Thus, several intermittent treatments with such drugs will provide a prolonged period of chemoprophylaxis and prevention against repeated hematological insults. This strategy, called intermittent preventive treatment (IPT), consists of the provision of several doses of antimalarials given intermittently (e.g. with intervals of at least one month) irrespective of the presence of malaria parasites or symptoms (presumptively) (Schellenberg et al. 2001).

IPT may have important implications in the treatment or prevention of malaria-associated anemia in areas with intense malaria transmission. One study from an area with very low malaria transmission on the Thai-Burmese border indicated that it takes about 42 days for full hematological recovery to occur in patients after an acute episode of uncomplicated falciparum malaria (Price et al. 2001). Although fever and inflammation can reduce RBC survival, anemia in malaria lasts longer than in most other systemic infections (Karle 1974). The rapidity with which anemia develops is likely due to hemolysis of both parasitized and non-parasitized RBCs. The slow recovery from malaria-associated anemia, on the other hand, may be attributable to continued destruction of non-parasitized RBCs after clearance of parasitemia due to reduced membrane deformability, as well as dyserythropoiesis (Dondorp et al. 1999; Price et al. 2001). This may suggest that new infections that occur within 42 days are likely to have a cumulative effect on the patient's hematological status. This is particularly relevant in areas with intense malaria transmission where children get re-infected with very high frequencies. Furthermore, low-density infections may also cause anemia, which may not be associated with symptoms and thereby remain undetected and untreated (McElroy et al. 2000). Thus, IPT may have a role in treating these infections that may otherwise go untreated in the context of policies that rely on early detection and prompt treatment of symptomatic malaria (i.e. febrile episodes).

In order to reduce the rate of development of drug resistance, short periods of targeted
prophylaxis with treatment doses are preferable to mass prophylaxis with low drug concentrations (WHO 1993). This approach is particularly justified in areas where a small proportion of the population is at the highest risk of adverse effects from malaria and where effective antimalarials still exist (Greenwood 1991).

Recently, following promising results of IPT with an effective antimalarial in the control of malaria in pregnancy (Garner and Güimezoglu 1999), interest has been generated in the use of IPT for the prevention of malaria and malaria-associated severe anemia in young children (Schellenberg et al. 2001; Massaga et al. 2003). In a study in Tanzanian infants, conducted in the context of routine vaccinations, IPT with SP halved the incidence of severe anemia in an area with intense malaria transmission (Schellenberg et al. 2001). Similar results have recently been reported for IPT with amodiaquine (Massaga et al. 2003). These results have created much excitement and suggest that IPT can provide an innovative and powerful new tool in the limitedly available arsenal to control malaria and malaria-associated anemia in malaria endemic Africa (WHO 2001; RBM 2003). However, the role of intermittent therapy in the treatment, rather than prevention, of all cause anemia in young children in malaria endemic areas remains to be established.

Towards integrated control of childhood anemia
The relative contributions of malaria and iron deficiency and their interaction in the pathogenesis of anemia determine whether the (1) control of malaria alone, (2) iron supplementation alone, or (3) a combination of both strategies, is required for optimal control of anemia in malarious areas. IPT, when given in combination with iron supplementation, has the additional potential to control any adverse effects of iron on malaria. While combined iron supplementation and malaria control may be more effective and safer than single interventions, it is also more expensive and it is unclear whether the enhanced efficacy of the combined approach is sufficient to be cost-effective in areas where a single cause predominates.

Study site in western Kenya
The studies in this dissertation were conducted in Asembo, a one-hour drive (50 km) southwest of the city of Kisumu, which is situated north east of Lake Victoria in western Kenya. The total population is approximately 55,000 Luo people, including 8,250 children less than 5 years of age. This was also the site of a large community-based study on the effect of ITNs on childhood mortality (Phillips-Howard et al. 2003a). Asembo, with an area covering 200 km², consists of 76 villages (Figure 1). During the above-mentioned ITN trial, 15 of these villages ("cohort area") were used for longitudinal follow-up of mothers and infants, and morbidity cross-sectional surveys were
conducted in the other 60 villages ("non-cohort area"). There are 15 peripheral health facilities (public and private) operational in the study site. This area is representative of many parts of sub-Saharan Africa with intense perennial malaria transmission. In 1986-87 between 80% and 95% of young children in this area experienced recurrent parasitemia within 84 days of having their parasitemias cleared with effective doses of sulfadoxine-pyrimethamine (Beadle et al. 1995). The median time between birth and first detectable *P. falciparum* infection is approximately 3 to 4.5 months (McElroy et al. 2000; ter Kuile et al. 2003a). The two randomized trials reported in chapters 5-7 were conducted in the context of area-wide distribution of ITNs (Phillips-Howard et al. 2003a; Phillips-Howard et al. 2003b), with adherence to net use being approximately 70% (Alaii et al. 2003). ITNs had a protective effect against child mortality, severe to moderate anemia, and high-density parasitemia even on children living in nearby compounds (within 300 meters) without an ITN (Hawley et al. 2003) suggesting an area-wide effect of ITNs on mosquito populations (Gimnig et al. 2003a). Thus, although malaria transmission in this area was previously reported to be intense and perennial (Beier et al. 1994), distribution of ITNs has caused a substantial reduction in transmission of *Plasmodium falciparum*; transmission was reported to be 90% lower in ITN intervention villages than in control areas (Gimnig et al. 2003b) and median time to first infection in infants was delayed from 4.5 to 10.7 months. This reduced the force of infection by 74% thereby delaying time to first infection to approximately 11 months (ter Kuile et al. 2003a).

Between 60-90% of the children less than five years of age are anemic at any time (Hb <11 g/dl) (Bloland et al. 1999; McElroy et al. 2000). Between 1990 and 1992, one-third of all pediatric hospital admissions to Siaya District Hospital had haemoglobin levels of <5 g/dL and this accounted for half of all the pediatric hospital deaths (Lackritz et al. 1992). Furthermore, in the treatment of anemic children with respiratory distress, blood transfusions administered 2 days after admission to a hospital had little benefit on survival outcome (Lackritz et al. 1992), which suggests an even higher burden of mortality associated with severe anemia in the community than in-hospital where prompt treatment may be available. Infant and under-five-year mortality rates are estimated to be 176/1000 and 257/1000 live births, respectively (McElroy et al. 2001). Malnutrition is an important health problem, especially in the months before the harvest (March-June). The prevalence of stunting, wasting, and being underweight in 6-59 months old children are estimated to be 30%, 4%, and 20%, respectively (Kwena et al. 2003). Between 1992 and 1996, the prevalence of HIV among pregnant women in the study area was estimated to be 18%. In the context of prolonged breastfeeding and lack of effective antiretroviral treatment, 7.2% of newborns were estimated to be infected with the virus during this period (De Cock et al. 2000; Phillips-Howard et al. 2003a).

Although iron supplementation for pregnant women is routine, at the time that these studies
were conducted there was no clear policy in western Kenya to address iron deficiency, through supplementation or food fortification in young children. Despite the high public health burden of anemia in Asembo and the known benefits of iron supplementation, most local clinics lack standardized guidelines for the use of iron supplementation. Clinic based surveillance in this area has shown that iron supplementation was not routinely given to children with mild and moderate anemia, and prescribed for only 12% of the children less than five years of age with clinically diagnosed severe anemia, while all received presumptive antimalarial treatment (Phillips-Howard et al. 2003c). The clinics that prescribe iron for severe anemia in children use short courses of relatively high doses of iron (3-6 mg/kg per day for 14 days). This is combined with presumptive antimalarial treatment to treat the malaria attributable component of anemia, while providing partial protection against potential adverse effects on malaria associated with iron (Gove 1997; Oppenheimer 2001). This 2-week regimen combined with antimalarial treatment is also used in other areas with similar intense malaria transmission (Menendez et al. 1997) reflecting the controversy on the safety of longer iron supplementation regimens in these malaria endemic areas (Oppenheimer 2001). The efficacy with this 2-week regimen is unknown, but the short duration of supplementation is likely to result in inadequate restoration of hemoglobin levels (which requires a minimum of 4-6 weeks) (Nestel and Alnwick 1996) and particularly iron stores, which may require iron supplementation for 12 weeks or longer (Stoltzfus 2001).

**Study infrastructure**

Detailed description of the field, laboratory and data management infrastructure for the study site have been provided elsewhere (Phillips-Howard et al. 2003a). The two intervention studies mentioned in chapters 5-7 were conducted in the “cohort area” (Figure 1, grey section of Asembo), where approximately 30 village monitors were trained to collect blood samples, perform anthropometric measurements, and administer standardized morbidity questionnaires. About 50 traditional birth attendants (TBAs) were also trained to administer iron during these studies. The cross-sectional studies mentioned in chapters 2-4 were conducted at central locations within villages in the “non-cohort area” (Figure 1, black section of Asembo). In both the cohort and non-cohort areas combined, a network of 38 field supervisors were assigned to a group of villages (average of six, range 4-9) that made up a sector. These sector supervisors, who lived in their respective sectors and were literate in English, were responsible for checking study forms completed by village monitors and TBAs before sending them to a central office. Study vehicles transported all forms, as well as blood smears, blood samples and stool samples, to the Kenya Medical Research Institute in Kisian, where the main administrative, laboratory, and data entry facilities were located (about 10 km out of Kisumu and 40 km from Asembo) (Phillips-Howard et al. 2003a). Automated internal consistency checks were executed upon data entry, and all
questionable forms were returned to the field for verification and correction.

**Aims and outline**

The overall objectives of the studies presented in this dissertation were to explore the extent of the problem of anemia among young children residing in an area of high malaria transmission, to identify the groups at highest risk, to improve the recognition of anemia, and to contribute to the development of control strategies to decrease the burden of anemia on child health.

Specific objectives include:

1. to determine the prevalence and severity of anemia in young children and identify subgroups at high risk of severe anemia within the community (chapter 2)
2. to examine whether live-attenuated measles vaccine is associated with an increased risk of anemia or malaria (chapter 3)
3. to identify the signs and symptoms of anemia that can be recognized by caretakers (chapter 4)
4. to compare the therapeutic efficacy and effectiveness of a short six-week course of twice-weekly versus daily iron supplementation in children with mild as well as moderate anemia (chapter 5)
5. to assess if the efficacy of a presumptive single dose of sulfadoxine-pyrimethamine (SP) in improving hemoglobin status can be enhanced by the addition of iron supplementation and/or monthly presumptive malaria treatment among mildly anemic children (chapter 6)
6. to determine if iron supplementation increases the risk of malaria, and if so, whether this can be controlled by the addition of monthly presumptive malaria treatment (chapter 6)
7. to determine the influence of the sickle-cell hemoglobin phenotype on hematological responses and malaria following iron supplementation in anemic children (chapter 7)

The fieldwork consisted of the following: a set of four cross-sectional surveys that were conducted between 1996 and 1999 as part of a larger controlled study of the impact of insecticide treated bednets (ITN) on childhood morbidity and mortality (Phillips-Howard et al. 2003a; Phillips-Howard et al. 2003b), and two independent anemia treatment studies conducted between 1999 and 2001. Data from the cross-sectional surveys were used to study objectives 1-3, results of which are described in chapters 2-4. An un-blinded cluster-randomized trial was undertaken to pursue objective 4, which is presented in chapter 5. Finally, a randomized placebo-controlled trial was conducted to achieve objectives 5-6 (presented in chapter 6) and objective 7 (presented in chapter 7).

**Ethical approval**

These studies were approved by the ethical review boards of the following institutions: Kenya
Medical Research Institute (KEMRI), Nairobi, Kenya, Centers for Disease Control and Prevention (CDC), Atlanta, USA, and Academic Medical Center at the University of Amsterdam, Amsterdam, The Netherlands.

Figure 1: Study site in western Kenya
References


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