Vitamin A and public health: challenges for the next decade

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Since 1980, there has been a revolution in our understanding of the major role which vitamin A plays in mortality and morbidity from infectious diseases. In the present paper, the results of the epidemiological studies which have led to this revolution are reviewed, and used as the basis to set challenges for the next decade.

Vitamin A deficiency and mortality and morbidity in older infants (≥ 6 months) and young children

A series of large, community-based, randomized controlled trials have shown that improving the vitamin A intake of children in populations in which vitamin A deficiency is prevalent substantially reduces their risk of death (Sommer et al. 1986; Muhilal et al. 1988; Rahmathullah et al. 1990; Vijayaraghavan et al. 1990; West et al. 1991; Daulaire et al. 1992; Herrera et al. 1992; Ghana VAST Study Team, 1993; Table 1). A meta-analysis of these eight trials concluded that, in similar populations to those in which the trials were conducted, one could reasonably expect a reduction in mortality of children aged 6 months–5 years of between 1 and 40 (mean 23)%, if similar levels of intervention coverage were achieved (Beaton et al. 1993).

Most (Sommer et al. 1986; Rahmathullah et al. 1990; Vijayaraghavan et al. 1990; West et al. 1991; Daulaire et al. 1992), but not all (Ghana VAST Study Team, 1993), of the trials which found a significant impact on mortality

suggested sex-specific differences in the effect of vitamin A supplementation, but the direction of these differences was not consistent. A meta-analysis of all eight trials showed no significant difference by sex, or by age (Beaton et al. 1993). However, there do appear to be important differences in the impact of vitamin A on different causes of death. Meta-analyses of data from those trials which collected cause of death information, showed that there was a substantial impact on diarrhoea-related deaths (Beaton et al. 1993), but no significant impact on acute lower respiratory tract infection-related deaths (Vitamin A and Pneumonia Working Group, 1995). Only the study in Ghana had a substantial number of deaths thought to be due to malaria, but there was no suggestion of an impact on either malaria-related deaths or morbidity in this trial (Binka et al. 1995).

Improving children's vitamin A intake may also reduce their risk of severe morbidity (Arthur et al. 1992; Ghana VAST Study Team, 1993; Barreto et al. 1994), although the results from trials of the impact of vitamin A supplementation on the incidence, prevalence, severity or duration of morbidity have been less consistent than those for mortality (Beaton et al. 1993). Furthermore, clinical trials of vitamin A supplementation of African children with severe measles have demonstrated significantly decreased mortality (Barclay et al. 1987; Hussey & Klein, 1990) and morbidity (Hussey & Klein, 1990; Coutsoudis et al. 1991). Even though similar clinical trials in children with less-severe measles (Rosales et al. 1996), diarrhoea (Henning et al. 1992; Bhandari et al. 1994), and pneumonia (Kjolhede et al. 1995; L Nacul, personal communication) have failed to show clear-cut, short-term beneficial effects, the overall mortality-sparing effects of vitamin A are now beyond dispute (Beaton et al. 1993).

One of the major challenges to all public health and nutrition programmes in developing countries in the next decade will be to turn this new knowledge into effective, large-scale intervention programmes in vitamin A-deficient populations. There are three major approaches to achieve this: supplementation; food fortification; food-based dietary interventions. The best choice of approach or combination of approaches, and the specific strategies which should be employed (e.g. fortification of a staple food or a food additive) will require careful study in each setting. There is

Table 1. Results of eight major trials of the impact of prophylactic vitamin A on child mortality (Data from Beaton et al. 1993)

Study	Rate ratio, vitamin A : placebo	
	Mean	95 % CI
Indonesia: Aceh	0·73	0·56–0·95
MSG	0·70	0·58–0·85
India: Tamil Nadu	0·46	0·31–0·67
Hyderabad	0·94	0·61–1·46[NS]
Nepal: Sarlahi Child	0·70	0·57–0·86
Jumla	0·74	0·60–0·91
Sudan	1·06	0·82–1·37[NS]
Ghana: VAST Survival	0·81	0·68–0·98
Overall estimate	0·77	0·71–0·84

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no universal best solution, and the choice should be based on an assessment not only of technical issues, but also of socio-cultural and political issues. However, such assessments must be carried out quickly so that effective programmes can be initiated without delay, because it has been shown that improving the vitamin A status of a very high proportion of the young children in the developing countries can be one of the most cost-effective interventions available to public health (Levin et al. 1993; World Bank, 1993).

Over the past 15 years, nutritional interventions have not been given a high priority by many governments and international donors. The clear evidence that improving the vitamin A status of young children can have such a major impact on their survival should be enough to reverse this neglect over the next decade. The demonstration that mild and moderate growth deficit is also associated with a substantial proportion of child mortality in developing countries (Pelletier, 1994), and the evidence that other micronutrient deficiencies, including Fe, I, and Zn, are also underlying causes of both morbidity and mortality in poor children (Levin et al. 1993; Sazawal et al. 1996), means that nutritionists have all the evidence they need to insist that nutritional interventions are integrated into health programmes in all developing countries. It should not be added as a token afterthought, but as a fundamental priority, alongside immunization and management of diarrhoea, acute lower respiratory tract infections, and malaria. Over the next decade, this unique opportunity to greatly improve the health, development, and survival of future generations of young children in developing countries must not be missed.

The safety and efficacy of vitamin A supplementation in early infancy

A current research challenge is the elucidation of whether similar benefits to those in older infants and young children should be expected from vitamin A supplementation in early infancy (i.e. aged less than 6 months). Three randomized controlled trials have examined the impact of vitamin A supplementation of young infants on their subsequent mortality and morbidity; two trials were conducted in Nepal (Daulaire et al. 1992; West et al. 1995), and one trial in Indonesia (Humphrey et al. 1996). The two trials in Nepal were community-based trials in which high doses of vitamin A were given to all children aged less than 6 months. Neither trial found a significant impact on mortality. The trial in Indonesia included all infants born within a large hospital in Bandung, who were either given a 15 mg dose of vitamin A or a placebo within 12 h of birth (Humphrey et al. 1996). The infants were then followed-up at home until they were 12 months old. The mortality rate was 64 % lower in the vitamin A group ($P < 0.01$). The mortality reduction appeared to be confined to the post-neonatal period when infectious diseases are more prevalent.

An alternative approach to supplementing the vitamin A intake of breast-fed infants is via their mothers' breast milk. Unfortunately, high doses of vitamin A can be teratogenic,

especially when given early in pregnancy; therefore, they are not recommended in women, except within 6 weeks after delivery (International Vitamin A Consultative Group, 1986). A randomized controlled trial in Indonesia showed that a single 90 mg dose of vitamin A to mothers significantly increased the serum retinol concentration of their infants for at least their first 8 months of life (Stoltzfus et al. 1993). A placebo-controlled trial in Matlab, Bangladesh, went on to test the impact on infant mortality during the first 6 months after the dose (de Francisco et al. 1994). Despite including a total of 8735 infants, the trial was still too small to be able to detect all but a very substantial impact on mortality in the infants. Although the mortality was 18 % lower in the infants whose mothers were supplemented, this difference was not statistically significant (95 % CI 0.58, 1.14). On the other hand, both suspected acute lower respiratory tract infection (i.e. cough plus measured rapid breathing; rate ratio 1.44, 95 % CI 1.10, 1.87) and reported diarrhoea (rate ratio 1.56, 95 % CI 1.29, 1.89) were substantially and significantly increased in the infants whose mothers had been allocated vitamin A.

In summary, with the notable exception of the trial in Bandung, Indonesia, the results of these trials of improvements in the vitamin A intake of young infants (either directly or via their mothers' breast milk) have tended to be disappointing compared with those in older infants and young children. Although this may have been related to the results having insufficient power to give a definitive answer, a clear-cut answer as to whether vitamin A supplementation in early infancy is safe and efficacious is important for two main reasons. First, mortality and morbidity rates are highest in this age-group; therefore, any beneficial effect will be particularly important. Second, a high proportion of young infants have several contacts with health services during infancy, often receiving an immunization at these contacts. The potential exists, therefore, for reaching these infants at very low marginal cost. At least three relevant trials (in Ghana, India, and Peru) are due to complete their data collection during 1997. These placebo-controlled trials are evaluating the impact of vitamin A on the incidence of immediate potential side effects, vitamin A status, and the incidence, duration and severity of morbidity in infants up to the age of 9 months (P Arthur, personal communication). These trials should greatly improve our understanding of the safety and efficacy of vitamin A supplementation in early infancy, although they may not have the power to detect important impacts on mortality, and none of the three study sites is in a population with a high prevalence of xerophthalmia.

These trials will also provide important data on whether high-dose vitamin A supplements cause functionally important side effects in this age-group when administered at the same time as routine infant immunizations. Concern about this possibility arose from trials in Matlab, Bangladesh, which found an increased incidence of bulging fontanelle in young infants given either 15 mg (de Francisco et al. 1993) or 7.5 mg (Baqui et al. 1994) vitamin A with each dose of diphtheria–pneumonia–tetanus and poliomyelitis vaccine at approximately 6, 10 and 14 weeks of age. The increase in transient bulging fontanelle was confirmed in trials in Nepal (West et al. 1992, 1995)

and in Indonesia (Humphrey *et al.* 1996). However, the functional significance of transient bulging fontanelle has been questioned, especially as it appears to be due to a transient increase in cerebrospinal volume in the absence of increased cerebrospinal pressure (Humphrey *et al.* 1996). Further data will come from the trials in Ghana, India, and Peru mentioned previously, and from developmental follow-up of the infants involved in the Bandung trial (J Humphrey, personal communication).

Further worries about potential side effects of vitamin A given at the same time as infant vaccines came from the results of a placebo-controlled trial in Indonesia of the effect of a single 30 mg dose of vitamin A given at the same time as measles vaccine when the infant was aged 6 months (Semba *et al.* 1995). Although, overall, there was no significant difference in the immune response to the vaccine, a subgroup analysis showed that the response was lower in those infants who still had substantial concentrations of maternal measles antibody. Arguments that this was less likely to occur when the vaccine was given at the more usual age of 9 months and above (Ross, 1995) have been borne out by the results of a recent trial in infants in Guinea-Bissau (Benn *et al.* 1997). In fact, there was a suggestion from this trial that the vaccine response at this age may have been increased by concurrent vitamin A supplementation in boys.

It seems likely, therefore, that it will become possible to give clear-cut recommendations about vitamin A supplementation of young infants (either direct or via the mother's breast milk) within the next year or so. In the meantime, it is safest to restrict this to 30 mg for infants aged 6 months or more, with a minimum interval of 4 months between doses. Fortunately, it now appears to be safe to give a dose at the same time as measles vaccine, when this is administered at the usual age of 9 months and above.

The safety and efficacy, in both mother and infant, of vitamin A supplementation in pregnancy

Studies in Asia have shown that vitamin A deficiency can be common in both pregnant and lactating women (Dixit, 1966; Mandal *et al.* 1969; Bloem *et al.* 1995; Katz *et al.* 1995). However, until very recently, attention has focused on the dangers of high doses of vitamin A to the fetus (International Vitamin A Consultative Group, 1986), and the restrictions this imposes on supplementation, or even consumption of vitamin A-rich foods such as liver, during pregnancy (Hathcock *et al.* 1990; Sommer & West, 1996). On the other hand, vitamin A deficiency has also been *shown* to adversely affect embryogenesis (Olson, 1972, 1996; Hofman & Eichele, 1994). Improving the vitamin A intake of deficient pregnant women, therefore, may have benefits both to the woman herself and to her fetus and the young infant. The efficacy of frequent low-dose vitamin A supplements administered to pregnant women is currently being tested within a large-scale community-based trial in Nepal (KP West, personal communication). The results of this trial will be crucial in guiding policy and programmes. If they show a clear benefit to the woman, her fetus or young infant, they will challenge health and nutrition

services to devise feasible and sustainable interventions to improve the vitamin A intake of pregnant women, while avoiding the potential risks of toxicity to the fetus.

Vitamin A and human immunodeficiency virus infection

Recent studies in adults in developed countries (mainly in the USA) have demonstrated a consistent association between human immunodeficiency virus (HIV)–acquired immune deficiency syndrome (AIDS) and vitamin A deficiency (Bogden *et al* 1990; Calle *et al.* 1991; Baum *et al.* 1992; Beach *et al.* 1992; Semba *et al.* 1993; Ward *et al.* 1993; Ward & Semba, 1994). A cohort study in 126 HIV-1 seropositive and fifty-three HIV-1 seronegative adult intravenous-drug users in Baltimore, MD, showed that mortality over a mean follow-up period of 22·8 months was significantly higher in the HIV-1 seropositive adults whose initial serum retinol concentration was $< 1·05$ µmol/l relative to those whose serum retinol concentration was $\geq 1·05$ µmol/l (relative risk 4·3 (95 % CI 1·1, 17·8 after adjusting for a wide range of potential confounders; Semba *et al.* 1993).

In another cohort study in Baltimore and Washington, DC, HIV-1 seropositive homosexual and/or bisexual men whose total dietary vitamin A intake was two to four times the recommended dietary allowance had substantially lower rates of progression to symptomatic AIDS, both in comparison with men whose intake was lower and higher than this (Tang *et al.* 1993). The number of men who had intakes likely to lead to deficiency was too small to allow the impact of vitamin A deficiency on disease progression to be examined.

The same cohort of HIV-1 seropositive homosexual and/or bisexual men has been used to examine the association between serum retinol concentration at enrolment and risk of progression to AIDS over a 9-year period. No significant association was found in this cohort, but serum retinol concentrations were uniformly in the normal to high range (median 2·44 µmol/l; Tang *et al.* 1997).

Unfortunately, none of the studies to date have measured acute-phase proteins, or adequately adjusted for the effects of concurrent infections on the measurements of serum retinol concentration. However, they indicate that vitamin A status may be associated with the progression of HIV-1 infection in adults, at least in some populations.

Additional indications that retinoids may be important in HIV–AIDS come from clinical reports that several of the conditions which are frequent complications in HIV-positive individuals (psoriasis, Reiter's syndrome, Kaposi's sarcoma, lichen planus, papillomavirus infection, and oral hairy leukoplakia) respond to retinoid supplements (Ward & Semba, 1994).

This evidence from multiple sources has led some workers to suggest that vitamin A and the retinoids may have a potential role in the treatment of HIV infection (Poli *et al.* 1992). However, *in vitro* studies have shown conflicting results. Several studies have indicated that retinoic acid and other retinoids can significantly increase HIV replication (Yamamoto *et al.* 1986; Kitano *et al.* 1990; Poli *et al.* 1992; Poli & Fauci, 1992; Turpin *et al.* 1992) or

Table 2. Relative and attributable risks of vertical transmission of human immunodeficiency virus infection according to maternal serum retinol concentration during pregnancy in Malawi (Data from Semba *et al.* 1994)

Serum retinol concentration of mother during pregnancy (μmol/l)	Relative risk of vertical transmission		Attributable risk of vertical transmission	
	Mean	(95 % CI)	Mean	(95 % CI)
< 0·70	4·4	(+1·6, +12·0)	0·25	(+0·12, +0·37)
0·70–1·05	3·6	(+1·3, +9·6)	0·19	(+0·09, +0·29)
1·05–1·40	2·2	(+0·8, +6·3)	0·09	(−0·01, +0·19)
≥1·40	1·0		0·00	

enhance transcription from the HIV-1 long terminal repeat (Collins, 1988; Maio & Brown, 1988) in human monocytes and monocyte-like cells, and Poli *et al.* (1992) have reported that retinoids can also block HIV expression in infected monocytes. Ultimate answers, as to whether or not vitamin A status is related either to HIV incidence or to the progression of HIV disease if an individual is infected, will have to come from community-based and clinical trials respectively. The former will need large sample sizes.

A cohort study in 338 HIV-1-infected pregnant women in Malawi showed a strong inverse correlation between the maternal serum retinol concentration during pregnancy and vertical transmission of HIV infection to the infant (Semba *et al.* 1994; Table 2). This was assessed in women whose infant survived to 12 months of age, and whose infant's HIV serostatus at that age was known. The odds ratio of vertical transmission was 0·56 (95 % CI 0·37, 0·85) for each 0·45 μmol/l increase in serum retinol, after controlling for maternal age, BMI, and CD4 cell count (Semba *et al.* 1994). The mean serum retinol concentration during pregnancy of HIV-1-infected mothers whose infants died before they reached 12 months (0·78 (SE 0·3) μmol/l) was similar to that of the mothers whose infants survived to 12 months but were HIV-1 seropositive at that age (0·86 (SE 0·03) μmol/l), but was lower than that of mothers whose infants survived to 12 months and were HIV-1 seronegative at that age (1·07 (SE 0·02) μmol/l; $P < 0·0001$). Several trials of the impact on vertical transmission of HIV infection of low-dose vitamin A supplements given to HIV-1-infected pregnant women are currently underway in Africa (RD Semba, personal communication). If these report positive results, this will provide one of very few interventions for the prevention of HIV infection.

The importance of vitamin A deficiency in older children and adolescents

Vitamin A deficiency frequently extends into later childhood, adolescence, and even into adulthood in affected developing country populations (Sommer & West, 1996). In fact, the prevalence of mild forms of xerophthalmia (night-blindness and/or Bitot's spot) has usually been found to be higher among school-age children than among younger children in Asia (Solon *et al.* 1978; Khan *et al.* 1984; Brilliant *et al.* 1985; Upadhyay *et al.* 1985; Hennig *et al.* 1991; Gopaldas, 1992). This is in contrast to the more severe, potentially-blinding corneal xerophthalmia which is

rare after the sixth birthday (Sommer & West, 1996). Two large hospital series in Asia have found that less than 10 % of cases of active corneal xerophthalmia were in children aged 6 years or more (Sommer, 1982; Hennig *et al.* 1991).

Very few studies have been conducted among older children or adolescents on the importance of vitamin A deficiency, or the potential of vitamin A supplementation. This has been mainly because until recently the focus of attention in relation to vitamin A deficiency was on blinding xerophthalmia, and because absolute mortality (and most morbidity) rates decline with age from infancy through childhood and into adolescence. However, a small placebo-controlled trial in schoolboys aged 7–15 years attending a school for slum children in Baroda, India, found that high doses of vitamin A given twice at 6-month intervals substantially reduced both the prevalence of xerophthalmia, and the proportion of children with severe or moderate biochemical deficiency (Pant & Gopaldas, 1987). A subsequent placebo-controlled trial in 210 schoolboys (aged 9–15 years) attending four primary schools in the same city has reported that children receiving 60 mg vitamin A on three occasions at 4-month intervals had a significantly lower prevalence, incidence and duration of several common childhood morbidities, although surprisingly not for diarrhoea (Bakshi & Gopaldas, 1990). Unfortunately, this trial has only been reported as an abstract, and details of the study design, its execution and results are not available.

One of the recent trials of the impact of vitamin A supplementation on mortality in young children included children aged 6–7 years (Ghana VAST Study Team, 1993). In this large trial in northern Ghana, there was no evidence of a trend by age in the impact on mortality of high-dose vitamin A supplements given every 4 months; in fact, the impact among children aged 72–95 months (a 61 % mortality reduction) was higher (although not significantly higher) than that in any other age group (Ghana VAST Study Team, 1993). It is possible, therefore, that the reductions in mortality associated with vitamin A supplementation may persist throughout childhood and beyond, and be coupled to substantial reductions in severe morbidity from infectious diseases, especially from diarrhoea. Intervention studies are urgently needed to confirm or refute this hypothesis, and to provide guidance for school health programmes, in which there is uncertainty about whether or not to include vitamin A supplementation in their package of interventions.

The potential of dietary interventions to improve vitamin A status

Recent work has thrown into question previous assumptions related to the bioavailability of vitamin A precursors in vegetable foods (de Pee et al. 1995), and their retention in processed and stored foods (Rodriguez-Amaya, 1997). It may well be that the bioavailability of vitamin A from vegetable sources is much lower than had been thought previously. Studies are now underway to investigate this possibility (CE West, personal communication), but such studies are often difficult to design and interpret. The reasons for this are: the enormous variety of vegetables and fruits which exists; the different vitamin A content of local strains of each species, and of the same strain at different stages of maturity; the variable losses through storage, processing and cooking; and the impact on carotenoid bioavailability of other foodstuffs (e.g. oil, phytates) which are eaten at the same time. At the population level, there have been very few studies of the impact of dietary-based interventions on vitamin A status. Such studies are urgently needed to complement the bioavailability studies mentioned previously.

Conclusions

The present review has highlighted seven major challenges which face those of us working in public health and nutrition in developing countries over the next decade:

1. the implementation of effective and sustainable, large-scale interventions to prevent the substantial burden of mortality and severe morbidity which is attributable to vitamin A deficiency in older infants and young children;
2. further studies of the safety and efficacy of vitamin A supplementation in early infancy, and incorporation of appropriate vitamin A interventions targeted at young infants into maternal and child health care programmes, if the results are positive. This may include incorporating vitamin A supplementation into the standard postnatal care of both mothers and neonates and/or administering vitamin A supplements alongside early infant immunizations such as Bacillus Calmette-Guérin, poliomyelitis, and diphtheria–pneumonia–tetanus;
3. studies of the safety and efficacy, in both mother and infant, of vitamin A supplementation in pregnancy, and incorporation of appropriate vitamin A interventions into maternal health programmes, if the results are positive;
4. randomized controlled field trials of the impact of vitamin A supplementation on the transmission and progression of HIV;
5. the completion of a series of current trials of the impact of low-dose vitamin A supplementation on vertical transmission of HIV, and incorporation of vitamin A supplementation into the standard care of HIV-infected pregnant women, if the results of the trials justify this;
6. investigation of the functional importance of vitamin A deficiency in older children and adolescents, and the design and implementation of suitable interventions for both school-going and non-school-going children;
7. studies of the bioavailability of vitamin A precursors in vegetable foods, and of the potential of dietary interventions to improve the vitamin A status of populations.

This list is by no means exhaustive. Further, unexpected challenges will come to light over the next decade, based on the results of the large volume of innovative research which is currently in progress or planned. The international nutrition community must rise to these challenges. Never before have we been armed with such compelling evidence that nutritional interventions have the potential to make a huge impact on the survival and health of poor populations. The greatest challenge of the next decade will be to ensure that this evidence is translated into effective action and, thereby, into a substantial reduction in the burden of ill-health and mortality in vitamin A-deficient populations throughout the developing world.

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