Vitamin A prophylaxis

It has been little more than a decade since the initial observation of the dose dependent relation between the severity of vitamin A deficiency and childhood mortality,1 quickly followed by the publication of a controlled trial in which children of preschool age, randomised to receive large doses of vitamin A every six months, died at only two thirds (or less) the rate of control subjects.2 In the short interval since this trial, an initially sceptical scientific community has declared control of vitamin A deficiency a major international goal3 and potentially one of the most cost effective of all health interventions.4

The story did not begin in the 1980s. A host of animal studies and anecdotal clinical reports during the first third of the century, soon after vitamin A was discovered, suggested a close, potentially causal relation between vitamin A status and morbidity and mortality from infection. These are detailed elsewhere.5

Vitamin A prophylaxis and mortality

For ethical and logistic reasons the observational study6 has never been repeated, though a large number of intervention trials have been carried out. Eight were initially considered to be suitably rigorous for inclusion in an independently commissioned meta-analysis (table 1).7 The results were remarkably similar, particularly given the wide differences in culture, dietary habits, disease patterns, and malnutrition of the populations studied, the differences in study design, and the variation in the potential effectiveness of the strategies used to improve vitamin A status.8-10

On an intent to treat basis, six of the eight studies recorded a statistically significant reduction in mortality among children assigned to receive vitamin A supplements (19 to 54%), even though not all those assigned vitamin A complied with the treatment.8-10

Negative results

Two ‘outlier studies’, in which no reduction in mortality was observed, deserve mention. The Hyderabad trial11 had a series of problems that only became apparent after publication from an exchange of letters to the editor: children were routinely examined and treated for disease each week by specially trained health workers. This may explain why both the treatment and control arms experienced mortality much lower than anticipated. This general reduction in mortality drastically reduced the power of the study to detect an effect attributable to the vitamin A supplement (mean reduction 6%, 95% confidence interval
In addition, the study had a large and differential loss to follow up and low levels of compliance.

The Sudan trial probably did not establish a meaningful difference in vitamin A status between its two study groups. It is likely that the study children were not particularly deficient to begin with: almost half lived in homes with sanitary facilities and piped-in water, hardly representative of the economic status and living conditions of most children in the developing world.

Importantly, the senior authors of both these studies have subsequently supported the value of improving vitamin A status as a means of reducing childhood mortality.4 15

**Infectious morbidity and mortality**

Longitudinal observational data have suggested that vitamin A status can affect the incidence of infectious diseases.4 16 19 Intervention trials, however, have not confirmed a causal relation; instead, improving vitamin A status primarily reduces the severity of infectious episodes, particularly life threatening diarrhoea and measles (table 1).

**Measles**

In the four community based prophylaxis trials in which cause specific mortality was ascertained, mortality from measles was reduced by roughly 50% (table 2).12 14 15 In the one trial which did not arrive at this conclusion,15 the data presented in the published paper clearly prove otherwise (though given the sample size the large clinical difference was not statistically significant). Remarkably, the treatment with high doses of vitamin A of children admitted to hospital with moderate to severe measles reduces mortality to a similar extent,21-25 strongly suggesting that the beneficial impact is secondary to the correction of the underlying vitamin A deficiency and not to a non-specific adjuvant response related to the large dose.9 Treatment with large doses of vitamin A (200 000 IU on two successive days) also reduces the severity and persistence of complications related to measles.22-25

**Diarrhoea**

Children assigned to the vitamin A supplementation arms of the community based mortality trials had one third fewer deaths attributable to diarrhoea than the control subjects (table 2). Community based studies on the effect of supplementation on morbidity support these results: although supplementation did not reduce the incidence of diarrhoea, it did reduce the severity of subsequent diarrhoeal episodes.4 20 The lack of apparent impact on incidence may be real; alternatively, it may reflect an inadequate sample size given the high frequency of trivial diarrhoeal episodes among children in the developing world.8

**Respiratory disease**

Despite evidence for an association between vitamin A deficiency and the prevalence and incidence of respiratory disease,8 14 the prophylaxis trials did not show a consistent impact on death from respiratory disease (table 2). Indeed, it has been suggested that vitamin A supplementation may increase the risk of respiratory infection, though a World Health Organisation Consultative Group, after reviewing all available data, concluded that this was unlikely.26 Some workers have suggested that the apparent contradiction may reflect the reversal of squamous metaplasia of the epili-
We now know, however, that vitamin A regulates the measles among children supplemented with vitamin A, as illustrated by the 50% reduction in mortality from growth.

Apart from infectious disease, vitamin A status appears to play an important part in growth and haemoglobin synthesis. Human data on growth, particularly from controlled intervention trials, are confusing: from no impact at all to a clear-cut protection is evident by the age of 5 months.

Mechanism of action
The protective effects of vitamin A supplementation seem to be entirely related to restoring normal vitamin A status. This, in turn, increases resistance to (severe) infection through at least two mechanisms: the restoration of normally differentiated epithelia, providing a more effective barrier to infection; and up-regulation of immune competence.

For example, children admitted to hospital with severe measles who were randomised to vitamin A supplementation developed a far greater immune response than control subjects. The speed of the protective response, graphically illustrated by the 50% reduction in mortality from measles among children supplemented with vitamin A after admission to hospital, seems at first glance surprising. We now know, however, that vitamin A regulates the expression of at least 300 different genes and that the nasogastric administration of vitamin A to deficient rats results in detectable alterations in gene products within an hour. Hence the dramatic clinical response observed in hospital and field studies has a readily demonstrable biological basis, even if it is only currently partially understood.

Recommendations for prophylaxis
The ultimate goal of prophylaxis is to restore normal vitamin A status to deficient children. The most effective means for accomplishing this urgent task will depend on the vagaries of local culture, the available foods, and the local health system. Ideally, every child (and woman) should receive adequate vitamin A as part of their regular diet. Small daily doses are more efficiently absorbed and stored than large periodic supplements. Unfortunately, the population of those countries in which the problem is most severe and extensive subsist primarily on vegetable diets, containing little, if any, preformed vitamin A (aside from breast milk, which is an excellent source for the young infant). Provitamin A carotenoids found in many fruits and vegetables are inefficiently converted to the active agent and one of the best, most widely available sources of provitamin A carotenoids, dark green leafy vegetables, is commonly eaten in only small amounts, if at all, by young children.

Many wealthier countries rid themselves of the problem through the fortification of dietary staples, particularly margarine and bread. Fortification of sugar has proved to be an effective approach for dramatically reducing the prevalence and severity of vitamin A deficiency in Guatemala and is now being instituted in a number of other Latin American countries. Where the problem is most severe, however, particularly in Africa and Asia (India, Bangladesh, Pakistan, Indonesia, and the Philippines), periodic supplementation of every child once every three to six months (100,000 IU at less than 1 year of age; 200,000 IU for older children) is recommended. Children at special risk (for example severe protein energy malnutrition, chronic diarrhoea, repeated respiratory infection) are provided with an additional dose if they have not received routine prophylaxis within the past month. Measles is treated with a 200,000 IU supplement on two successive days as a medical emergency. To boost maternal stores and the amount of vitamin A in breast milk, women are advised to receive 200,000 IU within four to six weeks of delivery.

Over 60 countries are now planning, or have instituted, programmes to control vitamin A deficiency. Periodic supplementation as a special endeavour generally achieves sustainable coverage rates of 40–60%, though some countries (and most demonstration projects) attain far higher levels. In Indonesia, where distribution has been integrated into a burgeoning health service system and mass media has been used to educate the public and change dietary patterns, a 90% reduction in the prevalence of overt deficiency has been achieved.

Unquestionably, the major challenge remains the design and implementation of effective population based intervention programmes.

Conclusions
Although there is a great deal more to be learnt about the value of vitamin A status and childhood morbidity and mortality, there is no longer any credible doubt that deficiency is inimical to optimum health and survival. These effects begin to occur even before the appearance of ocular disease (‘xerophthalmia’).

Key messages
- Vitamin A deficiency increases the severity of and mortality from measles and diarrhoea
- Increased infectious morbidity and mortality is apparent even before the appearance of xerophthalmia
- Improving the vitamin A status of deficient children aged 6 months to 6 years can dramatically reduce their morbidity and mortality from infection
- Prompt administration of large doses of vitamin A to children with moderate to severe measles, particularly if they may be vitamin A deficient, can reduce individual mortality by 50% and prevent or moderate the severity of complications
Routine male neonatal circumcision and risk of infection with HIV-1 and other sexually transmitted diseases

Routine male neonatal circumcision as policy excites strong medical opinions both for and against. In the USA over 70% of all males have been circumcised while the UK’s national survey of sexual attitudes and lifestyles found in 1990/1 that 21% of adult males (aged 16–59 years) reported having been circumcised. The percentage was 13% among those aged 16–24 years but 32% for those 45–59 years indicating that British rates have declined recently, as they may also have done in the USA. Circumcision rates are intermediate in Canada but very low in the Nordic countries. However when weighed against the irreducible procedure of uncertain effectiveness, they are best explained on grounds of medico/social culture and fashion, as is the case for some other elective surgical procedures of uncertain effectiveness.

The case for routine male circumcision has rested most firmly on the observation that rates of infant urinary tract infection and adult penile cancer are lower in circumcised males. However when weighed against the irreducible complication rates and costs of the procedure, these are thought insufficient grounds to recommend routine circumcision. Recently added is the observation that circumcised males seem less likely to acquire infection with HIV-1, or other sexually transmitted diseases (STDs).

Four explanations have been suggested: firstly that the exposed glans penis may develop a protective layer of keratin (sometimes referred to as a ‘natural condom’); secondly that the foreskin may be especially susceptible to minor balanitis and trauma during intercourse, allowing movement of HIV-1 through the dermatological barrier; thirdly that the warm microclimate under the foreskin may permit micro-organism survival increasing exposure to potential infections; and fourthly that lack of circumcision may predispose to a coinfection with other STDs that are known to facilitate heterosexual HIV-1 transmission.

Many observational studies provide data relevant to the relationship of HIV-1 infection and circumcision, and these have been the subject of two reviews and one meta-analysis of multiple studies within one region of an African country. The studies have been of types described as cross sectional or retrospective (observing the relative risk of acquiring HIV-1 infected among circumcised and uncircumcised men, or their female partners), prospective observational (observing the risk of becoming HIV-1 infected among circumcised and uncircumcised men), and ecological (comparing the association between circumcision status and prevalence of HIV-1 in different populations). Heterosexual partnership studies have also looked at sexual partners of men or women diagnosed HIV-1 infected in relation to the male’s circumcision status. The reviews note the data’s limitations. Most were gathered in African or other developing countries where incidence and prevalence of HIV-1 was sufficiently high to investigate possible effects of circumcision. None of the studies was experimental (no-one has dared ‘trial’ circumcision), nor were they primarily designed to investigate the HIV-1 and circumcision relationship. Therefore most are subject to confounding factors and many lack optimal statistical power. That said most, but not all, the African studies found the risk of HIV-1 infection was reduced among circumcised men. The reductions were modified by location, social status, religion, and background HIV-1
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