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Anemia in adolescent schoolgirls in Western Kenya

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CHAPTER 1

Introduction
Introduction

Adolescent Health

A fifth of the world population (1.2 billion) is adolescent (10-19 years) and 85% lives in developing countries. Because mortality rates in adolescence are low, it has long been regarded as one of the healthiest periods of life and as a result little attention has been given to adolescent health and nutrition. However, the intense physiological, psychological and social changes adolescents go through, predisposes them to significant health problems ranging from sexually transmitted diseases and HIV/AIDS to substance abuse and mental health problems to nutritional deficiencies. Because adolescents are tomorrow’s societies’ economic and political players and tomorrow’s parents, understanding of their health situation is of great importance. Particularly, because adolescence offers a last window of opportunity to correct problems inflicted in childhood and to prepare for the demands of adult life.

Due to socio-economic pressure and lack of information many adolescents are likely to engage in sex (often unprotected) relatively early and unprepared, running the risk of contracting a sexually transmitted disease or becoming pregnant. The current African HIV/AIDS epidemic is a prime example of the grave risk some adolescents face. In several African cities the prevalence of HIV in adolescent girls aged 15–19 years is as high as 24%. Moreover, adolescent pregnancies are at increased risk of severe anemia, preterm deliveries, still births, low birth weight and neonatal deaths. An estimated 60 out of every 1000 adolescent girls will give birth each year resulting in 17 million babies with an increased risk of dying in their first year of life. Partly responsible for this increased risk is poor coping and inexperience of these frequently socio-economically deprived mothers, but physical immaturity is an important additional factor.

Additionally, important consequences of poor adolescent health (including teenage pregnancy, malnutrition, iron deficiency anemia and malaria) involve the effect on school performance and attendance and physical work capacity. Furthermore, poor education and physical work capacity will in the long run have negative economic and health consequences for the individual, their offspring and the society they live in. Investing in adolescent health is investing in the future of struggling nations.

Anemia in women of childbearing age

Iron deficiency anemia is a large public health problem world wide, with young children and pregnant women the most affected, the majority living in developing countries. It is estimated that around 40% of women of childbearing age and 50% of pregnant women in Africa are anemic. The consequences of iron deficiency range from impaired work performance and child development to increased mortality rates when anemia is severe.

Little data is available about the functional consequences of mild anemia in pregnancy, but there is consensus that maternal mortality is greatly increased with severe anemia.
Severe anemia and iron deficiency in pregnancy have been associated with pre-term and low birth weight deliveries and consequently neonatal mortality, but causal evidence is lacking.\textsuperscript{19} In addition, intra-uterine growth retardation due to maternal malnutrition, including maternal anemia, has been associated with poor health later in life.\textsuperscript{20,21}

Pre-pregnancy hemoglobin and iron status are important determinants of anemia related morbidity and mortality during pregnancy.\textsuperscript{8,22} Additionally, maternal anemia early in gestation has been associated with poor pregnancy outcome.\textsuperscript{23} Therefore, strategies preventing anemia and building iron stores would preferably take place before conception. However, most pregnant women in sub-Saharan Africa will generally visit an antenatal clinic relatively late (>20 weeks) into their pregnancy.\textsuperscript{8,24,25} Because a significant number of women will have their first child before the age of 20 years\textsuperscript{2,8} optimizing iron stores in adolescence could be an effective strategy to reduce maternal and neonatal morbidity and mortality.

**Anemia in adolescent girls**

Few studies have focused on the prevalence, severity and risk factors of anemia in adolescent girls. 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. A 1985 World Health Organization review of the global prevalence of anemia found only six studies in Sub-Saharan Africa involving this age group (cumulative sample size = 652) and estimated that approximately half of adolescents were anemic, with the highest prevalence in eastern Africa.\textsuperscript{26} More recently additional studies in sub-Saharan Africa reported similarly high prevalences.\textsuperscript{27-29}

The etiology of anemia in adolescents in sub-Saharan Africa is complex and multifactorial with nutritional deficiencies, infectious diseases and hemoglobinopathies all coexisting. Nutritional deficiencies, most importantly iron deficiency, are regarded as the most important cause of anemia in adolescents, followed by helminth infections, most importantly hookworm and schistosomiasis.\textsuperscript{30} Whether malaria is a contributor to anemia in adolescents, as it is in young children, is unknown as there is a scarcity of data regarding the adverse consequences of malaria in adolescence.\textsuperscript{31}

**Malnutrition**

Linear growth retardation is an important marker reflecting the cumulative inadequacies in nutrition and health.\textsuperscript{12} The long-term physiological and economic consequences of stunting reflect the direct effect of impaired body size (reduced basal metabolism and physical work capacity) or the indirect, carried-over, secondary effects of associated causes of growth faltering (e.g. poor intellectual and behavioral development due to micronutrient deficiency).\textsuperscript{12}

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. Moreover, adolescent pregnancies are at increased risk of severe anemia, preterm deliveries, stillbirths, and neonatal deaths, due to competition between nutritional requirements of the developing fetus and the mother's requirement for continuing growth.

Unlike the wealth of information available on the nutritional status of children <5 years of age, little data is available from adolescents in sub-Saharan Africa. Approximately 40% of under-fives is stunted and approximately 35% is underweight. The main time window for linear growth retardation to occur is early childhood and stunting generally persists into adulthood. In addition, recent studies in primary schools in sub-Saharan Africa suggest that children continue to grow at a slower rate during the school-age years and continue to diverge from reference populations. However, there is evidence that catch-up growth is possible during adolescence if maturation is substantially delayed. When the causative environmental factors of growth faltering drastically improve (e.g. nutritional supplementation or adoption into an affluent society), catch-up growth in young children is also possible. However, a potential adverse effect of successful interventions is that the improved nutritional status can trigger endocrinological response accelerating maturity and early menarche, thus limiting total height gain and the potential for complete catch-up growth. There is some evidence that iron supplementation promotes linear growth in young children and adolescents, though several recent supplementation trials in adolescents have failed to confirm these findings and only showed an effect on weight gain.

**Malaria**

Plasmodium falciparum malaria remains among the most important causes of morbidity and mortality in sub-Saharan Africa, accounting for up to one million deaths per year, mainly young children. Additionally, malaria has a great limiting effect on the economic development of endemic countries.

The epidemiology of malaria depends on the level of transmission. Under epidemic conditions all ages are at risk of severe disease and death. In areas with stable transmission, sufficient immunity is acquired in the first years of life for older children to be protected from severe malaria. Parasite densities are controlled with increasing age and school aged children, adolescents and particularly adults are at a markedly reduced risk of developing symptoms when they become infected. 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. Persistent low-grade parasitemia is thought to be important to maintain immunity, but whether these infections are truly a-symptomatic or have adverse hematological consequences, as in young children, is not known. A recent analysis of malaria in Kenyan school-aged children suggests that a significant fraction of overall morbidity in school-aged children is still attributable to malaria, including among adolescents.
Pregnant women are more susceptible to malaria than non-pregnant women. The adverse consequences also vary based on the pre-existing level of immunity against malaria and range from severe complicated malaria resulting in maternal and fetal death in areas of epidemic and unstable transmission, to predominantly low-grade, sometimes sub-patent parasitemia in areas with stable malaria transmission. These latter infections frequently do not result in acute symptoms, and remain therefore undetected and untreated. They are, however, a substantial cause of maternal anemia, and may be responsible for 30–35% of preventable low birth weight. Primi- and secundigravidae are most at risk, but in areas with a high prevalence of HIV, women of higher gravidity are also affected. There is some evidence that teenage pregnant women, independent of the number of previous pregnancies are at particular risk of malaria and its adverse consequences.

The age-related decline in parasite density, morbidity, and mortality observed during childhood may suggest that years of cumulative exposure, potentially to multiple parasite strains, are necessary for the production of protective immune responses. Recently, studies of transmigrant populations in Irian Jaya (now West Papua) and longitudinal cohort studies in Kenya have challenged this hypothesis. Baird and colleagues demonstrated that non-immune, adult, transmigrants moving from non-endemic Java to endemic areas of Irian Jaya acquired immunity faster than their transmigrant children. Kurtis and colleagues demonstrated in Kenyan males that resistance to reinfection following anti-malarial treatment increased during puberty, but not before puberty, and was predicted by levels of the pubertal steroid dehydroepiandrosterone sulfate (DHEAS) independent of age and, by proxy, cumulative exposure. These findings imply that apart from cumulative exposure to the parasite per se, developmental changes in the host during puberty are essential for the expression of maximal resistance to malaria. If supported by further research, these findings would be of particular relevance to the development and implementation of a malaria vaccine, as it implies that vaccination of pre-pubertal children may not result in adult-like immunity. So far, little new data supporting this hypothesis is available from field studies.

Preventing and treating anemia

Iron supplementation, together with food-based approaches, is the mainstay of the control of iron-deficiency anemia. Though many programs have been implemented world wide, iron supplementation programs have not resulted in a dramatic decrease of the global burden of anemia. Even though iron supplementation is highly effective when given during controlled trials, when supplementation programs become operational they have often failed. Poor compliance (due to side-effects and the long duration of required daily intake), infrastructural restraints, high maintenance costs and the coexistence of other causes of anemia (parasitic infections, other micronutrient deficiencies) are important factors leading to failure. As a result, attention has gone out to alternative strategies to combat anemia, including food...
fortification, mass-treatment with anthelmintics, malaria control (insecticide treated bed nets and intermittent antimalarial treatment), multi-micronutrient supplementation and intermittent iron treatment.

Because the number of children surviving the preschool years and consequently the number of children attending school have increased in the last decades, schools have been considered as good centralized settings from which to implement health interventions aiming to reach large numbers of school-aged children. Furthermore, school health programs are thought to be among the most cost effective public health interventions.

Intermittent iron supplementation, as a cheap and due to less gastro-intestinal side effects better tolerated and adhered to alternative to daily supplementation, was promoted after the finding that intermittent supplementation resulted in similar or greater absorption than daily supplementation in iron-depleted laboratory rats and a randomized trial in humans that found superior hematological response to weekly over daily supplementation. Since then, many studies have shown intermittent treatment to be effective in the prevention of iron deficiency anemia under controlled conditions, albeit less effective than conventional daily regimens, as recently concluded in a meta-analysis by Beaton & McCabe.

Vitamin A deficiency, even when sub-clinical, may cause anemia through the modulation of iron metabolism. Randomized controlled trials of iron supplementation in anemic vitamin A deficient subjects have shown limited hematological response when iron was given alone but significantly better response when vitamin A was added. Improved effects on hematological recovery together with reports that vitamin A supplementation offers protection against infectious diseases have led to increased interest in combined supplementation with vitamin A and iron.

Insecticide treated bed nets have been shown to be effective in preventing all-cause mortality and morbidity, including severe malarial anemia, in children under five years of age. Similarly, insecticide treated bed net significantly reduce malarial anemia in pregnant women. No data is available on the efficacy of impregnated bed nets in preventing malaria and anemia in adolescents.

**Study sites (Figure 1)**
The studies presented in this thesis were conducted in three different areas of western Kenya.

**Kenya**
Kenya is a relatively stable and economically well-off country compared to most of it’s neighbors. After independence Kenya enjoyed strong economic growth, but this has declined since the 1970s from 6.5 percent to about 2.2 percent in the last decade, below the average population growth rate of 2.5 percent. GDP was about 10.4 billion dollars in 2000 and 50% of Kenyans (total population ~30 million) is estimated to live below the poverty line. In the 1980’s Kenya was among the major foreign aid recipients in Africa, but due to poor governance
and mismanagement foreign aid has steadily declined since. Large scale corruption and deterioration of public goods and infrastructure (schools, hospitals and roads) in the last decade have lead to a feeling of disparagement in many Kenyans (personal observations). In 2000, infant and child mortality rates (per 1000 live births) were 77.0 and 120.0, respectively, and life expectancy at birth was 47.0 years.91

The 2000 UNICEF End of Decade Assessment reported that approximately 75% of school-age girls in Kenya attend primary school.93 Primary school starts at the age of five years and teaches children from standard 1 through to standard 8. Tuition is charged each trimester and parents decide when their child will start school. Until recently, some parents have waited for their child to reach the age of seven before sending them to school. If children fail exams or miss schooling, for example when unable to pay tuition, they may repeat years, with the result that some children remain at primary school up to the age of 18.94

Asembo

Asembo (Rarieda Division) is located in Bondo District, on the shores of Lake Victoria in Nyanza Province, western Kenya. The study site and the resident population have been described in detail elsewhere.47,95 Briefly, Asembo comprises an area of 200km² with a widely dispersed ethnically homogeneous population of approximately 55,000 people. The main occupation (74%) is in cultivation and limited animal husbandry. The rainfall pattern is bimodal, with the long rains falling between March and May, and the short rains from October to December, though in the latter half of 1998 there was less rainfall than usual.95 Malaria is holoendemic and since some rain falls in each month, transmission occurs throughout the year.96 Over 90% of malarial infections are due to \textit{P. falciparum}; infection with \textit{P. malariae} making up most of the balance along with an occasional \textit{P. ovale} infection. High-grade chloroquine resistance is widespread; in the early 1990's, 75% of patients with acute \textit{P. falciparum} infections treated with the standard 25 mg/kg regimen had RII/RIII type responses.97 At the time of study, the prevalence of HIV among pregnant women attending antenatal clinics in nearby Kisumu city was 25%.98 Infant and under-five mortality are considerably higher than in other parts of Kenya (176/1000 and 275/1000).99 Between 60—90% of the children under five years are anemic at any time (Hb <110 g/L) and 30% and 20% are stunted or underweight.47,100

No data are available of the prevalence of anemia in adolescents. A recent study of vitamin A status conducted in a rural area 20 km north-west of Asembo found the prevalence of sub-clinical vitamin A deficiency (serum retinol ≤70 μmol/L) to be 55.2% and 17.5% in preschool and primary school girls, respectively, and none with signs of xerophthalmia.101 Asembo was also the site of a large community-based group randomized controlled study on the effect of Insecticide Treated bed net (ITNs) on under-five mortality.95 Half of 79 villages in this study area were randomly assigned to the intervention group and each household in these villages received permethrin treated bed nets during the 4th quarter of 1996. Full details of their

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impact on malaria, anemia and nutritional parameters in the younger children in this study population have been reported elsewhere. The large community based bed net study provided a unique opportunity to assess the impact of ITNs on malaria in adolescents.

**Mumias**

Mumias (Mumias Division, Kakamega District, Western Province) is one of the most densely populated areas in Kenya and mainly rural. The predominant ethnic group in the area are the Luhya. Sugarcane is the main cash crop, and has replaced previously grown food crops as maize, beans and cooking bananas. The main rainy seasons are from April to June and from October to November. Malaria transmission is low but perennial with the highest transmission in the rainy seasons. Malaria is by far the most common diagnosis and cause of death in adults and children admitted to St Mary's Hospital, the local mission hospital. Infant and under-five mortality rates are 41/1000 and 53/1000, respectively, and the prevalence of malnutrition in children 12–23 months old is ~35%.

**Kisumu**

Kisumu, located on the shores of Lake Victoria, in Nyanza Province, western Kenya, is the third largest city in Kenya with a population of ~320,000. Most inhabitants are from the Luo tribe followed by the Luhya and the Kisii. Most urban people work as casual laborers in the informal sector, but some work in the industry or small businesses sector. Malaria transmission in this area is largely uncharacterized, but is perennial with highest transmission during peak rainfall from April-July and October-December. Exposure to infective mosquitoes is likely to vary from the city center to the peri-urban areas as entomological inoculation rates are dependent on level of urbanization and socio-economic factors. A recent study of pregnant women attending the hospital antenatal clinic reported an overall parasitemia prevalence in teenage pregnancies of 25%. HIV infection is highly prevalent and approximately 24% of 15 to 19 year old girls are estimated to be infected. Detailed information on the nutritional status of adolescents or young children in Kisumu is lacking.

![Figure 1. Study sites Asembo, Kisumu & Mumias](image-url)
Aims and outline of this thesis

The studies in this thesis aim to define the magnitude and main risk factors of anemia, malnutrition and malaria in adolescents schoolgirls in western Kenya, and to assist in the design of suitable interventions to reduce and prevent anemia in this age group.

Chapter 1 presents the background to the studies presented in this thesis.

Chapter 2 describes the results of two cross-sectional surveys assessing the prevalence, severity and risk factors of anemia and iron deficiency in 12–18 year-old 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.

Chapter 3 describes the prevalence, severity and main risk factors of malnutrition and the age at menarche as assessed by a series of cross-sectional surveys of adolescent schoolgirls in two areas of western Kenya with different levels of malaria transmission and malnutrition.

Chapter 4 describes the impact of insecticide treated bed nets on malaria and malaria-associated anemia and growth in adolescent girls as part of a large scale community-based group-randomized controlled trial. Data from the same cross-sectional surveys as described in chapter 2 are used.

Chapter 5 presents the results of a study that tests the hypothesis that levels of the pubertal hormone DHEAS are associated with reduced parasite density and other malaria related outcomes such as anemia, independent of age, and by proxy, cumulative exposure.

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.

Chapter 7 summarizes the results presented in this thesis and discusses the implications for public health programs and future research.
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