DEVELOPMENT AND FIELD TEST OF A PROTOCOL FOR THE RAPID ASSESSMENT OF ANAEMIA

G D Ndossi, H Gebreselassie, S Kimboka

It is estimated that more than 1 billion people suffer from anaemia globally,[1] with the highest prevalence in South Asia and sub-Saharan Africa. In eastern and southern Africa the prevalence ranges from 40% to 49% in most countries except for South Africa, Namibia, Botswana, Lesotho and Swaziland, which have prevalence rates of less than 40%.[2] Women of reproductive age, infants and children are particularly affected by anaemia and its sequelae.

The major sequelae of anaemia include delay in psychomotor development, impairment of cognitive performance, neurological malfunction, reduced work capacity, decreased tolerance to infection and birth complications. In spite of the far-reaching consequences of anaemia, its prevention and control in general and that of iron deficiency in particular, has received little attention. This situation is true for eastern and southern African countries, where the multicausal nature of the problem and lack of national epidemiological data on the problem have posed specific challenges.

In order to have appropriate strategies for addressing anaemia it is important to have a clear picture of the contribution of the various factors, namely diet, malaria, intestinal parasites and other factors, in different settings and age groups.[3] However, currently available multiple haematological and biochemical tests have imposed limitations both in terms of cost and operational complexity for wider application. In order to overcome these limitations, the development of simplified and rapid appraisal techniques is imperative and timely. In so doing, it is of paramount importance to take into consideration the implication of the newly developed protocol in terms of simplicity, cost, time and accuracy.

Recognising the need to have a standardised rapid anaemia assessment tool, the Nutrition Network for East and Southern Africa Region (NUTRI-NET ESAR) has taken the initiative in developing and piloting such a protocol. It is envisaged that the protocol will provide data at community, district, regional, and/or national level that can eventually be used by programme managers to design, implement and monitor anaemia intervention programmes.

Tanzania Food and Nutrition Centre, Dar-es-Salaam, Tanzania
G D Ndossi, PhD
S Kimboka, MD, MSc
Ethiopian Health and Nutrition Research Institute, Addis Ababa, Ethiopia
H Gebreselassie, MD, MPH, PhD

DESCRIPTION OF THE PROTOCOL

This protocol has been specifically developed for the rapid appraisal of the extent and nature of anaemia in a given population. The protocol takes into account that the prevalence of anaemia can serve as the index of the severity of iron deficiency. This is supported by the differential shift in haemoglobin distribution[4] among different segments of a population where poor dietary iron intake plays a major role.

In order to optimise the performance of the protocol, blood smear for malaria parasitaemia, stool examination for hookworm and other helminth infestations as well as simplified dietary assessment are incorporated (in addition to the determination of haemoglobin).

Major components of the assessment procedure are described as follows:

Unit of survey. The unit of survey can be an administrative or geographical area such as a district, region or the whole country. Refugee camps, disaster areas and the like can also form survey units according to this protocol. The design is developed so as to ensure the generation of adequate information per unit of interest.

The underlying assumption of focusing on a unit, especially a district (or its equivalent depending on the country), is that the district is the most active functional level in the administrative structure of a country, occupying a place between national and grassroots levels. Moreover, it is assumed that the pattern of anaemia, unlike many other health problems, does not vary much within the same agro-ecological zone. It is therefore felt that there is no compelling reason to cover all or many smaller areas in order to characterise a large area.

Sample size requirement. In calculating the sample size (number of households to be surveyed) the model survey for the assessment of the protein-energy malnutrition through anthropometry is adopted.

Sample size $(N) = t^2 \times P\,(100\text{-}P)/d^2$, where t = level of probability that the true prevalence of anaemia in vulnerable households is within the chosen d; P = estimate of percentage of anaemia in vulnerable households in the area; and d = level of precision required of the results.

Owing to the possibility of drop-outs (non-compliance or refusal to participate), the sample size can be raised by about 10%.

Sampling procedure. The model of '30 by 40 cluster sampling' is to be used for each survey unit of interest. In this model of sampling, 30 small communities (representing for instance agro-ecological conditions) are selected based on a random sample scheme to represent the survey unit. From each cluster a total of 40 households is randomly selected; alternatively, if village population data are available, the number of households per village can be based on proportionate probability sampling.

Variables or measurements to be collected. Variables to be included for the rapid assessment of anaemia were identified primarily on the basis of whether they could easily be obtained and processed within the limits of time and the available meagre resources. Consequently five major components are considered: (*i*) haemoglobin level, which should be measured according to three categories of household members, namely all children aged 6 - 36 months, the mother (or female caretaker) and the father (or any adult male above the age of 14 years in the household); (*ii*) screening for malaria parasitaemia among children aged 6 - 36 months; (*iii*) stool examination of mothers (or caretakers) in the selected households; (*iv*) dietary assessment based on 7-day recall of selected foods using a simplified food-frequency questionnaire; and (*v*) assessment of anaemia control programmes in place, especially those activities that could possibility have an effect on anaemia, such as maternal and child health (MCH) services including iron/folate supplementation, nutrition education, malaria and helminth control, and dietary diversification efforts.

Data collection tools. Collection of data can be undertaken by nutritionists or any field workers who are given training as to the nature of the survey and the methods to be employed in carrying it out. Microscopy should be done by laboratory technologists. Semi-structured questionnaires are developed and administered at two levels, namely household level and health facility level.

According to this protocol, the method to be used for the assessment of the blood haemoglobin level is the HemoCue blood test system (Sweden) involving fingerpricks using disposable lancets. Staining for the detection of malaria is to be done by use of field stains A and B. In addition, presence of ova or parasites in wet preparations of stool samples are to be examined by direct microscopy.

Data processing and analysis. There should be checks for inconsistencies of data. Unreasonable entries and impossible entries should be checked. These and other checks for the validity of the data should preferably be done by the field workers themselves. Following this, data may be entered and analysed using any statistical package such as Epi-Info, SPSS-PC + or dBase.

Interpretation of results. Data on haemoglobin levels are analysed to describe the presence and severity of anaemia in accordance with World Health Organisation (WHO)-recommended age- and sex-specific cut-offs. Furthermore, in order to evaluate the nature and possible causes of anaemia, the haemoglobin distribution of children, women and adult men must be plotted and contrasted with the respective reference haemoglobin distribution. If poor dietary iron is the major cause of the anaemia, one will expect to observe a differential shift in haemoglobin distribution among children and women.[4,5] In case all three groups are observed to have a shift in haemoglobin distribution, the interpretation needs to incorporate the rest of the data (dietary, malaria parasitaemia and worm infestation data).

PRELIMINARY RESULTS OF THE APPLICATION OF THE PROTOCOL IN TANZANIA

Subjects and methods

The survey was conducted in Bagamoyo district of the coastal region in Tanzania. Residents of the study area are mainly of the Wakwere, Wazaramo and Wazigua tribes and their principal occupation is subsistence crop farming, fishing and petty trade. Malaria was endemic in the study area. Overall, 1 203 households were included in the study. The study participants were men and women, and children between the age of 6 and 36 months. In order to have sufficient representation of each sex and age category, households with at least a mother and a child were purposefully selected. Information about the survey was communicated to district, ward and village leaders. The village leaders, in turn, informed households in their respective villages.

A household questionnaire that had sections on identity of household members, socio-demographic information (age and gender), food frequency questionnaire for the assessment of the consumption of selected foods, and a section on the prevailing practices related to the prevention of anaemia was administered to the women by trained field workers.

Fingerprick blood was obtained from men, women and children in order to assess haemoglobin levels. A thick blood smear stained by the field stain A and B method was taken from all children and examined for malaria parasites. The number of parasites per 200 leucocytes was counted under high-power microscopy. Mothers were provided with stool cups to collect a stool sample for the determination of ova or parasites.

The survey team consisted of 1 nutritionist, 1 medical assistant, 4 laboratory technicians, 2 supervisors and 2 drivers. In addition, it was necessary to have at least 2 community leaders from each village to guide and identify the households to be surveyed.

Preliminary results

A total of 2 841 individuals were recruited into the study. Of this number, 447 (15.7%) were men (mean age 38.8 (SD 14) years; range 14 - 85), 1 129 (39.7%) were non-pregnant women (mean age 26.7 (SD 7.5) years; range 14 - 70), 42 (1.5%) were pregnant women, and 1 223 (43.1%) were children (mean age 20.6 (SD 9.2) months; range 6 - 36).

Table I shows the haemoglobin profile of the surveyed population. The mean haemoglobin concentrations of all categories were found to be lower than the WHO cut-off points set to define normal values. Children and pregnant women were by far the worst affected by anaemia. Over 93% of the children and approximately 73% of the pregnant women had mild-to-severe anaemia. Moreover, a large proportion of men (approximately 52%) and non-pregnant women (approximately 65%) were also found to be anaemic.

Among children aged 6 - 36 months, 551 (45%) had a positive smear for malaria. Of this number, only 59 (10.7%) had a parasite density count of over 4 000 per µl (Table II). The overall prevalence of intestinal worm infestation among women was 42.9% (494/1 171). Of the 494 women with worm infestation, 262 (53%) were anaemic.

Table III shows how frequently selected foods were consumed during the 7 days before the interview. The diet of this population was largely plant-based, although being a coastal community fish was also commonly consumed. In addition tea, considered to be an inhibitor of iron absorption, was consumed in large quantities.

Discussion

The above results need further in-depth analysis; however the major thrust of this study was to demonstrate the applicability of the protocol in a field situation.

The major strengths of the protocol, as observed in the field, were that it lends itself to rapid assessment and that it is easy to

Table I. Haemoglobin profile of the surveyed population

		Anaemia					
Group	Mean haemoglobin (SD)	Very severe *N* (%)	Severe *N* (%)	Moderate *N* (%)	Mild *N* (%)	Normal *N* (%)	Total *N* (%)
Children	8.4 (1.9)	6 (0.5)	283 (23.1)	706 (57.7)	144 (11.8)	84 (6.9)	1 223 (100)
Pregnant women	9.7 (1.7)	–	5 (11.6)	20 (46.5)	8 (18.6)	10 (23.3)	42 (100)
Non-pregnant women	11.1 (1.8)	2 (0.2)	25 (2.2)	267 (23.6)	437 (38.7)	399 (35.3)	1 129 (100)
Men	12.6 (2.0)	–	6 (1.3)	46 (10.3)	179 (40.0)	216 (48.3)	447 (100)

Table II. Prevalence of malaria parasitaemia in children aged 6 - 36 months

Malaria parasite load				
40 - 4 000/µl	> 4 000 - 8 000/µl	> 8 000 - 12 000/µl	> 12 000/µl	Total
492 (89.3%)	17 (3.1%)	5 (0.9%)	37 (6.7%)	551 (100%)

Table III. Frequency of consumption of selected foods during the 7 days before interview

Food items	Number of days on which the food was consumed per week			
	Nil	1 - 3	4 - 5	5 - 7
Dark-green leafy vegetables	64	596	234	309
Legumes	236	743	112	85
Sweet potato leaves	382	720	53	48
Egg plant	1 045	141	6	11
Citrus fruits	299	403	103	398
Meat	838	332	15	18
Sorghum	995	127	18	63
Wheat products	220	386	133	464
Fish	254	614	144	191
Poultry	805	378	14	6
Milk	934	130	14	125
Liver	1 157	36	2	8
Tea	139	193	61	810

apply, even by field workers who are not fully trained. Compared with other comprehensive community-based anaemia surveys, which incorporate detailed haematological and biochemical tests, this protocol was found to be relatively inexpensive. Furthermore, the protocol can easily be incorporated into other large-scale nutrition and health surveys.

However, some limitations of the protocol need to be mentioned. House-to-house visits by fieldworkers, in situations where households are scattered — the rule rather than exception in almost all African countries — are tiring and may potentially compromise the timing of completion of the study. This, in turn, may increase the cost of the field work. Nevertheless operational costs will be far lower than those of comprehensive surveys based on batteries of haematological and biochemical tests. Another limitation, not unique to this protocol but common to all cross-sectional surveys, is that it is prone to seasonal influence, particularly when it is applied to monitor programme achievements. Similarly, this protocol, like other cross-sectional surveys, is also prone to selection bias, which may have implications in terms of estimating the magnitude of the problem.

In conclusion, it is recommended that the protocol be used in developing countries that have a need for rapid appraisal of anaemia, with minor adaptations to the circumstances of each country.

References

1. West CE. Iron deficiency: The problem and approaches to its solutions. *Food Nutr Bull* 1996; **17:** 37-41.
2. Csete J. Global overview on anaemia. In: Proceedings of the Eastern and Southern Africa regional consultation on anaemia. 17 - 19 November 1997, Arusha, Tanzania. Micronutrient Initiative and UNICEF.
3. Johnston J. Opening remarks. In: Proceedings of the Eastern and Southern Africa regional consultation on anaemia. 17th - 19th November, 1997, Arusha, Tanzania. Micronutrient Initiative and UNICEF.
4. Yip R. Iron deficiency: Contemporary scientific issues and international programmatic approaches. *J Nutr* 1994; **124:** 1479S-1490S.
5. Yip R, Stoltzfus RJ, Simmons WK. Assessment of the prevalence and nature of iron deficiency for populations: the utility of comparing hemoglobin distributions. In: Hallberg 6, Asp Nile-George, eds. *Iron Nutrition and Disease*. London: John Libbey, 1996: 31- 48.

SAFETY OF MICRONUTRIENTS

Reneé Blaauw

Micronutrients and their role in the prevention and treatment of disease are currently enjoying tremendous growth and interest. These nutrients may have functions other than the ones accepted up to now (i.e. gene regulatory functions) and their requirements for the maintenance of optimal health may be different from those for the prevention of conventional deficiency states.[1] Marginal micronutrient status can adversely affect morbidity and mortality, and although increased micronutrient intakes (in the form of dietary supplementation) in excess of the recommended dietary allowances (RDAs) may have beneficial effects in specific situations, such high intakes demand extreme caution in terms of long-term safety.

Since there is no satisfactory internationally accepted standard for the intake of micronutrients, the RDAs are used by most. These levels are by definition safe, but are designed to meet the needs of practically all healthy individuals. Various studies have been performed to determine a safe daily level for prolonged intake of vitamin supplementation in adults. Table I summarises the proposed safe level of intake in relation to the RDA for a specific vitamin. There appears to be a considerable margin of safety with most of the vitamins and, with the exception of adverse reactions after the long-term excessive ingestion of vitamins A, D and B_6, most of the side-effects that occur with vitamin supplements are rapidly reversible on withdrawal of the supplementation and leave minimal or no lasting effects.[2]

Table I. RDAs and safety levels in adults

Vitamin	RDA	Safe level of intake
Fat-soluble vitamins		
Vitamin A	1 000 µg RE	Approx 10 x RDA
Vitamin D	5 µg	Approx 10 x RDA
Vitamin E	10 mg	Over 100 x RDA
Vitamin K	70 - 140 µg	Approx 50 x RDA
Water-soluble vitamins		
Thiamin	1.4 mg	Over 100 x RDA
Riboflavin	1.6 mg	Over 100 x RDA
Niacin	18 mg NE	Approx 100 x RDA
Pyriodoxin	2.2 mg	100 x RDA
Folic acid	400 µg	Over 50 x RDA
Vitamin B_{12}	3 µg	Over 100 x RDA
Vitamin C	60 mg	Approx 100 x RDA

Adopted from reference 2.

Department of Human Nutrition, University of Stellenbosch and Tygerberg Hospital, Tygerberg, W Cape

Reneé Blaauw, PhD

VITAMIN A

Clinical vitamin A deficiency (VAD) is one of the leading causes of childhood blindness.[3] It is, however, not only clinical vitamin A deficiency that is considerd of importance. In recent years, even marginal vitamin A deficiency has been linked to decreased immune function with subsequent increased predisposition to infections, poor growth, and iron deficiency anaemia (IDA). Vitamin A deficiency therefore plays an important role in child survival not only because it affects the severity of infections,[3-5] but also because vitamin A supplements administered to improve vitamin status are well documented to impact beneficially on childhood mortality.[3,6-8]

Treatment of clinical VAD

The treatment schedule for all stages of xerophthalmia, per age category, is outlined in Table II. The doses should be administered orally and should start immediately after diagnosis.

Table II. Treatment schedule for xerophthalmia for all age groups

Timing	Vitamin A dosage
Immediately after diagnosis	
< 6 months of age	50 000 IU
6-12 months of age	100 000 IU
> 12 months of age	200 000 IU
Next day	Same age-specific dose
2-4 weeks later	Same age-specific dose

Adopted from references 14 and 26.

Prevention of subclinical VAD

Various approaches to the prevention and treatment of subclinical VAD are available. They include, among others, supplementation, food fortification, dietary diversification/modification, promotion of breast-feeding, addressing conditions of public health importance, i.e. measles immunisation, parasitic control and oral rehydration,[7,9] and education on nutrition and health, with special emphasis on vitamin A. An interpersonal approach, the mass media, teacher programmes and medical personnel[10] are used to educate the public.

Periodic high-dose supplementation of vitamin A, whereby vitamin A reserves in the body are maintained at an optimal level, can only be considered a short-term solution to the problem of VAD.[9,11] Up to 30 - 50% of a 200 000 IU dosage is stored in the body for approximately 180 days (a protection period of about 6 months).[10]

Vitamin A supplementation programmes can be divided into two categories. Firstly, universal/mass supplementation programmes, which involve the periodic administration of large doses of vitamin A to all preschool-age children, children and adults living in high-risk areas, or all mothers living in high-risk areas within 4 weeks after delivery (Tables III, IV). Secondly, targeted or selective supplementation programmes, which are aimed at repleting vitamin A reserves drained by chronic or repeated infections, thereby protecting the high-risk child from vitamin A deficiency. Such programmes, therefore, target (*i*) susceptible age groups through the existing health services infrastructure; (*ii*) specific diseases in children (i.e. measles, protein-energy malnutrition, acute respiratory infections, and diarrhoeal disease); (*iii*) children with intestinal infestation with accompanying impairment of the absorption of supplementary retinol;[12] and (*iv*) very-low-birth-weight children.[9,13,14]

Table III. Prevention of vitamin A deficiency

Age category	Vitamin A dosage
Universal/mass supplementation programmes	
Infants < 6 months of age	
Non-breast-fed infants	50 000 IU orally
Breast-fed infants whose mothers have not received vitamin A supplements	50 000 IU orally
Infants 6-12 months of age	100 000 IU orally (every 4-6 months)
Children > 12 months of age	200 000 IU orally (every 4-6 months)
Targeted/selective supplementation programmes	
VLBW babies	1 500 - 2 800 IU/kg/day
Infants < 6 months of age	50 000 IU orally (every 4-6 months)
Infants 6-12 months of age	100 000 IU orally (every 4-6 months)
Children > 12 months of age	200 000 IU orally (4-6 months)

Adapted from references 14 and 26.

A single oral dose of vitamin A should be sufficient for 8 - 12 weeks.[15] However, whether vitamin A supplements should be given every 6 months or 4 months depends on a number of factors which may influence compliance. Moreover, the protective effect of supplementation seems to be greater with smaller frequent doses as compared with one large dose.[16] It would also appear that the effect of repeated (weekly) supplements is cumulative with the protective effect increasing after every dose.[11,17-20] Unfortunately, this mode of more frequent, small-dose supplementation can only be effective in the presence of an optimal infrastructure so as to ensure compliance.

Side-effects of vitamin A

Certain individuals are more susceptible to vitamin A toxicity than the general population owing to predisposing conditions such as viral hepatitis, cirrhosis and other forms of liver disease.[21] The dose and duration of exposure, as well as the age

Table IV. Vitamin A supplementation during pregnancy and lactation

Period	Vitamin A dosage
Safe vitamin A dosage during pregnancy	
Prevention	10 000 IU daily or 25 000 IU weekly
Treatment of night blindness/Bitot's spots	5 000 - 10 000 IU daily for 4 weeks
Treatment of severe xerophthalmia	200 000 IU divided in 3 dosages (as per Table II)
Safe vitamin A dosage postpartum	
Breast-feeding mothers	200 000 IU within first 60 days
	100 000 IU daily thereafter
Non-breast-feeding mothers	200 000 IU within the first 28 days
	10 000 IU daily thereafter

Adapted from reference 25.

of the individual, affects the adverse symptoms experienced. Vitamin A toxicity can be categorised as either acute, resulting from high doses (500 000 IU or 100 times the RDA) consumed over a short period of time, or chronic, as a result of long-term intakes of lesser amounts (50 000 - 100 000 IU per day for adults and 18 000 - 60 000 IU per day for children) and the tendency of vitamin A to accumulate.[21-23]

Acute intoxication, occurring within hours or at most a day or two after intake of a very large dose, is almost always accompanied by headache, as a result of increased intracranial pressure.[23] Other signs and symptoms in children include anorexia, bulging fontanelles, drowsiness, irritability and vomiting.[21] These symptoms should disappear within 12 - 24 hours without any specific treatment apart from stopping the next dose.

The essential feature of chronic hypervitaminosis A is peeling of the skin and bone pains, especially in the long, tubular bones.[23] Chronic vitamin A toxicity in children presents with alopecia, anorexia, bulging fontanelles, craniotabes, premature epiphyseal closure, pruritus and skin desquamation. Hepatomegaly and liver cirrhosis can also occur owing to excessive deposition of retinyl esters in the liver, leading to collagen deposition.[21]

Vitamin A in pregnancy

Since vitamin A is essential for growth and development, increased requirements occur during pregnancy. Breast-milk from vitamin A-deficient mothers is likely to contain insufficient vitamin A to maintain vitamin A stores in the infant. Since 90% of vitamin A in human milk is absorbed,[24] the vitamin A status of infants has been shown to improve with maternal supplementation. Advantages of maternal supplementation as opposed to direct supplements to the infant include improved safety (since the infant receives relatively low doses of vitamin A through breast-milk over a long period of time, instead of a single large dose), improved compliance, because of a reduced number of contacts necessary, and benefits accruing to both mother and child.[24]

In 1998, the WHO[25] recommended (Table IV) a safe vitamin A dosage for supplementation during pregnancy and lactation in areas where VAD is endemic. Treatment of clinical signs of VAD depends on the severity of the deficiency. Women of childbearing age with nightblindness or Bitot's spots should receive a daily oral dose of 5 000 - 10 000 IU vitamin A for at least 4 weeks. If severe signs of xerophthalmia are present, irrespective of whether the woman is pregnant or not, the high-dose treatment schedule (Table II) is advisable.

Vitamin A supplementation to postpartum mothers living in vitamin A-deficient areas is regulated by the safe period of postpartum infertility. In breast-feeding mothers, high-dose vitamin A supplementation can be administered up to 60 days postpartum. Thereafter, the daily intake should not exceed 10 000 IU. In the non-breast-feeding mother, the high-dose supplement can be administered up to 28 days postpartum, thereafter 10 000 IU daily.[25]

Excessive doses of vitamin A administered during pregnancy have been controversially associated with teratogenic effects, depending on the concentration and stage of gestation. Women exposed to high doses of preformed retinoic acid derivates (> 10 000 IU retinol daily) within the first 6 weeks of pregnancy, are reported to have a higher incidence of spontaneous abortion, premature delivery and babies with central nervous system, craniofacial and cardiac development malformations. This probably results from the fact that retinoic acid acts as a ligand that binds to a nuclear hormone receptor, thereby affecting gene function at the critical periods of organogenesis and embryonic development.[25,26] The current recommendation of a daily intake of 10 000 IU retinol throughout pregnancy is considered to be safe for women who do not habitually take vitamin A at the level of the RDA (8 000 IU). There is no justification for a vitamin A supplement in cases of adequate dietary vitamin A intake.[27]

Vitamin B_6

Vitamin B_6 is a water-soluble vitamin required for the metabolism of protein, fat and carbohydrate. Because vitamin B_6 is required for amino acid metabolism, the need for the vitamin is related to protein intake. Symptoms of vitamin B_6 deficiency

in humans include poor growth, anaemia, impaired immune response and convulsions.[27,28]

Vitamin B_6 is well known to be associated with alleviating symptoms of the premenstrual syndrome. Recently a relationship between vitamin B_6 and cardiovascular health has also been suggested on the basis of abnormal homocysteine metabolism. The metabolism of homocysteine to methionine involves three enzymes, namely vitamin B_6, vitamin B_{12} and a folic acid-containing enzyme. A defect in any of these enzymes (especially for vitamin B_6-dependent enzymes) can cause homocystinaemia. The latter may contribute to atherosclerosis in humans.[27]

Large intakes of pyridoxine (2-6 g/day) have been associated with the development of sensory neuropathy. The neuropathy is usually reversible on discontinuation of pyridoxine.[2] An intake of 50 - 100 X the RDA for up to 6 months appears to be safe.[27]

Folic acid

Folic acid is a precursor of certain important enzyme cofactors required for the synthesis of nucleic acids and the metabolism of certain amino acids. An insufficient intake results in the inability to produce deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and certain proteins, resulting in impaired cell growth. Because the demand for folic acid is highest during periods of rapid growth, the risk of deficiency is highest during growth phases and is therefore prevalent in newborn infants, pregnant women and adolescents. The elderly is another high-risk group because their dietary intake is often inadequate.[29] Folic acid supplementation is associated with a decreased incidence of neural tube defects[30] as well as reduced risk for cardiovascular disease by lowering homocysteine levels.[28]

Very high levels of intake have been associated with reduced zinc absorption, although much controversy exists on this matter, since there are studies that do not confirm such an effect. It can also mask the clinical signs of pernicious anaemia, thus making its timely diagnosis difficult. A safety level of 50 - 100 X RDA is recommended.[2,29]

Iron

Anaemia is the most common nutritional disorder in developing and developed countries. According to current estimates approximately 2 billion people worldwide are classified as anaemic, with iron deficiency being considered to be the principal cause.[31]

Complications of iron deficiency anaemia (IDA) are population-specific and are thought to be associated with pregnancy outcome (increased maternal and fetal morbidity and mortality, as well as premature delivery); physical growth (low birth weight and retarded physical development); mental development (retarded cognitive development) and physical performance (fatigue, decreased work capacity and decreased resistance to infections/impaired immunity).[31-36]

In view of the claimed extent and important consequences of iron deficiency, a number of strategies for its 'elimination' have been developed and include, at population level, improved sanitation, control of parasitic infestations, food fortification, improved breast-feeding and dietary practices.[37-39] At the individual level, though, the most important strategy is to identify and treat those at risk[37] by means of iron supplementation. The latter has been a key strategy for the short-term control of IDA for more than 70 years.

Treatment of IDA

In children, iron supplementation should be targeted to those individuals with poor iron status (Table V). Known high-risk groups include low-birth-weight babies, preterm babies, infants breast-fed for less than 6 months without the addition of adequate complementary foods and infants with protein-energy malnutrition.[40] In adults, at-risk groups for IDA include women who are pregnant, of low socio-economic status, with low levels of education, with high parity and multifetal gestations and those who consume diets low in meat and meat products and who are frequent blood donors.[41]

Table V. Treatment schedule for IDA

Category	Elemental iron dosage
Children	
VLBW infant (< 1 000 g)	4 mg/kg/day
VLBW infant (1 000 - 1 500g)	2-3 mg/kg/day
LBW infant	2 mg/kg/day
Full-term infant	1-2 mg/kg/day
Children 3-6 years	2 mg/kg/day 3 mg/kg/week
Pregnant women	
Treatment of IDA	60-120 mg/kg/day or 120 mg per week
Prevention of IDA	30 mg/day

Adapted from references 31, 33, 41, 44.

Studies on the effect of iron supplementation on growth have shown that supplementation of anaemic, underweight children resulted in increased weight gain, increased appetite and decreased morbidity.[34] Furthermore, supplementation of iron combined with vitamin A is reported to protect against any harmful effects of iron supplementation in communities where infections are highly prevalent, owing to the immuno-enhancing role of vitamin A.[42] Iron supplementation during pregnancy benefits the mother by improving maternal iron stores within 3 months. The improved maternal iron status has been documented to last up to 6 months postpartum.[43,44] In this regard, it is also suggested that maternal iron status during pregnancy is a strong predictor of infant iron status later in life.[43]

Frequency of dosing

Emerging evidence indicates that a weekly or twice-weekly iron supplementation regimen produces similar results to the one employing daily dosing; the former dosage schedule is associated with a lower prevalence of side-effects and improved compliance.[31,45,46] This has been ascribed to the fact that in iron-deficient individuals, iron absorption is about 30 - 40% after a single dose. The absorption of iron decreases to about 3 - 6% with a daily dose regimen. It has also been proposed that dosing once a week allows the renewal pattern of intestinal mucosal cells to occur, thereby increasing iron absorption and decreasing the possibility of mucosal iron overload that is thought to be responsible for the side-effects usually reported with iron supplementation. In view of the better iron absorption attained with a weekly dosing regimen, the supplemental dose can be smaller, thus reducing costs and improving compliance.[31] Iron supplements are optimally taken at bedtime or between meals to facilitate absorption. If the supplement contains only an iron salt, the absorption is also better than when it is part of a multivitamin.[41]

Possible adverse effects of iron supplementation and/or excessive iron intake

In the short term, the prevalence and severity of side-effects following iron supplements are dose-related and vary depending on the individual. Side-effects of supplementation include heartburn, nausea, abdominal discomfort, constipation and diarrhoea. These side-effects are reported to subside after a few days of treatment.[41]

In the longer term a few important complications have been associated with inappropriate iron supplementation practice:

1. Retarded growth — routine supplementation of iron to iron-sufficient children is reported to result in a significantly lower rate of weight gain.[47]

2. Bacterial growth — iron supplements given to iron-deficient individuals living in an area with inadequate sanitation and socio-economic circumstances has been associated with an increased incidence and longer duration of diarrhoea. This could be ascribed to the contamination of the environment by bacteria and parasites and the fact that these organisms require iron to proliferate.[48]

3. Catabolism of vitamin C — iron deposits lead to increased catabolism of vitamin C, resulting in reduced release of iron into the circulation from the reticulo-endothelial cells and inappropriately low serum ferritin concentrations.[49]

4. Haemochromatosis — dietary iron overload, resulting from the consumption of alcoholic beverages with a very high iron content (brewed in iron pots) is still reported to be a major problem in South Africa.[49,50]

Iodine

Iodine deficiency disorder (IDD) is one of the three micronutrient deficiencies that are currently recognised to be of public health significance,[51,52] since IDD is known to be one of the most common preventable causes of mental defects in the world.[53]

Salt iodisation is seen as a simple and cost-effective method to provide the iodine needs of any population. In South Africa salt iodisation has been voluntary for a number of years and has normally been in the region of 20 ppm. Compulsory legislation for iodisation of table salt at the level of 40 - 60 ppm has been in place since December 1995.[54]

Iodine intakes of < 1 mg/kg are probably safe for the majority of the population, but may cause adverse effects in some individuals.[55] Those most likely to respond adversely to excessive intakes of iodine include inhabitants of endemic goitre areas, those with habitual low dietary intakes of iodine, those with other forms of thyroid diseases and pregnant women.[55]

Adverse or side-effects to excessive exposure to iodine include thyroiditis, goitre, hypo- and hyperthyroidism and hypersensitivity reactions. Various reports of increased incidence of thyrotoxicosis in endemic goitre areas after increased iodine ingestion following supplementation programmes have been reported. Some of these cases resulted in heart failure and death. The importance of some form of biochemical monitoring of target populations in cases of universal salt iodisation has been emphasised repeatedly.[56,57]

Conclusion

The first rational approach to optimal health has been, and should be, food. When food/nutrient intake is inadequate, significant health benefits have been shown to accrue from supplementation. The latter, however, must be practised with great circumspection and with due consideration to the desired endpoint as well as to the possibility of doing harm. Future developments promise to provide us with a more sound scientific basis both for the recommendations we make in terms of healthy eating and well-defined indications for nutrient supplementation.

References

1. Labadarios D, Blaauw R. Micronutrients: are supplements necessary? *Micronutrients* May 1996; 5-8.
2. Marks J. *Vitamin Safety*. Basle, Switzerland: Hoffmann-La Roche, 1989: 1-26.
3. Labadarios D. Vitamin A — time for action. *S Afr Med J* 1994; **84:** 1-2.
4. Wahed MA, Alvarez JO, Khaled MA, Mahalanabis D, Rahman MM, Habte D. Comparison of the modified relative dose response (MRDR) and the relative dose response (RDR) in the assessment of vitamin A status in malnourished children. *Am J Clin Nutr* 1995; **61:** 1253-1256.
5. West KP jun. Vitamin A deficiency: Its epidemiology and relation to child mortality and morbidity. In: Blomhoff R, ed. *Vitamin A in Health and Disease*. New York: Marcel Dekker, 1994: 585-614.
6. Filteau SM, Morris SS, Abbott RA, *et al*. Influence of morbidity on serum retinol of children in a community-based study in northern Ghana. *Am J Clin Nutr* 1993; **58:** 192-197.
7. Solomons NW. Vitamin A and developing countries. *Intern Child Health* 1995; **6:** 33-47.
8. Hussey G. Public health significance of vitamin A deficiency and its control: Bellagio Conference. *S Afr Med J* 1992; **82:** 135-136.
9. Gillespie S, Mason J. Controlling vitamin A deficiency. Report based on the ACC/SCN Consultative Group Meeting on strategies for the control of vitamin A deficiency, 28-30 July 1993, Ottawa, Canada.
10. WHO Control of Vitamin A deficiency and xerophthalmia. WHO Technical Report Series 672. Geneva: WHO, 1982.
11. Anon. Vitamin A and malnutrition/infection complex in developing countries. *Lancet* 1990; **336:** 1349-1351.
12. Marinho HA, Shrimpton R, Giugliano R, Burini RC. Influence of enteral parasites on the blood vitamin A levels in preschool children orally supplemented with retinol and/or zinc. *Eur J Clin Nutr* 1991; **45:** 539-544.

13. Shenai JP, Kennedy KA, Chytill F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. *J Pediatr* 1987; **111:** 269-277.
14. WHO/UNICEF/IVACG Task Force. *Vitamin A Supplements: A Guide to their Use in the Treatment and Prevention of Vitamin A Deficiency and Xerophthalmia.* 2nd ed. Geneva: WHO, 1997.
15. Carlier C, Etchepare M, Ceccon J-F, Mourey M-S, Amédée-Manesme O. Efficacy of massive oral doses of retinyl palmitate and mango (Mangifera indica L) consumption to correct an existing vitamin A deficiency in Senegalese children. *Br J Nutr* 1992; **68:** 529-540.
16. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. A meta-analysis. *JAMA* 1993; **269:** 898-903.
17. Lie C, Ying C, En-Lin W, Brun T, Geissler C. Impact of large-dose vitamin A supplementation on childhood diarrhoea, respiratory disease and growth. *Eur J Clin Nutr* 1993; **47:** 88-96.
18. Herrera MG, Nestel P, Amin AE, Fawzi WW, Mohamed KA, Weld L. Vitamin A supplementation and child survival. *Lancet* 1992; **340:** 267-271.
19. Sommer A. Vitamin A: Its effect on childhood sight and life. *Nutr Rev* 1994; **52:** Suppl, S60-S66.
20. Rahmathullah R, Babu G. Reduced mortality among children in Southern India receiving small weekly dose of vitamin A. *N Engl J Med* 1990; **323:** 929-935.
21. Hathcock JN, Hattan DG, Jenkins MY, McDonald JT, Sundaresan PR, Wilkening VL. Evaluation of vitamin A toxicity. *Am J Clin Nutr* 1990; **52:** 183-202.
22. Florentino RF, Tanchoco CC, Ramos AC, *et al.* Tolerance of preschoolers to two dosage strengths of vitamin A preparation. *Am J Clin Nutr* 1990; **52:** 694-700.
23. Biesalski HK. Comparative assessment of the toxicology of vitamin A and retinoids in man. *Toxicology* 1989; **57:** 117-161.
24. Stoltzfus RJ, Hakimi M, Miller KW, *et al.* High dose vitamin A supplementation of breast-feeding Indonesian mothers: Effects on the vitamin A status of mother and infant. *J Nutr* 1993; **123:** 666-675.
25. World Health Organisation. Safe vitamin A dosage during pregnancy and lactation. WHO/NUT/98.4, 1998: 1-34.
26. World Health Organisation. Safe vitamin A dosage during pregnancy and lactation. Preliminary report. WHO NUT/96.14, 1997.
27. Gaby SK. Vitamin B6. In: Gaby SK, Bendich A, Singh VN, Machlin LJ, eds. *Vitamin Intake and Health.* New York: Marcel Dekker, 1991: 163-174.
28. Pietrzik K, Bronstrup A. Homocysteine and cardiovascular disease. *Asia Pacific J Clin Nutr* 1996; **5:** 157-160.
29. Gaby SK, Bendich A. Folic acid. In: Gaby SK, Bendich A, Singh VN, Machlin LJ, eds. *Vitamin Intake and Health.* New York: Marcel Dekker, 1991: 175-188.
30. Cziezel AE. Folic acid in the prevention of neural tube defects. *J Pediatr Gastroenterol Nutr* 1995; **20:** 4-16.
31. Stephenson LS. Possible new developments in community control of iron-deficiency anemia. *Nutr Rev* 1995; **53:** 23-30.
32. Hercberg S, Galan P. Nutritional anaemias. *Bailliere's Clin Haematol* 1992; **5:** 143-168.
33. Oski FA. Iron deficiency in infancy and childhood. *N Engl J Med* 1993; **329:** 190-193.
34. Angeles IT, Schultink WJ, Matulessi P, Gross R, Sastroamidjojo S. Decreased rate of stunting among anaemic Indonesian preschool children through iron supplementation. *Am J Clin Nutr* 1993; **58:** 339-342.
35. Duggan MB, Steel G, Elwys G, Harbottle L, Noble C. Iron status, energy intake, and nutritional status of healthy young Asian children. *Arch Dis Child* 1991; **66:** 1386-1389.
36. Shrestha M, Chandra V, Singh P. Severe iron deficiency anaemia in Fiji children. *NZ Med J* 1994; **107:** 130-132.
37. Ballot DE, MacPhail AP, Bothwell TH, Gillooly M, Mayet FG. Fortification of curry powder with NaFe (111)EDTA in an iron-deficient population: initial survey of iron status. *Am J Clin Nutr* 1989; **49:** 156-161.
38. Layrisse M. Iron deficiency in Latin America, causes and prevention. In: Hanck A, Hornig D, eds. *Vitamins — Nutrients and Therapeutic Agents.* Toronto: Hans Huber Publishers, 1995: 105-116.
39. Svanberg U. Dietary interventions to preview iron deficiency in preschool children. In: Nestel P, ed. *Iron Interventions for Child Survival.* London: OMNI Proceedings, 1995: 31-44.
40. Brabin B. Iron supplements to control anaemia. In: Nestel P, ed. *Iron Interventions for Child Survival.* London: OMNI Proceedings, 1995: 67-71.
41. Menard MK. Vitamin and mineral supplement prior to and during pregnancy. *Obstet Gynecol Clin North Am* 1997; **24:** 479-498.
42. Ribayo-Mercado JD, Mayer J. Importance of adequate vitamin A status during iron supplementation. *Nutr Rev* 1997; **55:** 306-307.
43. Allen LH. Pregnancy and iron deficiency: Unresolved issues. *Nutr Rev* 1997; **55:** 91-101.
44. Viteri FE. Iron supplementation for the control of iron deficiency in populations at risk. *Nutr Rev* 1997; **55:** 195-209.
45. Palupi L, Schultink W, Achadi E, Gross R. Effective community intervention to improve hemoglobin status in preschoolers receiving once-weekly iron supplementation. *Am J Clin Nutr* 1997; **65:** 1057-1061.
46. Gross R, Schultink W, Juliawati. Treatment of anaemia with weekly iron supplementation. *Lancet* 1994; **344:** 821.
47. Idradinata P, Watkins WE, Pollitt E. Adverse effects of iron supplementation on weight gain of iron-replete young children. *Lancet* 1994; **343:** 1252-1254.
48. Brunser O, Espinoza J, Araya M, Pacheco I, Cruchet S. Chronic iron intake and diarrhoeal disease in infants. A field study in a less-developed country. *Eur J Clin Nutr* 1993; **47:** 3117-3126.
49. Friedman BM, Baynes RD, Bothwell TH, *et al.* Dietary iron overload in southern African rural Blacks. *S Afr Med J* 1990; **78:** 301-305.
50. Walker ARP, Walker BF, Labadarios D. The benefits of iron supplementation and prophylaxis in Africa. *Nutr Res* 1994; **14:** 513-521.
51. Jooste PL, Marks AS, Schurink CvE. Factors influencing the availability of iodised salt in South Africa. *SA J Food Sci Nutr* 1995; **7:** 49-52.
52. Kretchmer N. Deficiency of iodine: A striking example of malnutrition of a micronutrient. *Int Child Health* 1995; **VI:** 63-69.
53. World Health Organisation. Global prevalence of iodine deficiency disorders. WHO Working paper, July 1993.
54. Jooste PL, Blaauw R. Micronutrient malnutrition in South Africa as seen in an African context. *SA J Food Sci Nutr* 1995; **7:** 87-88.
55. Pennington JAT. A review of iodine toxicity reports. *J Am Diet Assoc* 1990; **90:** 1571-1581.
56. Todd CH, Allain T, Gomo ZAR, Hasler JA, Ndiweni M, Oken E. Increase in thyrotoxicosis with iodine supplements in Zimbabwe. *Lancet* 1995; **346:** 1563-1564.
57. Bourdoux PP, Ermans AM, Mukalay A, Filetti S, Vigneri R. Iodine-induced thyrotoxicosis in Kivu, Zaire. *Lancet* 1996; **347:** 552-553.