The epidemiology and treatment of childhood anemia in western Kenya
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Summary
One to two-thirds of children < 5 years of age in sub-Saharan Africa are estimated to be anemic and severe anemia contributes substantially to child morbidity and mortality. The etiology of childhood anemia is multifactorial, with iron deficiency and malaria being the predominant causes in most of sub-Saharan Africa. Anemia in early childhood has profound short term (reduced physical activity, suppressed immune system) as well as long term implications (impaired physical growth and mental development).

The studies presented in this thesis aimed to: define the prevalence of severe anemia in an area with intense malaria transmission; identify subgroups at high risk of severe anemia within the community which could benefit from interventions; assess the ability of caretakers to recognize severe anemia in their children; and contribute to the development of strategies to decrease the burden of anemia on child health.

Chapter 1 presents an overview of the problem of childhood anemia, with an emphasis on its global prevalence as well as impact in sub-Saharan Africa. The epidemiology and consequences of malaria and iron deficiency are discussed, followed by a review of strategies in the treatment and control of anemia with a focus on use of iron supplementation and intermittent preventive treatment (IPT) with an effective antimalarial. Specific issues that are discussed include: rationale for intermittent iron supplementation; increased risk of malaria following iron supplementation; the concept of IPT; and integrated control of anemia using a combination of iron supplementation and IPT.

A series of cross-sectional surveys conducted between 1996 and 1999 as part of a large insecticide treated bednet (ITN) study provided an opportunity to determine the prevalence and severity of anemia in children less than 3 years of age (Chapter 2). It also provided the opportunity to examine the factors that are associated with hemoglobin levels, as well as socio-demographic and clinical indicators of anemia that may assist in identifying children at risk for anemia and who could benefit from interventions. The prevalence of anemia (Hb <11 g/dL) was 76.1% and 71%, respectively, in villages without and with insecticide treated bednets (ITNs); severe-moderate anemia (Hb <7 g/dL) was observed in 11% (non-ITN) and 8.3% (ITN). The prevalence of anemia, high-density malaria parasitemia (21.7%), microcytosis (34.9%), underweight (21.9%), and diarrhea (54.8%) increased rapidly from 3 months onwards and remained high until 35 months. Even very low-density malaria parasitemia was associated with severe-moderate anemia (Odds ratio [95% CI]: 3.11 [1.12, 8.61]). Helminth infections were present in only 8.3% of the children and not associated with Hb levels in this young age group. In multivariate analyses, family size, history of fever, 'pale body', general body weakness, diarrhea, soil eating, concurrent fever, stunting, and malaria parasitemia were associated with Hb. It was inferred from these data
that a high prevalence of malaria, malnutrition and diarrhea overlap placing children between 3-24 months at a particular risk of severe anemia. Prevention of severe anemia should start early in infancy and include a combination of micronutrient supplementation, malaria control, and possibly interventions to prevent diarrheal illness.

Mild viral illness, including that following immunization with live attenuated measles virus (LAMV), has been associated with transient decreases in hemoglobin (Hb) that may persist for several weeks. Immunization with LAMV is also associated with a temporary decrease in cellular immunity. In areas of intense malaria transmission infants are known to experience a progressive drop in Hb until age 9-10 months and one-third may have Hb <8 g/dL. These children may thus be at a higher risk of developing severe anemia with further hematological insult. Therefore, data from four cross-sectional surveys, and the two intervention studies described in chapters 5 and 7 were analysed retrospectively to determine if immunization with LAMV was associated with increased risk of transient anemia and malaria infection (Chapter 3). Measles vaccination coverage between 12-23 months of age ranged from 44.8% to 62.7%, and was lower than the national coverage rate for Kenya in 1999 (79%). Hemoglobin concentrations in children aged 6-24 months with documented measles immunization within the previous 14 or 30 days (n=103) were similar to those with no history of measles immunization in the previous 90 days (n=996). The risk of malaria parasitemia or severe to moderate anemia was also not different. These findings do not suggest that the transient decrease in hemoglobin and cellular immune response following immunization with LAMV results in clinically significant changes in the risk of subsequent severe to moderate anemia or malaria in young children.

In Chapter 4, the same set of cross-sectional surveys was used to explore physical signs of anemia that can be recognized by primary caregivers to help improve care-seeking practices. Comparisons of the sensitivity and specificity at a range of hemoglobin cut-offs showed that Hb concentrations <5 g/dL was associated with the greatest combined sensitivity (75.6%) and specificity (63.0%) for pallor at any anatomical site. Corresponding figures for the detection of Hb <7 g/dL were 59.1% and 64.3%, respectively. Furthermore, as indicated in chapter 2, soil eating is a common phenomenon in the study area; one in four children were reported to be geophageous. Combining a history of soil eating with anatomical pallor improved the sensitivity to detect severe anemia (87.8%) with only a small reduction in specificity (53.3%). It was concluded that primary caregivers can recognize severe anemia (Hb <5 g/dL) in their children with reasonable accuracy, but not moderately severe anemia (Hb <7 g/dL). The effect of training caretakers to improve the recognition of severe anemia and care-seeking behavior at the community and household-level should be assessed in prospective studies.
With respect to control of anemia, successful implementation of daily iron supplementation has been hindered by inadequate iron supplies, low coverage, and poor tolerance and adherence to the lengthy duration of required daily dosing. In search of strategies to reduce costs and improve compliance and effectiveness, a series of studies was conducted in the early 1990s to determine if intermittent iron supplementation (weekly or twice-weekly) is as effective in the prevention or treatment of anemia as the conventional daily iron supplementation. Such intermittent regimens are potentially better tolerated and may therefore improve compliance compared with daily dosing. These studies were based on findings from earlier animal models that showed reduced iron absorption and transport with daily exposure to high doses, explained in part by an apparent inhibitory mucosal block, which can be overcome by giving iron intermittently. A recent meta-analysis of 14 clinical trials indicated that daily, compared with intermittent iron supplementation resulted in significantly greater hematological improvement in pregnant women. In pre-school children, however, there was large inter-study variation and the differences were inconclusive. 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. In Chapter 5, we present the results of an un-blinded cluster-randomized intervention study assessing the efficacy and effectiveness of daily versus twice-weekly iron supplementation in the treatment of anemia among children between 2 and 59 months of age. Results showed that in the supervised groups hemoglobin concentrations at 6 weeks and 12 weeks (6 weeks post-supplementation) were significantly higher with daily than twice-weekly iron (mean [95% CI] difference at 6-weeks: 4.0 g/L [2.0, 6.0]; 12-weeks: 5.3 g/L [3.1, 7.6]). Among the unsupervised groups, hemoglobin concentrations were not different at 6 weeks (mean [95% CI] difference: 1.1 g/L [-0.9, 3.2]), but higher at 12 weeks for those assigned daily iron (mean [95% CI] difference: 2.5 g/L [0.2, 4.7]), though this difference was not statistically significant after adjustment for multiple testing ($P = 0.06$). These findings indicated that, similar to earlier recommendations for pregnant women, daily dosing should be the regimen of choice in the treatment of mild and moderate anemia in pre-school children regardless of the level of compliance that can be ensured.

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. Several studies have shown that iron supplementation is associated with an increase in the risk of falciparum malaria. Iron supplementation combined with malaria control may be more effective and address concerns of the increased risk of malaria associated with iron supplementation. Chapter 6 presents the results of a randomised placebo-controlled treatment trial that was conducted among 546 anemic (hemoglobin 7-11 g/dL) children between 2-36 months of age. All children used ITNs and received a single-dose of sulfadoxine-pyrimethamine.
(SP) at baseline followed by either: intermittent preventive treatment with SP (IPT) at 4 and 8 weeks combined with daily iron (Iron) for 12 weeks; Iron + placebo-IPT; IPT + placebo-Iron; or double-placebo. The difference [95% CI] in mean hemoglobin at 12 weeks from the double-placebo group was 1.14 [0.82–1.47], 0.78 [0.46–1.10], and 0.17 [0.15–0.49] g/dL, respectively. IPT halved the incidence of malaria parasitemia. However, in contrast to the promising results with IPT in the prevention of severe anemia in infants in areas with intense malaria transmission, our data suggests only a modest beneficial effect of IPT with SP on hemoglobin concentrations when given for the treatment of moderate or mild all-cause anemia in addition to a single dose of SP and in the context of wide-spread use of insecticide-treated bednets. Iron supplementation is clearly efficacious in increasing hemoglobin concentrations in young children with mild anemia, and this is likely to outweigh any potential adverse effects caused by increased risk of malaria.

A remaining concern has been whether the sickle cell trait phenotype, as well as other hemoglobinopathies that offer protection against malaria, modify the effect of iron supplementation. A study among pregnant Gambian women showed that iron supplementation is associated with increased susceptibility to malaria and decreased hematological responses among those with sickle cell trait (HbAS) compared to those with normal (HbAA) phenotype. Therefore, a sub-analysis of the trial described in chapter 5 was conducted to determine the influence of the sickle-cell hemoglobin phenotype on hematological parameters and malaria following iron supplementation (Chapter 7). The mean difference in hemoglobin concentrations at 12 weeks between children assigned iron and placebo-iron, adjusting for the effect of IPT, was 9.1 g/L (95% confidence intervals [CI]: 6.4-11.8) and 8.2 g/L (95%CI: 4.0-12.4) in HbAA and HbAS children respectively (P-value interaction term=0.68). The interactions between the effects of iron and hemoglobin phenotype on malaria parasitemia (P=0.70) or clinical malaria (P=0.20) were also not significant. Thus, our findings indicated no evidence for a clinically relevant modification by HbS phenotype of the response associated with iron supplementation in the treatment of mild anemia.

Conclusion

In light of the studies presented in this dissertation and other published literature, it is evident that even after decades of attempts to curb the problem of childhood anemia in sub-Saharan Africa, its prevalence remains unacceptably high even in this area with widespread use of ITNs. Our data suggest that caregivers, following minimal instructions, can recognize severe anemia in their children with reasonable accuracy. Prospective studies aimed at caretakers to improve diagnosis and treatment of severe anemia at the household level therefore seem justified.
Results from our treatment studies presented in this thesis are consistent with recent findings by others in Tanzania and eastern Kenya, and highlight the importance of iron deficiency as a cause of childhood anemia in this area and that control programs that aim to treat or prevent severe anemia in young children in malaria endemic areas should include iron supplementation. Although the prospect of intermittent iron supplementation appeared a promising alternative to daily iron in the early 1990s, our study, consistent with studies in pregnant women by others, suggest that daily iron should remain the treatment schedule of choice. Efforts should instead focus on improving compliance to long-term daily iron supplementation.

In this area of intense malaria transmission, iron supplementation is combined with a single presumptive treatment dose of SP. Our studies show that adding two additional doses of SP at monthly intervals approximately halves the incidence of malaria infections, but in the context of widespread use of ITNs, is restricted in rendering further hematological improvement over that of iron supplementation and a single dose of SP. In addition, our observations indicate that children with HbAS are equally likely to benefit from iron supplementation as children with HbAA phenotype.