

The Summer Meeting of the Nutrition Society was held at the University of Glasgow on 29 June–2 July 1999

Clinical Nutrition and Metabolism Group Symposium on 'Clinical nutrition in childhood'

Malnutrition, morbidity and mortality in children and their mothers

Andrew Tomkins

Centre for International Child Health, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

While being underweight or stunted is recognized as an important risk factor for increased prevalence and severity of infection and high mortality rates, there is increasing evidence for an independent role for micronutrient deficiency. Improving vitamin A status reduces mortality among older infants and young children and reduces pregnancy-related mortality; it also reduces the prevalence of severe illness and clinic attendance among children. Improving Zn status reduces morbidity from diarrhoeal and respiratory infection. Treatment of established infection with vitamin A is effective in measles-associated complications, but is not as useful in the majority of diarrhoeal or respiratory syndromes. Zn supplements, however, have significant benefit on the clinical outcome of diarrhoeal and respiratory infections. Concerns that Fe supplements might increase morbidity if given in malarious populations appear to be decreasing, in the light of new studies on Fe supplements showing improved haemoglobin without an increase in morbidity. Breast-feeding, well known to protect against diarrhoea, is also important in protecting against respiratory infection, especially in the young infant. Transmission of human immunodeficiency virus (HIV) in breast milk is recognized, but new data showing reduced transmission in infants who receive exclusive breast-feeding rather than mixed feeding reinforces the importance of promoting this practice in areas where environmental contamination precludes the safe use of other infant feeding regimens. The presence of subclinical mastitis, now recognized to occur in approximately 20 % of mothers in several developing countries, has been shown to increase the concentration of HIV in breast milk. Preliminary findings suggest that the prevalence of subclinical mastitis is reduced by dietary supplements containing antioxidants. Governments and international agencies now have a strong scientific basis to be much more active and innovative in the introduction of focused nutrition interventions especially micronutrients, for the control of infection.

Micronutrients: Infection: Pregnancy: Human immunodeficiency virus: Mastitis: Growth

The interaction between nutrition and infection among children and their mothers in less-developed countries is currently the focus of much research. The experimental, clinical and epidemiological framework for this interaction has been described in reviews (see Scrimshaw *et al.* 1968; Tomkins & Watson, 1989), and there has been a massive increase in knowledge in the last decade. Unfortunately, the development of policies and programmes, in the light of this knowledge, for the reduction of morbidity and mortality among children and their mothers has been rather slow. High rates of mortality among children with severe protein–

energy metabolism, including kwashiorkor and marasmus, are now recognized to be the result of a combination of severe metabolic disturbances and the presence of systemic and intestinal infection (Golden & Golden, 1979; Waterlow *et al.* 1992). Improved dietary management and greater awareness and better treatment of systemic and intestinal infection have resulted in a striking reduction of mortality among children with severe protein–energy malnutrition, even among those children in homecare management programmes (Khanum *et al.* 1994). Where high mortality rates continue, they are usually the result of failure to

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; IDD, iodine-deficiency disorders; MTCT, mother-to-child transmission.

Corresponding author: Professor Andrew Tomkins, fax +44 (0)207 404 2062, email a.tomkins@ich.ucl.ac.uk

implement knowledge and good practice due to limitations in resources, training and skills (Schofield & Ashworth, 1996).

Severely malnourished children make up approximately 1–3 % of the population of under-5-year-old children in many African and Asian countries, and even more in times of civil unrest and drought, or rapid changes in economic and social policies (United Nations Children's Fund (UNICEF), 1998a). However, only a proportion of these children manage to reach and be admitted to a nutrition rehabilitation centre or a paediatric ward where malnutrition is treated properly. The impact of severe protein–energy malnutrition is therefore not seen in hospital statistics on malnutrition; rather, its effect is hidden in the high admission rates and case fatality rates from common childhood infections such as pneumonia, diarrhoea, malaria, septicæmia and measles (Costello, 1997).

Many more children, however, are moderately malnourished. On the basis of a range of anthropometric criteria, over 150 million children are underweight globally, with a particularly high prevalence in Sub-Saharan Africa (nearly 30 million children) and South Asia (over 85 million; UNICEF, 1998a). When these issues were discussed a decade ago, some nutritionists proposed that such children were 'metabolically adapted' to a chronic low nutrient intake (for review, see Beaton, 1989; Waterlow, 1989). Indeed, some nutritionists held that this was a 'healthy' adaptation to chronic food shortage such that the smaller body size as an adult would reduce the nutrient requirements, claimed to be advantageous in conditions of chronic food shortage. However, data from carefully-performed epidemiological studies and the results of randomized controlled clinical trials have not supported this view. It is now clear that stunted and underweight children have a significantly increased risk of illness and death, even after controlling for the poorer physical and socio-economic environment in which they live (Pelletier, 1994; Vella *et al.* 1994). It is also clear that malnutrition increases risk of infection, independently of socio-economic status (Tomkins *et al.* 1989), although the way in which the data is recorded has a considerable influence on the assessment of nutrition–infection relationships (Pickering *et al.* 1987). It is now particularly evident that micronutrient deficiency is a major risk factor for morbidity and mortality, and that timely provision of supplements, fortified food or a better diet is followed by a reduction in the prevalence, severity and mortality from certain key infections among children and mothers (Filteau & Tomkins, 1999). The immediate challenge is to use this information to formulate new more effective policies within national and international health and development programmes.

Lack of nutrition components within health and development policies in less-developed countries

It is important to reflect on why nutrition has not been taken more seriously by national governments and international agencies who seek to reduce childhood mortality. It is unfortunate that many agencies have asserted that the multiplicity of factors that contribute to malnutrition in poor countries make it too complicated to address malnutrition

other than by implementation of economic development policies aimed at increasing food production and/or employment and wealth. Such governments and donors have insisted on the over-riding importance of social and economic policies, which involve quite detailed structural adjustment, anticipating that as a result of wealth creation, malnutrition rates would improve. Others have emphasized the importance of safety nets and food baskets, anticipating that social welfare programmes would enable efficient targeting towards the most vulnerable groups. It is now fashionable to emphasize 'sector wide approaches' in which governments and donors support the management of the whole portfolio of activities within sectors such as health, education or environment, aiming to strengthen the capacity of entire ministries rather than focusing on specific biomedical or socio-economic problems. While there are certainly enormous management and administrative needs within such organizations, without clearly defined nutrition-related policies and programmes within a sectoral portfolio, nutrition is often neglected. In practice, few governments or donors have shown sustained commitment to the reduction of mortality through specific programmes which focus on nutrition as a means of improving immunity, health, development and survival of children and their mothers. To nutrition professionals this situation is very surprising, as results of research, in the last decade particularly, have shown major health gains following focused interventions, especially from micronutrient supplements. The present paper will review some of the evidence that may be used to encourage national and international agencies to include focused nutritional components within health, economic and social policies. However, there are several hurdles to overcome before nutrition interventions are taken more seriously.

First, there is lack of recognition of the importance of malnutrition, especially mild or moderate underweight and stunting, as a threat to child survival compared with the more clinically-obvious critically-ill children who present with severe acute infectious disease. WHO and UNICEF have been successful in publicising common causes of mortality among children using highly-effective, graphic illustrations. These causes of mortality have included important diseases such as diarrhoea, measles, malaria, tetanus, pertussis, diphtheria and pneumonia (Claeson & Merson, 1990). The last decade has seen a considerable commitment to preventing these infections through better immunization coverage and improved treatment regimens. In addition, the prevention of the clinically-visible tragic disability resulting from poliomyelitis has also been successfully promoted by universal vaccination, often assisted by National Immunization Days. The introduction of oral rehydration solutions, extremely effective in reducing death from many dehydrating diarrhoeal diseases, has been promoted by governments and donors alike (Bern *et al.* 1992; Victora *et al.* 1996). There is new emphasis on vaccines, such as those protecting against *Haemophilus influenzae* B, pneumococcus and hepatitis B. The integration of prevention through vaccines and better management through clearly-formulated diagnostic and treatment algorithms has been promoted through the new programme of Integrated Management of Childhood Illness

by WHO and UNICEF (Bern *et al.* 1997). All these medical technologies are important, but most of them focus on the treatment of sick children seen at clinics or hospitals; the prevention of severe illness and mortality through specific community-based nutrition programmes has not been taken seriously enough.

Second, most of the previously described health technologies, such as vaccines, can be given on a single occasion, whereas nutrition interventions require a more sustained approach. This approach often leads to the dismissive conclusion that nutrition programmes are 'too complicated', because nutrition interventions often need to be given more frequently, sometimes three times per year, or even daily. If health workers alone are expected to administer these programmes they will indeed be insufficient for the task. However, most nutrition technologies do not need health professionals to administer them (Jennings, 1991; Kibona *et al.* 1995). Whether it is vitamin A capsules given to a young child three times per year or a multiple micronutrient mixture on a daily basis, informed motivated committed parents and community leaders can take the lead in distributing nutritional supplements, promoting improved dietary intakes and encouraging the use of fortified foods (Bloem *et al.* 1995; Darnton-Hill, 1999). Most of the successful programmes have been established initially in small-scale projects, often with a lively non-governmental organization to initiate and drive the project. There are now good examples of how, particularly with respect to vitamin A, these programmes can be taken to scale nationally (Bloem *et al.* 1996). There are now many opportunities for the development of culturally-acceptable programmes of nutritional interventions, especially focusing on micronutrient supplementation. There are many opportunities for professionals to work with local communities such that they discover their own enormous potential for the reduction of morbidity and mortality of their children through community-based activities (English *et al.* 1997). There are positive experiences from the Philippines, carefully reviewed in a recent monograph (Heaver & Hunt, 1995).

Third, there has been an over-optimistic viewpoint that infections can be treated more efficiently by the development and increased availability of modern antimicrobials. Unfortunately, the microbes responsible for pneumonia, dysentery and malaria (White *et al.* 1999) are becoming increasingly resistant to available anti-microbials, and disease-specific case fatality is now increasing in many areas (Salam *et al.* 1995). Furthermore, while oral rehydration has reduced the numbers of children dying from acute dehydrating episodes of watery diarrhoea, there are increasing numbers of children becoming infected with dysentery and persistent diarrhoea syndromes, many of them related to underlying malnutrition (Bhutta *et al.* 1997). A major reduction in mortality from diarrhoeal disease was anticipated following the introduction of oral rehydration, but this reduction has not been achieved. Thus, there is now a considerable urgency in preventing these infections in the first place, especially by regular supplementation with micronutrients (Tomkins, 1991; Tomkins *et al.* 1993; Black, 1998).

Fourth, despite the best efforts by governments, agencies and communities to reduce the prevalence of morbidity and

mortality from infection there is a potentially devastating impact of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) on infant and child survival (Gregson *et al.* 1997; Brocklehurst & French, 1998; Timaeus, 1998). Preventing and managing the complications of HIV now requires major resources which may divert attention away from non-HIV-related infection in infants, young children and their mothers. Current predictions on the impact of HIV and AIDS on infant and young child mortality depend to a great extent on the prevalence of mother-to-child transmission (MTCT) of HIV. Recent studies have shown that combinations of anti-retrovirals in pregnancy, microbicides in delivery, safer delivery practices, anti-retrovirals postnatally and certain feeding patterns all contribute to reduce the transmission rate from over 25 % (as was reported in several countries in Sub-Saharan Africa) to less than 10 % (Newell, 1999). However, even if the transmission of HIV *in utero* and during delivery can be reduced there is still a high risk of transmission through breast milk postnatally, and there is an urgent need to clarify and implement infant feeding policies in populations where HIV is highly prevalent. Unless these policies are made widely available, the mortality rates of infants and under-5-year-old children are predicted to rise to those rates seen over 30 years ago (Boerma *et al.* 1998). While current attention is focused on Sub-Saharan Africa, similar demographic change is also anticipated in parts of Asia as the HIV epidemic starts to spread. Until now the importance of nutrition in the prevention of HIV has been somewhat overshadowed by the expectation that anti-viral treatment will reduce MTCT. There is, however, considerable interest in the role of micronutrients and promotion of appropriate patterns of infant feeding. UNICEF/WHO/United Nations AIDS have developed generic guidelines for the prevention and management of HIV and AIDS in infants, and these guidelines now need to be implemented within the context of cultural and economic environments of high-risk communities (UNICEF, 1998*b,c,d*).

Fifth, in recognition of the tragic consequences of the very high rates of maternal mortality in less-developed countries, there has been a strong emphasis on the provision of better antenatal care and improved care during and after delivery within an overall programme of 'Safer Motherhood'. These programmes have been active in improving the levels of diagnosis, referral and obstetric care. However, few programmes have included any consideration of nutrition other than to promote regular consumption of Fe and folic acid in the antenatal period. Many of the component parts of the 'Safer Motherhood' programme rely on improving technical aspects of midwifery and surgical intervention, including better access to obstetric care, including Caesarean section. Despite intense, often successful, programmes of 'Safer Motherhood', reduction in maternal mortality has not been achieved globally. Indeed, in some countries the maternal mortality rate is actually increasing. There is considerable potential for micronutrient interventions for the reduction of pregnancy-related morbidity and mortality.

It is now increasingly recognized that economic policies and medical technologies in themselves have not been

sufficient to achieve the national and international goals for reduction in child and maternal mortality. While there is considerable opportunity for the inclusion of specific nutrition interventions, the proponents need clarity and persuasive powers. They also need to recognize that policy and programme staff face many competing demands for resources. While ensuring adequate dietary intake has often been campaigned for using a 'human rights' approach, the reality is that when anything new or additional is considered in programme terms, costs and benefits need to be calculated. There is at present a steadily increasing body of knowledge which enables these calculations to be made for nutritional interventions (Murray & Lopez, 1994). At the very least they provide 'good value for money' compared with medical technologies. As new data becomes available it will be possible to provide a larger informed portfolio of nutrition interventions.

Vitamin A

After early studies showing a high risk of mortality among children with clinical and biochemical evidence of vitamin A deficiency (Humphrey *et al.* 1992; Sommer, 1993), a series of randomized controlled clinical trials have shown that regular administration of vitamin A capsules reduces mortality by approximately 20 % among infants and young children in vitamin A-deficient areas. In addition, there is reduction in morbidity, although not necessarily mortality, in the neonatal and early infant periods if doses are given in the postnatal period (West *et al.* 1995; Humphrey *et al.* 1996). Thus, in areas where vitamin A deficiency is defined, the regular supply of vitamin A capsules is increasingly given as part of Child Survival Programmes. While there is clear evidence of reduction in young child mortality overall if regularly given on a 3–4-monthly basis, it is not exactly clear which diseases are affected by vitamin A.

In Ghana (Ghana VAST, 1993) regular supplementation with vitamin A reduced, by approximately 15 %, the prevalence of episodes of infection which were severe enough to require a clinic attendance. This situation was particularly noticeable for children presenting with severe dehydrating episodes of diarrhoea. In South Africa (Hussey & Klein, 1990) and Tanzania (Barclay *et al.* 1987) vitamin A has a major impact on the clinical outcome and the mortality from pneumonia following measles. In a comparison of international studies, however, the impact of vitamin A on the outcome of non-measles pneumonia was negligible (Pneumonia Working Group, 1995). Regular supplementation with vitamin A also had an impact on malaria in a recent study in Papua New Guinea (Shanker *et al.* 1999). There was a 30 % decrease in the number of febrile episodes with a high parasite count. Parasite density was also reduced. The study was not able to examine whether there was any impact on child mortality. In the Ghana study of vitamin A supplementation and child survival (Ghana VAST, 1993) there was no evidence of a decrease in morbidity or mortality from malaria as assessed by reports of febrile episodes, but there was a 20–30 % reduction in the prevalence of malaria slide-positive episodes in the vitamin A-supplemented group. In view of the proven benefits of vitamin A on mortality in vitamin

A-deficient communities it is now difficult, on ethical grounds, to examine the effect of vitamin A supplementation on malaria prevalence, morbidity and mortality. On the available evidence, the benefits of vitamin A supplementation have been compared, in cost effectiveness terms, with current malaria control programmes including insecticide-treated bed nets and malaria vaccines.

The impact of vitamin A on diarrhoea complicating measles has been demonstrated in South Africa (Hussey & Klein, 1990), but the impact on other diarrhoeal syndromes depends on the pathogen and the type of diarrhoea. There is rather variable evidence on the impact of vitamin A supplementation on the epidemiology of disease in terms of incidence or duration. Studies of vitamin A prophylaxis in Ghana showed reductions in the prevalence of severe diarrhoea (Ghana VAST, 1993), but interpretation of the data is complicated by the fact that many children who present to health facilities with diarrhoea have accompanying systemic diseases such as septicaemia, pneumonia or malaria. Thus, the beneficial effects of vitamin A may reflect an impact on these infections rather than on the intestinal tract directly. Overall, there is little effect of vitamin A supplementation on the outcome of watery diarrhoea from infections such as rotavirus and enterotoxigenic *Escherichia coli* (Henning *et al.* 1992). However, the duration of dysenteric diarrhoea was shortened in studies in Bangladesh and India. From the perspective of improving vitamin A status by regular administration of large doses, it is evident from trials in South Africa that the timing of the dose of vitamin A (during an acute episode of diarrhoea) does not influence the levels of vitamin A when assessed 8 weeks later; neither does it have any impact on the clinical outcome or the extent of intestinal damage assessed by lactulose and mannitol excretion (S Filteau, NC Rollins and AM Tomkins, unpublished results). In India, however, children with diarrhoea who were treated with a rigorous regimen of rehydration and antibiotics showed benefit, in terms of clinical duration and intestinal permeability, if they received vitamin A (McCullough *et al.* 1999). The duration of respiratory infection and febrile illness was decreased among infants of mothers who received a large dose of vitamin A after delivery (Roy *et al.* 1997a). There was no effect of vitamin A on respiratory infection among Brazilian children receiving vitamin A, but overall child mortality and the prevalence of severe diarrhoea were reduced (Barreto *et al.* 1994). Among severely-ill children in an Indian slum, those who received a large dose of vitamin A (60 000 retinol equivalents) had a significant reduction in severity and duration of diarrhoea compared with controls. However, administration of vitamin A did not alter the clinical course of those with severe respiratory infection (Bhandari *et al.* 1994). Some benefits were observed in different indicators of morbidity for infants of HIV-positive mothers if the women received vitamin A during pregnancy (Coutsoudis *et al.* 1995). There was no clinical benefit from adding vitamin A to the intake of adults with persistent diarrhoea from AIDS in Zambia (Kelly *et al.* 1999).

In view of the well-recognized effect of vitamin A deficiency on epithelial surfaces, it is of interest that shedding of HIV from the reproductive tract is greater

among women with low serum retinol levels in Kenya (John *et al.* 1997; Mostad *et al.* 1997). There is also an association between low levels of vitamin A and high rates of MTCT transmission of HIV in Malawi (Semba *et al.* 1994). It is difficult to know whether these relationships between low serum retinol levels and pathological change are causal, as low levels of plasma retinol are often indicative of an acute-phase response. Thus, the women with the highest viral load and clinical manifestations of HIV-related disease, and therefore more likely to shed or transmit the virus, are also likely to have low serum retinol levels. It was hoped that intervention with vitamin A prophylaxis of pregnant HIV-positive women would in fact reduce the prevalence of MTCT transmission (Nduati *et al.* 1995). Unfortunately, preliminary results of such studies have failed to show such a beneficial effect of vitamin A supplementation among pregnant women in South Africa (Coutsoudis *et al.* 1997). Results of studies in other countries are awaited.

The association between vitamin A deficiency and puerperal infection has been recognized since the pre-antibiotic era, but this crucial fact has been largely ignored. 'Safer Motherhood' policies and programmes have mainly emphasized the primary importance of improved midwifery and surgical practices as a means of decreasing maternal morbidity and mortality. There has until recently been no data on the impact of vitamin A supplementation on pregnancy outcome. A recent study of the impact of vitamin A or β -carotene given regularly to women of reproductive age on the mortality related to pregnancy in Nepal showed approximately 47 % reduction in mortality from either form of supplementation (West *et al.* 1999). It is not possible because of study sample limitations to perform statistically significant sub-analyses on whether particular causes of mortality are less frequent in the intervention groups. However, the study gives important data on the causes, assessed by verbal autopsy, of mortality. It is of considerable interest that supplementation was not particularly associated with a difference in rates of mortality from infectious disease. Other studies, particularly in malarious areas and those areas where sepsis is common, will be important to establish. However, the finding that daily vitamin A or β -carotene supplements reduce mortality by approximately 50 % is very striking. Various nutritional interventions for the prevention of maternal morbidity have been reviewed (Kulier *et al.* 1998), but they concluded that there is a need for trials with sufficient statistical power in order to conclude what micronutrients should usefully be given as supplements during pregnancy.

The benefits of regular doses of vitamin A should not overshadow the many opportunities there are for increasing intake of dietary vitamin A and integrating supplementation with improved dietary intake (de Pee *et al.* 1998; Filteau & Tomkins, 1999). However, the problems of achieving satisfactory improvement in vitamin A status using fruits and vegetables have been highlighted recently (de Pee *et al.* 1999).

Zinc

The effects of Zn deficiency on the immunity, growth and survival of children with severe protein-energy malnutrition

are well described (Golden & Golden, 1981; Roy *et al.* 1997b). Zn supplements are now recommended for the routine management of children with severe protein-energy malnutrition, whether they are in wards, nutrition centres or refugee camps. Experimental studies of Zn deficiency show a marked effect on intestinal morphology and function. There is villous atrophy and a heightened secretory response to diarrhoeal pathogens, such as the toxin from *Vibrio cholerae*. Early clinical studies of the effect of Zn supplementation among malnourished children in Bangladesh showed a reduction in the loss of intestinal fluid among children with acute diarrhoea and a shortening of the duration of diarrhoea (Roy *et al.* 1997b). Similarly, among malnourished Bangladeshi children with persistent diarrhoea syndrome there was a beneficial effect of Zn supplementation on the duration and severity of diarrhoea. There was also a lower mortality among the Zn-supplemented group (Roy *et al.* 1998). In both studies there was an improvement in the intestinal structure, as assessed by urinary excretion of lactulose and mannitol after an oral test dose (Roy *et al.* 1992). When these children were followed up for 12 weeks by regular home visits it was noted that the Zn-supplemented children had fewer episodes of diarrhoea and respiratory infection. There is no data on the impact of Zn supplementation on mortality from diarrhoea, but case fatality rates among malnourished children with persistent diarrhoea range from 5 to 15 %. Thus, reducing the prevalence of diarrhoea, especially from persistent diarrhoea or dysentery, may result in improved child survival.

Recent studies have examined the effect of daily doses of Zn-containing syrup among malnourished children in an urban slum in India. Children who received daily doses of Zn experienced a decrease, approximately 45 %, in the incidence of respiratory infection (Sazawal *et al.* 1998). Among low-birth-weight full-term infants in Brazil there was a 28 % decrease in the prevalence of diarrhoea and a 33 % decrease in the prevalence of cough in a Zn-supplemented group (Lira *et al.* 1998). While there have not been large community-based studies of regular prophylaxis with Zn and assessment of mortality, the case fatality from pneumonia is more than 5 % in many countries, and the reduction in prevalence as a result of daily supplements would be expected to reduce child mortality.

While these results are impressive, it is important to recognize that all studies of Zn supplementation do not show benefit. A study of severely-malnourished Pakistani children who were receiving a rehabilitation diet of lentils, rice and milk, did not show any benefit in terms of diarrhoea morbidity or weight gain if Zn supplements were given (Bhutta *et al.* 1999). It may be that the addition of Zn salts to the local high-phytate diet impairs their bioavailability, or the Zn content of the rehabilitation diet might be satisfactory anyway. Severely-malnourished children in a nutrition rehabilitation centre in Bangladesh showed an increased mortality when given large doses of oral Zn (Doherty *et al.* 1998). Several explanations are possible. Cu deficiency is recognized during large-dose Zn supplementation; the Zn impairs absorption. Cu deficiency may cause a severe leucopenia with a consequent decrease in immune function (Percival, 1998).

Zn deficiency may also contribute to decreased immunity and increased morbidity and mortality during pregnancy. Experimental studies show major changes in reproductive performance and outcome, with considerably increased mortality, but it is difficult to know how relevant these changes are to human reproduction. There are several reviews of the association of Zn deficiency and a series of complications in pregnancy and their contribution to maternal mortality (Caulfield *et al.* 1998). However, assessment of the role of Zn deficiency is difficult, as very few supplementation studies have been performed and most of the published data has been from studies among women with marginal Zn deficiency (Caulfield *et al.* 1999). Several studies show an improvement in birth weight following Zn supplementation (Goldenberg *et al.* 1995). Other studies reviewed by Ramakrishnan *et al.* (1998) show an association between Zn deficiency and increased risk of pregnancy-related morbidity such as prolonged labour, toxæmia and blood loss, but there is no convincing information on the impact of Zn supplementation on these aspects of maternal health and morbidity. Again, there is no information on whether Zn supplementation, given on a regular basis in Zn-deficient populations, will result in a reduction in maternal mortality.

Most studies have examined syrup preparations of Zn which are convenient but not always available. The importance of including an adequate dietary Zn intake is emphasized by studies from Malawi, but the considerable difficulties in obtaining Zn from high-phytate cereals are a remaining challenge (Gibson *et al.* 1998; Huddle *et al.* 1998).

Iron

Severe Fe deficiency causes suppression of several aspects of the immune system (Bhaskaram & Reddy, 1975). These factors can result in increased susceptibility to infection, specifically bacterial infection. There are considerable interactions between infection and plasma levels of micronutrients which make it difficult to assess nutritional status, and controlled trials of interventions are necessary (Filteau & Tomkins, 1994; Friis *et al.* 1996; Friis & Michaelsen, 1998). The increased mortality associated with severe anaemia is well established among children and pregnant women, and many public health programmes include Fe supplements to pregnant women, but very few provide Fe supplementation for infants and children. There have been several theoretical or empirical reasons why Fe has not been advised in populations where infections are endemic. First, experimental studies showed an increased bacterial growth when Fe was added to the culture medium (Andrews, 1998; Brochu *et al.* 1998). Second, there were reports of increased intestinal parasitic infection during refeeding of refugees, although these studies were observational and there were confounding variables (Murray *et al.* 1978). Third, there was increased respiratory morbidity and mortality when Fe was given intramuscularly to anaemic infants in Papua New Guinea (Oppenheimer *et al.* 1986). Fourth, there have been reports that Fe supplementation increased susceptibility of infants and children to

malaria. However, there are also many other reports which fail to show such a hazardous interaction (Oppenheimer, 1998).

The conflict between the approach which allows the administration of Fe supplementation in order to prevent disability and death from anaemia, and the approach which restricts Fe supplementation in order to prevent morbidity and mortality from infection has not really been resolved, because many of the studies have been experimental and theoretical rather than clinical and epidemiological. A recent rigorous study of supplementation of Tanzanian infants (Menendez *et al.* 1997) with different prophylactic regimens has shown that those who received daily Fe supplements had a lower rate of anaemia than those who received malarial prophylaxis alone. The data showed a protective efficacy of 28.8 % compared with a control population that did not receive Fe. Their attack rate for anaemia, as assessed by regular anaemia surveillance, was 0.62 cases per child per year compared with 1.0 cases per child per year in the controls. Moreover, they did not experience different attack rates of clinical malaria. The frequency of malaria episodes in unsupplemented *v.* supplemented children was 0.87 *v.* 1.00 cases per child per year. In comparing the relative contributions of malaria or Fe deficiency to the high frequency of anaemia noted in a longitudinal study, it was proposed that about 60 % of all episodes of anaemia were attributable to malaria and about 30 % were due to Fe deficiency. Similar estimates were made in studies of the cause of anaemia among infants in The Gambia, West Africa (Menendez *et al.* 1994), where Fe deficiency was calculated as being present in 28 % of cases of anaemia. Supplementation of older children with a mixture of several micronutrients, including Fe, improved biochemical status but did not increase the frequency or severity of clinical episodes of malaria (Bates *et al.* 1987; Fuller *et al.* 1988). These recent studies therefore indicate that the provision of regular Fe supplements not only contributes to the prevention of anaemia, with little or no increased risk of malaria, but has an important impact on the immune strength of the host.

Iodine

Iodine-deficiency disorders (IDD) are still common in many endemic areas of the world, despite calls by international agencies such as UNICEF for universal iodization of salt (Hetzel, 1989), and the devastating effects on cognitive function are well documented (Huda *et al.* 1999). There has been considerable progress in implementation, but there are still many millions who are I deficient. I deficiency does not affect immunity, but there are increased perinatal and infant morbidity and mortality rates among children with IDD. This situation probably reflects the poor survival of hypothyroid infants who have impaired neurological development. In addition, there is a significant effect of IDD on birth weight, accounting for an approximately 155 g difference between euthyroid and hypothyroid neonates in Bangladesh (US Anwar, ZR Anwar, M Fischer, KR Sullivan and AM Tomkins, unpublished results). The impact of a low birth weight might have an impact on immunity, which is

independent of IDD itself. There may be factors other than I which contribute to goitre and hypothyroidism (Filteau *et al.* 1994).

The importance of I deficiency as a risk factor for stillbirths and miscarriages is well documented in cross-sectional studies (Hetzl *et al.* 1990). As many of these women are at risk of sepsis following such pregnancy failures, it seems likely that maternal mortality might be increased, but there is no data on whether IDD results in increased maternal mortality. Considering that many areas afflicted by I deficiency are remote from maternal health services, it seems important to investigate the impact of miscarriages and stillbirths from IDD on maternal mortality. The evidence for improved pregnancy outcome is so strong that iodization of salt should be an obligatory part of 'Safer Motherhood' programmes which are in place in an IDD community.

Mixed micronutrients

In view of the evidence that individual micronutrients have quite marked effects on morbidity and mortality, there is increasing interest in combining micronutrients. There are important interactions between micronutrients such that large doses of one may inhibit the absorption of another, and these interactions need to be considered in interpreting the results of multiple micronutrient intervention. However, at present, there are remarkably few studies on the effect of multiple micronutrient interventions on immunity or morbidity in mother and child health. One of the most recent studies is an evaluation of the impact of multiple micronutrients on the pregnancy outcome of HIV-positive women in Tanzania (Fawzi *et al.* 1998). Mothers received either a placebo, vitamin A alone, or vitamin A with a range of additional micronutrients, which consisted of thiamin, riboflavin, vitamins B₆, B₁₂, C and E, niacin and folic acid.

There were several important findings. First, there was an increase in numbers of CD3, CD4 and CD8 lymphocytes among the mothers receiving multiple micronutrient interventions, whereas supplementation with vitamin A had no effect. Similarly, there was no effect of vitamin A supplementation on pregnancy outcome. However, multiple micronutrient supplementation was associated with significant reduction in the percentage of women who had fetal deaths (9.6% *v.* 5.9%), stillbirths (6.1% *v.* 3.5%), low birth weight (15.8% *v.* 8.8%), a composite of preterm birth or low birth weight (8.8% *v.* 3.8%) or an infant who was small-for-gestational age (17.6% *v.* 10.0%). These rather striking findings are important for HIV-positive women, but there is no evidence yet that such improvements would be expected in women who are HIV-negative.

Mixtures of micronutrients have been investigated in many studies where the focus has been on nutritional outcomes (Ndossi & Taylor, 1999). Variable responses in haemoglobin, plasma Zn and retinol levels with increase in linear growth have been observed in China (Lie *et al.* 1993) and Vietnam (Thu *et al.* 1999), although effects on morbidity were not recorded.

Breast-feeding

The benefits of breast-feeding are extensive and well documented (Victora *et al.* 1989). The benefits have mostly focused on the reduction in the incidence, severity, duration and mortality from diarrhoea, especially among malnourished children (Brown *et al.* 1989). Several studies have also emphasized the protective effect of breast-feeding against pneumonia, which is fast becoming the most important cause of death among children under 5 years of age globally. A recent study from Brazil (Cesar *et al.* 1999) showed that infants who were not being breast-fed were seventeen times more likely to be admitted to hospital for pneumonia. The benefits of breast-feeding were considerably reduced if infant formula was added to breast milk. Rates of pneumonia were much higher in those receiving solids, fluid supplements and/or formula milk. The excess risk was particularly pronounced in infants less than 3 months of age, but was still present among older infants. These findings support the promotion of exclusive breast-feeding, especially during the first 3 months of life.

The demonstration of MTCT of HIV through breast milk presents a tragic dilemma. Millions of children have now been infected with HIV, most of them live in Sub-Saharan Africa (Newell, 1999). Transmission can be attributed in about equal proportions to infection *in utero*, during delivery or from breast milk, although the relative contribution of each of the opportunities for infection varies considerably (Dunn *et al.* 1992; Bertolli *et al.* 1996).

Whereas in industrialized countries MTCT has been dramatically reduced by the use of anti-retroviral agents during pregnancy, appropriate obstetric care and exclusive formula feeding after delivery, these options are usually not available or feasible for women in less-developed countries. The cost and availability of anti-retroviral therapy in pregnancy, such as zidovudine, is still so high that only a very small proportion of the population will be able to access it. Some of the options have been reviewed (Kuhn & Stein, 1997). Recent data on the use of nirsevimir, a much cheaper drug, given as two single doses (one in labour and the other to the infant) show a striking reduction in MTCT. However, even with nirsevimir, transmission by breast milk is still significant. Unfortunately, from the perspective of transmission, the cost and safety of infant formula in poor socio-economic conditions is such that the potential benefit of preventing postnatal transmission of HIV by using infant formula may result in increased mortality from infectious disease as a result of the lack of breast-feeding. An added dilemma is caused by the lack of diagnostic facilities. Currently, the only tests widely available are for HIV antibodies rather than the virus; it is not possible to establish whether an infant is truly HIV-positive or -negative until at least 12 months of age, and feeding advice based on knowledge of infectious status is not possible on an individual basis.

Although it is estimated that about one-third of cases of paediatric HIV globally contract their infection from breast milk, these numbers vary considerably from country-to-country. A meta-analysis (Dunn *et al.* 1992) showed that transmission was much higher (29%) if the HIV infection

was acquired during lactation than if the mother was already HIV-positive during pregnancy (15 %). An important factor contributing to the transmission rate is the duration of breast-feeding; if breast-feeding is of long duration then the risk of transmission is higher. If transmission is more common in early lactation these data would tend to overestimate the proportion of infants with HIV who acquire their infection from breast milk. Recent calculations using pooled data from African children who were known to be HIV-negative at 3 months postpartum indicate a risk of transmission of 3.2 cases per 100 child years of breast-feeding (Leroy *et al.* 1998). In their analysis of breast-fed infants from a single African country Leroy *et al.* (1998) showed that approximately 10 % of children who were HIV-negative at 7 weeks became HIV-positive subsequently, but there is insufficient data to assess the relative risk of breast-feeding at individual time points after delivery. In a subgroup analysis of the study, the additional risk of transmission from breast-feeding was 2.5, 7.4 and 9.2 % at 12, 24 and 36 months of age respectively.

The HIV load is highest in colostrum (Markham *et al.* 1994) and in early lactation (Van de Perre, 1999), but breast-milk immune factors are also higher at these times. The relationship between viral load in breast milk and transmission via this route needs further study. Other risk factors are likely to be important in the postnatal transmission of HIV. These factors include deficiency of some of the many immunological-active components of breast milk. The presence of sulfated glycosaminoglycans is of potential importance because of their inhibition of binding of CD4 cells to the HIV-envelope glycoprotein. (Newburg *et al.* 1992). Impaired immunity in the mother, assessed by clinical staging of HIV and AIDS and CD4-CD8 counts as a result of HIV itself, breast abscesses or cracked nipples, systemic maternal infection (from pelvic inflammation or malaria) or increased viral shedding in vitamin A deficiency have all been proposed.

There may also be altered immune function and viral uptake by the intestinal mucosa of the infant. These factors could be influenced by dietary antigen stimulation and malnutrition (including Zn and vitamin A deficiency which are known to affect immunological competence and mucosal structure and function). Other factors which could enable increased viral uptake include candidal lesions of the buccal mucosa and intestinal damage from infections.

An additional novel hypothesis has been put forward during studies of breast-milk immunology among women in Bangladesh (Filteau *et al.* 1996, 1999) and South Africa (Willumsen *et al.* 2000). It was noted that approximately 20 % of women in these countries have subclinical mastitis, as assessed by high levels of Na:K and interleukin 8 levels in breast milk. This condition is especially important within the HIV context because of the association between high numbers of HIV particles and subclinical mastitis (Filteau *et al.* 1999). The veterinary literature has recognized subclinical mastitis for several decades. It is known to be associated with a high load of a range of bacteria, and is especially common among cattle being fed on antioxidant-deficient pastures. Subclinical mastitis has been noted to be associated with poor milk volume and growth faltering in farm animals, and these factors were also present in the

study of infant growth in relation to subclinical mastitis in Bangladesh. A recent study in South Africa shows that there are certain patterns of occurrence of subclinical mastitis. Bilateral subclinical mastitis is of a typical mild form with low Na:K values, whereas unilateral subclinical mastitis is more common and is often more severe with high Na:K values and elevated levels of interleukin 8; there are higher viral loads in samples from women with subclinical mastitis in Durban, South Africa (Willumsen *et al.* 2000). The association between subclinical mastitis, viral load and MTCT has been demonstrated in Malawi, although no information on the pattern of subclinical mastitis was provided (Semba & Neville, 1999).

The demonstration that HIV viral load is increased among women with subclinical mastitis has enormous implications for the transmission of HIV in the breast milk. It puts great emphasis on the reduction of the prevalence and severity of subclinical mastitis by whatever means possible. A recent study among women in Tanzania shows that the prevalence of subclinical mastitis is lower among women who received dietary supplements with sunflower-seed oil during pregnancy and lactation (Filteau *et al.* 1999). Sunflower-seed oil has a high level of vitamin E; the potential antioxidant capacity of this oil may be extremely relevant to the decrease in levels of mastitis.

Among the women studied in South Africa, those mothers who feed their infants with breast milk exclusively have a lower prevalence of subclinical mastitis than those mothers who use mixed feeding. It is postulated that milk stasis, attributable to the introduction of mixed feeding, might contribute to the establishment of subclinical mastitis. Thus, a combination of infection, micronutrient deficiency and mechanical issues such as placement, may be important in the development of subclinical mastitis (Willumsen *et al.* 2000).

Rates of MTCT in relation to type of infant feeding have been studied recently in an urban community in Durban, South Africa (Coutsoudis *et al.* 1999). Transmission was 18.8 % among never-breast-fed children (i.e. those who received infant formula alone). This value compared with 14.6 % among exclusively breast-fed infants and 24.1 % among infants receiving mixed feeding. Even after allowance for potential confounders such as maternal CD4:CD8 cells, syphilis screening results and premature delivery there was a significantly lower risk of HIV transmission (hazard ratio of 0.52) among exclusively breast-fed infants compared with those receiving mixed feeding. There are several possible explanations. First, the protective effect of exclusive breast-feeding may be due to lower levels of subclinical mastitis, and therefore a decrease in the accompanying viral load in breast milk (Willumsen *et al.* 1999). Second, the delay in introduction of dietary antigens may cause a lower immunological response in the intestinal mucosa; this lower response may decrease the uptake of virus from the gut into the circulation. Third, the addition of microbes in a mixed diet may damage the intestinal mucosa; indeed, this possibility is suggested by previous studies of intestinal permeability in different dietary groups (Udall *et al.* 1981).

The findings from Durban (Coutsoudis *et al.* 1999) suggest that the risk of transmission is relatively low if

infants are breast-fed exclusively for 3 months. However, the infection rates thereafter, not yet available from the Durban study, are quite high in other studies (UNAIDS/World Health Organization/UNICEF, 1998), and in the absence of more data it seems that after 3 months breast milk should not be given if accompanied by other foods. It is hoped that with more widespread availability and effectiveness of new anti-retroviral drugs the MTCT rates are likely to fall. Even so it will still be necessary to promote the reduction of transmission of HIV by dietary means. At present it seems that the appropriate advice in poor communities is to reinforce existing messages promoting the exclusive use of breast-feeding until 3–4 months of age. Thereafter, the message is not so clear. In the absence of carefully-controlled studies examining the postnatal transmission of HIV using different regimens of stopping breast milk, it is not possible to calculate the additional risk of MTCT if breast milk is continued after 4–6 months. If early cessation of breast-feeding is promoted there may be considerable deficiencies of Fe, Zn and other micronutrients. Growth faltering, anaemia, impaired immune response and increase in the prevalence of severe infection are all possible in the non-breast-fed child. In addition, the loss of the contraceptive benefits of breast-feeding increase the risk of early further pregnancies with associated detriment to maternal health.

Conclusion

The importance of nutritional interventions in mothers and children as a means of reducing morbidity and mortality has never been so clear. Considerable improvement in mortality rates has come from interventions with single micronutrients. The next few years are likely to see assessments of the impact of multiple micronutrients given at levels at which biological interactions are minimal and their immunological benefits are facilitated. It would, from purely academic purposes, be of great interest to establish studies where various combinations of individual micronutrients could be assessed carefully with respect to morbidity and mortality. There may well be opportunities for such research, but the enormous expense of community studies make it, in the author's view, inappropriate to examine the impact on morbidity and mortality, micronutrient-by-micronutrient. Existing knowledge now needs to be used to design combinations of micronutrients which should be tested in rigorously-designed epidemiological trials. While the benefits of micronutrients have been substantial, there are also enormous issues in relation to child and maternal nutrition that cannot be addressed by single or multiple micronutrient programmes alone. Programmes which also enhance intake of energy and protein, together with infection control, particularly for malaria, pneumonia, diarrhoea and intestinal helminths, are essential if maximum health gains from nutrition interventions are to be achieved.

The challenge to researchers and practitioners alike is to develop and evaluate the best combination of affordable sustainable interventions which can be made regularly available within poor communities. The challenge for policy

makers is to identify specific focused nutrition interventions within a portfolio of activities aiming to increase survival, development and human capacity, without which poverty will never be eradicated.

References

- Andrews SC (1998) Iron storage in bacteria. *Advances in Microbial Physiology* **40**, 281–351.
- Barclay AJ, Foster A & Sommer A (1987) Vitamin A supplements and mortality related to measles: a randomised clinical trial. *British Medical Journal* **294**, 294–296.
- Barreto ML, Santos LM, Assis AM, Araujo MP, Farenzena GG, Santos PA & Fiaccone RL (1994) Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* **344**, 228–231.
- Bates CJ, Powers HJ, Lamb WH, Gelman W & Webb E (1987) Effect of supplementary vitamins and iron on malaria indices in rural Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **81**, 286–291.
- Beaton GH (1989) Small but healthy? Are we asking the right question? *European Journal of Clinical Nutrition* **43**, 863–875.
- Bern C, Martines J, de Zoyza I & Glass RI (1992) The magnitude of the global problem of diarrhoeal disease: a ten-year update. *Bulletin of the World Health Organization* **70**, 705–714.
- Bern C, Zucker JR, Perkins BA, Otieno J, Oloo AJ & Yip R (1997) Assessment of potential indicators for protein-energy malnutrition in the algorithm for integrated management of childhood illness. *Bulletin of the World Health Organization* **75**, Suppl. 1, 87–96.
- Bertolli J, St Louis ME, Simonds RJ, Nieburg P, Kamenga M, Brown C, Tarande M, Quinn T & Ou CY (1996) Estimating the timing of mother-to-child transmission of human immunodeficiency virus in a breast-feeding population in Kinshasa, Zaire. *Journal of Infectious Diseases* **174**, 722–726.
- Bhandari N, Bhan MK & Sazawal S (1994) Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity *British Medical Journal* **309**, 1404–1407.
- Bhaskaram C & Reddy V (1975) Cell-mediated immunity in iron- and vitamin-deficient children. *British Medical Journal* **3**, 522.
- Bhutta ZA, Nizami SQ & Issani Z (1999) Zinc supplementation in malnourished children with persistent diarrhea in Pakistan. *Pediatrics* **103**, E42.
- Bhutta ZA, Nizami SQ, Thobani S & Issani Z (1997) Risk factors for mortality among hospitalized children with persistent diarrhoea in Pakistan. *Journal of Tropical Pediatrics* **43**, 330–336.
- Black RE (1998) Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries. *American Journal of Clinical Nutrition* **68**, 476S–479S.
- Bloem MW, Huq N, Gorstein J, Burger S, Kahn T, Islam N, Baker S & Davidson F (1996) Production of fruits and vegetables at the homestead is an important source of vitamin A among women in rural Bangladesh. *European Journal of Clinical Nutrition* **50**, Suppl. 3, S62–S67.
- Bloem MW, Hye A, Wijnroks M, Ralte A, West KP Jr & Sommer A (1995) The role of universal distribution of vitamin A capsules in combatting vitamin A deficiency in Bangladesh. *American Journal of Epidemiology* **142**, 843–855.
- Boerma JT, Nunn AJ & Whitworth JA (1998) Mortality impact of the AIDS epidemic: evidence from community studies in less developed countries. *AIDS* **12**, Suppl. 1, S3–S14.
- Brochu V, Greinier D & Mayrand D (1998) Human transferrin as a source of iron for *Streptococcus intermedius*. *FEMS Microbiology Letters* **166**, 127–133.

- Brocklehurst P & French R (1998) The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. *British Journal of Obstetrics and Gynaecology* **105**, 836–848.
- Brown KH, Black RE, Lopez DR & Creed DK (1989) Infant-feeding practices and their relationship with diarrheal and other diseases in Huascar (Lima), Peru. *Pediatrics* **83**, 31–40 (erratum published in *Pediatrics* (1989), **83**, 678).
- Caulfield LE, Zavaleta N, Figueroa A & Leon Z (1999) Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. *Journal of Nutrition* **129**, 1563–1568.
- Caulfield LE, Zavaleta N, Shankar AH & Merialdi M (1998) Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. *American Journal of Clinical Nutrition* **68**, 499S–508S.
- Cesar JA, Victora CG, Barros FC, Santos IS & Flores JA (1999) Impact of breast feeding on admission for pneumonia during postneonatal period in Brazil: nested case-control study. *British Medical Journal* **318**, 1316–1320.
- Claeson M & Merson MH (1990) Global progress in the control of diarrheal diseases. *Pediatric Infectious Diseases Journal* **9**, 345–355.
- Costello A (1997) Integrated management of childhood illness. *Lancet* **350**, 1266.
- Coutsoudis A, Bobat RA, Coovadia HM, Kuhn L, Tsai WY & Stein ZA (1995) The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. *American Journal of Public Health* **85**, 1076–1081.
- Coutsoudis A, Moodley D, Pillay K, Harrigan R, Stone C, Moodley J & Coovadia HM (1997) Effects of vitamin A supplementation on viral load in HIV-1-infected pregnant women. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* **15**, 86–87.
- Coutsoudis A, Pillay K, Spooner E, Kuhn L & Coovadia HM (1999) Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. *Lancet* **354**, 471–476.
- Darnton-Hill I (1999) The challenge to eliminate micronutrient malnutrition. *Australian and New Zealand Journal of Public Health* **23**, 309–314.
- de Pee S, Bloem MW, Satoto, Yip R, Sukaton A, Tjiong R, Shrimpton R, Muhilal & Kodyat B (1998) Impact of a social marketing campaign promoting dark-green leafy vegetables and eggs in central Java, Indonesia. *International Journal of Vitamin and Nutrition Research* **68**, 389–398.
- de Pee S, Bloem MW, Tjiong R, Martini E, Satoto, Gorstein J, Shrimpton R & Muhilal (1999) Who has a high vitamin A intake from plant foods, but a low serum retinol concentration? Data from women in Indonesia. *European Journal of Clinical Nutrition* **53**, 288–297.
- Doherty CP, Sarkar MA, Shakur MS, Ling SC, Elton RA & Cutting WA (1998) Zinc and rehabilitation from severe protein-energy malnutrition: higher-dose regimens are associated with increased mortality. *American Journal of Clinical Nutrition* **68**, 742–748.
- Dunn DT, Newell ML, Ades AE & Peckham CS (1992) Risk of human immunodeficiency virus type 1 transmission through breastfeeding. *Lancet* **340**, 585–588.
- English PM, Badcock JC, Giay T, Ngu T, Waters AM & Bennett SA (1997) Effect of nutrition improvement project on morbidity from infectious diseases in preschool children in Vietnam: comparison with control commune. *British Medical Journal* **315**, 1122–1125.
- Fawzi WW, Msamanga GI, Spiegelman D, Urassa EJ, McGrath N, Mwakagile D, Antelman G, Mbise R, Herrera G, Kapiga S, Willett W & Hunter DJ (1998) Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet* **351**, 1477–1482.
- Filteau SM, Lifschitz CH, Munjoma M, Bingham SA, Hermus RI & Tomkins AM (1999) Milk cytokines and subclinical breast inflammation in Tanzanian women: effects of dietary red palm oil or sunflower oil supplementation. *Immunology* **97**, 595–600.
- Filteau SM, Rice AL, Ball JJ, Chakraborty J, Stoltzfus R, de Francisco A & Willumsen JF (1996) Breast milk immune factors in Bangladeshi women supplemented postpartum with retinol or beta-carotene. *American Journal of Clinical Nutrition* **69**, 953–958.
- Filteau SM, Sullivan KR, Anwar US, Anwar ZR & Tomkins AM (1994) Iodine deficiency alone cannot account for goitre prevalence among pregnant women in Modhupur, Bangladesh. *European Journal of Clinical Nutrition* **48**, 293–302.
- Filteau SM & Tomkins AM (1994) Micronutrients and tropical infections. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **88**, 1–3 and 3b.
- Filteau SM & Tomkins AM (1999) Promoting vitamin A status in low-income countries. *Lancet* **353**, 1458–1459.
- Friis H & Michaelsen KF (1998) Micronutrients and HIV infection: a review. *European Journal of Clinical Nutrition* **52**, 157–163.
- Friis H, Ndhlovu P, Kaondera K, Sandstrom B, Michaelsen KF, Vennervald BJ & Christensen NO (1996) Serum concentration of micronutrients in relation to schistosomiasis and indicators of infection: a cross-sectional study among rural Zimbabwean schoolchildren. *European Journal of Clinical Nutrition* **50**, 386–391.
- Fuller NJ, Bates CJ, Hayes RJ, Bradley AK, Greenwood AM, Tulloch S & Greenwood BM (1988) The effects of antimalarials and folate supplements on haematological indices and red cell folate levels in Gambian children. *Annals of Tropical Paediatrics* **8**, 61–67.
- Ghana VAST (1993) Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. Ghana VAST Study Team. *Lancet* **342**, 7–12 (erratum published in *Lancet* (1993), **342**, 250).
- Gibson RS, Ferguson EL & Lehrfeld J (1998) Complementary foods for infant feeding in developing countries: their nutrient adequacy and improvement. *European Journal of Clinical Nutrition* **52**, 764–770.
- Golden BE & Golden MH (1979) Plasma zinc and the clinical features of malnutrition. *American Journal of Clinical Nutrition* **32**, 2490–2494.
- Golden BE & Golden MH (1981) Plasma zinc, rate of weight gain, and the energy cost of tissue deposition in children recovering from severe malnutrition on a cow's milk or soya protein based diet. *American Journal of Clinical Nutrition* **34**, 892–899.
- Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, DuBard MB & Hauth JC (1995) The effect of zinc supplementation on pregnancy outcome. *Journal of the American Medical Association* **274**, 463–468.
- Gregson S, Anderson RM, Ndlovu J, Zhuwau T & Chandiwana SK (1997) Recent upturn in mortality in rural Zimbabwe: evidence for an early demographic impact of HIV-1 infection? *AIDS* **11**, 1269–1280.
- Heaver RA & Hunt JA (1995) *Improving Early Child Development*. Washington, DC and Manila: World Bank and Asian Development Bank.
- Henning B, Stewart K, Zaman K, Alam AN, Brown KH & Black RE (1992) Lack of therapeutic efficacy of vitamin A for non-cholera, watery diarrhoea in Bangladeshi children. *European Journal of Clinical Nutrition* **46**, 437–443.
- Hetzel BS (1989) *The Story of Iodine Deficiency an International Challenge to Nutrition*. Oxford, New York and Tokyo: Oxford University Press.
- Hetzel BS, Potter BJ & Dulberg EM (1990) The iodine deficiency disorders: nature, pathogenesis and epidemiology. *World Review of Nutrition and Dietetics* **62**, 59–119.

- Huda SN, Grantham-McGregor SM, Rahman KM & Tomkins A (1999) Biochemical hypothyroidism secondary to iodine deficiency is associated with poor school achievement and cognition in Bangladeshi children. *Journal of Nutrition* **129**, 980–987.
- Huddle JM, Gibson RS & Cullinan TR (1998) Is zinc a limiting nutrient in the diets of rural pregnant Malawian women? *British Journal of Nutrition* **79**, 257–265.
- Humphrey JH, Agoestina T, Wu L, Usman A, Nurachim M, Subardja D, Hidayat S, Tielsch J, West KP Jr & Sommer A (1996) Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *Journal of Pediatrics* **128**, 489–496.
- Humphrey JH, West KP Jr & Sommer A (1992) Vitamin A deficiency and attributable mortality among under-5-year-olds. *Bulletin of the World Health Organization* **70**, 225–232.
- Hussey GD & Klein M (1990) A randomized, controlled trial of vitamin A in children with severe measles. *New England Journal of Medicine* **323**, 160–164.
- Jennings J (1991) *Managing Successful Nutrition Research Programmes. ACC/SCN State-of-the-Art Series: Nutrition Policy Discussion Paper no.8*. Geneva: ACC/SCN.
- John GC, Nduati RW, Mbori ND, Overbaugh J, Welch M, Richardson BA, Ndinya AJ, Bwayo J, Krieger J, Onyango F & Kreiss JK (1997) Genital shedding of human immunodeficiency virus type 1 DNA during pregnancy: association with immunosuppression, abnormal cervical or vaginal discharge, and severe vitamin A deficiency. *Journal of Infectious Diseases* **175**, 57–62.
- Kelly P, Musonda R, Kafwembe E, Kaetano L, Keane E & Farthing M (1999) Micronutrient supplementation in the AIDS diarrhoea-wasting syndrome in Zambia: a randomized controlled trial. *AIDS* **13**, 495–500.
- Khanum S, Ashworth A & Huttly SR (1994) Controlled trial of three approaches to the treatment of severe malnutrition. *Lancet* **344**, 1728–1732.
- Kibona N, Doland C, Watson FE, Alnwick D & Tomkins A (1995) An evaluation of a project to improve child nutrition in Tanzania. *International Journal of Food Science and Nutrition* **46**, 233–239.
- Kuhn L & Stein Z (1997) Infant survival, HIV infection, and feeding alternatives in less-developed countries. *American Journal of Public Health* **87**, 926–931.
- Kulier R, de Onis M, Gulmezoglu AM & Villar J (1998) Nutritional interventions for the prevention of maternal morbidity. *International Journal of Gynaecology and Obstetrics* **63**, 231–246.
- Leroy V, Newell ML, Dabis F, Peckham C, Van de Perre P, Bulterys M, Kind C, Simonds RJ, Wiktor S & Msellati P (1998) International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection. Ghent International Working Group on Mother-to-Child Transmission of HIV. *Lancet* **352**, 597–600 (erratum published in *Lancet* (1998), **352**, 1154).
- Lie C, Ying C, Wang EL, Brun T & Geissler C (1993) Impact of large-dose vitamin A supplementation on childhood diarrhoea, respiratory disease and growth. *European Journal of Clinical Nutrition* **47**, 88–96.
- Lira PI, Ashworth A & Morris SS (1998) Effect of zinc supplementation on the morbidity, immune function, and growth of low-birth-weight, full-term infants in northeast Brazil. *American Journal of Clinical Nutrition* **68**, 418S–424S.
- McCullough FSE, Northrop-Cleaves CA & Thurnham DI (1999) The effect of vitamin A on epithelial integrity. *Proceedings of the Nutrition Society* **58**, 289–293.
- Markham RB, Coberly J, Ruff AJ, Hoover D, Gomez J, Holt E, Desormeaux J, Boulos R, Quinn TC & Halsey NA (1994) Maternal IgG1 and IgA antibody to V3 loop consensus sequence and maternal-infant HIV-1 transmission. *Lancet* **343**, 390–391.
- Menendez C, Kahigwa E, Hirt R, Vounatsou P, Aponte JJ, Font F, Acosta CJ, Schellenberg DM, Galindo CM, Kimario J, Urassa H, Brabin B, Smith TA, Kitua AY, Tanner M & Alonso PL (1997) Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* **350**, 844–850.
- Menendez C, Todd J, Alonso PL, Francis N, Lulat S, Ceessay S, M'Boge B & Greenwood BM (1994) The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **88**, 590–593.
- Mostad SB, Overbaugh J, DeVange DM, Welch MJ, Chohan B, Mandaliya K, Nyange P, Martin HL Jr, Ndinya AJ, Bwayo JJ & Kreiss JK (1997) Hormonal contraception, vitamin A deficiency, and other risk factors for shedding of HIV-1 infected cells from the cervix and vagina. *Lancet* **350**, 922–927.
- Murray CJ & Lopez AD (1994) Global and regional cause-of-death patterns in 1990. *Bulletin of the World Health Organization* **72**, 447–480.
- Murray MJ, Murray AB, Murray MB & Murray CJ (1978) The adverse effect of iron repletion on the course of certain infections. *British Medical Journal* **ii**, 1113–1115.
- Ndossi G & Taylor AM (1999) *Multiple Micronutrient Supplementation in Tanzania – A Literature and Policy Review by UNICEF*. Dar es Salaam, Tanzania: UNICEF.
- Nduati RW, John GC, Richardson BA, Overbaugh J, Welch M, Ndinya AJ, Moses S, Holmes K, Onyango F & Kreiss JK (1995) Human immunodeficiency virus type 1-infected cells in breast milk: association with immunosuppression and vitamin A deficiency. *Journal of Infectious Diseases* **172**, 1461–1468.
- Newburg DS, Viscidi RP, Ruff A & Yolken RH (1992) A human milk factor inhibits binding of human immunodeficiency virus to the CD4 receptor. *Pediatric Research* **31**, 22–28.
- Newell ML (1999) Infant feeding and HIV-1 transmission. *Lancet* **354**, 442–443.
- Oppenheimer SJ (1998) Iron and infection in the tropics: paediatric clinical correlates. *Annals of Tropical Paediatrics* **18**, Suppl., S81–S87.
- Oppenheimer SJ, Gibson FD, Macfarlane SB, Moody JB, Harrison C, Spencer A & Bunari O (1986) Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **80**, 603–612.
- Pelletier DL (1994) The potentiating effects of malnutrition on child mortality: epidemiologic evidence and policy implications. *Nutrition Reviews* **52**, 409–415.
- Percival SS (1998) Copper and immunity. *American Journal of Clinical Nutrition* **67**, 1064S–1068S.
- Pickering H, Hayes RJ, Tomkins AM, Carson D & Dunn DT (1987) Alternative measures of diarrhoeal morbidity and their association with social and environmental factors in urban children in The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **81**, 853–859.
- Pneumonia Working Group (1995) Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. The vitamin A and Pneumonia Working Group. *Bulletin of the World Health Organization* **73**, 609–619.
- Ramakrishnan U, Manjrekar R, Rivera J, Gonzales-Cossio T & Martorell R (1998) Micronutrients and pregnancy outcome: a review of the literature. *Nutrition Research* **19**, 103–159.
- Roy SK, Behrens RH, Haider R, Akramuzzaman SM, Mahalanabis D, Wahed MA & Tomkins AM (1992) Impact of zinc supplementation on intestinal permeability in Bangladeshi children

- with acute diarrhoea and persistent diarrhoea syndrome. *Journal of Pediatric Gastroenterology and Nutrition* **15**, 289–296.
- Roy SK, Islam A, Molla A, Akramuzzaman SM, Jahan F & Fuchs G (1997a) Impact of a single megadose of vitamin A at delivery on breastmilk of mothers and morbidity of their infants. *European Journal of Clinical Nutrition* **51**, 302–307.
- Roy SK, Tomkins AM, Akramuzzaman SM, Behrens RH, Haider R, Mahalanabis D & Fuchs G (1997b) Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. *Archives of Disease in Childhood* **77**, 196–200.
- Roy SK, Tomkins AM, Mahalanabis D, Akramuzzaman SM, Haider R, Behrens RH & Fuchs G (1998) Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. *Acta Paediatrica* **87**, 1235–1239.
- Salam MA, Seas C, Khan WA & Bennis ML (1995) Treatment of shigellosis: IV Cefixime is ineffective in shigellosis in adults. *Annals of Internal Medicine* **123**, 505–508.
- Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A & Bhan MK (1998) Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. *Pediatrics* **102**, 1–5.
- Schofield C & Ashworth A (1996) Why have mortality rates for severe malnutrition remained so high? *Bulletin of the World Health Organization* **74**, 223–229.
- Scrimshaw NS, Taylor C & Gordon JE (1968) *Interactions of Nutrition and Infection*. Geneva: WHO.
- Semba RD, Miotti PG, Chipangwi JD, Saah AJ, Canner JK, Dallabetta GA & Hoover DR (1994) Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet* **343**, 1593–1597.
- Semba RD & Neville MC (1999) Breast-feeding, mastitis, and HIV transmission: nutritional implications. *Nutrition Reviews* **57**, 146–153.
- Shankar AH, Genton B, Semba RD, Baisor M, Paino J, Tamja S, Adiguma T, Wu L, Rare L, Tielsch JM, Alpers MP & West KP Jr (1999) Effect of vitamin A supplementation on morbidity due to *Plasmodium falciparum* in young children in Papua New Guinea: a randomised trial. *Lancet* **354**, 203–209.
- Sommer A (1993) Vitamin A, infectious disease, and childhood mortality: a 2 solution? *Journal of Infectious Diseases* **167**, 1003–1007.
- Thu BD, Schultink W, Dillon D, Gross R, Leswara ND & Khoi HH (1999) Effect of daily and weekly micronutrient supplementation on micronutrient deficiencies and growth in young Vietnamese children. *American Journal of Clinical Nutrition* **69**, 80–86.
- Timaeus IM (1998) Impact of the HIV epidemic on mortality in Sub-Saharan Africa: evidence from national surveys and censuses. *AIDS* **12**, Suppl. 1, S15–S27.
- Tomkins A (1991) Recent developments in the nutritional management of diarrhoea. 1. Nutritional strategies to prevent diarrhoea among children in developing countries. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **85**, 4–7.
- Tomkins A, Behrens R & Roy S (1993) The role of zinc and vitamin A deficiency in diarrhoeal syndromes in developing countries. *Proceedings of the Nutrition Society* **52**, 131–142.
- Tomkins AM, Dunn DT & Hayes RJ (1989) Nutritional status and risk of morbidity among young Gambian children allowing for social and environmental factors. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **83**, 282–287.
- Tomkins AM & Watson FE (1989) *Malnutrition and Infection: A Review*. Geneva: WHO.
- Udall JN, Pang K, Fritze L, Kleinman R & Walker WA (1981) Development of gastrointestinal mucosal barrier. I. The effect of age on intestinal permeability to macromolecules. *Pediatric Research* **15**, 241–244.
- UNAIDS/World Health Organization/United Nations Children's Fund (1998) *HIV and Infant Feeding. A Review of HIV Transmission Through Breast Feeding 1998*. WHO/FRH/NUT/CHD/98.3. UNAIDS/98.5 UNICEF/PD/NUT/(J) 98–3. New York: UNICEF.
- United Nations Children's Fund (1998a) *The State of the World's Children*. New York: Oxford University Press.
- United Nations Children's Fund (1998b) *HIV and infant Feeding – Guidelines for Decision Makers*. WHO/FRH/NUT/CHD/98.1, UNAIDS/98.3 UNICEF/PD/NUT/(J)98–1. New York: UNICEF.
- United Nations Children's Fund (1998c) *HIV and Infant Feeding – A Guide for Health Care Managers and Supervisors*. WHO/NUT/CHD/98.2, UNAIDS/98.4, UNICEF/PD/NUT/(J)98–2. New York: UNICEF.
- United Nations Children's Fund (1998d) *HIV and Infant Feeding – A Review of HIV Transmission Through Breast Feeding*. WHO/NUT/CHD/98.3, UNAIDS/98.5, UNICEF/PD/NUT/(J)98–3. New York: UNICEF.
- Van de Perre P (1999) Transmission of human immunodeficiency virus type 1 through breast-feeding: how can it be prevented? *Journal of Infectious Diseases* **179**, Suppl. 3, S405–S407.
- Vella V, Tomkins A, Ndiku J, Marshal T & Cortinovis I (1994) Anthropometry as a predictor for mortality among Ugandan children, allowing for socio-economic variables. *European Journal of Clinical Nutrition* **48**, 189–197.
- Victora CG, Olinto MT, Barros FC & Nobre LC (1996) Falling diarrhoea mortality in Northeastern Brazil: did ORT play a role? *Health Policy and Planning* **11**, 132–141.
- Victora CG, Smith PG, Vaughan JP, Nobre LC, Lombardi C, Teixeira AM, Fuchs SC, Moreira LB, Gigante LP & Barros FC (1989) Infant feeding and deaths due to diarrhea. A case-control study. *American Journal of Epidemiology* **129**, 1032–1041.
- Waterlow JC (1989) What do we mean by adaptation? In *Nutritional Adaptation in Man* [KL Blaxter and JC Waterlow, editors]. London: John Libbey.
- Waterlow JC, Tomkins AM & Grantham-McGregor SM (1992) *Protein Energy Malnutrition*. London: Edward Arnold.
- West KP Jr, Katz J, Shrestha SR, LeClerq SC, Khatri SK, Pradhan EK, Adhikari R, Wu LS, Pokhrel RP & Sommer A (1995) Mortality of infants < 6 mo of age supplemented with vitamin A: a randomized, double-masked trial in Nepal. *American Journal of Clinical Nutrition* **62**, 143–148.
- West KP Jr, Katz J, Khatri SK, LeClerq SC, Pradhan EK, Shrestha SR, Connor PB, Dali SM, Christian P, Pokhrel RP & Sommer A (1999) Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. The NNIPS-2 Study Group. *British Medical Journal* **318**, 570–575.
- White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, Kokwaro G, Ouma J, Hien TT, Molyneux ME, Taylor TE, Newbold CI, Ruebush TK, Danis M, Greenwood BM, Anderson RM & Olliaro P (1999) Averting a malaria disaster. *Lancet* **353**, 1965–1967.
- Willumsen JF, Filteau SM, Coutoudis A, Underwood BA, Newell ML & Tomkins AM (2000) Subclinical mastitis as a risk factor for mother-infant HIV transmission. *Proceedings of 9th International Conference of the International Society for Research in Human Milk and Lactation, Bonn, Germany* (In the Press).