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Nutritional Anemia in Developing Countries

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1. Introduction

As described in earlier chapters, anemia is characterized by an insufficient concentration of the protein hemoglobin in the circulation, causing a lack of oxygen transporting capacity. Hemoglobin is the principal component of red blood cells, erythrocytes, and is synthesised in the bone marrow with iron as the key oxygen binding site. Before discussing causes and consequences of nutritional anemia in developing countries, it is important to consider briefly how anemia is diagnosed.

Anemia can be diagnosed clinically, for example by looking at the paleness of the skin or mucosa or by a history of weakness and dizziness. This clinical assessment is often the only method available in resource-poor settings, but unfortunately has a low sensitivity and specificity (Critchley and Bates 2005). A more direct and thus more sensitive and specific approach is to measure hemoglobin concentrations in the blood, using one of many different techniques in blood samples obtained by either finger prick or vena-puncture. The obtained values are then compared to those from a matching, normal population, using pre-defined cut-offs for anemia. It is important to realize that different cut-off thresholds are used for different situations. For example, there are different cut-off points for young children, pregnant women, non-pregnant women and men, as well as ethnic differences and differences between smokers and non-smokers. Moreover, altitude affects hemoglobin concentrations and hence cut-offs for anemia. Therefore, it is very important to select the correct reference population for the subjects studied. Cut-off thresholds are normally chosen as the point at which 2.5% of the normal population (or 2 standard deviations) has a value that is lower. Hence, in a normal population, 2.5% of the people will be anemic according to this definition. From an epidemiological viewpoint, this means that if a survey finds a prevalence of anemia close to 2.5%, the studied population can be regarded as normal. From an individual viewpoint however, if a subject from that same population was diagnosed with anemia, s/he would not regard this as normal, would like to know the cause, and if indicated, s/he would like to be treated! Moreover, cut-offs are certainly not absolute or unequivocal, rather, they should be regarded as a proposed value that is accepted by consensus, and are sometimes challenged if found insufficiently accurate. For example, there is currently discussion regarding the cut-off for anemia in infants. Domellof et al. have proposed more precise, stratified cut-off thresholds for anemia at hemoglobin

concentrations of <105 g/L for infants 4 – 6 months of age and <100 g/L for infants 9 mo of age (Domellof et al. 2002a), but as shown in Table 1, these revised cut-offs have not been implemented by the public health community yet.

Reference group	cut-off (g/L)	Categories of anemia (g/L)		
		Mild	Moderate	Severe
Pregnant women	110	100-110	70-99	<70
Non-pregnant women	120	110-119	80-109	<80
Children 6 – 59 months of age	110	100-109	70-99	<70
Children 5 – 11 years of age	115	110-114	80-1-9	<80
Children 12 – 14 years of age	120	110-119	80-109	<80
Men	130	110-129	80-109	<80

Table 1. Cut-off values used by the World Health Organization to define anemia in different population groups (WHO 2001).

There are many different causes of anemia. Pathophysiologically speaking, anemia occurs either through a) blood loss in quantities higher than the body can replete through synthesis, b) an increased breakdown in the body of erythrocytes or c) a defect in the synthesis of hemoglobin protein or of new erythrocytes. An increased breakdown of erythrocytes occurs for example in sickle cell disease (sickle cell anemia) and in malaria. However, almost all anemias caused by nutritional deficiencies affect the production of new erythrocytes or hemoglobin, thereby causing anemia.

A large part of the human population is affected by anemia, with an estimated 1.6 billion people being anemic. Iron deficiency (ID) is most often, but certainly not the only cause of nutritional anemia. Indeed, many studies have shown that iron deficiency accounts roughly for only half of the anemia cases (Wieringa et al. 2007a), meaning that improving iron status in an anemic population will only reduce the prevalence of anemia to a certain extent. On the other hand, more people have insufficient iron stores than anemia, as anemia only occurs at the end stage, when iron deficiency eventually leads to so-called iron-deficiency anemia (IDA). Indeed, the World Health Organization (WHO) estimates that roughly twice as many people are affected by iron deficiency than by iron deficiency anemia (WHO 2001).

Prevalences of anemia and iron deficiency are much higher in developing countries than in affluent countries. However, large differences in anemia prevalence exist among different continents and among different countries on the same continent. Reasons for these differences are many and include differences in basic health and nutrition characteristics (such as diet, prevelance of nutritional deficiencies, prevalence of anemia-causing illnesses such as intestinal parasites or malaria) and other factors affecting hemoglobin and erythrocyte concentrations such as sickle cell anemia or other hemoglobinopathies and altitude. To appreciate the extent of anemia as a public health problem, one only has to review the data on anemia prevalence around the world.

The highest burden of anemia and ID is found in Africa and South Asia, with many studies showing the significant public health impact of anemia in these populations. In India, the prevalence of anemia is >50% in both pregnant and non-pregnant women (WHO 2008). Low birth weight and perinatal mortality increase two-fold when hemoglobin concentrations are <80 g/L during pregnancy. Not surprisingly, anemia is estimated to be responsible for 40% of maternal deaths in India (Kalaivani 2009). In rural Bangladesh, more than 30% of

nulliparous married women were anemic when entering pregnancy, with 15% being iron deficient and 11% having IDA (Khambalia et al. 2009). And already more than 80% had inadequate iron stores, which was defined as <500 mg of iron. In Pakistan, anemia prevalence was even higher: in a large prospective observational study in ~1400 pregnant women, 90.5% were anemic (Hb<110 g/L) (Baig-Ansari et al. 2008). In Africa, the prevalence of anemia in women of reproductive age (WRA) is estimated to be ~47% and in pregnant women ~57% (WHO 2008), although prevalence rates differ widely from country to country (Lartey 2008). In Mali, anemia was present in 47% of pregnant women (Hb<110 g/L), but only 13% of the women had ID (serum ferritin <12 µg/l) (Ayoya et al. 2006). Infectious diseases were a major contributor to anemia in this study. Among pregnant women in northern Nigeria, 30% was classified as anemic (Hb< 105 g/l); Here, the major contributing factor to anemia was ID (ferritin<10 µg/L) (Vanderjagt et al. 2007). Besides ID, vitamin B12 and folic acid deficiencies were probably prevalent also. In Ghana, anemia (Hb < 110 g/L) was observed in 34 % of the pregnant women from urban areas, with 16% of the women having ID (ferritin≤ 16 µg/l) and only 7.5% having IDA (Engmann et al. 2008). Malaria was a greater risk factor than ID for being anemic in this study. Hence, in Sub-Saharan Africa ID is prevalent, but not as strongly related to anemia, as other causes of anemia such as malaria infection are also prevalent in vulnerable groups. Other areas in the world are affected by a high prevalence of anemia also. In Vietnam, more than half of 900 women investigated in a representative community survey in healthy women of reproductive age were anemic (Trinh and Dibley 2007). In contrast, in Thailand in a similar survey only 14.1 % of 590 women was found to be anemic (Hb< 11g/dl), and 6.0% had IDA, according to the WHO criteria (Sukrat et al.). These last figures are more typical for developed countries. IDA was found in 4% of French children <2 yrs (Hercberg et al. 2001), and in the USA iron deficiency was found in 14.4% of children between 1 and 2 yrs, and in 9.2% of women of reproductive age (Cogswell et al. 2009). Worryingly, there appears to be no decrease in the prevalence of iron deficiency in young children over the last decades, with especially overweight children at risk for ID (Cogswell et al. 2009).

From above data, it is clear that anemia is widespread throughout the world, and given the negative effects of anemia on health and development, a world-wide public health concern. Indeed, for decades the urgent need for interventions to reduce the prevalence of anemia has been recognized, but most interventions have had little impact (Stoltzfus 2008; Yip 2002). From the above studies, it is also clear that the distinction between anemia, IDA and ID is important, not only because of differences in prevalence and health effects of these entities, but also because the etiology and underlying determinants are distinct and call for different intervention strategies. Anemia, IDA and ID are of course interrelated and overlapping diagnoses but do not constitute a complete continuum, and specific factors, causes and determinants play a different role in each entity. Furthermore, the above studies also show that prevalence patterns of anemia and iron deficiency indicators can vary widely among populations, depending on baseline health and nutritional determinants. Below, some key aspects of the etiology, the measurement and the public health impact of anemia will be reviewed, before discussing what can be done to reduce the global burden of anemia.

2. Nutritional causes of anemia with special reference to developing countries

For some micronutrients, such as iron and vitamin B_{12}, there is a clear understanding on why deficiency leads to anemia. For others, such as selenium or vitamin A, the underlying

mechanisms are less clear. Moreover, it appears that some nutrients act synergistically, where deficiency of one micronutrient might either aggravate or mask the effects of deficiency of another micronutrient, such as is the case for Vitamin B_{12} and folic acid. Furthermore, anemia is the end result of a long process, often with a multi-factorial etiology, with other health determinants often also playing a role. Therefore, anemia has been difficult to address from a public health point of view, and remains present in many populations despite countless intervention efforts.

As the etiology of anemia has been covered extensively in previous chapters and in other books, this chapter will focus mainly on strategies to prevent anemia from nutritional causes and reduce the prevalence in various populations, especially in those vulnerable groups that have the largest burden or the largest health impact of anemia. For more detailed information on the etiology of nutritional anemia, interested readers can freely download the book 'Nutritional Anemia' from the Sight and Life website (Sight_and_Life 2007). However, as some nutritional aspects of the etiology of anemia are important for understanding the ratio behind certain interventions, these are highlighted in this chapter when necessary.

Anemia is often considered a synonym for iron deficiency. However, as described above, anemia and iron deficiency are distinct, albeit overlapping, conditions. Anemia occurs in the later stages of iron deficiency, when iron stores are completely depleted. However, before anemia occurs, iron deficiency is already affecting other functions, such as the immune system and the nervous system, leading to reduced immunocompetence, decreased physical activity and cognitive impairment (Beard 2001). Physiologically, iron deficiency occurs when requirements exceed the amount of iron absorbed from the diet. Requirements are increased by rapid increases in body mass (such as in pregnant women, young children) or by high losses of iron (menstruation, hookworm infection). This explains in part the high prevalence in vulnerable groups such as children and pregnant women, and on the other hand, the association of anemia with poverty and poor health. A special situation is sequestration of iron in the body, making it less available for utilisation for e.g. hemoglobin synthesis, such as happens in (chronic) infection by the acute phase response or in massive erythrocyte breakdown (such as in malaria). Looking at the uptake of iron, it is found that in general iron absorption is low (~5%) from plant-based diets (developing countries) because of iron-uptake inhibiting factors (phytates, polyphenols) and iron absorption is higher (~15%) from diets containing more meat and fish (developed countries) because iron in animal products is often bound in heme protein structures that greatly facilitates absorption. This explains in part the much higher prevalence of ID in developing countries.

Other nutrients in the diet are also important, and deficiencies of other nutrients can directly or indirectly contribute to anemia and sometimes even to ID. The role of vitamin A in iron metabolism was recognized already in the 1980's (Mejia and Chew 1988), when studies showed that the effect of iron supplementation on hemoglobin concentrations could be enhanced by the addition of vitamin A (Suharno et al. 1993). The mechanisms by which vitamin A enhances hemoglobin formation are not completely understood, but vitamin A is thought to play a role in the absorption of iron and/or in the utilization of iron stores for new heme production (Zimmermann et al. 2006). Because interactions are probably on the level of gene expression and protein synthesis, it is an intricate and finely balanced interplay and deficiencies or excess can have indirect and sometimes unanticipated effects. In the latter case, this means that providing vitamin A to subjects with a marginal iron status

would make these subjects more iron deficient, as extra iron would be used for the production of hemoglobin, and is no longer available for other tissues such as the brain. Indeed, we showed in a large multi-country trial in SE Asia that vitamin A supplementation in infancy, without interventions to improve iron status, was associated with anemia (Wieringa et al. 2007a). This is an important reminder that understanding of the underlying mechanisms is important, even though the final public health effect is the objective of an intervention.

Nutrient	(proposed) mechanism leading to anemia	Ref
Iron	Essential part of heme. Deficiency: reduced production of hemoglobin	(Bates et al. 1989)
Folic Acid	Deficiency: Impaired DNA synthesis leading to reduced number of erythrocytes	(Koury and Ponka 2004)
Vitamin B_{12} (Cobalamin)	Deficiency: Interference with folic acid metabolism (see above)	(Koury and Ponka 2004)
Vitamin B_2 (Riboflavin)	Likely involved in iron absorption in gut mucosa	(Powers 2003)
Vitamin B_6 (Pyridoxal)	Possibly involved in heme biosynthesis	(Sight_and_Life 2007)
Vitamin A	Possibly involved in heme biosynthesis, perhaps also involved in regulating availability of iron from liver stores	(Roodenburg et al. 1996; Zimmermann et al. 2006)
Vitamin E	Deficiency: Oxidative stress of the erythrocytes leading to increased hemolysis	(Sight_and_Life 2007)
Vitamin C	Availability in gut enhances conversion Fe3+ to Fe2+ , increasing iron bioavailability.	(Bates et al. 1989)
Selenium	Deficiency: Possibly oxidative stress or increased inflammation	(Van Nhien et al. 2008)
Copper	Deficiency: Interference with red cell maturation and iron absorption	(Sight_and_Life 2007)

Table 2. Nutrients associated with anemia in developing countries.

Other deficiencies clearly related to the development of anemia are vitamin B_{12} and folic acid deficiency. Deficiency will lead to a characteristic megaloblastic anemia, meaning larger than normal erythrocytes, with poorly differentiated nuclei (Sight_and_Life 2007). Neither vitamin B_{12} nor folic acid deficiency is a rare condition in developing countries, and both contribute to the overall high rates of anemia seen in developing countries. Folic acid is also involved in the neural development of the fetus, and deficiency can result in very distinct malformations. Indeed, flour fortification with folic acid in the USA has resulted in a dramatic decrease in neural tube defects (Berry et al. 2010), making it a very cost-effective intervention (Grosse et al. 2005). The role of vitamin E and selenium in the etiology of anemia is less clear. Suggested mechanisms involve increased oxidative stress, leading to earlier breakdown of erythrocytes or increased inflammation.

Inflammation itself is associated with anemia, and this is often referred to as the 'anemia of chronic disease'. Immune activation leads to a decrease in erythropoiesis (synthesis of new erythrocytes), which eventually will lead to lower hemoglobin concentrations and

anemia. Immune activation, and especially the so-called acute-phase response, which is the generalized reaction of the body to infection or trauma, also results in a re-distribution of many nutrients in the human body. This re-distribution makes it more difficult for pathogens to replicate, and has been termed 'nutritional immunity' (Weinberg 1975). However, this re-distribution of nutrients such as iron, vitamin A and zinc by the acute phase response also distorts the measurement of micronutrient status by changing the plasma concentration of indicators commonly used to assess status. We and others have been trying to quantify the extent of this distortion by the acute phase response on several indicators (Wieringa et al. 2002), and have proposed factors (Table 3) to correct for the effects of inflammation (Thurnham et al. 2010; Thurnham et al. 2003). This is important for the estimation of the prevalence of micronutrient deficiencies in populations. If inflammation prevalence is high, e.g. in areas with endemic malaria, the perceived prevalence of vitamin A and zinc deficiencies will be significantly higher, as plasma retinol and zinc concentrations are reduced by inflammation. On the other hand, the perceived prevalence of ID and IDA will be significantly lower, as ferritin concentrations are increased in inflammation. Hence, the acute phase response should be taken into account when using indicators of micronutrient status sensitive to it by concomitantly measuring concentrations of acute phase proteins such as C-reactive protein (CRP) and α1-acid glycoprotein (AGP).

	Incubation phase (only CRP elevated)	Early convalescence phase (CRP and AGP raised)	Late convalescence phase (only AGP raised)
Ferritin ratios compared to no inflammation	1.30	1.90	1.36
Proposed correction factors for ferritin concentrations	0.77	0.53	0.75

Table 3. Effect of different phases of inflammation on ferritin concentration, and proposed factors to correct for the effect of inflammation on ferritin concentrations. Adapted from (Thurnham et al. 2010).

3. Interventions to reduce the prevalence of anemia

Unfortunately, efforts in the last decades to reduce the prevalence of anemia and iron deficiency have not been too successful. As anemia has a multi-factorial etiology, reasons for success or failure of interventions are also many. One striking feature of all public health interventions is the huge difference between the efficacy of studies done in a controlled research setting and the effectiveness of strategies implemented on a national scale. Unfortunately, anemia and iron deficiency interventions also demonstrate this difference compellingly. Whereas there are many studies published showing excellent efficacy of interventions to improve iron status in pregnant women or other risk groups, the few studies reporting effectiveness of large-scale iron interventions show little or no impact. Indeed, even the INACG (International Nutritional Anemia Consultative Group) was forced to conclude that although both daily and weekly iron supplementation regimens have been

demonstrated to be efficacious in vulnerable population groups, existing data do not demonstrate that large-scale programs with iron supplementation are generally effective (INACG 2004).

3.1 Evidence-based intervention development and implementation: Moving policy forward

Globally, most efforts to reduce anemia have focused on pregnant women, with millions of iron and folic acid tablets being provided to pregnant women all over the world annually. There are several reasons for this specific attention during pregnancy. Looking more closely at the reasons shows how science, health care and policy interact together resulting in the development and implementation of interventions. First of all, iron requirements during pregnancy increase by more than two-fold, to >4 mg Fe/day (Steer 2000), an amount that is almost impossible to meet with a diet with low available iron (Yip 1996). Indeed, it is even difficult to meet this requirement with a Western-style diet (with meat) with high iron-availability. Thus interventions would be useful in this situation, and direct effects can be expected. Furthermore by targeting pregnant women, one hopes to break the negative inter-generational vicious circle of poor intra-uterine growth leading to low adult height predisposing to poor intra-uterine growth. . So interventions in this target group can also contribute more indirect, long-term effects. Thirdly, during pregnancy women are encouraged to access health services, offering opportunities for targeted interventions such as iron supplementation. Often, health care access for pregnant women is already part of national public health policy, with encouraging antenatal care programs and registration in place. Finally, most published studies have been done in pregnant women; hence most evidence on impact of interventions such as iron supplementation is available for pregnant women, driving policy towards strategies focusing on pregnant women. The available evidence informs and focuses policy interests, and as policy prefers predictable results this encourages policy development in this field. However, other closely linked groups also at risk for anemia such as young infants and children or women of reproductive age (WRA) are thereby often sidelined, as the available evidence for these groups is less complete and less clear, and effects less well documented. This results in less interest from policy, and less momentum to advocate and develop interventions for these groups. In this way, policy interests may drive science but science also steers policy interests. To remain updated on latest policy developments, specific sites such as eLENA from the WHO (www.who.int/elena/en) are available.

3.2 Interventions for pregnant women

A meta-analysis on the effects of iron and folic acid supplementation in pregnancy was recently done by Pena-Rosas and Viteri (Pena-Rosas and Viteri 2009). Their meta-analyses comprises 49 trials with >23,000 women. Data on anemia and IDA was available for 1108 women from 6 trials. In women taking iron supplements, 30.7% were still anemic at term, whereas only 4.9% had IDA. For women not receiving iron these figures were 54.8% and 15.5%. These findings clearly demonstrate the multi-factorial etiology of anemia. Iron deficiency and folic acid deficiency are only part of the problem. Hence, providing only iron and folic acid can only be expected to give a partial improvement in anemia prevalence, depending on the extent of the pre-existing deficiency of iron. Despite this remaining prevalence of anemia, the intervention significantly increased hemoglobin concentrations in

the pregnant women, and thereby reduced the risk at term for anemia (RR 0.27 CI 0.17 – 0.42). Surprisingly, the authors found no significant effects on important health outcomes such as premature delivery, low birth weight (RR 0.79 CI 0.61 – 1.03), birth weight (+36.1 g CI -4.8 – 77.0), perinatal death or infant hemoglobin concentrations at 6 mo of age. It is important to consider these conclusions. Currently, blanket iron and folic acid supplementation programs for pregnant women are in place in many countries, with the expectation that it will substantially improve maternal and infant health (Bhutta et al. 2008). But apparently, the benefits of only iron and folate supplementation during pregnancy are less substantial and not as clear-cut as hoped for.

One explanation for the lack of improvement in maternal and infant health outcomes could be that the number of studies providing data on outcomes such as perinatal mortality was too low to draw consistent conclusions. Dibley and colleagues examined Indonesian demographic data with >40,000 pregnancies and showed that the iron and folic acid supplementation program protected against neonatal death in the first week after birth (RR: 0.53; 95% CI: 0.36–0.77) (Titaley et al. 2010b). And this beneficial effect also holds true in countries with endemic malaria, provided that it is combined with intermittent malaria treatment (Titaley et al. 2010a). Another explanation could be that other nutritional deficiencies, such as vitamin A deficiency or zinc deficiency, hampered a beneficial effect of the intervention. Perhaps, providing only iron (and folic acid) is not enough. Are multiple micronutrient supplements during pregnancy more effective? It is known that multiple micronutrient deficiencies often coexist (Dijkhuizen et al. 2001). Indeed, deficiency of multiple micronutrients in one individual is more common than single micronutrient deficiency (Thurlow et al. 2006). And given the multi-factorial etiology of anemia, a greater benefit might be expected from multiple micronutrient supplementation than from supplementation with iron and folic acid alone.

In the last decade, several large studies on the efficacy of multiple micronutrient supplementation during pregnancy on improving anemia and health outcomes have been conducted. However, results have been conflicting or confusing, partly because studies used different combinations of micronutrients, different amounts of micronutrients or different outcomes. An 2006 Cochrane review of 9 trials with >15,000 women showed that multiple micronutrient supplementation decreased the prevalence of low birth weight and maternal anemia (RR 0.61 CI 0.52 – 0.71) (Haider and Bhutta 2006). However, the effect of multiple micronutrient supplementation was not different from iron (+folic acid) supplementation alone and there was no effect on preterm births or peri-natal mortality. Hence, from this review, there appears to be no additional benefit of multiple micronutrient supplementation over only iron + folic acid during pregnancy. However, more recently, another meta-analysis using different criteria and inclusion of 2 recently published large trials, concluded that prenatal multi-micronutrient supplementation was associated with a significantly reduced risk of low birth weight and improved birth weight per se when compared with iron–folic acid supplementation (Shah and Ohlsson 2009). Some studies suggest that different combinations of micronutrients have different effects on the birth weight distribution curve, with iron and folic acid affecting the lower end of the distribution curve, meaning that there is only a specific effect on low-birth weight, without a change in overall birth weight. In contrast, supplementation with multiple micronutrients appears to shift the whole distribution curve to higher birth weights (Katz et al. 2006). Although this seems more beneficial, this could also have a downside. The shift towards higher birth weights

after multiple micronutrient supplementation could possibly also increase the number of obstructed deliveries. Hence, the potential benefits on infant survival by reducing the number of low birth weight infants, might be nullified by increasing the number of large-for-gestational age infants (Katz et al. 2006). Also, there are indications that supplementation with micronutrients (especially zinc and vitamin A) during pregnancy might affect the immune system of the newborn, and that these effects might be long-lasting and may not be only beneficial (Raqib et al. 2007; Wieringa et al. 2010; Wieringa et al. 2008). It is unclear at present whether these concerns also hold true with a weekly multiple micronutrient supplement given during pregnancy, with supplements given before conception, or with food-based interventions such as fortification, but these strategies, by being more physiological, could well have less negative or nullifying effects and therefore be more effective overall. However, results of such interventions are scarce and not very clear yet at this moment.

Besides safety concerns, there are other aspects of supplementation programs which need to be taken into account. In a study in China, effects of micronutrient supplementation during pregnancy on outcomes such as birth weight were only significant when supplementation started *before 12 weeks* of gestation (Zeng et al. 2009). Neither iron + folic acid nor multiple micronutrient supplementation started after 12 weeks of gestational age had an effect on birth weight. Other studies confirm that hemoglobin concentrations early in pregnancy are related to low birth weight in a U-shaped curve. Women between 4 and 8 weeks of pregnancy with hemoglobin concentration between 90 and 99 g/L had a 3.27 (CI 1.09 – 9.77) higher risk for a low birth weight baby than the reference category (110 – 119 g/L), whereas risks for low birth weight and preterm birth also increased with hemoglobin concentrations >130 g/L (Zhou et al. 1998). However, it is unlikely that the conditions of the study (high compliance, very early start of supplementation) can be met by standard national programs, where women are more likely to report to the health system for the first time at around 16 weeks of pregnancy. Based on the above observations, it can be expected that the effects of supplementation programs for pregnant women, whether providing iron, iron + folic acid or multiple micronutrients, will be disappointingly small or absent.

3.3 Interventions for women of reproductive age

Surprisingly, only few studies have investigated the effects of pre-conception supplementation with iron or multiple micronutrients on maternal or neonatal health, even though improving micronutrient status before or early in pregnancy seems to be most effective, and nutritional status around conception is a very important determinant of pregnancy health and outcome. This is especially clear for folic acid, where pre-conceptual increases in status have a strong effect on the reduction of neural tube defects, with possibly >70% of neural tube defects prevented by adequate intakes of folic acid. For other micronutrients such as iron, the exact effect of pre-conception status on maternal and child health is less clear, mainly due a lack of studies in humans. To meet iron needs during gestation, women need an iron reserve of at least 300 - 500 mg prior to conception so as not to become iron deficient after the first trimester (Milman et al. 2005; Viteri and Berger 2005). Many women in developing countries will have much lower iron reserves than this and hence are at risk of becoming iron deficient during pregnancy. Indeed, even many women in affluent countries fail to enter pregnancy with adequate iron stores. Studies suggest that

56% of non-pregnant women in the USA had iron stores <300 mg (Viteri and Berger 2005) and <20% of Danish women were estimated to have adequate (>500 mg) iron stores before pregnancy (Milman et al. 2005). A multi-country trial in SE-Asia examined long-term effects of supplementing women of reproductive age with iron and folic acid by following the women through pregnancy and delivery (Cavalli-Sforza et al. 2005). In the non-pregnant women, iron status significantly improved over the intervention period. In Vietnam for example, anemia prevalence decreased from 45% at baseline to <20% after 9 months to 1 year. Moreover, longer pre-pregnancy supplementation was associated with less anemia and better iron status during the first and second trimester of pregnancy. Indeed, there was no IDA in the first and second trimester of pregnancy in women who started taking supplements >3 months before conception (Berger et al. 2005). Another important observation was that although anemia prevalence rose in the 3rd trimester of pregnancy, there was almost no severe anemia (Hb< 95 g/L). Severe anemia is directly associated with increased perinatal risk for mothers and newborns, whereas mild anemia is often physiological in the third trimester and is a sign of the hemodilution normally seen in pregnancy. Unfortunately, data on birth weight was available for only 200 infants, but there was a tendency towards higher birth weights per se (+81 g) in the weekly supplementation group (P=0.15) and towards lower prevalence of low birth weight (<2500 g; 3% and 9% respectively, P=0.08) (Berger et al. 2005). In Vietnam, weekly supplementation of iron and folic acid in combination with deworming has been continued as pilot to improve iron status of WRA and has been shown to be successful as such: provision of weekly iron and folic acid for free has resulted in significant reductions in anemia (from 38% to 19%) and ID (ferritin<15 μg/L) (23% to 9%) prevalence in Vietnamese WRA (Casey et al. 2009). Nowadays, the World Health Organization (WHO 2009) recommends weekly iron and folic acid in WRA as one of the strategies to reduce anemia during pregnancy.

Similar to pregnant women, deficiencies of more than one micronutrient are also likely in women of reproductive age. However, until now no studies have documented the long-term effects of providing women of reproductive age with multiple micronutrients.

3.4 Interventions for young children

Infants and young children are especially at risk of anemia and iron deficiency as growth increases nutrient requirements. Iron deficiency not only leads to anemia, but may, even before the onset of anemia, cause impairment of psycho-motor development which is in part irreversible (Beard 2001; Black 2003). In many developing countries, over 50% of infants are anemic by 1 year of age (Dijkhuizen et al. 2001). Although blanket iron supplementation for young children has being considered as an option to reduce anemia prevalence in childhood, studies comparing the effects of iron supplementation on infants in Sweden and Honduras suggested that iron supplementation in iron-replete infants may not be beneficial, and can cause growth faltering (Dewey et al. 2002). Furthermore iron supplementation in children living in malarious areas increased morbidity and mortality (Sazawal et al. 2006), iron supplementation may negatively influence zinc uptake and zinc status (Wieringa et al. 2007a), and iron supplementation in infancy may cause a redistribution of vitamin A (Wieringa et al. 2003) . Therefore, as public health interventions must operate from the '*Non Nocere*' (Do No Harm) principle, these potential adverse effects make global blanket iron supplementation for under-five children unfeasible.

Four parallel studies on iron and zinc supplementation in infants were conducted in South-East Asia (Thailand, Vietnam and Indonesia) to investigate effects on micronutrient status and growth. These studies showed that although iron status and anemia prevalence were significantly improved, no overall effect on growth could be found (Dijkhuizen et al. 2008). Also, despite iron supplementation for 6 mo, at least 25% of the infants remained anemic in the iron-supplemented groups. The prevalence of iron deficiency anemia, however, was less than 2.5% after iron supplementation. Hence, the anemia remaining after supplementation may be due to unresolved deficiencies of other nutrients such as vitamin B_{12} or folic acid, to chronic inflammation, or to hereditary hemoglobinopathies. Estimates of for example α-thalassemia prevalence in the region ranges from 3 to 11% (Weatherall and Clegg 2001) and could explain at least part of the remaining anemia. However the data itself could also be interpreted differently perhaps. As discussed earlier, cut-off values for anemia in infancy are being reconsidered, and using other newly proposed (lower) cut-offs on these study results will give lower estimates of the prevalence of anemia. This is an important consideration whenever cut-off thresholds are used, the threshold that is used determines the prevalence found. Cut-off values for anemia that are currently used may not be appropriate for infants and may thus lead to an overestimation of anemia prevalence in this age group (Domellof et al. 2002a). Another interesting finding in the 4 studies in SE Asia, is that the effect of iron supplementation on hemoglobin concentrations was almost twice as large in boys than in girls (Wieringa et al. 2007b). Although hemoglobin concentrations differed between genders at recruitment, the differences were not as large as at the end of the study. Hence the largest part of the difference in hemoglobin concentrations between boy and girl infants developed during the second half of infancy. One possible explanation for these gender differences may be the higher growth rate of boy infants, leading to increased iron requirements. An important implication is that boy infants are more at risk for anemia and iron deficiency (Table 4), a finding that has been reported elsewhere also (Domellof et al. 2002b). We estimated that daily iron intake of boy infants should be almost 1 mg/d higher than that of girl infants to achieve similar iron body stores (Wieringa et al. 2007b). These considerations on age and gender related differences in iron status complicate the development of interventions, and together with the potential adverse effects of iron, make appropriate dosing and targeting important aspects to consider in intervention strategies for infants and under-five children. Also, approaches with lower, more physiological dosing such as weekly dosing and food based interventions such as fortification may have significant advantages here, as will be discussed below.

	Relative Risk for Boy infants
Anemia	1.6 (1.3 – 2.1)
Iron Deficiency Anemia	3.3 (2.1 – 5.0)

Table 4. Relative risk for boy infants to be anemic or have iron deficiency anemia at 11 months of age when not receiving iron supplements. Table adapted from (Wieringa et al. 2007b).

Besides supplementation, other strategies to improve anemia prevalence and micronutrient status of young children need to be considered. One noteworthy strategy is the provision of complementary foods fortified with micronutrients. In a series of studies in Vietnam, we showed that micronutrient-fortified complementary foods significantly improved iron status and reduced the prevalence of anemia (Phu et al. 2010). Importantly, the intervention showed that when infants received fortified complementary food from 5 months of age onwards, iron status remained at the same level, whereas iron status in the control group deteriorated over the 6 month intervention period. Other important strategies are delayed cord-clamping and the promotion of exclusive breastfeeding during the first 6 months of life (Dewey and Chaparro 2007). Indeed, iron stores can be increased by 33% by a 2-minute delay in clamping the umbilical cord (Dewey and Chaparro 2007)! De-worming is probably a less effective strategy in this age-group in Vietnam as the prevalence of parasitic infestation is still low, and only increases rapidly when the child starts to venture outside. However, large differences in the prevalence of parasitic infestation exist among cultures, so this intervention is also worth considering, and often added as an adjuvant measure in older children.

To conclude, although iron supplementation benefits hemoglobin concentrations and reduces the prevalence of anemia in infancy, potential adverse effects such as increased morbidity and mortality and growth-faltering in iron-replete infants make blanket supplementation unfeasible. Therefore, targeting is warranted, e.g. by screening infants prior to implementing iron supplementation. Appropriate and more physiological dosing is another important concern. Provision of high-quality complementary foods improves micronutrient status and reduces the prevalence of anemia, probably without the risk of detrimental effects on health or growth as seen with supplementation.

3.5 Interventions for school-aged children

School-age children are a neglected group with regard to interventions to reduce the prevalence of anemia or improve micronutrient status. One of the few interventions widely implemented is deworming. Helminthic infections have been shown to be major contributors to anemia and malnutrition in the developing world through effects on digestion and absorption, chronic inflammation and increased nutrient losses (Stoltzfus et al. 2000; Stoltzfus et al. 1997). However, many children only receive deworming every 6 months, a frequency which might not be enough to bring down parasite infestation if the infection rate is high. And only deworming might not be enough to restore depleted micronutrient stores (Hall 2007). Food provided at school that is fortified with multiple vitamins and minerals, in combination with regular deworming could be a more effective strategy to reduce anemia in school-aged children, and will supply the children with a whole range of nutrients necessary to grow and learn. The school food often also provides an additional motive for school attendance, which is an important concern in many countries. Indeed several studies have shown significant improvements in hemoglobin concentrations and micronutrient status from such combined programs (Faber et al. 2005; Nga et al. 2009; van Stuijvenberg et al. 1999). Besides improvements in micronutrient status, these studies also resulted in important improvements in cognitive function, thus showing also functional benefits of the intervention. Interestingly, in one study in Vietnam there was a high prevalence of anemia, but the prevalence of iron deficiency and iron deficiency anemia was low. Yet, biscuits fortified with multiple micronutrient decreased anemia

prevalence by 40%, again highlighting the importance of other nutrients than only iron in the etiology of anemia (Nga et al. 2009). The same study reported an enhanced effect of deworming on Ascaris and Trichuris infection when combined with multi-micronutrient fortified biscuits, suggesting also improvements in immune function in school children who received fortified food (Nga et al. 2011). Given the low cost of food fortification (for example, fortifying a meal of rice per day for 1 school child would cost less than US$1/year), and the potential benefits, food fortification should be given high priority for this age group.

3.6 Interventions for adolescent girls

Finally, another often-forgotten age group is that of adolescent girls. Anemia prevalence is often high in adolescents girls due to blood loss through menstruation combined with an increase in growth rate. Reaching adolescent girls through existing health programs has been proven difficult, as often the most vulnerable groups are no longer attending school (Ahluwalia 2002), whereas anemia prevalence in these girls can be extremely high (Bulliyy et al. 2007). Otherwise, programs through schools have been shown to be effective in increasing hemglobin concentrations of adolescent girls (Tee et al. 1999), and as discussed above, multiple micronutrient supplementation is more beneficial than only iron and folic acid supplementation in reducing anemia prevalence as other nutritional causes of anemia are also addressed (Ahmed et al. 2010). The cultural context with regard to education, access to health care and other important aspects of the position of women play a disproportionally important role for this group, making the development and implementation of interventions especially challenging. However, as this group is poised to progress to WRA it is at the same time extremely urgent to reach this group.

There rests a special case for anemia in malaria endemic areas. This anemia is in part due to malaria infection, as there is an increased breakdown of erythrocytes. But as malaria itself is associated with poverty, nutritional deficiencies are also an important cause of anemia in these populations. However, interventions are not so easy, as the malaria infection is fuelled by iron and erythropiesis (Oppenheimer 2001). This makes for a dangerous combination, and indeed, many studies have found that iron supplementation increased morbibity and mortality in malaria endemic populations. The consensus for the moment is that iron supplementation interventions need to be combined with adequate bed-net usage and intermittent anti-malarial therapy (WHO/UNICEF 2007). Surprisingly, the increase in morbidity and mortality after iron supplementation in the study in Pemba was not only due to malaria but to a whole range of common childhood infections (Sazawal et al. 2006) suggesting a complex interplay between (sub-clinical) malaria infection, immune function and nutritional status. Again, food based interventions to improve iron status such as fortification and dietary diversification also seem to carry less risk to increase morbidity and mortality in malaria endemic areas, perhaps because the more physiological approach does not lead to an increase in the so-called non-transferrin bound iron (NTBI) (Troesch et al. 2011).

4. Conclusion

Anemia is major public health problem in many developing countries. Nutritional deficiencies of iron and also of other micronutrients underlie an important part of this, but

are certainly not the sole contributor. Anemia is often regarded as nutritional anemia, however other causes of anemia include hemoglobinopathies (such as sickle cell trait and thalassemia), chronic infections (such as malaria and tuberculosis) and intestinal parasites. Anemia is also often equated to iron deficiency. However, WHO estimates that less than half of the anemia in the world is due to iron deficiency. Indeed, as shown by several studies from Vietnam, anemia prevalence remains high in vulnerable population groups whereas the prevalence of iron deficiency has decreased rapidly over the last decade. Other micronutrient deficiencies, such as vitamin B_{12}, folic acid or vitamin A deficiency, might underlie this paradox, although parasitic infestation certainly contributed to the anemia observed in this population. Many interventions with the potential to be effective in reducing anemia prevalence in vulnerable groups exist. Iron supplementation has been promoted for decades as a cost-effective strategy. However, care should be taken when implementing this intervention, as interactions with other micronutrients (zinc, copper, vitamin A) and infectious diseases (malaria) might lead to adverse effects, and correct timing of the intervention (early in pregnancy) appears to be of major importance for success. Interventions with multiple micronutrients have the benefit of addressing multiple causes of anemia, and have been shown to be successful in improving hemoglobin and micronutrient status of school children, with the additional benefit of improving cognition and immune function. Additional benefits of multiple micronutrient supplementation during pregnancy are unclear at the moment, with small gains in birth weight reported, but with no benefits for neonatal survival. New strategies such as weekly supplementation of women of reproductive age with multiple micronutrients need to be investigated urgently. For the long-term, food fortification to improve overall micronutrient status of populations is the most cost-effective strategy, with adverse effects less likely to occur, and targeting or differential dosing often automatically incorporated in the choice of food vehicle. Effective interventions directed at all stages of the life cycle are urgently needed and both policy and science should work in concert. Not only to explore new approaches, but also to critically evaluate existing evidence and efforts, and gain understanding in the complex physiological, nutritional and social factors involved in anemia as a public health problem. This will allow the development of evidence-based effective strategies that are tailored to specific populations, vulnerable groups and cultural settings, providing improved and more accurate tools to reduce anemia.

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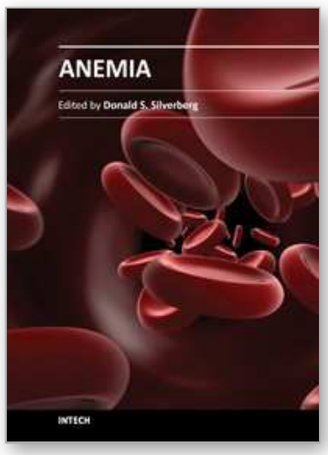

Anemia

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This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

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