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Can supplements help meet the micronutrient needs of the developing world?

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Supplementation has many potential advantages over fortification and dietary approaches for improving micronutrient intake. Pregnant and lactating women and infants are most likely to benefit from supplementation. Recent experience with vitamin A supplementation in young children has proved to be remarkably successful. Demonstrated efficacy of vitamin A supplements for improved child survival in many settings and a technical consensus on how to implement interventions were major factors in achieving this success. Bilateral and UN agencies worked together so that in 1999 80 % of children under 5 years of age in the least-developed countries received a vitamin A capsule in the last 6 months. At least one million child lives saved were associated with the increase in coverage in the last 2 years of the 1990s. Experience with Fe–folate supplements has not been as successful. Whilst a technical consensus has been reached on how to implement programmes to control Fe deficiency, the lack of convincing evidence of efficacy of Fe–folate supplements in terms of maternal and child survival outcomes has undoubtedly contributed to the limited pursuit of effective action. A new multiple micronutrient supplement for use amongst women of reproductive age in developing countries has been formulated. UNICEF is employing the supplement in programmes aimed at helping to prevent low birth weight. The new supplement is likely to be more efficacious than Fe–folate supplements for both maternal and child survival and development outcomes. Successful completion of rigorous efficacy trials will be critical for creating the political support needed to achieve universal coverage.

Micronutrient supplementation: Iron and folate supplements: Vitamin A supplements: Survival outcome

In theory the answer to this question is of course yes, but in practice our experience is quite mixed. The present paper describes the use of dietary supplements as a programmatic option for increasing micronutrient intakes amongst vulnerable groups in populations of developing countries. The great progress achieved in the quest of virtually eliminating vitamin A deficiency using massive-dose capsules is reviewed, and the remaining constraints and challenges discussed. The lack of progress in tackling anaemia in women and the constraints and challenges involved in promoting the use of Fe–folate supplements are further considered. The rationale behind the development of a multiple micronutrient supplement as part of an approach for improving maternal nutritional status and preventing low birth weight is also described, including how such interventions are being pursued in several pilot countries.

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When to supplement?

The programmatic approaches available for increasing micronutrient intake include dietary modification, food fortification and supplementation. Whilst each approach has its inherent advantages and disadvantages, these different approaches for improving micronutrient status of populations are more often complementary options than competing options. The diet-based approach has the advantage that once the population changes its diet, it is likely to sustain this practice. The disadvantages are that very often it is difficult to change dietary practices, and that micronutrient-rich foods are often expensive, meaning that they may be beyond the reach of the poorest of the poor. Even in industrialized countries large segments of the population have adequate energy but inadequate micronutrient intakes (Kant 2000). Supplementation has the advantage that it can provide a rapid improvement in the nutritional situation of target groups, but has the disadvantage that the recipients are usually required to take the supplement with some regularity. Even if the issue of adherence is resolved, the challenge remains of ensuring the continuous distribution and local availability of the supplements.

Supplementation is the best option where the prevalence of a micronutrient deficiency in a population is high, and especially if the requirement for a nutrient is difficult to achieve through the normal diet. Supplements are normally provided to a well-defined target group, not the whole population, and for a limited period. Typically, pregnant and lactating women and infants represent the most-at-risk groups whose nutrient needs are highest, and who merit provision of micronutrient supplements during this period of increased nutritional vulnerability. Supplementation is especially indicated if a distribution system exists that will allow the target population to be fully covered at a reasonable cost. Even though supplementation is traditionally considered a short-term approach, in reality it may be a long-term one in many situations. In industrialized countries between 10 and 30 % of the population regularly take dietary supplements, with the result that dietary intakes of nutrients such as Fe and folate are enhanced in this segment of the population with no apparent risk or side effects (Dwyer *et al.* 2001; Kiely *et al.* 2001).

Vitamin A supplements

Although the elimination of vitamin A deficiency by year 2000 was one of the goals set at the World Summit for Children in 1990 (UNICEF, 1990*b*), little progress was evident at mid-decade. Clinical vitamin A deficiency was estimated to be affecting about 3·3 million children under the age of 5 years in 1995, with a further 100 million subject to subclinical deficiency. Although it was one of the mid-decade goals selected in 1993 by the WHO/UNICEF Joint Committee on Health Policy as a priority goal to be achieved by 1995, at mid-decade only ten countries had vitamin A supplementation programmes, and there was little evidence of any progress in tackling the problem of vitamin A deficiency.

The non-perception of vitamin A deficiency as a problem was a substantial barrier to establishing supplementation programmes. Governments, not unreasonably, are reluctant to introduce supplements without hard evidence that they have a problem. At only 0·5 %, the prevalence of clinical signs of frank vitamin A deficiency such as bitot spot and corneal lesions that make it a 'public health problem' is very small. Since clinical signs are often more common in rural populations and are not as evident in urban areas, a significant vitamin A deficiency problem can easily go undetected. Thus, national representative surveys were a prerequisite for getting action. However, many economically challenged governments in non-industrialized countries have difficulty tackling their perceived disease problems, such as tuberculosis and/or malaria, and will not easily spend money to find 'new' problems. Another barrier is the voice of those who only advocate food-based approaches, and see supplements as expensive technical fixes or golden bullets that might help to save lives but are of questionable sustainability and/or against national interests.

Convincing proof of the efficacy of vitamin A capsules for child mortality reduction helped to create increased momentum for supplementation programmes. A turning point for increasing the coverage of vitamin A supplements was undoubtedly the publication of the meta-analysis of the efficacy trials of massive-dose vitamin A capsules (Beaton *et al.* 1994). The analysis of eight mortality trials indicated that improving the vitamin A status of children aged 6 months–5 years by massive-dose capsule distribution reduced mortality rates by about 23 %. The observed effect of supplementation, described in terms of relative risk, did not differ by gender or age. However, the number of lives saved was greater at younger ages because of higher mortality. The important conclusion of this publication was that increased risk of mortality from vitamin A deficiency was not just limited to those populations with severe vitamin A deficiency problems.

Vitamin A supplementation has proved to be one of the most cost-effective health interventions. The World Development Report of 1993 (World Bank, 1993) found micronutrient programmes in general, and vitamin A supplementation in particular, to be among the most cost-effective of all health interventions. The costs per capsule delivered are between 25 and 45 US cents. The costs per life saved and life-years free of illness gained (disability-adjusted life-year gained) are ways of comparing the effectiveness of health interventions. For vitamin A supplements the cost per life saved is US $325 and the cost per disability-adjusted life-year gained is US $9 (World Bank, 1994).

What constituted 'the justification' for carrying out a vitamin A supplementation programme began to evolve during the second part of the 1990s. Many of these discussions were held at the biannual meetings of the International Vitamin A Consultative Group and the annual meetings of the working group on vitamin A of the Nutrition Forum of the UN (ACC/SCN). The main conclusion coming from these discussions was that where the mortality rates for under-5-year-olds were > 50 per 100 000 live births there was no need for survey data to demonstrate the existence of vitamin A deficiency as a prerequisite for introducing supplementation programmes. A technical consensus

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meeting held in 1997 finally accepted that the benefits of vitamin A supplements would be evident in populations where the mortality rates for under-5-year-olds were > 70 per 100 000 live births, together with evidence that there was a protein–energy malnutrition problem (UNICEF/Micronutrient Initiative/World Health Organization/Canadian International Development Agency/USAID, 1997). Subsequent to this consensus agreement on when and why to implement vitamin A supplementation programmes, a global policy to integrate vitamin A capsule distribution into regular immunization schedules was rapidly adopted (World Health Organization, 1998). Recommendations were made to include massive-dose vitamin A supplements as part of regular routine immunization schedules, and also incorporate vitamin A capsules into the national immunization campaign days being promoted to achieve the eradication of poliomyelitis.

Programmatic vitamin A interventions received considerable impetus from the Vitamin A Global Initiative, an informal inter-agency advocacy group that worked together to promote the adoption of vitamin A supplementation programmes. The initiative included WHO and UNICEF together with Canadian International Development Agency, Department for International Development from UK, American USAID, and the Micronutrient Initiative. Through their networks these various organizations worked together to convince governments with high mortality rates for under-5-year-olds to introduce vitamin A capsule distribution programmes. Vitamin A capsules were made available by the Canadian International Development Agency through UNICEF to any developing country that wanted them. A global communication campaign was developed by UNICEF and Micronutrient Initiative with USAID and Department for International Development funds, which put TV spots on global satellite television channels, developed ready-made television and radio spots for countries that wanted them at the national level, and sponsored several documentary programmes for airing in the industrialized nations. During the period building up to the end of the 1990s this inter-agency group held monthly conference calls to check on progress and to agree ways to increase the articulation of their individual efforts. At the country level local missions were requested to help with the advocacy work, often working in unison.

By the end of the decade vitamin A supplementation programmes had seen a remarkable expansion. Most countries with high mortality rates for under-5-year-olds adopted vitamin A supplementation programmes, although the most notable exception was India. The number of countries with vitamin A programmes increased from ten in 1995 to seventy-two in 2000. Although the ways in which the vitamin A capsule programmes were developed and implemented varied from country to country, the most common strategy was using national immunization days for poliomyelitis eradication to piggyback vitamin A supplements. The use of this approach doubled from thirty countries in 1997 to sixty in 1999. As the poliomyelitis eradication strategy requires two nationwide campaigns not more than 2 months apart, some countries also promoted separate micronutrient days, or child health days, so that children would get at least two capsules 6 months apart during the course of 1 year. On average UNICEF procured through its central warehouse in Copenhagen and supplied through its country programmes an average of 289 million capsules per year from 1993 to 1998, which was still estimated to be only 38 % of the need (Mason *et al.* 2001).

Estimating the coverage of children with vitamin A capsules has been attempted in various ways. Through its country offices UNICEF collects the coverage data from routine immunization activities, together with the coverage data reported through campaigns such as national immunization days and micronutrient days. In addition, the multiple indicator cluster surveys carried out in many countries at the end of the 1990s to measure progress towards the World Summit for Children goals (UNICEF, 1990*b*) have all included questions on recent consumption of vitamin A capsules by children under 5 years of age. Based on all these sources of information UNICEF estimates that half of all children in developing countries outside China and 80 % of children in the least-developed countries received a vitamin A capsule within the last 6 months of 1999. Coverage was highest in Sub-Saharan Africa, where 70 % of under-5-year-old children received a capsule in the last 6 months. Extrapolation of the protective effect of a 23 % reduction in child mortality shown by the meta-analysis to the increased coverage of capsules achieved between 1998 and 2000 suggests that one million extra lives were saved in this short period.

The challenges that remain for vitamin A supplementation are largely ones of sustainability. Although supplements are traditionally seen as a 'short-term' solution, in reality they need to be maintained during at least the medium term if continued gains in mortality reduction are to be realized. Increases in other sources of vitamin A, be it through diet and/or fortification, are unlikely to be achieved in the short term. The eventual phasing out of national immunization days, as poliomyelitis eradication becomes a reality, will cause problems for maintaining the high coverage of vitamin A capsules. Alternate strategies are needed and are being put in place in many countries. Bangladesh, amongst others, promotes biannual micronutrient days with large-scale social mobilization efforts. Nepal systematically goes house to house to deliver capsules in its most remote regions. Sustaining the provision of the vitamin A capsules is also likely to become a problem. Up until now supplements have predominantly been provided by the Canadian government and supplied through UNICEF. What will happen when Canadian funds dry up?

Iron–folate supplements

Despite the World Summit for Children goal (UNICEF, 1990*b*) to reduce anaemia in women by one-third, anaemia still affects 44 % of non-pregnant women and 56 % of pregnant women in developing countries, with little sign of any change during the 1990s (ACC/SCN, 2000*a*). Global policy recommendations to routinely provide Fe and folate supplements for women during pregnancy and lactation have changed little in approximately three decades, with recommendations that all women should receive Fe supplements during pregnancy in almost all contexts (World Health Organization, 1972; International Nutritional

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Anaemia Consultative Group/World Health Organization/UNICEF, 1998; UNICEF/United Nations University/World Health Organization, 2001). About half the developing countries in the world are reported to have national Fe supplementation policies (Mason *et al.* 2001).

There is ample evidence that Fe deficiency and the anaemia with which it is associated is a great burden on society, and especially on the poor. The median value of productivity losses due to Fe deficiency alone is about US $4 *per capita* or 0·9 % of the gross domestic product. The absolute losses in South Asia are estimated at approximately US $5 billion annually. The dominant effect for all countries is the loss associated with cognitive deficits in children (Ross & Horton, 1998). Whilst the efficacy of Fe–folate supplements for controlling anaemia is well documented, and there is a considerable amount of descriptive evidence linking maternal anaemia to both low birth weight and maternal mortality, there are no randomized controlled trials showing that Fe supplementation leads to improvements in these maternal and child survival and development outcomes. These conclusions need careful interpretation, however, since most trials have had a negative bias (Rasmussen, 2001). Indeed, it is difficult to carry out such trials, since the existence of global and national policies on Fe supplementation make placebo controls unethical. The bottom line remains, however, that the efficacy of Fe supplements during pregnancy for survival and development outcomes remains to be proved.

Many meetings and publications over the last few decades that have looked at the causes and solutions of Fe-deficiency anaemia conclude that lack of effectiveness of Fe supplementation programmes for anaemia control is mostly related to problems with supply of the supplement (Morrow 1990; Gillespie *et al.* 1991; World Health Organization, 1996; Gillespie & Johnston, 1998). Although the side effects of Fe pills are often raised as the reason why Fe supplementation programmes do not work, this situation rarely seems to be the case in reality (Schultink *et al.* 1993; Galloway & McGuire, 1995; Ekstrom *et al.* 1996). One of the biggest causes of non-adherence seems to be the lack of understanding of the benefits the supplements can bring amongst health staff that deliver the tablet. Where supportive community level delivery mechanisms are put in place, which encourage adherence, and the supply of supplements is assured, then high levels of coverage can be achieved and sustained.

Despite an international consensus that supplementation has a key role to play in the control of Fe-deficiency anaemia, there are still those who question such programmes. In late 1998 a technical consensus meeting made recommendations on what was needed to tackle the problem of Fe deficiency (UNICEF/United Nations University/World Health Organization/Micronutrient Initiative, 1999). However, the advisability of Fe supplementation programmes is still disputed (Rush, 2001; Sloan *et al.* 2002). Another complicating factor is undoubtedly related to the fact that adequate coverage of Fe supplements alone will not ensure anaemia control in many settings. A global review of anaemia causality reveals that perhaps only half the anaemia is wholly due to Fe deficiency (World Health Organization, 1992).

Despite a high cost-effectiveness, little or no priority has been given to Fe-deficiency-anaemia reduction programmes. At US $0.002 per tablet the Fe supplement is relatively cheap. The cost per disability-adjusted life-year gained of US $13 makes the supplementation of pregnant women with Fe a very cost-effective intervention (World Bank, 1994). However, anaemia reduction has received no special attention from the international community in the last decade. It was not included amongst the mid-decade goals of WHO and UNICEF, and support from bilateral agencies for Fe supplementation has been very low-key. At the national level, despite there very often being national policies, there is little political commitment, and rarely is there a budget line for the provision of supplements and/or supervision of Fe-deficiency-anaemia programmes (Gillespie, 1998). Although UNICEF is a major supplier of Fe–folate supplements to the developing world, the level of supply is far lower than that thought to be needed. In the period 1993–6 2·7 billion tablets were shipped through to 122 countries at a cost of US $7.5 million as part of UNICEF assistance to programmes aimed at tackling maternal anaemia (Alnwick, 1998). However, the amount of Fe–folate being supplied by UNICEF is < 5 % of that needed to cover all pregnancies in developing countries (Mason *et al.* 2001). There have been few, if any, attempts to gauge the coverage of Fe–folate supplements at any level, be it district, national or international level. Furthermore, there has not been any effort put into creating political accountability for ensuring that high coverage is achieved.

Multiple micronutrient supplements

In recent years the case has increasingly been made for providing multiple micronutrient supplements for women of reproductive age in developing countries instead of the Fe–folate supplements. A woman's diet that is deficient in Fe is likely to be deficient in many other micronutrients. Poor dietary quality rather than quantity has been found to be the major determinant of inadequate micronutrient status among women in developing countries. Intakes of Fe, Zn, folate, vitamin B_6, vitamin B_{12}, vitamin A, riboflavin and Ca are commonly below the recommended levels (Allen, 1995; Huffman *et al.* 1998).

While the incremental cost of distributing a multiple micronutrient supplement is likely to be small, the increased benefits could be large. The main cost of the delivery of a nutrient supplement for women of reproductive age is not the supplement itself, but the cost of the delivery system. Although it may not be working that well, a delivery system already exists for the Fe–folate supplements that could be used to provide these other micronutrients. There has been much speculation over what the costs of a multiple micronutrient supplement might be compared with the Fe–folate tablet currently procured and provided by UNICEF (Ladipo, 2000). Adding the extra nutrients to the Fe–folate tablets will add < 20 % to the cost of the tablet, as long as they are procured in bulk on the international market, as is the case for the current Fe–folate tablets supplied by UNICEF. The potential benefits for pregnant women from improving not only Fe and folate status, but also the status of Zn, vitamin A and other antioxidant nutrients are likely to be great.

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Providing women with vitamin A has been shown to improve the haematinic effect of Fe supplements in Indonesia and Bangladesh (Suharno *et al.* 1993; Ahmed *et al.* 2001). The findings that vitamin A supplements to women of reproductive age reduced maternal mortality by about 40 % in Nepal (West *et al.* 1999), and that Zn supplementation improved birth weight amongst poor women in USA (Goldenburg *et al.* 1995), point to the possible multiple benefits, beyond anaemia reduction, of introducing a multiple micronutrient supplement for use by women in developing countries.

The composition of a multiple micronutrient supplement for use in trials amongst pregnant and lactating women in developing countries has recently been agreed upon (UNICEF/World Health Organization/United Nations University, 2000). The proposed formulation contains physiological doses of the micronutrients based on the recommended daily allowance. The US and Canadian recommendations (National Research Council, 1989; Institute of Medicine, 1997, 1999) were used, being the most recent and best documented. The selection of nutrients included in the supplement was based on evidence of deficiencies, possible consequences of deficiencies for mother and child, weighing of risks and advantages, and on interaction between nutrients. Furthermore, information about toxicity levels, cost of nutrients, the size of the resulting supplement and possible side effects related to supplement intake were considered. The formulation agreed on includes fifteen micronutrients (vitamins A, D, E, B_6, B_{12} and C, thiamin, riboflavin, niacin and folic acid, and minerals Fe, Zn, Cu, I and Se), all at the recommended daily allowance (National Research Council, 1989; Institute of Medicine, 1997, 1999) level, except for folic acid, which was included at the 400 μg level, considered sufficient to prevent neural-tube defects if taken peri-conceptually.

The multiple micronutrient tablet formulation was developed with various users in mind. For pregnant women the tablet should be taken on a daily basis for as long as possible during pregnancy. For lactating women the supplement should be taken daily until 3 months post partum. The tablet can also be taken by adolescent girls on a once-weekly basis, as a way of improving micronutrient status before getting pregnant. Another possible target group is refugees, who can take the supplement according to their biological state (pregnant or not), and in the case of severe deficiency could take two tablets daily.

Although the supplement was not considered a dangerous product, it was still recommended for use in trials, with special attention to be paid to monitoring and evaluation. Tablets of similar composition are regularly prescribed by physicians and/or purchased by mothers in developed countries. Similar products are also commercially available in most non-industrialized countries and widely consumed by the richer segments of the population. Despite the relative safety of the supplement it was recognized that many issues related to multiple micronutrient supplements still remain to be investigated. Research topics identified included the assessment of risks, as opposed to benefits, of regular supplement intake in environments with many disease agents present. It was also considered necessary to investigate factors that influence adherence to tablet intake.

The need to carry out both efficacy and effectiveness studies of the multiple micronutrient supplements in various different populations is well recognized. The requirement for micronutrient supplementation in pregnancy is likely to be great, because of widespread maternal malnutrition. However, it has to be recognized that public health resources are always limited, and priority is given to interventions that are both efficacious and effective. Thus, establishing the efficacy of multiple micronutrient supplements is essential before their wide-scale use can be advocated (Ladipo, 2000). Care needs to be taken when deciding which outcomes should be assessed, since birth weight has its limitations (Stevens-Simon & Orleans, 1999), and on its own might not be the most important outcome to measure. Multiple micronutrient supplements are almost always going to be part of a package of interventions, especially in developing countries. Indeed, the micronutrient supplements will probably be most effective as part of a package that also seeks to control the major diseases afflicting the mothers (malaria, sexually transmitted diseases and/or intestinal parasites). Being part of a package obviously makes it difficult in field conditions to test the relative merits of the individual pieces, including the micronutrient supplement. For these reasons both 'plausibility'- and 'probability'-based approaches are recommended for measuring performance of the multiple micronutrient supplements (Habicht *et al.* 1999), so that experience can be gained in how to mount programmes that promote fetal and infant growth, as well as learning whether micronutrient supplements are truly efficacious in developing-country settings.

UNICEF is looking at the possibility of incorporating the multiple micronutrient supplements into ongoing programmes as part of a new initiative to prevent low birth weight. UNICEF is promoting programmes to reduce the prevalence of low birth weight in eleven countries, including Indonesia, The Philippines, Vietnam, China, Bangladesh, India, Pakistan, Nepal, Tanzania, Mozambique and Madagascar. The increased interest in preventing low birth weight stems from the recognition that preventing growth failure in children in the first 2 years of life largely depends on improving fetal growth (ACC/SCN, 2000*b*; Shrimpton *et al.* 2001; James *et al.* 2000).

Low-birth-weight prevention programmes are being fashioned to fit local circumstances, in accordance with the nutrition strategy approved by the UNICEF Executive Board (UNICEF, 1990*a*). The approach being developed in each country elaborates on the 'Care for Women' element of 'The Care Initiative' that has been developed to facilitate improvements in caring practices amongst families and communities. In addition to the multiple micronutrient supplement, other interventions that form part of low-birth-weight prevention efforts include attention to early marriage and childbearing, promotion of increased child spacing, increased rest and food for the mother during pregnancy, improved reproductive health, deworming and malaria control during pregnancy, as appropriate. Prepregnancy weight, weight gain during pregnancy and birth weight are all receiving special attention as the principal evaluative indicators of programme success.

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Conclusions

Supplements can play an important role in meeting the micronutrient needs of the developing world, but their full potential is still far from being realized. In the later part of the 1990s experience with vitamin A supplementation was very positive. As a result of the large-scale use of these supplements in the last few years of the 1990s it is likely that at least one million young child lives have been saved in a very cost-effective manner. A large part of the success in achieving such high coverage is attributable to the high priority and political support given by a few key bilateral donors and international agencies working together. However, experience with the use of Fe–folate supplements has not been as successful. Even though Fe deficiency is a much larger problem than vitamin A deficiency, and Fe supplementation has similar cost-effectiveness in terms of disability-adjusted life-year gains, Fe–folate supplementation programmes have not been given a priority, and political support has not materialized. Getting political support and a high priority for Fe supplementation programmes has been dogged by the lack of evidence for a clear-cut link between coverage of the supplements and maternal and child survival outcomes. A new multiple micronutrient supplement is currently being tested as an alternative to the Fe–folate supplement for use during pregnancy and lactation. Potentially, it is likely to have greater impact on both maternal and child survival and development than Fe–folate tablets. Documenting both the efficacy and effectiveness of the new multiple micronutrient supplements under programme conditions in developing countries thus assumes considerable importance for furthering the use of supplements to improve micronutrient status in developing countries.

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