SUMMARY

This thesis presents the results from studies defining the magnitude and main risk factors of anemia, malnutrition and malaria in 12-18 year old adolescent schoolgirls in western Kenya. Additionally, studies evaluating interventions to reduce and prevent anemia in this age group are presented.

In Chapter 1 we present the background to the studies presented in this thesis. Anemia remains a major public health concern in preschool children and pregnant women in the developing world. While many studies have examined these two at-risk groups, there is a paucity of data on anemia in adolescents living in developing countries in the complex ecologic context of poverty, parasitism and malnutrition. This relative omission is surprising considering that developmental processes of adolescence exert significantly increased demands on both micro and macronutrients, especially in girls entering menarche. It is estimated that approximately half of adolescent girls living in sub-Saharan Africa is anemic. Adverse effects of anemia range from severe morbidity to decreased physical work capacity to deficits in cognitive development and potentially school performance. A significant proportion of African women have their first pregnancy during adolescence and pre-pregnancy hemoglobin and iron status are important determinants of the risk of anemia related morbidity and mortality during pregnancy. Stunting is an important indicator reflecting the cumulative inadequacies in nutrition and health and has considerable long-term physiological and economic consequences. A direct consequence of short maternal height is obstructed labor due to cephalopelvic disproportion (incongruence between the head of the fetus and the pelvis of the mother), resulting in an increased risk of peripartum and maternal mortality. Teenage pregnancies are also at increased risk of severe anemia, preterm deliveries, stillbirths, and neonatal deaths, likely due to competition between nutritional requirements of the developing fetus and the mother’s requirement for continuing growth. Knowledge of the magnitude and main risk factors of anemia and stunting in this age group is of public health importance because adolescence offers a last window of opportunity to correct hemoglobin concentrations and growth deficits and to prepare for the demands of motherhood.
Chapter 2 describes the results of two cross-sectional surveys that assessed the prevalence, severity and risk factors of anemia and iron deficiency in adolescent schoolgirls in Asembo, an area with year-round intense malaria transmission and a high level of anemia and malnutrition in young children and pregnant woman. The prevalence of anemia (Hb <120 g/L) was 21.1%; only one girl had an Hb less than 70 g/L. The prevalence of iron deficiency (Ferritin < 12 ug/L) was 19.8% and 30.4% of anemic girls were iron deficient. Malaria and Schistosoma infections were the main risk factors for anemia in younger girls (12-13 yrs) while menstruation was the principal risk factor in older girls (14-18 yrs). There was a significant negative correlation between time since menarche and hemoglobin, suggesting that iron deficiency in menstruating girls is likely to increase with age. Iron deficiency and anemia in school attending girls in western Kenya were more prevalent than in developed countries, but considerably less prevalent than in pre-school children and pregnant women from the same study area.

In Chapter 3 we describe the prevalence, severity and main risk factors of malnutrition and the age at menarche in 12-18 year-old adolescent schoolgirls as assessed by a series of cross-sectional surveys conducted in two areas of western Kenya with different levels of malaria transmission and malnutrition. The prevalence of stunting and thinness was relatively high in young girls, but with age, the prevalence decreased and anthropometric z-scores converged towards the reference median. Menarche was delayed by 1.5 to 2 year relative to that of a US reference population, likely resulting in a prolonged period of growth, allowing girls to catch up on incomplete linear growth attained earlier in life. Parasitic infections (malaria and intestinal helminths) and socio-economic status were not associated with nutritional status.

Adolescents are at a markedly reduced risk of malaria-associated morbidity and mortality compared to young children and pregnant women. Though resistance to symptomatic malaria develops, sterilizing immunity does not and low-grade asymptomatic malaria infections are common in all inhabitants of malaria endemic areas. Whether these infections in adolescents are truly asymptomatic or have adverse hematological consequences, as in young children, is not known. Chapter 4 describes the impact of insecticide treated bednets (ITNs) on malaria and malaria-associated anemia and growth in adolescent girls as part of a large scale community-based group-randomized controlled trial. In 12 and 13-year-old schoolgirls, ITNs were associated with a reduced prevalence of all cause anemia (16.9% versus 31.4%; adjusted prevalence odds ratio [95% CI]; 0.38 [0.21 , 0.69]), and malaria associated anemia (3.2% versus 11.2%; adjusted prevalence odds ratio [95% CI]; 0.21 [0.06 , 0.72]). No significant beneficial effect on all cause anemia or hemoglobin concentrations was seen in older girls. No effect of bednets was seen on malaria parasite prevalence or density, clinical malaria, all-cause morbidity, standard measures of nutritional status and growth, or the use of antimalarials and other medication. This suggests that malaria is associated with mild anemia in young adolescent girls, but not in older girls, and that ITN use will improve Hb in this age group.

The age-related decline in parasite density, morbidity, and mortality observed during childhood has supported the view that years of cumulative exposure, potentially to multiple parasite strains, are necessary for the production of protective immune responses. However, recent transmigrant and cohort studies have implicated developmental changes in the host, apart from cumulative exposure to the parasite, in the expression of maximal resistance. Chapter 5 presents the results of a study that tests the hypothesis that levels of the dehydroepiandrosterone sulfate (DHEAS), an adrenal steroid whose concentrations parallel
pubertal development, are associated with reduced parasite density and other malaria related outcomes such as anemia, independent of age, and by proxy, cumulative exposure. In pubertal girls DHEAS was significantly associated with decreased parasite density after adjusting for age ($P=0.012$). DHEAS levels were also related to increased hemoglobin levels after accounting for age and other determinants of hemoglobin ($P=0.004$). These findings support the hypothesis that host pubertal development, independent of age and, by proxy, cumulative exposure, is necessary for maximal expression of resistance to malarial infection and morbidity as assessed by hemoglobin.

Chapter 6 describes a randomized double-blind placebo-controlled trial of the effect of weekly iron and vitamin A supplementation, alone or combined, on hemoglobin concentrations, nutritional parameters, malaria and non-malaria morbidity, cognitive function and school performance in adolescent schoolgirls in Kisumu. In menstruating schoolgirls, 21 weeks of iron supplementation was associated with a 11.5 g/L greater increase in hemoglobin concentrations relative to iron-placebo ($P<0.0001$). The effect of iron was independent of the effect of vitamin A and vice versa. No effect was evident in girls pre-menarche. No significant increase in hemoglobin was seen with weekly vitamin A, alone, or combined with iron. No effect of iron or vitamin A was seen on nutritional parameters. Iron supplementation was associated with a higher incidence of malaria parasitemia (rate ratio 1.43 [95% CI 1.15-1.79]), but vitamin A was not (rate ratio 1.08 [95% CI 0.86-1.35]). However, iron was not associated with an increased risk of clinical malaria or other infections. Iron supplementation had no beneficial impact on cognitive function or school performance. Weekly iron supplementation is effective in increasing hemoglobin concentrations in menstruating adolescent schoolgirls in this area in western Kenya and is likely to outweigh any potential associated adverse effects caused by increased risk of malaria.

Chapter 7 summarizes the results presented in this thesis and discusses the implications for public health programs and future research. Menstruating girls are a group at risk of iron deficiency anemia. School-based programs providing weekly supervised iron supplementation are likely to result in significant hematological benefit in girls at high risk of iron deficiency. Further research is needed to determine whether our findings in adolescent schoolgirls are representative of all adolescent girls in this area, including those not attending school. Further research is also needed to determine the long-term effects of iron supplementation programs in schoolgirls of reproductive age in the prevention of anemia-related adverse outcomes in pregnancy. Similarly, more research is needed to determine if iron supplementation in school-children and adolescents can reverse cognitive impairments due to iron deficiency earlier in life.

Prevention of malaria by ITNs would halve the prevalence of mild anemia in young adolescent girls in areas with intense malaria transmission. Although older adolescents are less likely to have direct benefit from ITN use, there are potential indirect benefits to distributing and promoting ITNs in schools; educating adolescent girls about the benefits of ITNs may ensure use of ITNs throughout a subsequent pregnancy. Moreover, distributing ITNs through schools will contribute to high population coverage which may enhance health and survival in infants, by contributing to the community wide effect of ITNs.

Finally, longitudinal studies are needed to further characterize the changes in acquired resistance to falciparum malaria during puberty and to evaluate more precisely the mechanisms behind these developmental changes.