PREVENTING AND TREATING ANAEMIA

Anaemia is defined as a low Hb concentration in blood, or less often, as a low haematocrit, the percentage of blood volume that consists of red blood cells. The limits which define anaemia are shown in Table 8[279]. Nutrition anaemias are caused when there is an inadequate body store of a specific nutrient needed for Hb synthesis.

TABLE 8: Haemoglobin (Hb) limits used to define anaemia[a] based on WHO/ UNICEF/UNU (1996) recommendations

Age or gender group	Hb below (g/L)	Haematocrit below (%)
Children 6 months -5 years	110	33
Children 5-11 years	115	34
Children 12-13 years	120	36
Nonpregnant women	120	36
Pregnant women	110	33
Men	130	39

Source: Stoltzfus RJ, Dreyfuss ML (1998) *Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia*. Geneva: International Nutritional Anaemia Consultative Group/UNICEF/WHO.

[a] These definitions are for populations living at sea level. To adjust for altitude, make the following additions to the values for Hb and haematocrit respectively: 3,000-3,999 ft (914 – 1,218 m) +2.0, +0.5; 4,000-4,999 ft (1,219 – 1,523 m) +3.0, +1.0; 5,000-5,999 ft (1,524 – 1,827 m) +5.0, +1.5; 6,000-6,999 ft (1,828 – 2,133 m) +7.0, +2.0.

Anaemia is usually caused by lack of iron, the most common nutrient deficiency. Iron deficiency anaemia (IDA) is typically diagnosed by low Hb, accompanied by biochemical evidence of iron deficiency, such as low serum ferritin concentration. Hb response to iron supplementation can also be used to confirm that the anaemia was caused by iron deficiency. Women and children have a higher prevalence of nutrition anaemias than men. Even in developed countries, about 20 to 30% of women of reproductive age have little or no stored iron. Malaria and hookworm, the major non-nutrition risk factors for anaemia, affect both men and women.

In addition to iron, several other micronutrients are important for Hb synthesis. VAD is a significant factor in many cases of anaemia and can contribute to incomplete Hb recovery after iron supplementation. Vitamin B_{12} deficiency is common in many regions, and folic acid deficiency has been reported in some areas. A relatively severe deficiency of either of these two vitamins can cause anaemia by impairing red blood cell synthesis. Riboflavin deficiency also occurs commonly in some regions, and impairs iron absorption. The relative contributions of these vitamin deficiencies to anaemia can be determined by comparing Hb response to supplementation with iron alone, or in combination with the other nutrients, although there is little information on this. Anaemia has multiple adverse effects on human function. These are independent of the other consequences of specific nutrient deficiencies.

The Prevalence of Anaemia and of Iron Deficiency

The World Health Organization[196] estimated that about 40% of the world's population (more than 2 billion individuals) suffer from anaemia. The groups with the highest prevalence are: pregnant women and the elderly, about 50%; infants and children of 1-2 years, 48%; school children, 40%; nonpregnant women, 35%; adolescents, 30-55%; and preschool children, 25%. Because few countries have collected representative data on the prevalence of anaemia, and because much of the information is from clinic records or small surveys, national or regional estimates of anaemia are not very precise. Nevertheless, it is apparent that the prevalence of anaemia in developing countries is about four times that of developed countries. Current estimates for anaemia in developing and developed countries respectively are: for pregnant women, 56 and 18%; school children, 53 and 9%; preschool children, 42 and 17%; and men, 33 and 5%[196].

The WHO has suggested the following classification of countries with respect to the level of public health significance of anaemia: a prevalence of <15% is "low", 15-40% is "medium" and >40% is "high". Asia has the highest rates of anaemia in the world. About half of the world's anaemic women live in the Indian subcontinent, and 88% of them develop anaemia during pregnancy. The situation in Asia has not improved in recent years[11].

Anaemia occurs at a late stage of iron deficiency, after stores are depleted. The prevalence of iron deficiency, which is usually detected by low serum ferritin concentrations, is estimated to be from 2.0 to 2.5 times the prevalence of anaemia. There are few data on the actual prevalence of iron deficiency in developing countries because of the resources required to measure the necessary biochemical indicators. In population groups with a high prevalence of anaemia, however, almost all individuals will be iron deficient, except possibly if the anaemia is caused predominantly by malaria.

Causes of Anaemia

Inadequate absorption of dietary iron is the main explanation for the much higher prevalence of anaemia in the developing countries of Asia and other regions, except where it is caused by infections such as hookworm and malaria. The best sources of dietary iron are meat, fish and poultry. These foods have a major influence on iron status, but intakes are low among poor people or when such foods are avoided for religious or cultural reasons. They contain more iron than cereals, dairy products, fruit or vegetables, and about 40% of their iron content is in the haem form, of which about 25% is absorbed. Only about 2-5% of the total iron is absorbed from cereals and legumes, and cereals contain much less iron than meat, fish or poultry[211].

At certain periods in life, iron requirements are particularly high, and therefore less likely to be met. Iron requirements are highest for pregnant women: 1.9 mg/1,000 kcal of dietary energy in the second trimester and 2.7 in the third. The figures for other groups are: infants, 1.0; adolescent girls, 0.8; adolescent boys, 0.6; nonpregnant women, 0.6; preschool and school children, 0.4; and adult men, 0.3[212]. Assuming that individuals within a household eat a similar diet, those with the highest iron requirements are at highest risk of becoming iron deficient. Women have a substantially higher prevalence of anaemia than men, because about half of their iron requirement is needed to replace iron losses in menstruation. This explains why most women in developing countries, and many in developed countries, enter pregnancy with depleted iron stores. Their high iron requirements, for maternal tissue synthesis and for transfer to the foetus, exacerbate their iron deficiency, as do: blood losses at delivery; short (less than 2 year) interpregnancy intervals; adolescent pregnancy; and multiple births.

In infancy, risk factors for anaemia include premature clamping of the umbilical cord[280] and maternal iron deficiency during pregnancy. In a comparative study of 6 month-old, exclusively breastfed infants in Honduras and Sweden, ferritin concentrations of the Honduran infants were half those of the Swedish infants, presumably illustrating the lower accumulation of iron *in utero* by the Honduran group[242]. The iron content of breastmilk is low and cannot supply enough for the full-term infant after the age of 6 months. Therefore, prolonged breastfeeding, as well as inadequate amounts of absorbable iron in complementary foods, explains the peak prevalence of anaemia between about 9 and 18 months of age. About half of the infants in developing countries become anaemic by 12 months[282].

In many countries, the prevalence of anaemia declines substantially starting at about two years of age, because iron requirements for growth fall after the first year of life. However, where intake of animal products is low, and parasites common, prevalence of anaemias may still be high. In adolescence, anaemia again becomes common: girls start to lose iron in menstrual blood, and both boys and girls deposit iron in lean tissue. Because adolescent boys gain more lean tissue than girls, the prevalence of anaemia may be similar between the genders.

A major cause of anaemia is infection with malaria or other parasites. *Plasmodium falciparum* is the primary cause of severe malaria in regions of the world where malaria is endemic. In tropical Africa, for example, malaria and anaemia explain the majority of visits to heath centres. In Tanzania, malaria causes about 60% of the anaemia, and iron deficiency only 30%[78].

An Expert Consultation on the determinants of anaemia, organized by the Micronutrient Initiative (MI) in September 1997, led to the design of a life cycle risk matrix as an aid in analyzing the etiology of anaemia. Such a matrix could also be used for deciding on appropriate action at each lifecycle stage[281].

Consequences of Anaemia

Anaemia impairs human function at all stages of life. Severe anaemia during pregnancy is thought to increase the risk of maternal mortality. A review of 21 studies[282] showed that anaemia explained 23% of the maternal mortality in Asia and 20% in Africa. However, these studies were retrospective and when anaemia is associated with mortality, both of these outcomes could be caused by a third problem, such as infection. There have been no large scale, placebo-controlled, prospective intervention studies to test the effect of iron supplementation on maternal mortality, partly for ethical reasons. Severe maternal anaemia, with Hb < 8 g/L, is almost certainly a greater mortality risk factor than mild or moderate anaemia[283].

Pregnancy anaemia has been reported to be associated with preterm delivery and a subsequently LBW in many studies[80]. For example, in a study of low income, predominantly adolescent women in the USA, IDA (but not anaemia without iron deficiency) predicted a 3-fold greater risk of preterm delivery[76]. The Hb concentrations of 829 Chinese women, at 4 to 8 weeks of pregnancy, predicted their risk of preterm delivery. The relative risks for preterm birth, by g/L of Hb, were: 2.52 for ≥130 g/L; 1.11 for 120-129 g/L; 1.64 for 100-109 g/L; 2.63 for 90-99 g/L; and 3.73 for 60-89 g/L[77]. However, the effect of iron status on actual duration of gestation has been measured in only two randomized, placebo-controlled, intervention trials, in France and in Finland. In neither did iron supplementation reduce preterm delivery or affect the duration of gestation[284, 285]. However, none of the women was severely anaemic and the severity of anaemia in general was far less than is usual in pregnant women in developing countries. As discussed further below, there is no strong evidence that anaemia in pregnancy causes LBW.

Associations between Hb concentration and psychomotor performance have been demonstrated at all stages of life. Although iron is required for the function of several brain neurotransmitters, an Expert Consultation[286] concluded that only anaemia, and not iron deficiency without anaemia, impairs the mental and motor development, and the behaviour of infants. A review of studies on the effect of iron deficiency on children's cognitive development concluded that there is sufficient evidence to show that iron supplementation of anaemic children aged >2 years improved their development, but that it remains uncertain whether supplementation of anaemic children <2 years old is beneficial[287]. Another concern for anaemic children is that they have a higher absorption of toxic heavy metals such as lead and cadmium, so they are at greater risk in polluted environments[288].

Anaemia has long been known to impair work performance, endurance and productivity[289]. In Indonesian women, Hb concentrations have been related to performance, even in tasks requiring only moderate activity. Anaemic women produced 5% less in factory work, and did 6.5 hours less housework per week[290]. In addition, iron deficiency impaired the work capacity of young American women, independently of Hb concentration[291]. It appears that iron deficiency does not have to progress to anaemia to affect work performance. Therefore, iron deficiency and anaemia may adversely affect the work performance of an even larger proportion of the world's population than that which suffers from anaemia.

Efficacy Trials of Iron Supplementation

Supplementation in Pregnancy

The WHO recommends that all pregnant women be supplemented with 60 mg iron daily, in a pill that also usually contains 400 µg folic acid[279]. This is the recommendation in most of the developing and many industrialized countries. Because of current concern about the apparent lack of effectiveness of large scale iron supplementation programmes intended to control pregnancy anaemia[212, 292, 293], it is important to know whether supervised, randomized, placebo-controlled, iron supplementation trials can prevent or treat anaemia and iron deficiency in pregnancy.

It is usually considered unethical to withhold iron during pregnancy where there is a high prevalence of anaemia. Therefore, randomized, controlled trials are rare, especially in developing countries. A recent meta-analysis included nine randomized, placebo-controlled, clinical trials of routine iron and folate supplementation in 5,449 pregnant women[294]. The women were recruited before 28 weeks of gestation and all had initial Hb concentrations >100 g/L. The usual dose was around 100 mg elemental iron plus 350 µg folic acid. The iron-folate supplements raised or maintained concentrations of serum iron and ferritin, and serum and red blood cell folate. There was a substantial reduction in the number of women with Hb concentrations <100 and <105 g/L in late pregnancy. No conclusions could be drawn about the effects of this supplementation on other maternal or foetal outcomes because few data were collected on these. An important limitation of these studies is that only three out of the nine trials in the analysis, at least two of which were in regions where malaria is endemic, were undertaken in areas where anaemia is a serious public health problem. However, this meta-analysis showed that iron supplementation improved maternal iron status, even in relatively well nourished populations. Another meta-analysis, using 24 randomized, controlled trials in developing countries, found that supplementation clearly reduced anaemia[295].

Other important information emerged from a Cochrane meta-analysis[294]. Hb and iron status improved with iron doses up to 60 mg/day and supplementation lasting up to 20 weeks. Longer term, small doses of iron were more effective than short term, large doses. These conclusions about the effects of timing and duration are supported by newer evidence. A meta-analysis of randomized, controlled iron supplementation trials that compared the efficacy of iron given daily or weekly[296], concluded that daily supplementation was most effective for preventing anaemia, especially severe anaemia during pregnancy. Given the short period during which pregnant women usually take supplements, and the high demands for iron during pregnancy, iron supplements should be given daily, if they are to have maximum impact on Hb and iron status. However, weekly doses certainly improve these measures as well. An analysis of supplementation trials in Tanzania confirmed that the total amount of iron consumed during pregnancy is the most important predictor of Hb response[297]. Likewise, in Bangladeshi pregnant women, Hb response per 60 mg iron tablet was the same whether the dose was taken daily or weekly. Most of the Hb response was produced by the first 20 tablets, and Hb plateaued after 40 tablets[298].

Among 21 randomized, controlled, iron intervention trials, in which the effect of iron treatment on birthweight was assessed, only trials in India[299] and The Gambia (for those women who took at least 80 iron pills)[78] found birthweights to be higher in the treatment group. Associations between both low and high Hb concentrations in gestation and LBW have been observed in many nonintervention studies; i.e., a U-shaped relationship between Hb and birthweight. However, given the lack of efficacy of iron supplementation on birthweight in most trials, these associations are probably artefacts of poor plasma volume expansion (for high Hb) or medical problems such as infection or haemorrhage (for low Hb).

Maternal iron status in pregnancy does influence the iron stores of the infant postpartum. In most association and intervention studies, in which maternal iron status in gestation and infant iron status postpartum were measured, cord blood ferritin was related to maternal Hb or ferritin, whereas maternal and infant Hb concentrations were rarely correlated[79]. Maternal iron supplementation in gestation may improve infant iron stores for some months after delivery. The iron status of iron-supplemented French women in late gestation remained correlated with the iron status of their infants at 2 months of age[284]. Infants born to anaemic mothers in Spain were almost six times as likely to become anaemic at 12 months of age, compared to infants born to nonanaemic mothers controlling for feeding practices, morbidity and socioeconomic status[300]. The logical conclusion is that maternal iron supplementation in pregnancy may provide the infant with some protection from iron deficiency postpartum. This is an important consideration, given the high prevalence of anaemia that develops during the first year of life, and its potentially permanent or long term effects on child development.

An additional benefit of iron supplementation during pregnancy is the opportunity to improve maternal iron stores postpartum. In Finland[301], and Niger[302], iron supplements during pregnancy increased maternal stores for 6 months postpartum compared to controls. This could reduce the risk of anaemia during lactation and in a subsequent pregnancy.

A combination of antimalarial prophylaxis and iron supplementation is particularly important for preventing maternal anaemia and LBW in areas where malaria is endemic[279]. In regions of endemic VAD, the simultaneous provision of low dose (for safety reasons) vitamin A supplements is likely to improve the Hb response of anaemic women to iron supplementation[303].

Iron Supplementation of Infants and Preschool Children

LBW infants are born with lower iron stores, and have higher iron requirements for growth. Their iron requirements cannot be met from breastmilk, and their iron stores are depleted by 2 to 3 months postpartum. The global recommendation is to supply such infants with supplemental iron drops starting at 2 months of age[304].

Randomized, placebo-controlled, efficacy trials with infants reveal that iron supplementation significantly improves Hb and ferritin concentrations. However, the usual age of onset of anaemia in infancy is controversial, in part because of uncertainty about setting Hb limits for anaemia. This is illustrated by randomized, controlled supplementation studies in Honduras and Sweden. The investigators supplied 1 mg iron/kg to infants between 4 and 9 months of age, or between 6 and 9 months[242]. The infants were all exclusively breastfed until 6 months of age and partially breastfed thereafter. Although the Honduran infants had substantially lower ferritin concentrations at baseline, the provision of iron supplements between 4 and 6 months increased Hb and ferritin concentrations equally in the two countries. This suggests that these responses were not due to iron deficiency. Supplements given from 6 to 9 months improved Hb and ferritin in Honduras, but only Hb in Sweden. A higher prevalence of diarrhoea in the iron-supplemented group gave cause for concern. The results of this study imply that the current Hb cut-off set for anaemia in infancy may be too high and the prevalence of anaemia in young infants overestimated. More needs to be learned about the appropriate age for starting iron supplementation in infancy, and the Hb and ferritin limits that signify true deficiency.

Several placebo-controlled intervention trials have demonstrated that iron supplements increase Hb concentrations of preschool children in developing countries. These include trials in Indonesia on children aged 12 to 18 months[305] and in Viet Nam[273]. In Indonesia, a home-based, weekly supplement was effective for increasing Hb concentration and reducing anaemia from 37% (placebo control) to 16%[306]. The supplements were 30 mg iron, given to children age 2 to 5 years, once a week, by their mothers.

Not all iron intervention trials succeed in improving the Hb concentration of young preschool children. A randomized, controlled efficacy trial was conducted in rural Mexico, for which 220 children were recruited between 18 and 36 months of age[307]. At baseline, about 70% of the children had anaemia, accompanied by iron deficiency. For a year, under supervision, the children were provided with either 20 mg iron/day or a placebo. Hb concentrations were slightly significantly higher after 6 months of supplementation with iron but, surprisingly, there was no significant difference after 12 months in Hb concentrations between the iron-supplemented and the placebo groups. Hb concentrations improved as the children became older, but 30% of them remained anaemic at 12 months in spite of normalization of ferritin concentrations. The lack of Hb response to iron supplementation was not obviously due to parasites or morbidity. Because the children suffered from multiple micronutrient deficiencies and those who did increase their Hb in response to iron supplements seemed to be generally better nourished, it is possible that other micronutrient deficiencies were limiting the Hb response to iron.

There has been only one trial to compare the efficacy of iron to improve Hb concentrations when given in a multiple micronutrient supplement, compared to when given as iron alone. In a region of rural Mexico where several micronutrient deficiencies occur simultaneously in preschool children, groups with low Hb concentrations were given iron alone, iron plus vitamin B_{12}, iron plus multiple micronutrients, or a placebo, every other day for 4 months. At the end of the study, Hb response was significantly greater in the iron alone or iron plus vitamin B_{12} groups than in the multi-micronutrient group[308]. A placebo-controlled trial on preschool children in Viet Nam measured response to daily iron supplements (8 mg/day) that also contained vitamin A and zinc[273], but there was no iron-alone control. The prevalence of anaemia fell from 51% at baseline to 6% after the 3-month intervention, when it was significantly less than the 43% in controls. A third group of these children took supplements containing higher levels of these nutrients (including 20 mg iron) once a week. The prevalence of anaemia fell from 48% at baseline to 9% after 3 months. The HA of children in both of the supplemented groups improved significantly compared to the placebo group. The authors concluded that consumption of the supplement once a week would be sufficient to reduce anaemia and to improve vitamin A and zinc status in this group.

There have been very few studies of the long term effects of IDA during infancy, and its reversibility by iron supplementation. An Expert Consultation[286] concluded that iron therapy for infants and children aged <2 years did not improve deficits in mental or motor performance, whereas iron supplementation for preschool children (2 to 4 years) was able to reverse the functional impairments. However, as described below, there have been very few intervention trials on infants and young children. At around 5 years of age, the cognitive performance of Costa Rican children was apparently still impaired, if they had been anaemic during infancy[309]. It is not yet certain that iron supplementation during infancy can reverse these effects. Iron supplementation , started at age 12 to 23 months, did not improve the developmental scores of anaemic Costa Rican children[310]. In contrast, iron supplementation did successfully reverse the motor and mental performance deficits of Indonesian children aged 12 to 18 months[305]. The mental and motor performance of infants in the USA was better at 9 and 12 months when they were raised on iron-fortified formula (12.8 mg/L) compared to a regular formula (1.1 mg/L) [311]. However, these differences disappeared by the time the children reached 15 months of age.

More than 22 countries have adopted iron supplementation of infants and preschool children as a public health policy[293]. The recommendation is to provide 12.5 mg of elemental iron plus 50 µg folic acid per day from age 6 months to age 12 months in regions where the anaemia prevalence is <40%, and from age 6 to 24 months where the prevalence of anaemia is

> 40%[279]. It is important that LBW infants receive this dose from 2 months of age up to 12 months. In reality, however, there are few national programmes to prevent or to treat anaemia in infants. India and some Caribbean countries are exceptions. Constraints include poor compliance, the relatively high cost of the iron solutions and droppers, and the lower stability of solutions, compared to tablets[312].

Iron Supplementation of School Children and Adolescents

A substantial amount of evidence confirms that iron supplementation of anaemic school children improves their school performance, verbal and other skills[286]. Iron supplementation of Israeli girls, aged 16 to 17 years, reduced tiredness and improved their ability to concentrate[313]. In the USA, iron deficient but non-anaemic girls, aged 13 to 18 years, had better verbal learning and memory abilities after 2 months of iron supplementation in a randomized, controlled trial[314]. In India, boys and girls, aged 15 to 18 years, improved their cognitive function after iron supplementation[315].

In Kenya, when iron supplements were provided to school children on school days for 32 weeks, there was a significant increase in weight, WH, arm circumference and skinfold thickness compared with the placebo group[316]. Hb levels also improved significantly.

As it has become increasingly apparent that it is difficult, if not impossible, to correct anaemia fully by iron treatment during pregnancy alone, more attention is being paid to the need to provide adolescent women with either daily, or weekly, low dose iron supplements. This strategy may prevent them being anaemic and iron deficient when they become pregnant, as long as the supplements are given for long enough and close enough to conception; however, where the usual intake of dietary iron is low, supplementation will still need to be continued during pregnancy[163]. Treatment of pregnant Nigerian adolescents with iron, folic acid and antimalarial prophylaxis, increased maternal height and lowered the incidence of cephalopelvic disproportion[115].

Frequency, Duration and Prioritization of Iron Supplementation

One of the main obstacles to obtaining good compliance of participants in iron supplementation programmes has been the perceived need to consume the supplements every day for at least a few months at a time. During the past few years, there has been considerable interest in the possibility that iron supplements do not have to be given as frequently as once a day to be effective. If this is correct, it opens many new possibilities for supplementation programmes. Costs could be reduced and compliance increased if supplements were provided once a week; for example, to children in schools, on the weekly day of rest, linked to religious events, or distributed by the community. These strategies may afford the possibility of preventing iron deficiency rather than the usual situation of trying to treat anaemia.

A recent meta-analysis[296] compared the efficacy of weekly and daily iron supplementation for improving Hb and serum ferritin concentrations. The three main conclusions were as follows. Both daily and weekly iron supplementation are efficacious as long as compliance is good: an important and exciting finding that creates new opportunities for programmeme delivery. Under almost all conditions and particularly where there was less control over the dose being consumed, daily supplementation was more effective than weekly: this, presumably, is because missing a weekly supplement will have a greater adverse effect on iron status than missing one or several daily supplements. The duration of supplementation was not an important determinant of efficacy, except in pregnancy, with its high demands for iron and short window of supplementation, in which case daily supplements are more effective.

Because efficacy trials usually improve Hb and iron status, the poor effectiveness of some iron supplementation programmes is likely to be caused predominantly by other barriers to compliance including: lack of perceived benefit of taking the supplements, by the intended recipients and by health care providers; perceived or actual side effects such as diarrhoea or constipation, which are unlikely unless the dose exceeds 60 mg/day; poor supply or limited access to supplements; and unattractive packaging etc.[212]: see also section on Effectiveness of Micronutrient Supplementation; iron (below).

With regard to prioritization of vulnerable groups for iron supplementation, current recommendations from the International Nutritional Anaemias Consultative Group (INACG), WHO and UNICEF[279] are that the main priority groups are pregnant and postpartum women and children aged 6-24 months, because of their greater risk of deficiency and the greater likely benefits of supplementation. Where anaemia is highly prevalent (usually considered to be >40%), supplementation would also benefit women of reproductive age, preschool children, school children, and adolescents. In these target groups, the decision to supplement will depend most likely on feasibility. This might be highest in a day-care or school setting for children and adolescents or in the workplace for women.

In populations with a high prevalence of anaemia, almost all women and children are iron deficient. This argues for universal supplementation. Where severe anaemia is relatively common (2% or more of a population group) then its detection and treatment in primary health care facilities is necessary, to prevent morbidity and mortality from severe anaemia[279].

Where resources are very limited, it will be necessary to prioritize supplementation prior to conception, which is difficult, and from as early as possible in pregnancy, and then through lactation, infancy, and early childhood. These stages should be approached as a continuum, with the most vulnerable period being from preconception to age 2-3 years. The specific situation dictates the setting of priorities and the level of investment. Where LBW prevalence is very high, then addressing this must be a priority.

The Role of Other Micronutrients in Anaemia

Vitamin A deficiency (VAD) also causes anaemia. When adult male volunteers in the USA were depleted of vitamin A, their Hb concentrations fell from about 150 to <110 g/L within 12 months[317]. Treating this anaemia with iron alone had no effect, whereas vitamin A plus iron readily restored Hb concentrations. In general, the Hb concentration of VAD individuals increases by about 10 g/L when vitamin A supplements are provided[318].

Riboflavin deficiency may be quite common in developing countries where intake of animal products is low, and especially during seasons when there is less intake of vegetables. It has been estimated[319] that 90% of adults in China were riboflavin deficient. There is a lack of information the prevalence of deficiency in other Asian countries. The few data on its prevalence in other countries include: 50% for elderly persons in Guatemala[320]; 77%, among anaemic, lactating women in Guatemala[321]; and almost 100% of pregnant and lactating women in The Gambia[322]. The high riboflavin requirements of pregnant and lactating women may put them at the highest risk of deficiency. Riboflavin deficiency lowers Hb concentrations, probably by impairing iron absorption[323]. It may also reduce synthesis of Hb, and cause storage iron to be trapped in ferritin. In efficacy trials, riboflavin supplements improved Hb response to iron supplementation in Gambian men and lactating women who were iron and riboflavin deficient[324, 325], and children in the former Yugoslavia[326]. Supplements containing both riboflavin and iron increased serum ferritin concentrations more than iron alone, in anaemic, lactating Guatemalan women[321].

Severe folic acid or vitamin B_{12} deficiencies can cause anaemia, but it is not clear to what extent the global prevalence of anaemia is influenced by such deficiencies. Folic acid has long been included in iron supplements for pregnant women on the assumption that this will treat folic acid deficiency anaemia. There is, however, little evidence that folic acid deficiency is a public health problem in many developing countries. No abnormal values for serum or red blood cell folate concentrations were reported in Thailand[327], Guatemala[328], or Mexico[329]. This may be explained by the considerable amount of folate in foods such as legumes, leafy greens and fruit, that are consumed in large amounts in developing countries. Moreover, in a WHO collaborative study in Myanmar and Thailand, there was no incremental effect on Hb of adding folic acid to iron supplements for pregnant women[82]. Small, nonsignificant increases in Hb, have been reported in pregnant women in Africa[330], India[331, 3332], Myanmar[333], and Thailand[334]: usually when folate plus iron supplements were compared to supplementation with iron alone. Increasingly, the inclusion of folic acid in iron pills for pregnant women is targetted at reducing neural tube defects in the small segment of the population who are genetically at risk for this problem. However, for folic acid supplements to be effective against these defects, they must be consumed prior to or up to six weeks after conception. Most pregnant women do not enter care during this time window. Other reasons to include folic acid in iron supplements include a probable reduction in risk of preterm delivery[43] and the association between elevated plasma homocysteine in pregnancy and a variety of adverse pregnancy outcomes[87]. Folic acid supplementation often lowers plasma homocysteine concentrations. Folic acid should also be administered to LBW or premature infants, because they are at greater risk of developing folate deficiency and megaloblastic anaemia. Folic acid improves Hb and folate status in such infants[335].

As with folic acid deficiency, a severe deficit of vitamin B_{12} results in megaloblastic anaemia. There are, however, limited data on the global prevalence of vitamin B_{12} deficiency. This vitamin, also called cobalamin, is found only in animal products. No forms of cobalamin found in plants or bacteria are biologically active in humans. Therefore, a low intake of animal products is certainly a risk for vitamin B_{12} deficiency. There are also some common situations in which absorption of vitamin B_{12} from food is impaired to the point that deficiency ensues; for example, gastric atrophy from *Helicobacter pylori* infection, which is common in the elderly, and overgrowth of bacteria in the small intestine. One third of individuals of all ages have been reported to have vitamin B_{12} deficiency in Mexico[336] and Guatemala[337]. Deficiency is common in the elderly, even affecting about 22% of elderly in the USA and Europe[338]. Its prevalence is undoubtedly higher in developing countries, where animal product intake is low and the prevalence of *H. pylori* is even more common. About 38% of Guatemalan elderly had severe deficiency[339]. More information is needed on the prevalence of vitamin B_{12} deficiency in Asia in and other parts of the world, and on its contribution to anaemia.

Given the high prevalence of VAD in Asia and other regions and the potentially high prevalence of deficiencies of other micronutrients that are required for Hb synthesis and other functions, it is logical to assume that supplementation with multiple micronutrients, rather than just iron or iron plus folate, is a rational public health strategy. The development and testing of such supplements, encouraged by UNICEF, WHO and other agencies, is ongoing in several countries including Bangladesh, Peru, and the Republic of South Africa.

Dietary Interventions to Reduce and Prevent Iron Deficiency

Iron absorption can be improved by changing the foods consumed or their composition. However, this has been demonstrated almost exclusively in small trials with single meals. Neither efficacy nor effectiveness has been adequately tested.

One way to improve the absorption of iron from food is to increase the intake of vitamin C. This enhances the absorption of non-haem iron if the two nutrients are consumed within an hour of each other[211, 340]. The efficacy of vitamin C in vitamin C-rich foods is the same as that of the synthetic form[340]. However, there are few data on the feasibility, and effect on iron status, of increasing intake of vitamin C from locally available foods.

To examine this question, trials were conducted in an area of rural Mexico where traditional maize and legume diets are high in non-haem iron but have poor iron bioavailability due to phytates. It was established, through isotope studies, that consumption of 25 mg of vitamin C was needed twice a day with meals, in order to double iron absorption. The only practical local source of this quantity of vitamin C was a lime-based drink. Iron deficient, nonanaemic women consumed this drink to obtain 25 mg vitamin C, twice a day with meals, for 8 months. At the end of the intervention, there was no improvement in any indicators of iron or Hb status[341].

In many locations, it may be difficult to find suitable, locally appropriate and affordable foods that can supply even 25 mg vitamin C per meal. Moreover, the improvement in iron absorption produced may not be sufficient to improve iron stores in iron deficient individuals. Vitamin C supplements (100 mg twice a day, with lunch and with dinner, for two months, vs a placebo group) did improve iron status in 27 anaemic preschool children[342]. The supplemented children showed a significant improvement in Hb and red cell morphology, whereas the controls had no change. Perhaps the difference in result compared to the Mexico trial[341] was the larger amount of vitamin C given in India. This amount would be almost impossible to obtain consistently from foods. Moreover, it is unlikely that vitamin C alone would be used as a supplement for iron deficient children.

Vitamin C is probably most effective for improving the absorption of fortificant iron added to foods. For example, the addition of vitamin C to iron-fortified dry milk in Chile reduced anaemia in preschool children more than the milk fortified with iron alone[343].

The addition of meat or fish to a meal provides not only more absorbable iron, but also increases the absorption of non-haem iron, including fortificant iron. For example, when fish was added to a typical plant-based, South-East Asian meal that had been fortified with 5 mg iron (as ferrous sulphate), the amount of iron absorbed from the fortificant was doubled[344]. Interestingly, there have been almost no trials of the effect of increasing meat intake on the iron status of humans. An efficacy trial funded by the Global Livestock Collaborative Research Support Programme (CRSP) is currently underway in Kenya, where school children are being given a meat supplement to their usual school lunch for one year. The promotion of animal products, to improve iron status and intakes of other micronutrients, has not been sufficiently explored. Although cultural, socioeconomic and environmental constraints exist, small amounts of animal products can often be targeted to the most needy (e.g., young children and women), and home production of chickens, small livestock, and fish can generate income as well as improving the nutrition status of the household.

A review of food-based programmes[345] examined what was known about the impact of recent efforts to improve iron status by increasing the intake of animal products. These efforts have included promotion of fishponds and animal production in Viet Nam[346], increased availability and promotion of liver and other organ meats in Peru[347], fishpond promotion in Bangladesh[348] and fishponds and chicken in Thailand[349]. In Viet Nam, the iron intake of children was increased but iron status not evaluated. In Peru, haem iron intake was improved and the prevalence of anaemia reduced. Analysis of the first stage of the

Bangladesh project show that it failed to increase fish or vegetable intake and there was no impact on iron status. In Thailand, both iron and vitamin C intakes were increased as intended, as well as serum ferritin in school girls, although they also received iron supplements and better school lunches.

There are opportunities on the horizon to improve iron status through genetic enhancement of plants. A maize variety that is low in phytate has been produced in relatively small amounts. The single efficacy trial of iron absorption from this source showed that iron absorption was improved from 5% in control maize to 8% in the low phytate maize[350]. Genetic modification to insert ferritin synthesizing genes into rice and other cereals is also being evaluated[351, 352].

Iron Fortification of Foods

Of all of the strategies used to deliver additional iron to humans, food fortification has the greatest potential to improve the iron status of the largest number of people. Refined cereals are iron-fortified in many developed countries. The characteristics of suitable food vehicles and approaches to fortification have been described[2]. Unfortunately, progress in iron fortification has been hindered not only by the usual constraints to fortification (such as the need for central processing) but also by the lack of useful iron fortificants. When added to refined cereals, iron salts such as ferrous sulphate and fumarate are reasonably well absorbed and are suitable, when storage is not expected to be long term. However, most soluble forms of iron cause oxidation and rancidity of fats and color changes in foods over time. For longer shelf lives, reduced iron is preferred, but this will not be well absorbed unless the size of the particles is very small.

NaFeEDTA has the potential to be a widely used iron fortificant. When consumed with cereals and legumes, its absorption is 2 to 3 times higher than ferrous sulphate. Its structure affords some protection against phytate inhibition of iron absorption. It is about one third as well absorbed as ferrous sulphate from sugar, but has the advantages of greater stability and of increasing the absorption of native non-haem iron and zinc in food. However, changes in the colour of wheat and maize can occur when NaFeEDTA is added. Food-grade EDTA has been difficult to obtain but this situation might soon improve; for example, facilities in the PRC may start to produce NaFeEDTA for use in fortification.

The absorption of iron from iron-amino acid chelates (ferrous bisglycinate or "Ferrochel") is substantially more protected from inhibition by phytate than that from ferrous sulphate. One radioisotope study showed that iron absorption from ferrous bisglycinate was six-fold higher than absorption from ferrous sulphate, when these iron compounds were added as fortificants to whole (high phytate) maize porridge[353]. Iron absorption from the chelate was normally down-regulated by higher iron stores. Absorption from the less soluble ferric trisglycinate in maize was poor. Better absorption of ferrous bisglycinate iron, compared to iron from ferrous sulphate or FeEDTA added to maize or white wheat flour, has also been reported[354]. The potential limitations of ferrous bisglycinate as a fortificant include its promotion of rancidity in whole maize meal, although this is readily inhibited by the addition of an antioxidant such as butylated hydroxyanisole (BHA) and did not affect the acceptability of fortified porridge to infants, preschool children or their parents[355]. Ferrous bisglycinate is added as a fortificant to dairy products and other foods in some countries, such as Argentina, Brazil, Chile, Italy and the Republic of South Africa.

Efficacy Trials

There are many examples of iron fortification programmes and iron-fortified products. The following section considers only those that have been tested in efficacy or effectiveness trials. Ideally, once the compatibility of the fortificant with the food vehicle has been tested, this should be followed by bioavailability trials, then by efficacy trials to measure impact on Hb and iron status, and finally by large scale effectiveness trials at the community or national level. Although there is a considerable amount of information on the compatibility of fortificants and on their bioavailability, there have been very few trials of either efficacy or effectiveness for improving iron status.

In an efficacy trial in the PRC, 5 mg of iron sodium EDTA (NaFeEDTA) per day was consumed as a soy sauce fortificant. It significantly improved Hb status (A. Malaspina, unpublished data). Double-fortified salt, fortified with both iron and iodine, has been developed in Canada. The potassium iodide is encapsulated with dextrin to prevent it from interacting with the ferrous fumarate. The iron and iodine in the salt are both well absorbed[356]. Efficacy trials are ongoing. The National Institute of Nutrition in India has also developed iron- and iodine-fortified salt. The effectiveness of the salt was tested in school children and increases in Hb and urinary iodine excretion were observed[357].

In an efficacy trial in Ghana[220] iron and other micronutrients were added to "Weanimix" (a cereal-legume blend) promoted by the government and by UNICEF. Infants, almost all of whom were partially breastfed, were given the foods between 6 and 12 months of age. Two levels of electrolytic iron were added (about 300 mg/kg and 120 mg/kg) to cover the needs of those consuming smaller and larger amounts of the food respectively. Unfortified Weanimix was used as a control. The foods were supplied weekly to the mothers, free of charge, and feeding three times per day was encouraged. Many other vitamins and minerals were added, including vitamin C (at 780 or 390 mg/kg). The prevalence of low ferritin concentrations increased from 19% at 6 months to 55% at 12 months in the unfortified group, but fell during this time from 18% to 11% for those receiving the fortified Weanimix.

Effectiveness Trials

Maize and Wheat Flour Fortification

In the 1980s, Venezuela underwent an economic crisis that adversely affected the quality and quantity of food consumed by the lower socioeconomic classes. This caused a deterioration in the iron status of the population. In 1993, the government started a national fortification programme in which precooked maize and wheat flours, which together provided 45% of the daily energy of the low income population, were enriched with 20 and 50 mg iron per kg respectively. Both flours contained added thiamine, riboflavin, and niacin, and the maize flour was also enriched with vitamin A. By 1994, the prevalence of anaemia in children age 7 to 15 years in Caracas had dropped from 19 to 9%, and iron deficiency from 37 to 16%[358]. There was no control group.

Other examples of national iron fortification programmes include: wheat and maize flour fortification in Chile[343, 359]; wheat fortification in Sri Lanka; iron fortification of noodles in Thailand and Indonesia; and a national programme of fortification of maize flour with iron and zinc in Mexico[359], which is seen as an appropriate strategy now that a larger proportion of the population lives in urban areas and purchases commercially produced tortillas and flour.

Condiment Fortification

Sugar can be fortified at the point of production. In Guatemala, NaFeEDTA was added to sugar at a concentration of 1 g /kg, i.e., 13 mg iron/100 g. Average sugar consumption was 40 g/day[360]. On average, iron intake increased by more than 3 mg/day. In the three communities that consumed iron-fortified sugar, iron stores increased significantly within 8 months compared to control communities, and further increases were still occurring at 32 months. Mean iron absorption was about 6%. There were no observable adverse effects of the intervention.

Fortification of salt has been problematic, due to: the relatively high ratio of fortificant to salt required; the need for the salt to have a minimum purity of 99% and a maximum moisture content of 2%; and the fact that iron will oxidize potassium iodate, added as a source of iodine. In India, 3.5 g ferrous sulphate was added per kg salt, where the average salt intake is 15 g/day. Bioavailability was assumed to be 5%. Fortification caused a significant improvement in Hb and a reduction in anaemia, especially among population groups with the highest prevalence of anaemia[357]. Iron fortification of salt is also being tested in Thailand and Indonesia.

In Thailand, fish sauce has been fortified with 1 mg/mL iron (as NaFeEDTA), to increase iron intake by 10 mg/day[361]. Absorption was 8% when the iron compound was added to meals. The sauce was produced in Bangkok and transported every two months to a rural village. The village head man distributed the bottles on request. The villagers were told that the sauce contained something which might make their blood more strong. Compared to a control village where there was no fortification, average haematocrits were significantly higher, by about 1.5%. In the control village 16% of the subjects became anaemic and 20% recovered. In the intervention village, 9% became anaemic and 35% recovered. Thus 25 to 35% of the recipients benefited from the iron. A study on a small subsample of the men suggested that their submaximal working capacity might have improved during the year of supplementation. The large number of producers of fish sauce may be a constraint to wider fortification.

In the Republic of South Africa, NaFeEDTA also improved Hb concentrations within two years, when incorporated into curry powder targeted to the population of South Asian descent[362]. The greatest increase in Hb occurred in the most anaemic individuals. The powder was fortified with 1.4 mg/g and the iron was 10% available. The average intake of absorbable iron increased by 0.8 mg/day.

Major efforts are underway to test the effectiveness of adding NaFeEDTA to soy sauce in the PRC and in Viet Nam, with the intention of reaching 75% of the population (A. Malaspina, personal communication). In soy sauce, iron from NaFeEDTA was twice as well absorbed as that from ferrous sulphate and, as stated above, improved Hb in a small efficacy trial in children. Community-based trials are in progress.

Fortification of Foods for Infants and Children

Ferrous fumarate, ferrous succinate and small particle size iron are suitable iron fortificants for infant cereals[363]. They are bioavailable yet, unlike ferrous sulphate, they do not cause fat oxidation or discolouration. Infant cereals are widely fortified in developed countries and this has led to a definite reduction in anaemia[364].

Chile supplies low fat milk to low income households as part of a National Supplementary Feeding Programme. The milk is distributed to mothers when they attend health clinics for routine immunization and growth monitoring. Milk powder was fortified to contain 15 mg/L ferrous sulphate (3 mg/L iron) when reconstituted. The prevalence of anaemia fell from 27% to 10% among children aged 3 to 15 months. The remaining anaemia was thought to be caused by the inhibitory effect of milk calcium on iron absorption. To improve absorption of the fortificant iron, vitamin C was added at 100 mg/L. Anaemia virtually disappeared[343]. The limitations of this approach are the additional cost of the vitamin C, and the need to prevent its oxidation, either by appropriate containers or coating.

Peru implemented a national school breakfast programme in which children were provided with an iron-fortified biscuit and milk. After one year, the prevalence of anaemia fell from 66 to 14% (G. de Romana, unpublished data). National programmemes have just been started in Mexico and in Indonesia to distribute fortified foods to low income pregnant women and young children.

Safety of Iron Fortification Programmes

Iron fortification poses no risk for the normal individual. Iron absorption falls, as iron stores increase, to protect against excessive iron accumulation. However, a small proportion of the population is susceptible to iron overload. This has been reviewed elsewhere[212, 293, 365, 366]. The conclusions are that iron fortification poses little, if any, risk to individuals with thalassaemia minor or other haemoglobinopathies, and that the impact of iron fortification in malarial areas should be monitored. Food fortification with iron has not significantly increased the prevalence of iron overload in the USA[367] or in Sweden[368]. Overall, it is true that: *"the potential benefit of an iron intervention to a predominantly iron-deficient population is likely to vastly outweigh any risk this may pose for a few individuals"* [212].

Oral iron supplements have not increased the risk of infection in any age group in nonmalarial countries. In malarial areas, the effects of iron supplements on clinical malaria attacks, lower respiratory tract infection, and nonmalarial, infectious diseases, have been inconsistent among studies. There remains concern that high dose iron supplementation, during the peak malaria transmission season, may increase the risk of clinical malaria[369]. However, prevention of iron deficiency anaemia and malaria in malarial areas reduces the risk of child mortality from malaria[283].

Complementary Parasite Control Strategies for Prevention of Anaemia

For areas with endemic parasitic infections that can affect Hb or iron status, the INACG, WHO, and UNICEF recommended the following complementary control measures[279]. Where hookworm is endemic (i.e., prevalence 20-30% or greater) adults and children over 5 years should be treated with at least an annual dose of albendazole, mebendazole, Levamisole or Pyrantel. For pregnant women treatment should be given after the first trimester. Where urinary schistosomiasis is endemic, annual treatment with Praziquantel should be given to school children who report having blood in their urine. If *Plasmodium falciparum* malaria is endemic and transmission of infection high, women in their first or second pregnancies should be given curative antimalarials at their first prenatal visit followed by locally recommended antimalarial prophylaxis. Insecticide-impregnated bed nets in communities decrease the prevalence of severe anaemia in young children. Other primary health care measures such as hand washing and the wearing of shoes in hookworm areas, can have a major impact on the prevalence of anaemia.

Summary and Conclusions

Asia has the highest prevalence of anaemia in the world. About half of all anaemic women live in the Indian subcontinent where 88% of them develop anaemia during pregnancy. Vast numbers of infants and children are also affected. Low intakes of absorbable iron, malaria, and hookworm are the main causes of anaemia. Intervention trials have demonstrated the benefits from improving iron status and reducing anaemia. The greatest benefits are to be anticipated in the most severely anaemic individuals.

- Randomized, controlled clinical trials show that iron supplementation of pregnant women improves haemoglobin and iron status, even in industrialized countries. Efficacy increases with iron doses up to 60 mg/day. Where iron supplementation has not been effective this has been due predominantly to programmatic constraints such as lack of available supplements, lack of information, education and communication campaigns, and poor counselling by health providers, resulting in poor compliance.

- No conclusions can be made about the benefits of iron supplementation during pregnancy on maternal or foetal health, function or survival. Most trials have been conducted on relatively small numbers of women in industrialized countries. Severe anaemia during pregnancy is thought to increase the risk of maternal mortality but there have been no controlled intervention trials on this question. An association between anaemia and preterm delivery has been reported in several large studies but most placebo controlled trials have been unable to confirm that anaemia causes prematurity.
- Maternal iron supplementation during pregnancy can improve both maternal and infant iron status for up to about six months postpartum.
- A recent meta-analysis comparing the efficacy of daily and weekly randomized controlled iron supplementation trials concluded that daily supplementation is most effective for preventing anaemia—and especially severe anaemia—during pregnancy. The total amount of iron consumed is the most important predictor of pregnant women's haemoglobin response. Antimalarial prophylaxis combined with iron supplementation is particularly important for preventing maternal anaemia and LBW in malaria-endemic areas.
- LBW infants are born with very low iron stores, which are depleted by 2 to 3 months postpartum. Because breastmilk cannot meet their iron requirements they should be supplemented with iron starting at 2 months of age.
- Anaemia during infancy could result in long term or permanent impairment of psychomotor function, although more studies are needed on this question. Iron supplementation of anaemic preschool children improves their cognitive and physical development. Improved growth of iron-supplemented preschool and school children was observed in some studies but not in others.
- Anaemia is associated with lower productivity, even in tasks requiring moderate effort such as factory work and housework. Iron deficiency that has not yet progressed to anaemia may also reduce work capacity. Efficacy trials have shown iron supplements to improve work performance of anaemic individuals.
- Except for iron fortification, there have been few attempts to assess the effectiveness of food-based strategies to improve iron status. Increasing ascorbic acid intake through local foods is probably an inadequate strategy to improve iron status where iron deficiency is prevalent. Targeting animal products to those with highest iron requirements, and supporting the production of small animals and fish, would increase the intake of absorbable iron and other micronutrients. There are strategies available to increase iron absorption through plant breeding but the efficacy and effectiveness of this approach have not been evaluated.
- Fortification of foods with iron has produced improvements in iron status in several countries. Iron fortification of maize and wheat in Venezuela is one such example. Electrolytic iron reduced anaemia and iron deficiency when added to a complementary food in Ghana. Double fortification of salt with iodine and iron has the potential to prevent both iron and iodine deficiencies and has been effective for improving Hb concentrations in India. Fortification of nationally distributed dry milk with ferrous sulphate and ascorbic acid in Chile lowered the prevalence of anaemia in infants from about 27% to close to zero.
- The search for better fortificants continues, and NaFeEDTA has good potential. When added to sugar it increased haemoglobin and ferritin concentrations in a community trial in Guatemala. Iron added to soy sauce as NaFeEDTA appears to be well absorbed and is being tested in large scale production and fortification trials in the PRC.
- Weekly delivery of iron supplements does improve iron status, almost as well as daily delivery in the case of children and adolescents. This programmatic approach may be a cheaper, more effective way to prevent iron deficiency. Ways should be sought to deliver weekly iron through schools, community-based programmes and other situations. However, daily supplements are still more effective for pregnant women because of their high iron requirements and the limited window of time available for supplementation.
- Supplements containing multiple vitamins and minerals could be more effective for improving Hb response than iron alone; multiple micronutrient deficiencies often occur simultaneously and should be prevented and treated, and several nutrients are required for Hb synthesis. Multiple micronutrient supplements are now being formulated and tested by international organizations.