Micronutrient Supplementation Throughout the Life Cycle

Report of a workshop held by the Ministry of Health, Brazil and UNICEF

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Edited by Rainer Gross

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EXECUTIVE SUMMARY

In many countries, populations suffer simultaneously from more than one micronutrient deficiency, and supplementation programmes addressing different micronutrient deficiencies are often implemented at the same time. Operational strategies and distribution systems can be similar for each micronutrient, and therefore efforts and resources are duplicated and cost-effectiveness is reduced.

Widespread micronutrient deficiencies in populations have a deep-rooted causality within the human life cycle. They are strongly associated with poverty and are passed on from one generation to the next. Multi-micronutrient supplementation has recently been suggested as a means of halting this vicious cycle.

There are, however, several technical and scientific aspects to be considered before recommending implementation of a multi-micronutrient supplementation programme. A first step was taken in a UNICEF/WHO/UNU workshop that made recommendations on a multi-micronutrient supplementation for women. Following on from that strategy, this workshop aims to provide a basis for a comprehensive micronutrient supplementation programme for populations in developing countries who suffer simultaneously from the deficiency of several micronutrients.

Thirty six representatives from government agencies, non-governmental organizations (NGOs), universities and the private sector from twelve countries of South and North America, Africa, and Europe participated in this three-day-workshop in Rio de Janeiro organized by the Ministry of Health, Brazil and UNICEF. Within the workshop, workgroups and the following plenary discussions focused on six issues:

- Multi-micronutrient composition for infants and children
- Product
- Distribution
- Communication programme planning to sustain high adherence
- Monitoring and evaluation
- Supplementation programme design

Composition and dosing: The micronutrient status of infants and small children was identified as the area of most vulnerability within the life cycle. Due to the limited time available at the workshop, recommendations were developed focusing this age group, although several recommendations are also applicable to other age groups. It was agreed that although infants and small children are the most vulnerable groups, with the highest relative requirements, it is also the group with the least available information concerning the efficacy and effectiveness of supplementation. Decisions on the selection and composition of micronutrients in a supplement had to be based on existing scientific and technical experiences.

It was decided that a supplement should contain the following 13 micronutrients: vitamins A, D, E, B1, B2, B6, B12, folic acid, niacin; Fe, Zn, Cu, I. The rationale for the composition of micronutrients in a supplement was based on the recommendations of the UNICEF/WHO/UNU workshop, ***Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries.*** Furthermore, available information about efficacy, toxicity levels, cost of nutrients and possible side effects related to supplement intake were considered. Based on these discussions, the 100% RDA approach was applied, using the USA/Canadian RDA reference as the best updated and documented basis for the amounts included for each nutrient. In case of daily application, it was recommended to add one RDA for age group 12 –24 months into a supplement for infants and young children (6 – 24 months). An exception was made for zinc, which was recommended at a lower dose adjusted for infants 6-12 months due a the possible risk of faster AIDS progression in HIV-positive children. In case of intermittent multi-micronutrient supplementation, two RDAs were recommended for a once-a-week administration. Although little experience is available on weekly dosing in infants and small children, support was expressed for further development of this alternative as a possible way of positioning the intervention more in the area of nutrition than of medicine.

Product development: The development of a new type of supplement has been proposed. This product should be a low density, dry, foam-like supplement, which is easily crushable into a dispersible powder, can be added to the final serving of infants' complementary food or milk, and can be chewed by older children or adults. The product should be larger and of different size than tablets, so it must be chewed rather than swallowed, and has a more food-like appearance.

Distribution: Sufficient access to supplements must be guaranteed through adequate distribution as a precondition for high adherence. Although health services will always play a key role in the distribution of supplements for infants and small children, all additional alternatives (resellers, education services, religious groups, community organizations, etc.) should be explored and utilized. Intermittent dosing could facilitate distribution and increase adherence.

Communication: One of the limiting factors to the efficiency of supplementation programs was inappropriateness or total lack of collateral communication programmes. Such programmes must not only address the primary but also secondary and tertiary audiences using consistent, relevant, and easy understandable messages, appropriate channels, and effective monitoring and evaluation.

Monitoring and evaluation: Adequate monitoring and evaluation (M&E) of processes and impacts is one key factor for the success of supplementation programmes. This is particularly relevant for multi-micronutrient supplementation in infants and small children, where up to now there is no programme experience available. Within the monitoring and evaluation process, the supply and distribution chain, training and communication are of special importance. Reported and observed adherence, effectiveness (using structural and functional indicators), and negative side effects related to collateral programmes (fortification and dietary changes) should be assessed. Inclusion of M&E costs is crucial in calculating required financial resources and the efficiency of multi-micronutrient supplementation programmes.

Supplementation programme design: The following issues were identified as key factors for efficient programme design:

- Decision on public health action (situation analysis), needs and etiology
- Identification of target group(s), frequency of intake (and hence dosage over a particular time)
- Duration of supplementation
- Design of the product
- Costs
- Channels of distribution
- Human resources (quantity, quality, and time)
- Communication
- Possible negative side effects (social, cultural, etc.)
- Monitoring and evaluation

For the present, a new supplement is being developed as outlined above and will be tested in efficacy and effectiveness trials in different countries. It is planned to exchange experiences in a follow-up workshop.

1

INTRODUCTION

1.1 Background

Rainer Gross

In the paradigm of "hidden hunger", deficiency of micronutrients was identified as the most prevalent nutritional problem. Vitamin A, iron and iodine deficiencies were the most important micronutrients for intervention programmes. As a result, several vertical programs such as vitamin A capsule distribution and iron supplementation of pregnant women were revitalized or newly implemented in many countries. Despite the success of some of these programmes, a number of experiences demonstrate that actions related to single micronutrients that address the most deficient groups may show only limited effectiveness. Limiting factors include lack of financial resources, inadequate distribution systems, and poor adherence. Interaction between micronutrients has also recently been identified as another factor that may reduce the effectiveness and efficiency of programmes.

In many countries, populations suffer from more than one micronutrient deficiency and supplementation programmes for different micronutrients are often implemented at the same time. Since operational strategies and distribution systems can be similar for each micronutrient, efforts and resources are duplicated and cost-effectiveness is therefore reduced.

Concerted efforts have recently been undertaken to overcome these problems. According to the current understanding, a newly emerging concept for the alleviation of micronutrient deficiencies can be summarized as follows:

Not just curative, but also preventive

Not just one strategy, but several

Not just distribution, but also information, education, communication

Not just action, but also monitoring and evaluation

Not just efficacy or effectiveness, but also efficiency

Not just single, but multiple micronutrients

In Brazil, several initiatives have incorporated these new concepts into micronutrient supplementation programmes. These initiatives are supported by two important factors. Firstly, improved nutrition has become an important human rights goal and therefore has broad political and public support. Secondly, decentralization allows municipalities to plan and implement their nutrition strategies according to their specific needs and resources.

This dynamism in the field of nutrition in Brazil has lead the Ministry of Health together with UNICEF, with the support of the Municipality of Rio de Janeiro, to organize a workshop on Micronutrient Supplementation through the Life Cycle. The workshop is part of an ongoing conceptual development process. In 1998, multi-micronutrient supplementation for women was addressed in a workshop in Singapore. In April 1999, the discussion was followed up in a working group session at the 26th ACC/SCN Session in Geneva, where another working group discussed the related area of the life cycle consequences of fetal and infant malnutrition. In July 1999 multi-micronutrient supplementation of pregnant women was discussed and recommendations were elaborated at a UNICEF/WHO/UNU workshop in New York. In October 1999, an International Zinc Conference took place at Davis in California and in November 1999 a workshop on the efficacy of daily and weekly dosing of iron supplementation took place in Washington DC. The Rio workshop presented an opportunity to build these experiences into a strategy on micronutrient supplementation throughout the life cycle.

1.2 Objectives of the workshop

The aim of this technical workshop was to provide the basis for a comprehensive micronutrient supplementation programme for populations in developing countries who suffer simultaneously from the deficiency of several micronutrients.

In particular, the objectives were to:

- Define micronutrient dosing for infants and children
- Identify gaps in knowledge and experiences necessary for the success of supplementation programmes
- Identify possible operational strategies (distribution systems) and formulate appropriate technical recommendations for each one
- Identify factors that influence adherence
- Formulate appropriate communication strategies to increase adherence
- Formulate indicators for the monitoring and evaluation of supplementation programmes

- Formulate a protocol for a comprehensive supplementation programme based on a life cycle approach

1.3 Programme of the workshop

Thirty-six experts from twelve countries of South and North America, Africa and Europe, working for international agencies (UNICEF, CIDA, GTZ); governmental organizations (Brazil, Italy, Peru, South Africa); universities (Brazil, Germany, USA); non-governmental organizations (AJCN, USA; CeSSIAM, Guatemala; HKI, USA; Instituto de Investigación Nutricional, Peru; Micronutrient Initiative, Canada); along with three specialists from the private sector invited by UNICEF, came together for three days in Rio de Janeiro to discuss recommendations for micronutrient supplementation.

The workshop was organized by the Ministry of Health, Brazil and UNICEF, and supported by the Instituto de Nutrição Annes Dias of the Municipality of Rio de Janeiro. Denise Coitinho, Ministry of Health, Brazil, Ines Rugani, Municipality of Rio de Janeiro, and Werner Schultink, UNICEF, New York welcomed the workshop participants. Rainer Gross, University of São Paulo, then outlined the background, objectives and expected process of the workshop.

The programme consisted of three sections. The first section, chaired by Carlos Monteiro, University of Sao Paulo, discussed aspects of micronutrient dosing during the life cycle. The second section, chaired by Flora Sibanda-Mulder, UNICEF, West Africa, was dedicated to distribution of and adherence to supplementation. The third section, chaired by Denise Coitinho, Ministry of Health, was devoted to the design of a life cycle supplementation programme.

Each section consisted of presentations followed by group work, the results of which were documented and subsequently presented and discussed in a plenary session with all participants. The rapporteurs considered additional comments from the plenary in their final report. The written reports are a core element of this publication (see part 2). The detailed program is shown in Annex 1. At the end of the workshop a smaller group developed a research protocol for a multi-centre study on multi-micronutrient supplementation in infants, which is attached to this document as Annex 4. The final report was edited by Rainer Gross.

2

WORKSHOP REPORTS AND OUTCOMES

2.1 Multi-micronutrient composition for infants and young children

Rapporteur: D'Ann Finley

It was agreed upon that the most vulnerable group in need of supplementation is children from ages 4-6 months to 24 months due to:

- High risk of being born with low micronutrient stores
- Insufficient levels of micronutrients in breastmilk due to low maternal nutritional status
- Inadequate complementary feeding
- Repeated episodes of infectious diseases and parasitism
- Relatively high need due to rapid growth

To prevent micronutrient deficiencies and to allow for normal growth to occur, all nutrients must be present simultaneously. Although supplementation is only one of several options to improve nutritional status of children, a supplementation formulation should be developed because it is useful in a variety of settings and is increasingly requested by authorities in developing countries.

Due to limited time, the following issues were not considered in this section of the workshop:

- Form of delivery–*chewable is desirable where possible because it does not require potentially polluted water for consumption, but children in this age group cannot chew or swallow pills*
- Low birth weight (LBW) babies–*even though 40-50% of births in some countries (e.g. India and Bangladesh) are LBW*
- Daily versus weekly supplementation
- Children older than 24 months

The formulation of a supplement has been recently developed for women of child-bearing age, and includes **Vitamins A, D, E, C, B-1, B-2, B-6, B-12, folic acid, niacin,** and **Fe, Zn, Cu, I, Se**.

The workshop agreed that caution must be exercised in developing a micronutrient formulation for use in developing countries. A strong case would need to be made if adding nutrients or using a different concentration of nutrients from those used in supplements in industrialized countries.

Nutrients not considered in the formulations

Biotin and pantothenic acid: No information is available that might suggest a deficiency of either of these nutrients in developing countries.

Vitamin K: It is unlikely that vitamin K deficiency occurs, except in newborns, but the possibility of vitamin K deficiency during early childhood needs to be explored further.

Calcium: Due to the high requirement for calcium, it is not practical to provide a meaningful portion of the calcium requirement through a multi-micronutrient supplement. However, some calcium can be included in the supplement as part of the carrier. Unfortunately, there is no soluble calcium salt available at reasonable cost that could be included in a liquid supplement. According to participants, the individual impact of calcium on bone development in young children is difficult to judge, since it cannot be separated from the influence of vitamin D. If calcium were added, the iron and zinc components of the supplement would be less available due to interactions with the calcium. For adults, 250 mg calcium in a supplement decreases the bioavailability of zinc and iron. Most infants obtain sufficient calcium via breastmilk. The amount of calcium in milk is little affected by maternal intake. Therefore supplemental calcium is probably not needed as long as the child is breastfed.

Phosphorus: If calcium is not included in the supplement, phosphorus should not be added, otherwise the calcium to phosphorus ratio will be disrupted and phosphorus absorption will be highly reduced. Furthermore, phosphorus in the form of phytates is a component of most complementary foods and supplementation is therefore not essential.

Magnesium: There is some evidence that magnesium deficiency may be a possible contributor to Sudden Infant Death Syndrome (SIDS), but SIDS is not a problem for children older than 4-6 months. Magnesium can become deficient in some malabsorption syndromes. However, there is no indication for a higher prevalence of magnesium deficiencies in developing countries. Magnesium has also been reported to decrease iron absorption in pregnant women. Addition of magnesium is therefore not recommended.

Potassium: Potassium content is high in staple food sources in developing countries as well as in complementary foods fed to young children. There is therefore no justification for adding this micronutrient.

Selenium: Selenium levels vary over large range within some countries. Some reports suggest the prevalence of goitre can be due not only to iodine deficiency but to combined iodine-selenium deficiency. Some US infant formulas have very high levels of selenium, but no problems have been reported relative to these levels. However, the addition of selenium to the supplement was not considered since there seemed to be insufficient information available on the negative side effects of the ingestion of high levels. Furthermore, a low bioavailability of selenium has been reported from some selenium sources such as yeast. There is a need to collect more information on the benefits and risks of including selenium in supplements.

Fluoride: Fluoride is the micronutrient with the smallest difference between required and the toxic levels. In some geographical areas (e.g. in Africa), there are naturally high levels of fluoride. Furthermore, increasingly this element is added to drinking water. For safety reasons, fluoride should not be added to the supplement.

References for quantities of included nutrients

The basis of the rationale for the concentration of micronutrients to be included in the supplement is the RDA, with the RDAs of the US and Canada (Table 1) as the basis of the formulation. The international panel that developed recommendations for multi-micronutrient supplementation of pregnant and non-pregnant women has already accepted this rationale.

Even children in poor conditions will always ingest some amount of all micronutrients via food. However, there is sufficient information available from many parts in the world that the situation with regard to micronutrient intake is so precarious that micronutrients should be provided at high concentrations as long as they are safe and edible. A supplement designed to be taken daily that contains 100% RDA is regarded as safe even when additional micronutrients are ingested with food.

TABLE 1.

US/Canada RDA values for young children

Micronutrient	Unit	Age group		Details of unit
		6-12 months	13-24 months	
Vitamin A	mg	375	375	retinol equivalents
Vitamin D	ug	5	5	
Vitamin E	mg	4	6	a-tocepherol equivalents
Vitamin B1	mg	0.3	0.5	
Vitamin B2	mg	0.4	0.5	
Vitamin B6	mg	0.3	0.5	
Vitamin B12	ug	0.5	0.9	
Folate	ug	80	150	dietary folate equivalents
Niacin	mg	4	6	
Vitamin C	mg	30	35	
Iron	mg	10	10	
Zinc	mg	5	10	
Copper	mg	0.4-0.5	0.6-0.7	
Iodine	ug	40	50	

Special consideration must be given to zinc. According to the results of most studies, zinc supplementation of 10 mg/d showed a positive effect on linear growth. However, 3 mg Zn/d has been shown to improve haemoglobin status. WHO has recommended 11.8 mg/d of zinc for toddlers consuming diets of "low" zinc bioavailability (WHO, 1996). In the US, it is likely that the RDA will be decreased below the current recommendation of 10 mg because endogenous losses have been overestimated. The RDA for zinc recommended by WHO and currently by US/Canada may be too high for children in several parts of the world. According to a study, high intakes might accelerate the progression of HIV to AIDS. In some populations a 25% transmission rate from mother to child has been observed, and therefore in areas with a high prevalence of AIDS, high zinc intakes should be avoided. To lower the risk, zinc levels in supplements should be restricted to below 100% RDA, until data that contradict such fears are available.

For infants up to one year, the US recommendation is to provide vitamin B6 only via food, because it is assumed that vitamin B6 intake is sufficient via breastmilk. However, in developing countries vitamin B6 content in breastmilk may be low. Therefore, vitamin B6 should be added to the supplement.

It was concluded that for children from 6 to 24 months of age, the higher, 13-24 months RDA levels should be used for the formulation of any generic multi-micronutrient supplement, except for zinc, for which the lower, 6-12 months RDA level should be used.

2.2 Product development

Rapporteur: Klaus Schümann

An optimal supplement should have the following characteristics: low production cost, long term stability of all added micronutrients, easy dosability and convenience for the mother to feed it to a suckling child. In addition, the product should preferably have a food-like appearance instead of a capsule-like appearance. None of the current galenic forms fulfills all of these requirements. A tablet is difficult to administer to a suckling child. However, the micronutrients in a liquid media such as syrup will tend to interact, leading to mutual destruction and decreasing shelf-life. Furthermore, the storage of syrup in a bottle with a dosing device or even in a sachet adds to costs.

An alternative solution would be a low density, foam-like supplement, which is easily crushable into a dispersible powder, can be added to the final serving of the babies' complementary food or milk, and can be chewed by older children.

The administration of the supplement with milk or complementary foods would give the supplement a more food-like character. To differentiate such a product from the current medical approach to supplementation, an appropriate name has to be identified. The name *"food-let"* (food + tablet) was proposed for the above-suggested galenic form. Since the suggested supplement would be chewed or dissolved rather than swallowed, size is not a critical issue. The dry form supports stability of micronutrient content, allowing for an estimated shelf-life of over a year. After crushing or dissolving, the product can be administered to suckling infants, while older children can chew it. Its production should be cheap and feasible with existing technology. The tablet will be too big to be swallowed in bulk or to cause choking, which adds to its safety. The external packaging should be water- and crush protected. Internally, the supplements could be packaged separately for better control of administration. However, blister packaging should not be used, because of its high cost, and to avoid giving the supplement a medicinal image. The form should preferably be flat and squared to ease packaging and to allow crushing. The taste of the supplement should depend on cultural preference and should be strong enough to hide the metallic taste of Fe, Zn and Cu as well as the taste of B-vitamins. The form in which the micronutrients are added was not defined in detail. It should be the cheapest form and at the same time being sufficiently bioavailable. Physico-chemical interactions between micronutrients during storage seem not to be an issue in a dry supplement.

As the “food-let” should be taken with food and as the RDA recommendations are made for micronutrients in food, the recommended RDA doses seem adequate. However, if taken on empty stomach, the availability of Zn, Cu and Fe will be higher.

A fat-based, no-water paste was discussed as an alternative, which should be able to avoid destabilization of the micronutrients. It could be dosed with a dispenser or in a sachet or hard gelatin capsule. Open questions are whether the product may become rancid over time, whether the out-oxidation of fat destabilizes fat-soluble vitamins, and whether the capsule would be small enough to cause choking in small children. Its convenience when opened and spread on food seems to be less than that of the “food-let”.

Participants identified the need for further research regarding weekly versus twice daily or daily dosing. There was a lack of information on the impact of such dosing pattern on micronutrient status as well as on compliance and cost-effectiveness as related to the improvement of status. It was felt that the “food-let” should be dosed for a daily administration, which decreases risk of overuse and increases flexibility of administration. If weekly administration is desired a defined multiple of “food-lets” could be used on the same day.

2.3 Distribution

Rapporteur: Barbara MacDonald

If multiple micronutrient policies are adopted in developing countries, every effort must be made to enhance adherence of recommended intakes. Adherence to iron supplementation programmes has been compromised in the past, due to unacceptable products, inadequate distribution channels and insufficient communication. All these factors are essential for successful programmes.

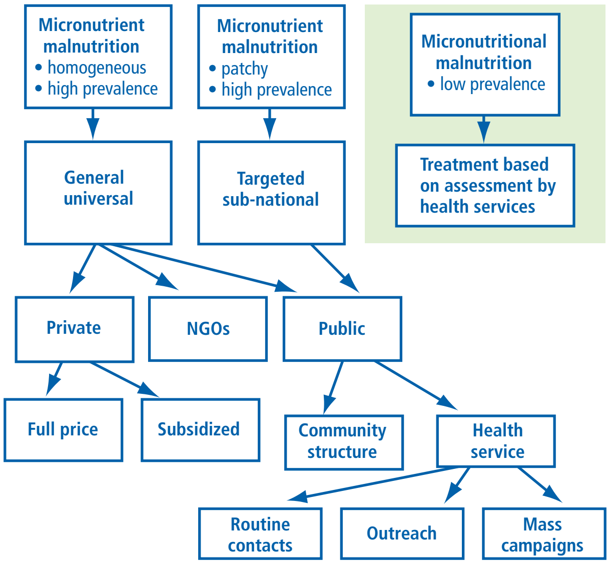
Although a life cycle approach is recommended for identifying the most appropriate target groups for supplementation programmes, it was decided that the working group should concentrate on reaching children aged 6 to 24 months. A similar exercise should be conducted for other vulnerable groups who may be best reached via other distribution channels. However, several points discussed below are relevant also for other age groups or are relevant for the entire community as such.

Supplementation is often required for a long duration and may involve ingesting tablets for preventative rather than curative purposes. These factors may reduce adherence compared to medications and may be partly addressed through the use of novel community-based approaches for distribution which may complement the health system. Drawing on public health experience with the promotion of cod liver oil and adherence to TB drug protocols, community participation and effective communication are critical for long-term success. Micronutrients, therefore, should be positioned not as “medicines” but truly as *supplements* to the diet that will help improve quality of life during critical periods of the life cycle. If it is found to be efficacious and effective, weekly micronutrient supplementation may help with this non-medical approach as medicines are normally ingested daily. It was recommended that a strong partnership between communities and the health system be promoted and that the potential role of existing community structures such as schools, religious institutions and private outlets should be explored. This partnership includes working with communities to develop specifications for the most acceptable products.

Optimal distribution channels and the desirability of universal versus targeted programmes will be context-specific and will depend in part on the prevalence of micronutrient malnutrition, geographic/socioeconomic/seasonal variability, periodicity of supplementation and the coverage of the existing health system. Figure 1 illustrates the variety of distribution channels available. Governmental and civil society struc-

Figure 1.

Potential micronutrient supplement distribution channels



tures are included, with special events such as outreach and campaigns among the possible options. As children in some countries have excellent routine contacts with the health system during the first year of life, efforts should be made to distribute take-home supplements during immunization and other contacts, especially for children aged 6 to 12 months. Depending on the socioeconomic status of those affected, the subsidized purchase of supplements through private outlets is possible.

Although universal recommendations regarding distribution are not possible, it is imperative that methodologies be developed and disseminated that will aid governments and agencies in identifying the most effective and sustainable channels. In choosing the best system, planners must be consider:

- Who will be reached via a given channel?
- What is the acceptability of that channel to the population?
- What is the cost of using that channel?
- What is the efficiency of that channel?

2.4 Programme planning to sustain high adherence

Rapporteur: Elizabeth Warnick and Ursula Gross

Communication: The assessment of the problem, i.e., the identification of the most affected and the magnitude of the problem, is the first step in designing a micronutrient communication plan. During this assessment, it is important to involve the local community to understand their perception of the problem. The second step is the identification of target audiences. Often, the beneficiaries of the intervention or the users of a product are considered as the sole primary audience—in the case of a micronutrient supplement for children, it would be the children themselves. Programmes must also consider other groups such as caretakers (in this case, mothers), who will administer or control supplementation to the target group, as well as other groups, such as policymakers and service providers, who can be very influential in the acceptance and delivery of the messages. To ensure successful programme results, it is necessary to get all three groups actively involved in the communication and implementation strategies. These groups and communication strategies are: primary, secondary, and tertiary audiences.

In the case of micronutrient supplements for children, the **primary audience** consists of those who are deficient who will take the micronutrients (children), and primary caretakers who will give the micronutrient to their children.

The following recommendations were made when designing messages for *primary audiences*:

1. Choose a simple attractive product name and promote the micronutrient supplements using the product name instead of calling it "vitamins" or "supplements".
2. Identify and use a simple message that emphasizes benefit and action. For example, use "Give XXX to make your child strong and healthy" rather than "XXX is good for your child's health". Both the product name and message should be tested among the primary audience.
3. Identify and use the channels of communication that are most effective and adequate for the groups to be targeted (e.g., community women's groups, schools, magazines, etc.).
4. Adapt the messages as needed to accommodate regional differences, minority groups, etc. Wording and visuals may affect how messages will be perceived and understood by the primary audience.
5. Use consistent messages across the target audiences.
6. Messages should be delivered frequently and not only once at the beginning of the programme.
7. A programme design implies various message strategies and stages of communication.

The **secondary audience** consists of those who influence the primary audience—health professionals, family, peers, opinion leaders (e.g. religious and community leaders, teachers, etc.).

In order to involve the secondary audience in achieving programme goals, communication should:

1. Create social acceptance by those who more likely to influence the primary audience—for example, if the users of the micronutrient supplements are schoolchildren, ensure that parents, teachers, and health professionals accept micronutrient supplements and understand their benefits.
2. Train the service providers (e.g. health workers) in communication skills and delivery of correct messages and actions—the service providers have a multiplier effect as they can influence many users. As part of a monitoring process, reassess knowledge and practices of service providers and retrain as necessary, reinforcing basic messages and delivery skills.

The **tertiary audience** consists of those who help to make the programme a success: policy and decision makers, donors, international agencies, academic and professional societies, civil groups, press/media.

For the tertiary audience, it is recommended to:

1. Provide relevant information and guidelines for advocacy and programme management—information more likely to influence decision makers includes cost-effectiveness figures, safety assurance, and proofs of efficacy and effectiveness;
2. Seek and inform of the endorsement and advocacy of micronutrient interventions by international organizations, which are more likely to positively influence decision makers; and
3. Provide consistent information among the tertiary audience groups.

2.5 Monitoring and evaluation

Rapporteurs: D'Ann Finley and Klaus Schümann

Monitoring and evaluation (M&E) will be handled differently in more affluent countries with a well-organized health system than in poorer countries with less organized systems, but is necessary no matter which is the case. M&E must be carried out on both the process and impact of a micronutrient supplementation programme. There are several areas in which M&E are required.

Supply and distribution chain: M&E is necessary at all points in the distribution chain, beginning with forecasting the amount of product needed to begin the project and continuing with routine control of inventory throughout the entire chain from the producer to the end user (caregiver in our example). Reorder forms need to be designed and then used at predetermined intervals. Outdated materials should be discarded and not included in the inventory.

Training and communication: The impact of training should be monitored particularly frequently at the beginning of the project. A validated instrument should be used, such as semi-structured interviews, to gain information from the individuals in direct communication with the caregiver and from the caregiver herself. This should measure knowledge and identify changes in practice and attitudes. When misinformation is identified, measures for correction must be implemented immediately. The determination of the amount of printed materials that had been distributed is a simple, indirect method to monitor training and communication. However, this does not ensure that the material has been used or read.

Measurement of impact: Under field conditions, potential biochemical markers for determination of the micronutrient status show different feasibility (i.e. in blood from finger pricks or in urine, reliability of the assay, danger of contamination). Monitoring vitamin A, thiamine, folate and Fe status would be feasible and highly desirable. In some locations it might also be desirable and feasible to monitor vitamin B12, iodine, Se and Vitamin C status. In addition, functional indicators such as anthropomorphic variables (e.g. height and weight, morbidity) should be assessed. If possible, children's morbidity should be monitored by biweekly recalling the caregiver. Mental development scores should be monitored under more sophisticated conditions. All of these markers should be studied in subpopulations during the run-in phase to measure the efficacy and effectiveness of the intervention and possibly to eventually fine-tune dosing of micronutrients.

Assessment of adherence: At the second and on each subsequent distribution, each caregiver should be asked how often the supplement has been given to the child and if there have been any problems with administering the supplement *(reported adherence)*. A semi-structured in-depth interview should be carried out on a sub-sample of users. Information obtained should include:

- Knowledge of the caregiver relative to supplement—why is it given?
- Ways in which supplement has been given - was it done correctly?
- Who received the supplement - was only the intended child given the supplement or was it given to other children within the family?
- Changes in behaviour and attitude of the caregiver and of the other household members

A biological test should be sought to measure adherence *(observed adherence)*. One possibility would be to add PABA (para-amino benzoic acid) to some of the supplements and to randomly distribute the marked supplements to caregivers. The urine of the children would subsequently be tested to determine whether they had received the supplement. This would complicate the distribution process because two kinds of supplements would need to be produced and distributed, and the identity of the caregiver receiving the special supplements would need to be recorded. However, it is not recommended to add PABA into all supplements due to increased costs. Furthermore, it is ethically questionable to expose a substance to all children, which is physiologically not a necessary part of the supplement. The described monitoring method of observed adherence may be too sophisticated for some distribution sites.

Negative side effects: Negative side effects should be monitored at three different levels:

- Individual - such as increased diarrhoea
- Household - such as decreased purchasing of fruits and vegetables
- National - such as, higher relative cost of this project compared to that of others for improving the health of the population

Advocacy: The results of M&E should be evaluated and this information should be distributed to policy makers, donors, other project sites (in decentralized system), and consumers themselves, and so the purpose and the targeted information groups for advocacy needed to be identified before establishing an M&E system and defining the indicators. M&E costs at programme initiation will be relatively high to ensure that the project is successfully launched. Subsequently, as available information increases, M&E will be less necessary and therefore costs will decrease. Nevertheless, M&E must always be a component of a programme and sufficient budget must be allocated.

Adequate budget planning for M&E requires the definition of a feasible programme at programme design. Then, the specific M&E budget, the process and impact indicators (structural and functional—e.g. the cut off levels for biochemical markers of nutritional status), the frequency of M&E, and the assignation for the responsibility for M&E should be defined.

2.6 Supplementation programme design

Rapporteur: Ian Darnton-Hill

Programmes should always consider more than one, and usually the conventional three, approaches to the prevention and control of micronutrient malnutrition (supplementation, fortification, dietary changes), and then look at prioritization depending on need. To assist in prioritizing it is necessary to identify the needs and current status of the different target groups throughout the life cycle. The most optimal in terms of sustainability would be diet diversification, then fortification, and then supplementation, but the actual mixture of the intervention design will depend on local circumstances, resources and needs.

Any programme recommendation on supplementation does not reduce the importance of the other two options. Since in most cases the planning and implementation of all three options needs to be initiated from the start of a programme, all recommendations on supplementation should be interwoven with those for the other two complementary options. This leads to such questions as: when should supplementation be used; what are the special cases such as refugee camps; what are the delivery options; and so forth?

The following agenda, used during the meeting, would be useful for programme design, monitoring and evaluation:

1. Decision on public health action (situation analysis)
2. Needs and etiology
3. Target group(s)
4. Frequency of intake (and hence dosage over a particular time)
5. Duration of supplementation
6. Design of the product
7. Cost issues
8. Channels of distribution
9. Human resources (quantity, quality, and time)
10. Communication to end-users
11. Side effects (social, cultural, etc.)
12. Monitoring and evaluation
13. Next steps

Situation analysis: There are four scenarios which characterize the situation of multi-micronutrient deficiencies:
- multi-micronutrient deficiencies both broad and highly prevalent (homogeneous);
- highly prevalent but patchy;
- not highly prevalent but homogeneous; and
- not highly prevalent and patchy.

Short-term and long-term needs may differ under the four different situations.

Using existing information and identifying what new information might be needed i.e. assessing the nutritional situation, should be the first step. There might be a need to identify the deficient micronutrients and which target group(s) is/are of concern. Program implementers may ask the following questions:

- Do we need to address more than one micronutrient?
- Should the situation analysis be conducted for each micronutrient—and then decide on mix of possible supplements?
- What possible interventions are feasible?
- What are the existing intakes—collected as consumption data (but which can be notoriously unreliable so can only indicate likely problems)?
- What are the other needs for information e.g. predicted changes in urban/rural ratios?

It was concluded that a situation analysis must be done (not least as one type of baseline information) but that although different countries' needs are likely to vary, UNICEF cannot make more than one formulation. Nevertheless the rationale remains that those who are micronutrient deficient in one vitamin or mineral, are more likely to have several deficiencies because of poor quality diets. Countries could, however, vary dose and/or administration frequency recommendations and guidelines. Countries would therefore need to decide for themselves if they are willing to use a multi-micronutrient supplement (offered for example by UNICEF) or feel the need to use a more 'tailored' intervention.

The situation analysis should be done throughout the life cycle and this life cycle approach addressed right at the planning stage and must look at the needs of the whole population.

Needs: There are groups in society, at different stages of the life cycle, with known greater relative needs. Consequently, in practical terms the planner may need to design interventions aimed at different age groups. Two evident paradigm shifts become obvious:
- taking a 'life cycle' approach means not only identifying greatest needs at a particular phase of life, but also that understanding the health and nutrition status at any point in a life stage will influence to a greater or lesser degree, the whole of the rest of the life cycle and will influence subsequent health and nutrition; and
- supplementation can be longer-term way of moving the micronutrient status of populations from left to right (inadequate to adequate) i.e. a classic public health approach.

The supplementation should be based on a population-based, public health approach that presumes multiple deficiencies based on available evidence (often the only data may be for iron deficiency anemia).

Young children (6-24 months) are the current priority for programmes. However, a programme should seek to address all age groups. It may be possible to do this with different sources of programme funding, so it is not a matter of addressing one target group to the exclusion of another.

Target groups: Taking into account all the above considerations, the specific age group of 6-24 months, in particular 6-12 months was identified as the primary target group for multi-supplementation. Considerations of factors such as cost, access to infants, physiological needs, environmental and sanitation factors all contributed to this conclusion.

Opportunities for access to infants and young children of different age groupings may need disaggregating during planning—e.g. health systems give priority to the first year of life- including immunization, while access during the second year is often more difficult. Programme design may therefore differ between age groups—for 6-12 months, 12-24 months, etc. However, it may prove possible in the future to simply use the same composition of micronutrients, but with differing dosages.

In principle, multi-micronutrient supplementation should be initiated in a deficient population in infants at 6 months, if their birth was normal and they are fed exclusively with breastmilk. Otherwise, supplementation should start from 4 months on. Low birth weight children have specific micronutrient needs, which may require supplementation to start already at the age of 2 months. However, when the prevalence of low birth weight is high, special programmatic arrangements have to be considered, taking the maternal and physical environmental, and national circumstances into account.

Considering cost constraints, feasibility, and convenience, a duration of supplementation for infants of 6 or 12 months was recommended, depending also on the type of dosing: daily or weekly. Generally the recommendation was to start at 6 months and continue at least until 12 months. Despite the greater information on iron status and supplementation as compared with other possible micronutrient deficiencies— and even this is limited—multi-micronutrient supplementation may require a different regimen from iron supplementation e.g. daily dosing may not be appropriate for some micronutrients.

Since in the poorer developing countries two thirds of all deaths occur during the first year of life, the major objective of multi-micronutrient supplementation is the reduction of mortality in this age group. Nevertheless, additional outcomes for the survivors such as reduction in morbidity and promotion of physical and cognitive development are critically important. Both physiologically and because of biological reasons, and that there are less other intervention alternatives after 12 months through clinics etc., priority was given to 6-12 months old infants. Other interventions can then complement this, and so there is less of a cost burden (as this does not include supplementation for 12-24 months olds). Countries may choose to continue longer depending on their resources. However, taking all the above into account, priority was given to 6-12 months.

Frequency of intake: Currently, there is not enough scientific evidence to establish the optimally effective utilization of all the constituents of a multi-micronutrient supplement under programme conditions. For metals such as iron and zinc, and fat-soluble vitamins, both daily and weekly dosing appear to be efficacious. The final decision for a daily or intermittent dosing must then be based on observed compliance, effectiveness, and available resources.

For the present it was agreed to recommend a daily dose. If there are severe resource constraints, ministries might try twice a week, but should monitor such intervention programmes closely. There is an urgent need for effectiveness data and for clarification of safety of giving a dose of twice the RDAs per week. In the meantime, as the frequency of administration is closely related to the concentration of micronutrients in the supplement, the daily administration of one RDA dose is suggested to be the most effective. However, under many circumstances (e.g. due to limited resources or distribution problems) once-a-week dosing may be more feasible. In this case, an administration of a two RDA dose is recommended. However, effectiveness needs to be closely monitored. There is an urgent need to investigate the efficacy and effectiveness of daily and weekly dosing in multi-micronutrient deficient infants.

Duration: Little information is available about the biological efficacy of micronutrients related to the duration of their administration, and sustainability of differing regimes. Yearly repeated short-term (3-6 months) administration may be less effective but offers the advantage of being cheaper and maybe less counteracting of efforts to encourage dietary change.

The outcome to be achieved is another issue to be considered for the definition of the duration of a supplementation programme. A short duration may be effective to reduce the prevalence of anemia but insufficient to reduce the rate of stunting, or some other micronutrient deficiencies.

Another factor to be considered with regard to the duration of supplementation is the most biologically sensitive window for supplementation during the life cycle. The amount of time needed to replenish deficient stores, the time of onset of stunting (although often already starting in intrauterine development), or the increasing prevalence of infectious diseases are factors which must be taken into account in the definition of the duration.

Given all the above it was recommended that the **minimum** should be to cover every child of 6-12 months where possible, preferably starting at 6 months. If supplementing older children, 3 months duration of supplementation was recommended. As an example, if a child first presents at a clinic at 8 months, then he/she might be presumed to be more at risk than an infant that has been receiving regular post-natal care and should therefore still receive supplementation for a further 6 months (i.e. until 14 months). At end of the six months dosage period, then any decision would be a clinical decision to continue, and the child should be reviewed three months later if the child's continued unhealthy environment means that problems are likely to recur.

Design of the product: Continuing experimentation and product development is blurring the line between supplements and fortified food products, e.g. what is a micronutrient-containing powder added to a drink? A 'cocktail' of micronutrients can be given in a variety of ways e.g. suspension, powder in milk, sprinkles. Suspensions are heavier, more expensive, more difficult to give adequate doses and carry the risk of becoming rapidly unstable. Dry formulations of supplements such as powders, sprinkles, or tablets may be more advantageous. Each country may need to develop and produce their own supplement considering international experiences and recommendation of organizations such as WHO and/or UNICEF. However, the formulation and all other data such as stability, expiry dates etc., must be in the public domain, and discussions and decisions on dosage should be freely available. There must be some maintenance of composition standards, and standards of best practice will need to be adapted and agreed upon to maintain quality assurance for effectiveness, and safety.

Cost issues: Information on the costs and effectiveness of multi-micronutrient programmes is urgently needed. Cost calculations should be made at least on a theoretical basis. Previous calculations for iron by the Micronutrient Initiative, for vitamin A by OMNI/USAID or PROFILES could serve as a model. Items that would need to be considered include the actual cost of constituent micronutrients, staffing needs, distribution, IEC materials, and M&E. However, by using existing systems and health frameworks some of the costs (such as salaries, building facilities etc.) would be incremental. There is no doubt that, compared to the costs of the supplement production itself, packaging and distribution by the health system, the incremental extra cost of adding all the suggested micronutrients is minimal. Nevertheless, taken together this relatively small extra could still dissuade some countries from the utilization of multi-micronutrients.

Channels of distribution: Health systems appear to be the most appropriate distribution channel for multi-micronutrient supplements. However, there is the risk that not enough attention will then be paid to utilizing private, public and private/public partnerships systems for delivering supplements.

Human resources: While much of this was discussed under costs and channels of delivery, there will be a need for specific efforts to be made towards human resource development to secure successful programme implementation. However, little systematic information is available on the effectiveness and efficiency of human resource development for micronutrient programmes, which are very often country and system specific.

Communication to end-users: The success of any micronutrient programme is closely linked to an effective communication programme to end-users. Such programmes will always depend on local circumstances and should be accompanied by formative research. Beside the end-user, communication must be addressed to policy makers, and this is often forgotten. Experiences have shown that some policy makers are likely to be most resistant to nutritional interventions in general and micronutrient supplementation in particular.

Side-effects of the programme: Any intervention will create the risk of unintended side effects, which could include social and cultural issues. A multi-micronutrient supplement programme can affect other programmes (e.g. diverting of resources, reduction of effectiveness, etc.). As a result, the risk of unintended negative side effects in supplementation is of particular relevance and need to be closely monitored, especially considering that a comprehensive micronutrient programme comprises simultaneously also fortification and dietary changes.

Monitoring and evaluation: Due to the lack of experience on multi-micronutrient supplementation, monitoring and evaluation (M&E) is of particular importance. Besides the general need for monitoring and evaluation, multi-micronutrient supplementation in particular, requires an on-going observation due to rapidly changing living conditions, sanitation, dietary behaviours, etc.

Next steps: It was agreed that the report of the meeting should be published and distributed as soon as possible. Furthermore, efforts will be made to organize in a year a follow-up workshop on multi-micronutrient supplementation and subsequently, a similar workshop on multi-micronutrient deficiency and fortification. Both these workshops would take advantage of the added information and data that should be available by then from early implementation studies.

ANNEX 1 PROGRAMME OF THE WORKSHOP

Wednesday, 17.11.1999

9:00	Welcome:	Denise Costa Coitinho, Ministry of Health, Brazil; Ines Rugani, Institute of Nutrition "Annes Dias", Rio de Janeiro; Werner Schultink, UNICEF, New York
9:15	Introduction:	Rainer Gross, University of São Paulo

Micronutrient dosing in the life cycle

Chairperson: Carlos Monteiro, University São Paulo

9:30	Presentations:	Cristina Lopriore and Francesco Branca, National Institute of Nutrition, Rome – *Multi-micronutrient fortified food reverses growth failure and anemia in 2-5 years old stunted refugee children*
10:00		Lindsay Allen, UCD, USA – *Are multiple micronutrient supplements for the treatment of anemia better than iron alone?*
10:30	Coffee Break	
11:00		Carmen Donangelo, UFRJ, Brazil – *Micronutrient status and supplementation in women in Rio de Janeiro*
11:30		Noel Solomons, CeSSIAM, Guatemala – *Interaction and toxicity considerations of micronutrients*
12:20	Lunch Break	
14:00		Nadia Trugo, UFRJ, Brazil – *Micronutrient dosing for women: an overview*
14:30		Spinnier Benade, MRC, Capetown, South Africa – *Micronutrient dosing for children: an overview*
15:00		**Plenary Discussion:** *Recommendations on dosing of multi-micronutrients for infants and children*
16:00	Coffee Break	
16:30		**Plenary Discussion:** *Recommendations on dosing of multi-micronutrients for infants and children*
17:30		**Wrap-up by the Chairperson**

Thursday, 18.11.1999

Distribution and Adherence

Chairperson: Flora Sibanda-Mulder, UNICEF, West Africa

9:00	Presentations:	Denise Costa Coitinho, Ministry of Health, Brazil – *Iron supplementation in children under 2 years of age in 512 of the most at risk municipalities of the Northeast of Brazil – the participation of Community Health Workers*
9:30		Elizabeth Warnick, Population Services International, Bolivia – *Social marketing of multivitamin supplements for women of reproductive age*
10:00		Ursula Gross, University of São Paulo, Brazil – *Communication strategies for micronutrient supplementation programmes*
10:30	Coffee Break	
11:00	Work groups:	**Recommendations on research and programme planning to sustain high adherence in supplementation programmes (product development, distribution, communication)**
12:30	Lunch break	
14:00	Work groups:	**Recommendations on research and programme planning to sustain high adherence in supplementation programs (product development, distribution, communication)**
15:30	**Coffee break**	
16:00	**Plenary Discussion:**	*Conclusions of the work groups*
17:30		**Wrap-up by the chairperson**

Friday, 19.11.1999

Design of the life cycle supplementation programme

Chairperson: Denise Costa Coitinho, Ministry of Health, Brazil

9:00	Presentation:	Guillermo Lopez de Romaña, INN, Lima, Peru – *Micronutrient supplementation in the life cycle*
9:30		Werner Schultink, UNICEF, USA – *State of the art monitoring and evaluation systems in micronutrient supplementation programmes*
10:00		France Begin, MI, Canada – *Delivering multiple micronutrients to vulnerable groups: Some innovations, challenges and opportunities*
10:30	Coffee Break	
11:00	Work groups:	**Recommendations on supplementation programme design, monitoring and evaluation**
12:30	Lunch break	
14:00	Work groups:	**Recommendations on supplementation programme design, monitoring and evaluation**
15:30		**Plenary Discussion:** Conclusions of the work group
16:30	Coffee Break	
17:00		**Wrap-up of the Chairperson**
17:30		Rainer Gross, University of São Paulo, Brazil
		Plenary Discussion: *Next Steps*
18:00	Closing remarks	**Werner Schultink, UNICEF**

ANNEX 2

DIETARY REFERENCE INTAKE (DRI) FOR SMALL CHILDREN AND ADULTS

from Calcium Panel Report 1997; B-Vitamins and Choline Panel Report 2000.

TABLE 2.

Dietary Reference Intake (DRI) values for Children (1-3 years).

Nutrient	EAR	RDA	AI	UL
Calcium	None	None	500 mg	2500 mg
Phosphorus	380 mg	460 mg	—	3.0 g
Magnesium	65 mg	80 mg	—	65 mg**
Vitamin D	None	None	5 ug (200 IU)	50 ug (2000 IU)
Fluoride	None	None	0.7 mg	1.3 mg
Vitamin B1	0.4 mg	0.5 mg	—	None
Vitamin B2	0.4 mg	0.5 mg	—	None
Niacin	5 mg NE	6 mg NE	—	10 mg NE
Vitamin B6	0.4 mg	0.5 mg	—	30 mg
Folate	120 ug DFE*	150 ug DFE*	—	300 ug folic acid None for folate from food
Vitamin B12	0.7 ug	0.9 ug	—	None
Pantothenic Acid	None	None	3 mg	None
Biotin	None	None	8 ug	None
Choline	None	None	200 mg	1 g

*DFE = dietary folate equivalents = 1 mcg food folate = 0.5 mcg synthetic folic acid on empty stomach = 0.6mcg synthetic folic acid with meals

** supplementary magnesium

EAR: Estimated Average Requirement (covering the requirement of 50% in a population group)

RDA: Daily dietary requirement (covering 97.5% of an individual in a population group); calculated from EAR · 1.2

AI: Adequate Intake (comparable to RDA, a surrogate for RDA, if not enough scientific evidence available to decide for a EAR)

UL: Tolerable upper level of intake (derived from NOAEL [no observed adverse effect level] or from LOAEL [lowest observed adverse effect level] by employing an uncertainty factor, usually between 1-10); the risk for an adverse effect is gradually increasing with intakes > NOAEL

TABLE 3.

Dietary Reference Intake (DRI) values for Children (4-8 years).

Nutrient	EAR	RDA	AI	UL
Calcium	None	None	800 mg	2500 mg
Phosphorus	405 mg	500 mg	—	3.0 g
Magnesium	110 mg	130 mg	—	110 mg**
Vitamin D	None	None	5 ug (200 IU)	50 ug (2000 IU)
Fluoride	None	None	1.0 mg	2.2 mg
Vitamin B1	0.5 mg	0.6 mg	—	None
Vitamin B2	0.5 mg	0.6 mg	—	None
Niacin	6 mg NE	8 mg NE	—	15 mg NE
Vitamin B6	0.5 mg	0.6 mg	—	40 mg
Folate	160 ug DFE*	200 ug DFE*	—	400 ug folic acid None for folate from food
Vitamin B12	1.0 ug	1.2 ug	—	None
Pantothenic Acid	None	None	3 mg	None
Biotin	None	None	12 ug	None
Choline	None	None	250 mg	1 g

*DFE = dietary folate equivalents = 1 mcg food folate = 0.5 mcg synthetic folic acid on empty stomach = 0.6 mcg synthetic folic acid with meals

TABLE 4.

Dietary Reference Intake (DRI) values for Children (9-13 years).

Nutrient	EAR	RDA	AI	UL
Calcium	None	None	800 mg	2500 mg
Phosphorus	405 mg	500 mg	—	3.0 g
Magnesium	110 mg	130 mg	—	110 mg**
Vitamin D	None	None	5 ug (200 IU)	50 ug (2000 IU)
Fluoride	None	None	1.0 mg	2.2 mg
Vitamin B1	0.5 mg	0.6 mg	—	None
Vitamin B2	0.5 mg	0.6 mg	—	None
Niacin	6 mg NE	8 mg NE	—	15 mg NE
Vitamin B6	0.5 mg	0.6 mg	—	40 mg
Folate	160 ug DFE*	200 ug DFE*	—	400 ug folic acid None for folate from food
Vitamin B12	1.0 ug	1.2 ug	—	None
Pantothenic Acid	None	None	3 mg	None
Biotin	None	None	12 ug	None
Choline	None	None	250 mg	1 g

*DFE = dietary folate equivalents = 1 mcg food folate = 0.5 mcg synthetic folic acid on empty stomach = 0.6 mcg synthetic folic acid with meals

** supplementary magnesium

TABLE 5.

Dietary Reference Intake (DRI) values for Children (14-18 years).

Nutrient	EAR	RDA	AI	UL
Calcium	None	None	1300 mg	2500 mg
Phosphorus	1055 mg	1250 mg	—	4.0 g
Magnesium	340/300 mg°	410/360 mg°	—	350 mg**
Vitamin D	None	None	5 ug (200 IU)	50 ug (2000 IU)
Fluoride	None	None	3.0 mg	10 mg
Vitamin B1	1.1/0.9 mg°	1.2/1.0 mg°	—	None
Vitamin B2	1.1/0.9 mg°	1.3/1.0 mg°	—	None
Niacin	12/11 mg NE°	16/14 mg NE°	—	30 mg NE
Vitamin B6	1.1/1.0 mg°	1.3/1.2 mg°	—	80 mg
Folate	330 ug DFE*	400 ug DFE*	—	800 ug folic acid None for folate from food
Vitamin B12	2.0 ug	2.4 ug	—	None
Pantothenic Acid	None	None	5 mg	None
Biotin	None	None	25 mg	None
Choline	None	None	550/400 mg	3 g

*DFE = dietary folate equivalents = 1 mcg food folate = 0.5 mcg synthetic folic acid on empty stomach = 0.6 mcg synthetic folic acid with meals

** supplementary magnesium

° males / females

TABLE 6.

Dietary Reference Intake (DRI) values for Children (19-50 years).

Nutrient	EAR	RDA	AI	UL
Calcium	None	None	1000 mg	2500 mg
Phosphorus	580 mg	700 mg	—	4.0 g
Magnesium				
19-30 y	330/255 mg°	400/310 mg°	—	350 mg
>31 y	350/265 mg°	420/320 mg°	—	(non-food only)
Vitamin D	None	None	5 ug (200 IU)	50 ug (2000 IU)
Fluoride	None	None	4/3 mg°	10 mg
Vitamin B1	1.0/0.9 mg°	1.2/1.1 mg°	—	None
Vitamin B2	1.1/0.9 mg°	1.3/1.1 mg°	—	None
Niacin	12/11 mg NE°	16/14 mg NE°	—	35 mg NE
Vitamin B6	1.1 mg	1.3/1.3 mg°	—	100 mg
Folate	320 ug DFE* 520 ug DFE* (pregnancy)**	400 ug DFE* 600 ug DFE* (pregnancy)**	—	1000 ug (synth.) None for folate from food
Vitamin B12	2 ug***	2.4 ug***	—	None
Pantothenic Acid	None	None	5 mg	None
Biotin	None	None	30 ug	None
Choline	None	None	550/400 mg°	3.5 g

*DFE = dietary folate equivalents = 1 mcg food folate = 0.5 mcg synthetic folic acid on empty stomach = 0.6 mcg synthetic folic acid with meals

**in addition to dietary folate 4g of folic acid as supplement is recommended for women capable of becoming pregnant to reduce the risk of neural tube defects

***adults > 51 years are advised to obtain most of this amount by taking foods fortified with vitamin B12 or vitamin B12 – containing supplements

° males / females

References

Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, D.C., 1997

Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Pre-publication, Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, D.C., 2000.

ANNEX 3

Multi-Micronutrient Research Topics

Category	Description
1	**Biochemical, physiological, and epidemiological determinants of multi-micronutrient deficiencies**
1.1	Age groups and physiological status (e.g. pregnancy, infection, contamination)
1.2	Socioeconomic status
1.3	Ethnicity
2	**Functional indicators**
2.1	Micronutrient status in different ages and physiological status and functional outcomes (e.g. iron status in infancy and functional outcomes to define cut-off of anemia)
3	**Efficacy of multi-micronutrient supplementation in different age groups and physiological status**
3.1	Efficacy of daily/weekly dosing of single micronutrients (B vitamins, folic acid, niacin)
3.2	Efficacy of daily/weekly dosing of combined micronutrients
4	**Effectiveness of multi-micronutrient supplementation**
4.1	Effectiveness of micronutrient supplementation in single population groups
4.2	Effectiveness of micronutrient supplementation in the whole population (life cycle approach)
5	**Communication**
6	**Efficiency of multi-micronutrient supplementation**
6.1	Costs of multi-micronutrient supplementation
6.2	Cost-benefit
7	**Assessment and impact monitoring**
7.1	Simple food intake/frequency indicators for multi-micronutrient deficiency
7.2	Simple biochemical markers for multi-micronutrient deficiency
8	**Product development of non-drug supplements**

ANNEX 4

International Research on Infant Supplementation (IRIS) Multi-Center Study on Efficacy of Multi-Micronutrient Supplementation in Small Children

Background

In many countries, populations suffer simultaneously from different micronutrient deficiencies and often supplementation programs for different single micronutrients are implemented at the same time. Since operational strategies and distribution systems can be similar for each micronutrient, efforts and resources are duplicated and cost-effectiveness is therefore reduced.

To overcome these problems, multi-micronutrient supplementation in different age groups has been suggested. Several studies have been conducted to test the efficacy in schoolchildren, adolescents and adults. However, little is known about the efficacy of multi-micronutrient supplementation in infants. It is this age group, which is mostly affected by these deficiencies.

Objective of the study

It is the objective of the study to examine the prevalence of multi-micronutrient deficiencies in infants from rural populations of four selected countries. Furthermore, the efficacy of multi-micronutrient supplementation shall be explored in infants from micronutrient deficient populations of different ethnic groups.

Region: Africa, Latin America, Asia

Population: infants 6 – 12 months, randomly chosen from a micronutrient deficient underfive population with at least 30% anemia (Hb <110 g/L) and 30% VAD (serum retinol < 20 µg/dL);

At least 65 infants per group + 5 infants in case of drop outs;

In case that more than one child in a family fulfils requirements to participate in the study, all children should be included and treated as separate cases. However, the children should join the same intervention group.

Duration of the study: 6 months

Study design:

Randomized, double blind case control study. Prior to the study all subjects shall be dewormed, using Albendazole if relevant.

Group	Type	Frequency of administration
1	Placebo	Daily
2	10 mg elementary iron as iron sulfate	Daily
3	Multi-micronutrients (1 RDA)	Daily
4	Multi-micronutrients (2 RDA)	Weekly

In all groups the supplements shall be administered on a daily basis for 7 days. Group 1 receives the placebo and Group 2 the iron supplement. Group 3 receives daily one multi-micronutrient supplement (1 RDA), whereas group 4 receives one 2 RDA multi-micronutrient supplement per week. On the other days the infants of this group receive a placebo supplement. Based on this distribution scheme, the need of supplements for each site is shown in the following table. This calculation considers 70 infants per group (65 + 5 drop-outs) and an additional amount of 2 RDA supplements for a weekly dosing of three months of the placebo group after the study.

TABLE 7.

Requirements of supplements per site.

Group	Micronutrient Supplement 1 RDA	Micronutrient Supplement 2 RDA	Iron	Placebo
1	—	—	—	12 740
2	—	—	12 740	—
3	12 740	—	—	—
4	—	1 820	—	10 920
Post-Need	—	910	—	
Total	**12 740**	**2 730**	**12 740**	**23 660**

It is desirable that the supplements are similar in form, taste and texture. All supplements and the placebo shall be produced using aformula developed by Roche and shall be used in all study sites.

The infants shall be visited in their households by the enumerators at least once a week. During the visit compliance of the administration of the supplement will be controlled.

Multi-micronutrient supplement

One multi-micronutrient supplement used shall have the dose of micronutrients of 1 RDA for children aged 1-2 years with exception of zinc, which is equivalent for 1 RDA for children aged 6-12 months.

Vitamin A	(µg RE)	375	Vitamin C	(mg)	35
Vitamin D	(µg)	5	Folic acid	(µg)	150
Vitamin E	(IU)	6	Niacin	(mg)	6
Vitamin B-1	(mg)	0.5	Fe	(mg)	10
Vitamin B-2	(mg)	0.5	Zn	(mg)	10
Vitamin B-6	(mg)	0.5	Cu	(mg)	0.6
Vitamin B-12	(µg)	0.9	I	(µg)	50

Anthropometric measurements

Children's weight and height shall be measured monthly. Weight should be recorded nearest 0.1 kg, while children are minimally clothed, with an electronic weighing scale (SECA, Hamburg, Germany). Length shall be recorded nearest 0.1 cm, with the children laying down; using the WHO recommended length-measuring board for infants (Ahrtag, London, UK).

Blood sampling

Blood shall be obtained from the vein. At least 800 µL blood are collected in heparinized tubes and centrifuged at 5000 g for 5 min within one hour after collection. The plasma is transferred to one or two 500 µL Eppendorf cups (at least 300 ul in one cup). After removing of the remaining plasma and the buffy coat the erythrocytes are also transferred to one or two 500 µL Eppendorf cups. Plasma and erythrocytes are frozen at –20° C and stored at –70° C until transportation on dry ice to Germany. All procedures should be done as fast as possible and protected from direct light.

Biochemical analysis

The blood samples collected in each site shall be analyzed in the Micronutrient Laboratory of the Institute of Biological Chemistry and Nutrition at the University of Hohenheim with exception of hemoglobin, which shall be determined on each site.

Hemoglobin concentration will be determined with the cyanomethemoglobin method (INACG, 1984) by using a portable photometer. Serum ferritin shall be measured by ELISA according to the above-mentioned specification. Serum retinol, ß-carotene, and tocopherol will be analyzed by HPLC according to Erhardt et al. (1999). Plasma zinc and copper concentrations shall be analyzed with flame atomic absorption spectroscopy (Versieck and Cornelis, 1980). Radio assay for folate determination (Floridi et al. 1985, Zempleni et al. 1992) and HPLC analysis for riboflavin shall be used (see Annex 1). Acute phase response shall be observed to monitor infectious status. C-reactive protein and AGP (a-1 acid glycoprotein) for short and long term effects, respectively, shall be measured (ELISA kits). If possible, a urine sample for the urine iodine excretion shall be collected from boys between 08.00 h and 12.00 h. Iodine concentration in urine will be analyzed based on alkaline digestion using the Sandell-Kolthoff reaction (Dunn et al 1993).

Exclusion criteria

Lack of signed informed consent
Premature birth of the child
Severe wasting: < -3 Z-scores
Fever: >39 C
Hemoglobin: <80 g/L
C-reactive protein: Positive cases will be excluded from the statistical analysis of serum ferritin, retinol and zinc.

Observation of different parameters

Weight	Monthly
Height	Monthly
Morbidity	At least weekly
Hemoglobin	Begin/end
Serum ferritin	Begin/end
Serum retinol	Begin/end
Serum ß-carotene	Begin/end
Serum tocopherol	Begin/end
Folate	Begin/end
Riboflavin	Begin/end
Serum zinc	Begin/end
Serum copper	Begin/end
C-reactive protein	Begin/end
Urinary iodine	At least 3 monthly

Statistical analysis:

The statistical evaluation of the data collected in all sites will be carried out by the MRC, South Africa. The complete data file shall be returned to the participating centers with the codes.

Ethical considerations:

The guidelines of the Council for International Organizations of Medical Sciences shall be followed (CIOMS, 1990). Before the study the mothers shall be informed about the purpose of the study and the research institution by the first author. Assurance will be given that participation is voluntary and that no negative consequences would result for those who decided not to participate in the study. The Ethical Committee of each research center must approve the study protocol.

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ANNEX 5 LIST OF PARTICIPANTS

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