VITAMIN A: DURBAN IVACG HIGHLIGHTS

INTRODUCTION

The XIX International Vitamin A Consultative Group (IVACG) meeting was held in the International Conference Centre in Durban, 8–11 March 1999. The theme of the IVACG meeting was "Vitamin A and other Micronutrients: Biologic Interactions and Integrated Interventions". The XIX meeting of IVACG was attended by almost 600 delegates from 66 countries. The aims of the
XIX IVACG meeting were:

- To provide up-to-date scientific support for effective policy decisions
- To encourage innovation in reaching populations at risk of vitamin A deficiency
- To improve understanding of the biologic interactions of vitamin A and other nutrients, infections and vaccines and their implications for programme integration
- To address the economic dimensions of the choice of vitamin A interventions and the development benefits of strengthening vitamin A status
- To identify knowledge gaps that are constraints to vitamin A deficiency control and prevention
- To provide an environment for dialogue and constructive information sharing between countries

INAUGURAL COMMENTS

At the inauguration ceremony, Dr Zweli Mkhize, Minister of Health, Kwazulu-Natal (KZN), reported that illiteracy, poverty, poor water and sanitation were all important factors contributing to poor health and nutrition. Those most affected by these social deprivations were the women and children of the rural and slum areas. This was also the case in South Africa, a country in which one out three children aged 6–72 months had a marginal vitamin A status and one out of four were stunted, as was documented by the South African Vitamin A Consultative Group in 1994. Dr Zweli Mkhize also reported on the increasing problem of HIV/AIDS in South Africa and predicted that if HIV continued to increase at the present rate there would be 3 million less people in KZN by the year 2014, the population of KZN now being 8.7 million. He referred to the government's Integrated Nutrition Programme, which had the long-term goal to enable communities to be self-sufficient for food, thereby giving household food security and improving the health of the most vulnerable groups within the population, the women and children. He concluded by saying that he hoped that the use of vitamin A might help to alleviate some of the nutritional problems encountered in the country. Mrs Cynthia Mgijima, Deputy Director, Directorate: Nutrition, Department of Health, outlined the aims and objectives of the national food consumption survey in children aged 1 – 9 years and indicated that serious consideration was being given to implementing a food fortification programme, as part of the Integrated Nutrition Programme, once the survey identified the most suitable vehicle. Mr William Rhodes, USAID Mission Director to South Africa, reported that vitamin supplementation was one of the most cost-effective ways to reduce child mortality, with a 25% reduction in mortality at a cost of only 0.02 US$/person/year. From such a small outlay the subsequent health benefits result in economic benefits of a US$ 146 increase in productivity/person/year. Because of the enormous potential advantages, USAID was currently supporting 50 countries to provide vitamin A supplementation. Dr Roger Shrimpton, Chief of the Nutrition Programme for UNICEF, said that more than 19 countries in sub-Saharan Africa had given at least one dose of vitamin A in the last 12 months resulting in

more than 80% coverage. In addition, more than 9 million children had been protected by vitamin A. National Immunisation Days (NIDs) for polio and measles vaccination have been the key to improving vitamin A coverage, and supplementation by this method has been shown to be cost-effective for as long as five years in some countries. For the future, Child Health Days or Vitamin A Weeks might be a possible route for achieving the continued high coverage of vitamin A supplements to children at risk. A problem of particular concern in South Africa, Dr Shrimpton said, was the rapidly increasing number of people with AIDS; three million people are infected, and the worst affected province was KZN. HIV/AIDS prevention has the highest support from UNICEF and Dr Shrimpton stressed that any way to reduce mother-to-child transmission must be pursued.

PREVALENCE OF VITAMIN A DEFICIENCY IN AFRICA

More than ever before, countries are trying to address the problem of vitamin A deficiency and its elimination as a public health problem, a goal which was set in the World Summit for children in 1990, and reaffirmed at the International Conference on Nutrition in 1992. African countries are particularly, adversely and uniformly affected by vitamin A deficiency as outlined at the Congress. Marginal vitamin A status of public health importance and/or overt vitamin A deficiency has been reported, apart from South Africa (33%), in Ethiopia (3.5 – 7% Bitot's spots), Ghana (27 – 34%), Lesotho (13%), Malawi (27%), Mali (93%), Mozambique (clinical 0.7%), Namibia (20%), Nigeria (56%), Senegal (57% low breastmilk retinol), Swaziland (50%) and Zambia (66% in under-fives and 22% in mothers). In correcting vitamin A deficiency of populations at large, two important concepts have been clearly reaffirmed, namely that of preventive supplementation and, in the longer-term, of food fortification.

FOOD FORTIFICATION

Food fortification has received increasing attention in the developing world as a main strategy to prevent and to control micronutrient deficiencies. As any other nutritional intervention, it has some advantages but also some limitations. Therefore, it is important to have a fair view of its characteristics in order to understand better its potential as a resource to reach the goal of overcoming preventable deficiencies.

Food fortification is a normal practice these days in the food industry of the developed countries. In the United States, for instance, during the years of the Second World War, wheat and other flours was fortified with iron, thiamin, riboflavin, niacin, and calcium. In developed countries, mostly in temperate zones of the Earth, selected food fortification was used to control rickets. Milk and its derivatives were fortified with vitamin D and vitamin A. In 1955, Switzerland introduced the fortification of salt with fluoride, and achieved a remarkable reduction in tooth decay. In addition to these examples, many other foods, for example breakfast cereals are fortified with micronutrients in amounts proportional to 10 to 25% of the RDA values per portion.

In the developing world, food fortification has also been adopted by many developing countries. For example, in Guatemala, since the 60´s several foods made with the combination of cereal and legume flours (composite flours) have been fortified. A serving size of these foods satisfies from 25 to 50% of the RDA of the micronutrients added to the selected food. In 1974, the fortification of sugar with vitamin A was launched in Central America because it was recognized that, in spite of the introduction of the fortified composite flours, a more aggressive intervention was needed to overcome the deficiency of this vitamin at the national level. The sugar fortification program has been continuous and enforced from 1987 in Guatemala, and from 1992 in El Salvador and Honduras. Nowadays, sugar provides between 50 to 125% of the RDA of vitamin A to the population older than 2 years of age, and 25% of the RDA to infants from 6 to 24 months old. In line with these developments and from 1997, some African countries such as Namibia, Zimbabwe and South Africa started adding vitamin A, iron, and some vitamins of the B complex to maize meal, with the purpose of supplying at least 25% of the RDA values of these micronutrients.

When properly implemented food fortification programmes are invariably associated with a marked improvement in micronutrient status. Data presented at the Congress indicate that, in the Philippines, for instance, the consumption of a popular bread, called "pandesal", made with wheat flour fortified with vitamin A, by school-age children produced in 6 months a reduction of vitamin A deficiency measured by means of the MRDR method. The percentage of cases with low liver reserves of retinol was reduced from 29 to 15%. In 1996 in South Africa, the fortification of a biscuit with B-carotene, which provided the equivalent to 50% of the RDA for Vitamin A, decreased the prevalence of marginal vitamin A deficiency from 39 to 12% in school going children after 12 months of consumption. Similar data were reported from Ghana as well as Guatemala and Honduras. The experience in the two latter countries, however, does underscore the importance of not relying on a single food vehicle or a single intervention policy to cover the whole population of a given country.

It is imperative that, for success, any fortification program must fulfill several technical requirements as follows:

- Appropriate food vehicles should be produced and controlled by adequately equipped factories
- The chosen food vehicle should be consumed by the target population
- Food intake variability among all consumers should be small
- The costs for fortification should be affordable
- Fortification should not affect the acceptability of the food
- The added nutrient should have adequate stability and not separate under normal conditions of storage and use, and
- The nutrient should be bioavailable

In addition to these technical requirements, there are also some crucial strategic and political requirements that need to be met for food fortification programmes:

- The coverage and effect of the programme should be continuously monitored
- Appropriate legislation is frequently needed for adequate compliance
- The public should be aware of the benefits of such a programme, and
- A reliable quality control and monitoring system must be implemented.

From the point of view of the food industry, many food companies have recognized that fortification is a way to improve the added value of its products. The food industry should be encouraged to continue adding micronutrients to its products, but the type of food to fortify and the amount of micronutrients to be added should be a matter of governmental regulation. In this regard, the creation of a seal of fortified food(s), which include **at least one third** of the RDA of the selected micronutrients would be considered advantageous. On the other hand, one should guard against a plethora of fortified food products not only because of the risk that some persons could reach the recommended maximum intake of some nutrients, but also because unnecessary addition of micronutrients would increase the cost of such a product.
A major future challenge regarding fortification programmes, thought as crucial at the Congress, was how best to harmonise the technical requirements and regulations about fortified foods among neighboring countries. It is important to reach consensus on the basic principles of labeling as well as enforcement criteria, and to obtain the approval of the Codex Alimentarius. If these efforts do not materialise, food fortification programmess will be at risk of being halted by sceptical policy makers who make powerful economic decisions.

SUPPLEMENTATION

Vitamin A supplementation programmes should be seen as being an integral part to addressing vitamin A deficiency. Indeed, the latter can only be addressed by coordinated efforts, which include multiple approaches, multiple partners and multiple interventions. A number of studies were presented, which indicated that administering vitamin A supplements during National Immunisation Days (NID) is a practical and cost-effective practice. A randomised trial in Ghana, India and Peru assessed the benefits and the safety of vitamin A supplementation linked to immunisation in early infancy (mothers received 200,000 IU of vitamin A 3–6 weeks post-partum, and their infants were given 25,000 IU with their DPT/Polio immunisations at 6, 10 and 14 weeks; and a further dose of 25,000 IU with their measles

immunisation). Although there were no differences in hospital admissions, diarrhoea or respiratory infections or cumulative infant mortality as compared to controls, the practice was shown to be safe with less than 1% of infants having bulging fontanelle. Importantly and contrary to previously reported findings, vitamin A supplementation was not associated with any adverse effects on the antibody response of the DPT (diptheria, pertussis and tetanus) and OPV (oral poliovirus vaccine) vaccines. Overall, the experience of linking micronutrient supplementation to immunisation was positive. It was also considered to be a promising tool for the future, particularly since over 450 million of the world's children less than 5 years of age were immunised and many countries reach more than 90% coverage using NIDs. The success of NIDs surprised many, and it was thought that it was due to the fact "that everything stops and immunisation receives priority". In 1998, 43 out of 64 countries incorporated vitamin A supplementation in NIDs, therefore they offered an excellent opportunity to provide each infant with at least one dose of vitamin A per year. However, with the global commitment to polio eradication, this practice may in future become less feasible, and new initiatives would need to be developed, such as "Child Health Days" or "Vitamin A Days" during the year.

Micronutrients in infectious diseases

A study in India found that children with lower plasma zinc concentration had higher rates of pneumonia. In this regard, analysis of 17 eligible studies, which assessed the effect of zinc supplementation, with half the RDA of zinc or more, in children aged 0 – 5 years, showed a 40% reduction in pneumonia with zinc supplementation. The protective effect was seen mainly in children less than 12 months of age. However, although there was a reduction in total mortality, there was no overall effect on pneumonia mortality. Vitamin A supplements had no effect.

A number of micronutrient (vitamin A, zinc, folate, riboflavin) deficiencies have been shown to influence the clinical outcome of diarrhoea in terms of severity and duration, but they have only minor effects on the incidence. Delegates were reminded of the findings of the Ghana Vast study, in which there was a reduction in mortality associated with acute diarrhoea and a significant reduction in clinic visits and admissions due to diarrhoea following vitamin A supplementation. In terms of the role of zinc in the management of diarrhoea, a number of studies have suggested that zinc supplementation was therapeutically effective and resulted in an overall reduction in the incidence of acute diarrhoea from 8% in children in India to as much as 38% in a study of persistent diarrhoea in Bangladesh. Zinc supplementation (20–40 mg/day) also resulted in a reduction in the duration of illness by between 9 and 23%. The clinical application of these findings, however, must await greater clarity and perspective, since in one study in children with persistent diarrhoea in Bangladesh zinc supplementation (6 mg/Kg/Day) was associated with a four-fold increase in mortality. It would therefore be essential to know whether the excess mortality was due to the zinc supplements or to other confounding factors.

Malaria caused by Plasmodium falciparium affects over 300 million people resulting in 2–3 million
deaths/year, mostly among children and pregnant women. Results from a double-blind placebo-controlled trial of vitamin A supplementation in Papua New Guinea indicated that vitamin A supplementation had no effect on serum retinol concentration, but reduced parasite attack rates by 30% and also reduced parasite density. Vitamin A had a significant impact on parasite density when the P. falciparum concentration was <10,000/mL blood, but the protective effect of vitamin A was not seen in heavy infections (>100,000 P. falciparum parasites/mL blood). The greatest protection was seen in children aged 12–36 months, where there was a 35% [14 – 50, 95% Confidence Interval (CI), $p<0.01$] reduction in P. falciparum clinical episodes and a 68% (28 – 85, 95% CI) reduction in P. falciparum density. Administration of 10 mg zinc to children (n=138) for 6 days/week reduced malaria-attributable health centre attendance by 38% (3 – 60, 95% CI), decreased the number of malarial attacks (40%) and reduced P. falciparum density by 35 – 40%. However, unlike vitamin A, the

protective effect of zinc was maintained even in heavy infections. No doubt further studies on this relationship will define the clinical significance of these findings.

Although iron supplementation is generally advocated for prevention and treatment of anaemia, uncertainties concerning the deleterious effects of iron on P. falciparum malaria have often made policy decisions in malarious areas difficult. A meta-analysis of 13 controlled studies on the impact of iron supplementation on malaria morbidity showed that iron supplementation was associated with:

- A non-significant increase in the risk of malaria attack (RR=1.1; 0.9 – 1.3, 95% CI)
- A significant increase in the odds ratio of being infected with P. falciparum (OR=1.4; 1.2 – 1.8, 95% CI)
- An actual increase in P. falciparum prevalence of 5.7%
- A non-significant increase in spleen enlargement (OR 1.2)
- An increase in haemoglobin levels of 1.25 g/dL

Even though the results of the meta-analysis indicated that iron could be used with benefit in malaria endemic areas, these conclusions should be interpreted against those of the Wellcome-USAID Conference in September 1998, which stated:

- The observed effect of vitamin A supplementation on childhood mortality is related to the underlying nutritional deficiency. It is not a physiological effect of pharmacological doses
- The mechanism of therapeutic and prophylactic effects of zinc on diarrhoeal disease is due to local gastrointestinal effects not via systemic effects associated with the alleviation of underlying zinc deficiency
- Iron status determines susceptibility to and severity of infection
- There are potentially significant toxic consequences of iron supplementation in infection

An interesting presentation reported on the use of urinary neopterin as a marker of infection and the influence of vitamin A supplementation on its excretion in infants. Neopterin, is an early sensitive and non-specific marker of cellular activation of the immune system. Neopterin was measured in three groups: (a) Pakistani infants given 8333 or 16,000 IU vitamin A or placebo weekly for 4 weeks; (b) Indian infants given 16,000 IU vitamin A weekly for 8 weeks and (c) healthy Irish infants with no intervention. Neopterin was expressed as a ratio with creatinine (N:C). At baseline the N:C ratio in the Pakistani (2.21) and Indian (2.19) infants was significantly higher than that in the Irish infants (0.78), confirming that the N:C ratio was higher in infants living in environments where exposure to disease is high. There was also some response to vitamin A. In the Indian infants, the N:C ratio was reduced at 4 weeks and remained low at 8 weeks. However, in the placebo group, although the N:C ratio fell during the first 4 weeks, it subsequently increased again probably reflecting the constant exposure to infection in the surrounding environment and increased susceptibility and disease in the placebo group.

Vitamin A: interactions with zinc and iron

In a study in the USA, non-smoking men were fed either a zinc-deficient diet or a diet with marginal zinc content (5.5 mg/day). Zinc concentrations decreased rapidly on the deficient diet but more slowly on the marginal diet. Serum vitamin A did not change on either diet. Retinol binding protein (RBP) decreased significantly on the zinc-deficient diet, but not on the marginal diet. The results were interpreted to suggest that in severe zinc deficiency, uncomplicated by other nutrient or protein-energy deficiencies, decreases in RBP concentration in healthy men possibly occur through the interaction between zinc and the retinoid-thyroid hormone superfamily. The lack of effect of marginal zinc deficiency on vitamin A metabolism might explain why so many scientists do not observe any evidence of the interaction in human epidemiological studies. This interpretation was supported by a randomised trial in Nepal involving 235 pregnant women with night blindness who received either 25mg zinc or placebo daily for 3 weeks. Zinc supplementation resulted in an increase in

serum zinc but had no effect on night blindness. A similar lack of interaction was also reported in a community-based, individually randomised, placebo-controlled trial from Indonesia. The trial employed a factorial design with four daily treatments: either vitamin A (2400 RE), 20 mg zinc sulphate, both or a placebo. Results showed that daily low-dose vitamin
A given during the second and third trimesters substantially reduced maternal postpartum infections in vitamin A deficient women. No impact was observed for zinc versus placebo. By contrast, in another study from Bangladesh, 147 marginally malnourished children (1–3 years of age) were randomly allocated to receive either 200,000 IU vitamin A, 40 mg elemental zinc, vitamin A plus zinc or placebo for 7 days. Diarrhoeal episodes were significantly lower in the zinc group compared to the zinc plus vitamin A group ($p<0.002$). Measles antibody titre was significantly higher in the zinc group after 2 weeks of supplementation. In all groups, except the placebo group, significant increases in weight were seen, but only the vitamin A group showed a significant gain in height. The Relative Dose Response (RDR) test showed a significant positive response in the vitamin A and the zinc plus vitamin A groups.

Anaemia and poor vitamin A status commonly coexist in Third World countries and supplementation with vitamin A is frequently followed by an increase in haemoglobin. Several studies examined the interaction between iron and vitamin A status in different communities. Haematological indices and serum retinol were measured in anaemic and non-anaemic women (non-pregnant, non-lactating). A positive correlation between serum retinol and haemoglobin was reported in the anaemic group but not in the controls. These findings were interpreted as being indicative of the haemopoietic effect of vitamin A. However, it is just as likely that infection was depressing the indices in the anaemic group. Thus to interpret this data more fully, some measures of infection should have been monitored. By contrast, in another placebo-controlled vitamin A supplementation study, haemoglobin was monitored in hospitalised infants and was shown to increase only in the vitamin A-supplemented group. Both groups received appropriate clinical treatment for their infections but the haemoglobin in the controls did not change throughout the study. These data suggest that vitamin A had a true haemopoietic effect, and the lack of response in the controls suggests that the anaemia was the result of poor vitamin A status. Furthermore, the relationship between ferritin and serum vitamin A was examined in children from the Central Plateau of Haiti. Vitamin A status was poor and plasma ferritin was relatively high (38.7 ± 47.4 mmol/L). There was no association between the two variables. Serum ferritin is sometimes difficult to interpret, since iron deficiency will suppress it, while infection increases its concentration. These data suggest that iron status was relatively good in the population. If the ferritin was high because of infection, then serum retinol would have been lower and inverse associations would have been found. As no such association was found, it is unlikely that infection was the cause of the high ferritin.

Vitamin A and iron deficiencies continue to be important problems in many countries throughout the world. The reason for the persistence of these deficiencies may be due at least in part to the complicated aetiology, which is frequently overlooked. The use of acute phase proteins to monitor clinical and sub-clinical infections was recommended so as to assist with the interpretation and to correctly diagnose the main factor responsible.

Vitamin A and HIV

The increasing problem of HIV/AIDS in South Africa can be appreciated by looking at the infection figures for women presenting at antenatal clinics: In 1990 2.4%, in 1995 18% and in 1998 34% of mothers were HIV-positive. Factors contributing to this increase are poverty, migration of the men from the household, unemployment and social distribution. The treatments available in the West are totally out of reach to the majority of the population of Africa. However, a number of studies have shown beneficial effects of vitamin A supplementation in HIV infection. In a study in South Africa where HIV-

infected mothers delivering full-term babies were given either placebo or vitamin A. Those given vitamin A showed an overall reduction in morbidity in their HIV-infected infants with the reduction in diarrhoea, especially severe diarrhoea, being the most notable. In another study

also in South Africa, a supplement of 200,000 IU vitamin A to children with AIDS induced increased immuno-competence as measured by an increase in absolute lymphocytes, CD4 (cluster of differentiation antigen), CD56 and CD29 counts. Pregnant HIV-infected women have lower serum retinol concentrations (1.05 mmol/L) than those who were not infected (1.58 mmol/L). Women with low vitamin A status have higher rates of vertical transmission. In an in-vitro study retinoic acid was found to increase HIV replication, but a placebo-controlled study in South Africa showed that vitamin A supplementation in pregnant HIV-infected women did not increase viral load.

On this basis, a random double-blind, placebo-controlled trial was conducted at King Edward VIII and McCords hospitals in Durban. Seven hundred and twenty eight pregnant women were given a daily dose of 5000 IU retinyl palmitate plus 30 mg β-carotene for a maximum of 12 weeks and then 200,000 IU retinyl palmitate at delivery. The women were HIV-positive with an average CD4 count of 500, but none had clinical AIDS and all but two were asymptomatic. A possible beneficial outcome of the trial was that only 11.4% of babies were delivered pre-term in the vitamin A group, compared with 17.4% in the placebo group. In addition, the percentage of pre-term births of women with anaemia was higher in the placebo (25%) than in the vitamin A group (13%). There was a difference in transmission rates from mother to infant according to the mothers' plasma retinol status and supplementation group. There was a 47% reduction in vertical transmission from mother to infant at 3 months in the supplemented group (34% placebo vs 18% supplemented group). However, this difference was not statistically significant probably because of the small number of subjects for the type of study that was undertaken. Nevertheless, one should bear in mind that premature infants have a poorer vitamin A status than full-term infants and consequently they could be at greater risk for vertical transmission. In addition, the epithelial surfaces of pre-term infants is very thin and may be more vulnerable to damage. It is possible, therefore, that the vitamin A supplementation may have helped to strengthen the epithelial tissue, hence, as way of explanation of these findings, the reduction in transmission in those infants who are most vulnerable and at greatest risk for vitamin A deficiency. Undoubtedly, the role of vitamin A supplementation in the prevention of the mother to child transmission of HIV remains to be elucidated and confirmed.

CONCLUSION

This was a very well attended and organised congress, the first of its kind in South Africa. It reminded delegates of the crucial importance of vitamin A and other micronutrients in the field of child and woman's health. It also imparted new knowledge, and new approaches to be deployed in our continued efforts to address the problem of the so called "hidden hunger" in the world successfully.