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VITAMIN A DEFICIENCY AND DIARRHOEA: A Review of Interrelationships and their Implications for the Control of Xerophthalmia and Diarrhoea

Richard G. Feachem

Department of Tropical Hygiene
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT

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1. INTRODUCTION

The purpose of this review is to explore the relationships between vitamin A deficiency and diarrhoea among young children. The major focus is on the implications of these relationships for policies towards the control of childhood diarrhoea and xerophthalmia. The possible benefits of giving vitamin A to children with diarrhoea are also considered. A recent monograph (SOMMER, 1982) and epidemiological overview (TIELSCH and SOMMER, 1984) on xerophthalmia provide a comprehensive background to this, more focused, review. The benefits and risks of vitamin A supplementation for pregnant and lactating women are not addressed here, but have been comprehensively reviewed by UNDERWOOD and WALLINGFORD (1980). This review is a part of a series of reviews on interventions for the control of diarrhoea among children under 5 years of age in developing countries (FEACHEM, 1986).

2. THE FREQUENCY OF XEROPHTHALMIA IN DEVELOPING COUNTRIES

Information about the person- and place-specific incidence and prevalence rates and sequelae of xerophthalmia is scarce. Global and regional gross estimates are used in the promotional literature (for instance, 10 million new childhood xerophthalmia cases per year world-wide with over 500 000 resulting in blindness; PATH, 1985) but these estimates derive from extrapolation from limited community data and are of limited value in the rigorous analysis of the impacts of interventions.

Table 1 shows the WHO classification scheme for the various forms of xerophthalmia. This classification is now widely adopted and will be used in this review. The categories nightblindness (XN), conjunctival xerosis (X1A) and Bitot's spots (X1B) are sometimes grouped under the term "mild xerophthalmia"; corneal xerosis (X2) and corneal ulceration (X3A/B) are sometimes described as "active corneal xerophthalmia"; and XN, X1B and X3A/B are sometimes referred to as "active xerophthalmia". In practice, X1A may be excluded from surveys of mild xerophthalmia because its poor diagnostic specificity makes it an inadequate measure of vitamin A deficiency.

Table 1 also shows the prevalence criteria for determining whether xerophthalmia and vitamin A deficiency are a significant public health problem in a given country or area. On the basis of these criteria, a list of countries, from all parts of the developing world where vitamin A deficiency is a significant public health problem, has been compiled. The list is growing as new survey data become available. The low level of the prevalence rate criteria shown in Table 1 is suggestive of the problems of targeting appropriate prophylactic measures.

The most commonly reported frequency data are prevalence rates of either mild xerophthalmia (XN, X1A or X1B) or active corneal xerophthalmia (X2 or X3) in pre-school aged children. Prevalence rates for mild xerophthalmia in pre-school aged children are seldom over 10%, and the range of 5-10% represents the worst end of the spectrum of frequency (TIELSCH and SOMMER, 1984). Prevalence rates of well under 1% for mild xerophthalmia among pre-school aged children are reported from many countries. Marked seasonal variations in prevalence rates have been reported (SINHA and BANG, 1976). Typically, prevalence rates of active corneal xerophthalmia are well below 0.5% among pre-school aged children. Most surveys report that mild xerophthalmia is significantly more common in boys than in girls (COHEN *et al.*, 1985).

The most detailed measurements of incidence and prevalence rates are those reported from Indonesia by SOMMER *et al.* (1981). The incidence rate of active corneal

Table 1.

Classification of forms of xerophthalmia and criteria for designation of a significant public health problem.*

Classification code	Clinical description	Prevalence rates among preschool children indicating significant public health problem
XN	Nightblindness	>1%
X1A	Conjunctival xerosis	-
X1B	Bitot's spots	>0.5%
X2	Corneal xerosis	} >0.01%
X3A	Corneal ulceration/keratomalacia involving less than 1/3 of the corneal surface	
X3B	Corneal ulceration/keratomalacia involving \geq 1/3 of the corneal surface	
XS	Corneal scar	>0.05%
XF	Xerophthalmic fundus	-
Biochemical criterion:	Plasma vitamin A \leq 0.35 μ mol/l (10 μ g/dl)	>5%

*From WHO (1982)

xerophthalmia (X2 or X3) in children aged 0-6 years in 6 villages in West Java was 0.5/100 each year. The incidence rate of mild xerophthalmia among the same children was 9/100 each year, with a spontaneous cure rate of about 50% (TIELSCH and SOMMER, 1984). Combining this information with the fact that about one-third of the mild xerophthalmia cases in this study had a history of previous mild xerophthalmia, SOMMER (1982) estimated that some 36% of these children experience mild xerophthalmia between birth and 6 years of age. The prevalence rates of active corneal xerophthalmia in pre-school aged children were 0.12% in West Java and 0.06% nationwide. In the same age group, a more recent survey in Sumatra (SOMMER *et al.*, 1986) found a prevalence rate of active xerophthalmia (XN, X1B or X3) of around 2%.

The only comparable data from Africa are those reported from the Lower Shire Valley in Malawi by TIELSCH *et al.* (1986). A total of 5441 children under 6 years of age living in 71 villages were surveyed. The prevalence rate of all signs of active xerophthalmia (XN, X1A, X1B, X2, or X3) was 3.9%. Prevalence rates rose with age to a maximum of 8.2% among those aged 48-71 months.

Few adequate data on the progression of various forms of xerophthalmia to spontaneous cure or to various degrees of chronic visual impairment, have been located. There are obvious ethical obstacles to the collection of data of this type. SOMMER *et al.* (1981) estimate that one-third to one-half of active corneal xerophthalmia cases result in bilateral blindness.

3. THE INTERRELATIONSHIPS AMONG VITAMIN A DEFICIENCY, XEROPHTHALMIA, MORTALITY AND DIARRHOEA

In understanding the interrelationships between these conditions 3 types of information are relevant. First are the well-established causal relationships that derive from an accumulation of laboratory, clinical, and epidemiological evidence. Second are certain associations observed during epidemiological studies in developing countries. Third are hypotheses about mechanisms for causality that come from clinical studies and work with laboratory animals.

Vitamin A deficiency results primarily from inadequate dietary intake of vitamin A. Vitamin A deficiency is the cause of xerophthalmia. This review concentrates on the evidence linking vitamin A deficiency with risk of disease or death from diarrhoea, and pays special attention to community-based epidemiological studies.

Animal studies are an important background to the epidemiological discussions in this review. Such studies have been reviewed elsewhere (MCLAREN, 1980; SOMMER, 1982). In summary, they show that adequacy of vitamin A intake is a determinant of growth, survival, resistance to infection, maintenance of epithelial integrity, and both humoral and cell-mediated immune competence, in a wide variety of laboratory animals, including many small mammals and fowl. Evidence of these relationships in humans is scarcer.

3.1 Is diarrhoea a risk factor for xerophthalmia?

There is clear evidence in the literature of decreased vitamin A absorption associated with various infections; especially diarrhoeas, intestinal helminthiases, and respiratory infections. This literature is not reviewed here but is reviewed in part by WEST and SOMMER (1984). In addition, infections may decrease vitamin A intake owing to anorexia. In children whose dietary vitamin A intake is low and whose body stores are marginal, it is plausible that repeated respiratory or intestinal infections may precipitate vitamin A deficiency and xerophthalmia (see, for instance, SIVAKUMAR and REDDY, 1972).

It is widely believed, therefore, that diarrhoea, especially repeated and prolonged diarrhoea, is a risk factor for vitamin A deficiency and xerophthalmia in children whose liver stores are low. Two types of evidence would help to confirm this belief; first data from observational studies showing that children with more frequent or prolonged diarrhoea have greater risk of xerophthalmia and, second, data from intervention studies showing that a reduction in diarrhoea incidence or duration is followed by a reduction in xerophthalmia. Firm evidence of either type has not, thus far, been published.

A high proportion (100% and 86%, respectively) of children in Bangladesh with xerophthalmia had diarrhoea in the month preceding the survey (COHEN *et al.*, 1985) or the month preceding the onset of the eye lesions (KHAN *et al.*, 1984). Control data were not reported and the authors appear to reach premature conclusions concerning the causative role of diarrhoea in xerophthalmia. Cohen *et al.* state "diarrhoea is, therefore, an important precipitant of severe lesions immediately threatening sight", and both sets of authors conclude that diarrhoea control might substantially reduce xerophthalmia. In a case-control study in Nepal, cases of xerophthalmia were matched with controls by age, sex, season and village, but not by socio-economic confounders (BRILLIANT *et al.*, 1985). Cases were nearly 30 times more likely than controls to have had diarrhoea in the previous month.

These studies in Bangladesh and Nepal, like several others including that of PATWARDHAN (1969), report an association in person and time between diarrhoea and xerophthalmia that could also be explained by confounding or by vitamin A deficiency being a cause of diarrhoea (TIELSCH and SOMMER, 1984). In support of

confounding, Cohen *et al.* found that both wealth and maternal education were independently and significantly associated with reduced risk of xerophthalmia. In Malawi, poorly educated and poorer families were more likely to have children with active xerophthalmia (TIELSCH *et al.*, 1986), and these socio-economic factors are likely to exert an independent influence on the risk of diarrhoea.

STOLL *et al.* (1985) found that diarrhoea patients (children aged 1-10 years in Dhaka, Bangladesh) with night blindness were significantly more likely to have prolonged and dysenteric disease (caused especially by *Shigella* and *Entamoeba histolytica*) than similar patients without night blindness. Stoll *et al.* conclude that these findings are more consistent with diarrhoea as a risk factor for xerophthalmia than vice versa. Confounding is, however, also suggested by the findings of Stoll *et al.*, since the diarrhoea patients with night blindness were significantly more likely to be <80% of reference weight-for-height than similar patients without night blindness.

A case-control study of children under 14 years of age in slum areas of Dhaka, Bangladesh (STANTON *et al.*, 1986) showed an association between protracted diarrhoea (more than 14 days of diarrhoea in the past month) and prevalent mild xerophthalmia (night blindness with or without conjunctival xerosis and/or Bitot's spots). This association (odds ratio 4, $0.05 < P < 0.1$) was controlled for gender, age and number of children in the family, following the exploration of a range of potential confounding variables. These results are presented in the context of a study of risk factors for mild xerophthalmia, but the reverse hypothesis (mild xerophthalmia as a risk factor for protracted diarrhoea) is also plausible.

This association between diarrhoea and xerophthalmia was not found in a hospital-based study in Bangladesh (BROWN *et al.*, 1979), or in community studies in Cebu, Philippines (SOLON *et al.*, 1978) and Malawi (TIELSCH *et al.* 1986). The most detailed attempt to unravel this relationship is the study in West Java reported by SOMMER *et al.* (1984). Their findings are more suggestive of xerophthalmia as a risk factor for diarrhoea than of diarrhoea as a risk factor for xerophthalmia or of both being caused by underlying poverty-related confounding factors. No evidence of the second type, from intervention studies which examined the effect on xerophthalmia of controlling diarrhoea, has been located.

3.2 Is vitamin A deficiency a risk factor for diarrhoea?

Clinical and laboratory studies suggest that vitamin A deficiency may increase the risk of bacterial colonization of the respiratory, gastrointestinal, and genitourinary tracts and may also interfere with immune competence. These findings suggest the hypothesis that vitamin A deficiency may predispose to illness and death from certain infectious diseases. Once again, both observational and intervention studies might throw light on this hypothesis.

A prospective study of 4600 children, aged 0-6 years at entry, was conducted in 6 villages in West Java, Indonesia, during 1977-78 (SOMMER *et al.*, 1983). Children were examined at 3-monthly intervals for 18 months. The mortality rate was 4 times higher among children with mild xerophthalmia (night blindness and/or Bitot's spots) at the examination before their death, than among those without. The risk of death increased with the severity of eye disease, being 3 times higher for those with night blindness only, 7 times higher for those with Bitot's spots only, and 9 times higher for those with both conditions. The relative risks of mortality by severity of mild xerophthalmia remained broadly similar when the data were controlled for respiratory infection, age, and weight-for-height. DIBLEY *et al.* (1983) suggested that this association between mild xerophthalmia and mortality might have been caused by the relationship of stunting (low height-for-age) with both of these variables. They point out that the use of wasting (low weight-for-height) by Sommer *et al.* to control for the confounding effects of nutritional status may have been inappropriate since

"wasting is not associated with mild vitamin A deficiency". SOMMER (1984) replied with arguments to show that the difference in height-for-age between the mildly xerophthalmic and non-xerophthalmic children could not have accounted for a difference in relative risk of mortality of greater than 3.

The same Javanese data set as reported by SOMMER *et al.* (1983) was analysed to explore the association between mild vitamin A deficiency and risk of diarrhoea and respiratory disease (SOMMER *et al.*, 1984). Children (0-6 years) with mild xerophthalmia (night blindness and/or Bitot's spots) at the start and end of the 3-month interval between examinations were 3 times more likely to report diarrhoea during the 1 month preceding the second examination than children with no xerophthalmia at the start or end of the 3-month interval. This relationship was maintained when the data were stratified by weight-for-height. Among non-xerophthalmic children, the risk of diarrhoea was independent of nutritional status. Among mildly xerophthalmic children, diarrhoea incidence rates were 50% greater among those less than 90% of standard weight-for-height than among others. Diarrhoea rates among well-nourished, mildly-xerophthalmic children were significantly higher than among poorly nourished children with normal eyes, although it should be noted that few study subjects were severely malnourished (<4% of children had weight-for-height <80% of standard). No other observational studies that bear directly on this hypothesis have been located.

Relevant intervention studies are those which controlled vitamin A deficiency and measured the impact on diarrhoea. One such study has been located (SINHA, 1976), in which oral administration of 100 000 IU of vitamin A every 4 months to children in rural West Bengal failed to produce a detectable reduction in diarrhoea rates. (A full report of this study has not been seen by the reviewer and it may be that sample sizes were too small to detect the expected impact on diarrhoea rates.)

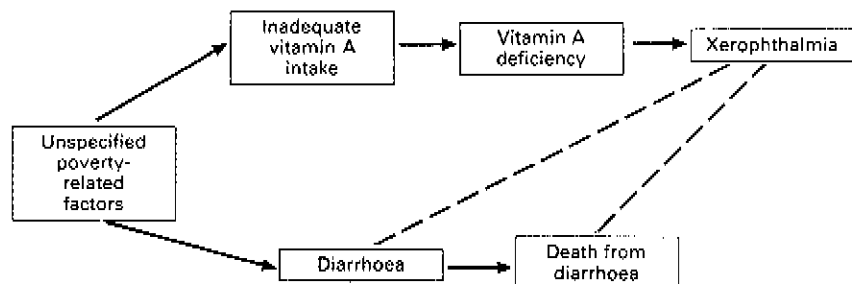
An intervention study of great interest, although one that did not measure diarrhoea morbidity or mortality as outcome variables, is the randomized, controlled, community trial on the effect of vitamin A supplementation on childhood mortality in Sumatra (SOMMER *et al.*, 1986). Overall mortality rates among children aged 12-71 months were 34% lower in the 229 villages receiving vitamin A supplementation (2 capsules of 200 000 IU per year) than in the 221 control villages. The impact on mortality rates for specific ages varied markedly: from an apparent excess of mortality in the supplemented villages among children aged 36-47 months, to a decrement of 72% among children aged 60-71 months. Diarrhoea, or other cause-specific mortality rates were not separately reported. Differences in overall mortality rates between supplemented and control villages in the first 2 years of life, the period when diarrhoea mortality rates are highest in other studies, were 17% for infants (a group not targeted for supplementation but 82% of whom, nonetheless, received at least one vitamin A capsule) and 15% for children aged 12-23 months.

Three letters to the *Lancet* (COSTELLO, 1986; GRAY, 1986; MARTINEZ *et al.*, 1986) cast serious doubt on the conclusion reached by SOMMER *et al.* (1986) that "supplements given to vitamin A deficient populations may decrease mortality by as much as 34%". Causes for concern included the lack of data on baseline mortality rates; atypical age structure and age-specific mortality rates suggestive of measurement error; the higher baseline prevalences of xerophthalmia, diarrhoea, stunting and wasting in the control compared with supplemented villages; a lack of placebo and of blinding; and certain shortcomings in analysis. A reply to these criticisms was published (SOMMER and WEST, 1986). COHEN (1986) and GOPALAN (1986) published further critiques, again casting serious doubt on the claim that the vitamin A supplementation *per se* caused a 34% decrease in mortality rate.

3.3 Modelling the interrelationships

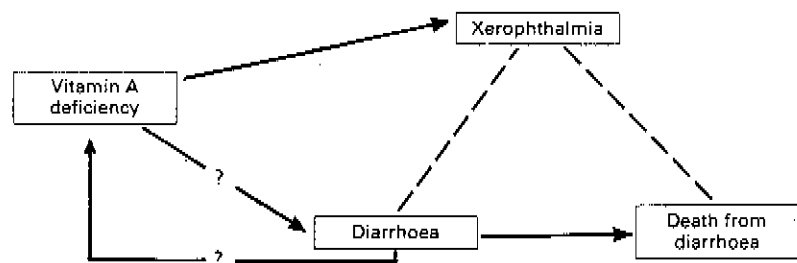
This limited information can be used to construct models of the interrelationships

among vitamin A deficiency, xerophthalmia, mortality, and diarrhoea. First, a conservative model, Model 1, which does not accept that any causal relationship has been demonstrated in either direction between vitamin A deficiency and diarrhoea. Model 1 can be portrayed as follows:



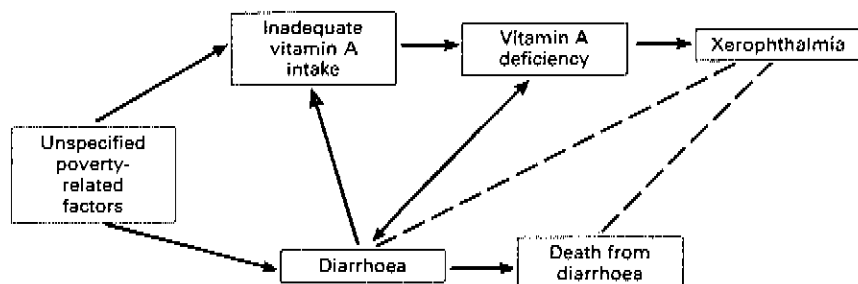
Unbroken lines indicate putative causal relationships with arrows showing a direction from cause to effect. Broken lines indicate observed associations which result from the effect of other variables in the model and are not causal in nature. Thus, in Model 1, the observed association between xerophthalmia and increased risk of diarrhoea and diarrhoea death is due entirely to the confounding influence of the poverty-related factors in the model. This model, therefore, predicts that reducing xerophthalmia by vitamin A supplementation will cause no change in diarrhoea rates and that reducing diarrhoea (by latrine construction, for instance) will cause no change in the prevalence of xerophthalmia.

Second, a model can be proposed that accepts either that diarrhoea predisposes to vitamin A deficiency, or vice versa, or both. This can be called Model 2 and is portrayed thus:



Broken and unbroken lines have the same meanings as before. SOMMER *et al.* (1983, 1984) found that the associations between mild xerophthalmia and both diarrhoea and death held good when the data were stratified for nutritional status, a variable likely to be highly correlated with the unspecified poverty-related factors in Model 1. This suggests that, at least in some circumstances, Model 2 may be correct. Model 2 predicts that either vitamin A supplementation will reduce diarrhoea and death, or that diarrhoea control will reduce xerophthalmia, or both, depending on which of the arrows with ? actually applies. The major reduction in mortality rate, some of which may have been due to a reduction in diarrhoea mortality, said to have been caused by vitamin A supplementation in Sumatra (SOMMER *et al.*, 1986) suggests that the arrow from vitamin A deficiency to diarrhoea may be operative in this community.

On the basis of all the fragmentary evidence, this reviewer believes that the best working model at this time is the combination of Model 1 and Model 2, dubbed Model 3 and depicted below:



The relative contribution of the various causal pathways is unknown but is of considerable practical importance in determining the likely impact of specific interventions. The vitamin A supplementation trial in Sumatra was said to have reduced mortality in children aged 1-5 years by 34% (SOMMER *et al.*, 1986).¹ This reduction suggests that vitamin A deficiency in the community is the "cause" of one-third of deaths in this age group and, possibly, of a similar proportion of diarrhoea deaths. This finding is at odds with much of the conventional wisdom on the aetiology of childhood death in developing countries. A second generation of vitamin A supplementation trials is being planned to determine whether the results obtained in Sumatra can be replicated in other communities.

4. POLICY IMPLICATIONS

The policy implications of the foregoing may be addressed by posing and attempting to answer 3 questions.

4.1 Will the control of vitamin A deficiency reduce diarrhoea morbidity or mortality rates?

If vitamin A deficiency predisposes to diarrhoea, the answer is "yes", if not, the answer is "no". The observational studies of SOMMER *et al.* (1983, 1984) suggest that vitamin A deficiency, as expressed by mild xerophthalmia, predisposes to increased diarrhoea incidence (relative risk: 3) and increased mortality from all causes (relative risk: 4), among pre-school aged children in West Java. Two intervention studies have further explored this relationship. SINHA (1976) found that vitamin A supplementation did not reduce diarrhoea rates in West Bengal, but this study was not designed primarily to detect such an impact and sample sizes may have been too small. SOMMER *et al.* (1986) claim that vitamin A supplementation decreased mortality from all causes by 34% among children aged 1-5 years in Sumatra. This reported impact is strikingly high and merits further discussion.

¹Subsequent dose-related analyses of these data suggest that the true impact of vitamin A supplementation on mortality was even greater than 34% (SOMMER, personal communication). This finding must be viewed in the light of the reservations concerning this study expressed by GOPALAN (1986) and others (see page R6).

Xerophthalmia is caused by vitamin A deficiency and therefore children with xerophthalmia have, or have had, vitamin A deficiency. The relationship between xerophthalmia and serum vitamin A levels in children is not closely defined but some general associations are discernible. Above a serum vitamin A level of 20 $\mu\text{g}/\text{dl}$, xerophthalmia is uncommon and it becomes increasingly common as serum concentrations of vitamin A fall below this figure (SOMMER, 1982). Active corneal xerophthalmia is found mostly in children with serum vitamin A levels below 15 $\mu\text{g}/\text{dl}$. However, there are many children with low serum concentrations of vitamin A who do not manifest signs of clinical xerophthalmia. In the study in West Java, SOMMER (1982) found that over 9% of children had serum vitamin A concentrations below 10 $\mu\text{g}/\text{dl}$, but the prevalence rate of Bitot's spots was only 0.8%.

In most surveys, the prevalence rate of vitamin A deficiency can only be estimated by the prevalence rate of xerophthalmia. The latter, however, may be much lower than the former. It is possible that there are many children with increased susceptibility to infection (due to damage to the epithelium and/or impairment of immune competence) caused by vitamin A deficiency who do not have xerophthalmia. If this is true, any estimation of the impacts of vitamin A supplementation on morbidity or mortality based on the prevalence rates of xerophthalmia will underestimate, perhaps greatly, such impacts.

With these thoughts in mind we may examine the 34% mortality reduction claimed by SOMMER *et al.* (1986). Suppose, first, that the prevalence rate of exposure to the risk factor is well estimated by the prevalence rate of active xerophthalmia. The prevalence rates of active xerophthalmia (XN, X1B, X3) were 1.9% and 2.3% at the baseline survey and declined to 0.3% and 1.2% at the repeat survey 1 year later, in the supplemented and control villages respectively. Assuming that the prevalence changes occurred instantaneously following the baseline survey (a conservative assumption for this purpose because it overestimates the difference in the prevalence rates of xerophthalmia between the supplemented and control villages) then, during the year of mortality rate measurement, the control villages had an excess prevalence of xerophthalmia of 0.9% (1.2% - 0.3%) compared with the supplemented villages. (Assuming that the xerophthalmia prevalence declined linearly through time between the baseline and the repeat surveys, the average excess rate of xerophthalmia in the control community is only 0.65%.) Then a 34% reduction in mortality rate due to a reduction in the prevalence rate of exposure from 1.2% to 0.3% implies a relative risk of death among children with active xerophthalmia of 70. This relative risk is almost 17 times higher than that found in West Java (SOMMER *et al.*, 1983). Suppose, second, that the relative risk of death is really 4, as found in West Java. A 34% reduction in mortality rate would be achieved if the prevalence of exposure to the risk factor in the control villages, as indicated by the prevalence rate of active xerophthalmia at the repeat survey, was in fact 18%, not 1.2%. Under this latter set of assumptions there are 1.2% of children with active xerophthalmia and a relative risk of death of 4, together with, either a further 17% of children with the same relative risk of death due to vitamin A deficiency but lacking eye signs, or a further proportion of more than 17% of children with milder vitamin A deficiency, no eye signs and relative risk of death of less than 4 but more than 1.

These calculations illustrate the possibility that the prevalence rate of children exposed to some increased risk of death due to vitamin A deficiency is greater than either the point or period prevalence rates of xerophthalmia. In other words, there may be children at increased risk of death due to vitamin A deficiency who are entirely undetectable by ophthalmic survey.

The report on the Sumatra mortality study (SOMMER *et al.*, 1986) gives no indication of cause of death in supplemented and control villages. For all children in the Sumatra study (ages 1-5 years), the mortality rate was 34% lower in the villages receiving vitamin A supplementation, but there were great, and unexplained variations with age. The difference was greatest (72% lower) in the sixth year of life when diarrhoea mortality rates are very low in most communities. Differences were 17%

and 15% in the first 2 years of life, respectively, when diarrhoea mortality rates are at their peak. Proportional mortality due to diarrhoea remains high throughout childhood, however, being responsible for about one-third of all deaths. It is likely, therefore, that there was a major difference in diarrhoea mortality rates between the supplemented and control villages.

Returning to the question posed at the head of this section, the answer is that we do not know but that the balance of evidence points towards a "yes" answer, at least for diarrhoea mortality. Further studies are urgently needed to define the magnitude of any reductions in diarrhoea morbidity or mortality rates that can be achieved through vitamin A supplementation. Such studies should pay special attention to investigating excess risk of diarrhoea due to vitamin A deficiency in children without eye signs and should seek to develop measures² of such deficiency states which can be used in community surveys.

4.2 Will the control of diarrhoea reduce the prevalence of xerophthalmia?

If diarrhoea precipitates xerophthalmia the answer is "yes", if not, the answer is "no". Studies on malabsorption of vitamin A due to intestinal infections and epidemiological evidence reviewed in section 3.1, suggest "perhaps". The evidence is weak, however, and further observational studies are required.

The priority to be attached to such studies may be low for the following reasons. First, diarrhoeal disease control is being pursued vigorously for other reasons and the discovery that it may also have benefits to the prevention of vitamin A deficiency may not greatly affect current policies or investment levels. Second, the prevention of vitamin A deficiency will surely rest on the 3 currently established approaches of vitamin A supplementation, food fortification, and community education coupled with self-sufficiency in foods rich in vitamin A. Diarrhoea control will never be a primary strategy for the prevention of vitamin A deficiency. Xerophthalmia has been successfully controlled by periodic massive dosing with vitamin A, in the absence of any diarrhoea control measures (VIJAYARAGHAVAN *et al.*, 1984).

4.3 Will the administration of vitamin A to children with diarrhoea reduce the prevalence of vitamin A deficiency or assist in the treatment or control of xerophthalmia or diarrhoea?

The 3 methods for preventing vitamin A deficiency that are normally advocated are the periodic distribution of massive oral doses of vitamin A, (200 000 IU every 4-6 months is normally recommended), the fortification of staple foods (such as sugar) with vitamin A, and nutrition education to encourage adequate consumption of locally-available foods which are rich in vitamin A. Periodic massive dosing has been successful when coverage is high (>65%) and has been comprehensively reviewed by WEST and SOMMER (1984).

The most commonly articulated objection to giving vitamin A to children with diarrhoea is that it will be poorly absorbed. Most of the literature shows that, indeed, absorption is considerably reduced during diarrhoea, perhaps to levels of only 30% of a large dose (NAGER, 1979; WEST and SOMMER, 1984). Absorption of both water-

²A debate concerning appropriate measures of vitamin A deficiency is underway. Serum retinol levels are still widely used (see Table 1), but are homeostatically maintained at the expense of liver stores and thus bear no clear relationship to vitamin A status except in extreme deficiency states. The relative dose response (RDR) test has attracted attention recently, but its interpretation and application in epidemiological investigations remain uncertain (FLORES *et al.*, 1985). Conjunctival impression cytology is under evaluation (SOMMER *et al.*, 1985; WITTPENN *et al.*, 1986), but would appear to be too sophisticated for large-scale survey work.

miscible and oil-soluble vitamin A is impaired, but the former is better absorbed than the latter. The practical question is whether, despite lowered absorption, a sufficient proportion of oral vitamin A is absorbed during diarrhoea to prevent or correct vitamin A deficiency. For comparison, an oral dose of 200 000 IU given to children without diarrhoea appears to prevent mild xerophthalmia for 4-6 months (WEST and SOMMER, 1984).

SOMMER *et al.* (1980) successfully treated xerophthalmia in children with acute diarrhoea by oil-soluble, oral vitamin A (200 000 IU on each of 2 consecutive days). This regimen was as effective as intramuscular administration.³ MOLLIA *et al.* (1983) produced significant increases in mean serum vitamin A, and improvement or cure of xerophthalmia, in children with acute diarrhoea and dehydration by giving 7500 IU/kg of water-miscible vitamin A by mouth. REDDY *et al.* (1986) found that over 70% of 100 000 IU of oral, water-miscible vitamin A given in oral rehydration salts (ORS) or water to children with acute diarrhoea was absorbed. Serum vitamin A levels rose significantly. This evidence suggests that, despite lowered absorption, clinically significant amounts of oral vitamin A can be absorbed during acute diarrhoea.

Assuming this to be correct, one may consider the 4 possible reasons for administering vitamin A to children with diarrhoea: to contribute to the community-wide control of vitamin A deficiency; to avert subsequent xerophthalmia in the children under treatment; to influence the course of the current diarrhoea episode; or to reduce the risk of subsequent diarrhoea in the children under treatment. The possible effect on vitamin A deficiency and xerophthalmia will be considered first. Most children have diarrhoea each year and many children have several episodes. A proportion of these episodes, especially the more severe episodes, receive treatment from a health worker. In high risk areas, perhaps 30-40% of children will experience xerophthalmia before 6 years of age. It is not known whether these children are also those most likely to experience severe diarrhoea or dysentery, and thus be likely to receive treatment from a health worker. Given the close interrelationships among the poverty-related determinants of nutritional deficiencies and infections, it is likely that children at special risk of xerophthalmia are also at special risk of diarrhoea and dysentery, the latter group being somewhat larger than the former. In an ideal situation in which all episodes of severe diarrhoea and dysentery in children are being treated by a health worker, if vitamin A were given at the time of treatment it would probably reach most children at risk of xerophthalmia and many other children besides.

To prevent xerophthalmia, children over 1 year, with marginal intakes and body stores, would have to ingest not less than about 400 000 IU of vitamin A per year in not less than 2 regularly spaced doses. It is most unlikely that this could be achieved entirely through vitamin A administration at the time of diarrhoea treatment. First, there will be children at risk of xerophthalmia who do not have 2 episodes of diarrhoea per year. Second, there will be many children with diarrhoea who do not receive treatment from a health worker; they may instead be treated by home-prepared oral fluids as advocated in many national diarrhoea control programmes. It is more plausible that vitamin A administration to children with diarrhoea would act to reinforce other vitamin A supplementation activities in the same community.

The administration of vitamin A to children with diarrhoea could thus be conceived as a contribution to the overall task of controlling vitamin A deficiency and its consequences in the community. Alternatively, it could be perceived as a therapeutic response to a putative, clinical consequence of severe diarrhoea; namely the precipitation of frank xerophthalmia in children with marginal body stores of vitamin A. The evidence that such precipitation occurs is weak even in children not receiving appropriate therapy. There is no evidence that acute diarrhoea may precipitate

³For further discussion of this study see NALIN and RUSSEL (1980) and SOMMER (1980).

xerophthalmia in children receiving oral rehydration and appropriate nutritional management (excluding specific vitamin A supplementation).

Separately from the above, the effectiveness of vitamin A administration during childhood diarrhoea as a means of controlling diarrhoea may be considered. A relatively small proportion of children have repeated episodes of severe diarrhoea, and it is these children who are most likely to suffer from serious nutritional consequences or to die. If vitamin A deficiency is a risk factor for these multiple attacks of diarrhoea, then treating severe diarrhoea cases with vitamin A, in addition to the conventional treatments, may reduce their subsequent risk of diarrhoea-associated morbidity or mortality. Such treatment may also reduce the severity or duration of the current episode. Studies to investigate this possibility are being planned.

It is not possible to advocate a clear policy towards administration of vitamin A to children with diarrhoea on the basis of current evidence. If the purpose is to contribute to the overall reduction of vitamin A deficiency in the community, the cost-effectiveness of administering vitamin A to children with diarrhoea, in comparison with other methods of administration, must be assessed in areas with different frequencies of vitamin A deficiency and diarrhoea. Some information on the cost-effectiveness of other means of preventing vitamin A deficiency is available (ARROYAVE *et al.*, 1979; WEST and SOMMER, 1984). If, on the other hand, the purpose is to treat a clinical consequence of diarrhoea, then the presence of this consequence must be demonstrated, as must the efficacy and cost-effectiveness of the treatment. Similarly, it remains to be demonstrated that children treated with vitamin A during severe episodes of diarrhoea are protected from subsequent morbidity or mortality relative to children receiving only conventional treatment.

If, for any of the above reasons, it is decided to administer vitamin A to children with diarrhoea, the method of administration must be selected. The first option is that health workers give a vitamin A capsule to each diarrhoea case which they treat. This policy allows the health worker to adjust the dose in accordance with the child's age and previous vitamin A supplementation. A second option is to attach a capsule of vitamin A to every packet of ORS. This policy may lead to over-dosing if many ORS packets are needed to treat a single child (an especially serious concern for young infants), or under-dosing if the child does not have access to, or does not need, ORS. It does, however, make vitamin A supplementation available to children who are treated by their mothers at home with purchased, or previously supplied, ORS and who are not brought to a health worker. The third option is to fortify the ORS powder with vitamin A. This option has advantages with respect to access similar to the previous option but is, if anything, more problematical with regard to control of the vitamin A dose.

Both the options that link the vitamin A directly to ORS, either by attaching a capsule to the packet or by fortifying the ORS, pose special problems of targeting. ORS is used by many people other than children and by many communities and countries where vitamin A deficiency is not a problem. This fact could lead to considerable expenditure on unnecessary vitamin A supplementation; especially since, although the ORS may be locally manufactured, most countries will import the vitamin A. In addition, young infants and pregnant women may be placed at risk of hypervitaminosis A if vitamin A is included with or within ORS packets.

For the fortification of ORS with vitamin A, specific practical issues remain to be resolved. The stability of vitamin A plus ORS in dry and hydrated forms must be determined. The costs of adding vitamin A to ORS must be calculated, including the costs of any modifications in packaging necessary to safeguard the stability of the new mixture. Protection against humidity may be especially important. Any effect on taste must be discovered and the consequences for acceptability determined.

5. RESEARCH NEEDS

The world-wide interest in vitamin A deficiency and infectious causes of morbidity and mortality, that has been generated by the Indonesian studies reviewed here, has created a favourable international climate for the funding and conduct of more research in this field. In designing this research it is important that clearly defined hypotheses of public health importance are addressed, that the designs are sufficiently sophisticated to account for the major confounding effects of economic, demographic and nutritional variables, and that ethical issues are carefully considered. Regarding ethics, it is this reviewer's opinion that it is unethical to prospectively follow children with *any* signs or symptoms of vitamin A deficiency without giving full vitamin A therapy. Some studies reviewed here have done this, and some studies currently being planned intend to do so. Three major research priorities, that have emerged from this review, are briefly presented below.

5.1 Vitamin A supplementation and diarrhoea-associated childhood morbidity and mortality

The study in Sumatra (SOMMER *et al.*, 1986) is, at the same time, pregnant with public health policy implications and fraught with uncertainty about the validity of its conclusions. Placebo-controlled, randomized trials of the impact of vitamin A supplementation on diarrhoea-associated, and other cause-specific, morbidity and mortality rates are, therefore, justified and necessary. Such studies might, most usefully, concentrate on morbidity, rather than mortality impacts and might also measure the impact on diarrhoea severity and duration and on the rates of diarrhoea caused by specific major enteric pathogens. In line with the comments on ethics made above, children with eye signs must be treated and this may be expected to reduce the magnitude of any protective effect of vitamin A supplementation that is shown.

5.2 The association between vitamin A status and risk of diarrhoea of varying severity and aetiology

Because of the remaining uncertainties surrounding vitamin A deficiency as a risk factor for diarrhoea, and the logistical and ethical problems inherent in randomized trials of vitamin A supplementation (see section 5.1), case-control studies may be usefully conducted. Cases could be children reporting to a clinic with diarrhoea of known aetiology and severity. Controls could be selected from appropriately matched children attending the same clinic for reasons not possibly connected with vitamin A deficiency (this excludes most infections and so the selection of sick controls may prove impossible). Preferably, controls might be selected randomly from appropriately matched healthy children in the community. Cases and controls would be compared with regard to their prevalent eye signs, history of eye signs and night blindness, and, possibly, conjunctival impression cytology. Potential confounding variables would be recorded, and controlled in the analysis. Such studies require most careful design and interpretation, especially with regard to the direction of any postulated causal association between vitamin A deficiency and diarrhoea.

5.3 The effect on risk of subsequent diarrhoea and xerophthalmia of giving vitamin A to children under treatment for diarrhoea

In this study, children attending hospitals or clinics for diarrhoea and lacking any signs of vitamin A deficiency would be randomized to receive all normal diarrhoea

therapy plus vitamin A or normal diarrhoea therapy alone. Any effect of vitamin A on the course of the current episode of diarrhoea would be measured and the children would be followed in the community for 2 to 3 months after discharge to assess the impact on risk of subsequent diarrhoea and xerophthalmia.

6. CONCLUSIONS

Limited evidence suggests that vitamin A deficiency predisposes to increased risk of diarrhoea illness, and to an increased risk of death, among pre-school aged children. It is possible that the prevalence rate of vitamin A deficiency that confers these increased risks is higher than the prevalence rate of xerophthalmia because there are children with physiologically important vitamin A deficiency but without eye signs. Further studies, some of which are already planned, are urgently needed to define the magnitude of any reductions in diarrhoea morbidity and mortality rates that can be achieved through vitamin A supplementation in areas where vitamin A deficiency is a significant public health problem. Such studies should pay special attention to investigating excess risk of diarrhoea due to vitamin A deficiency in children without eye signs and should seek to develop measures of such deficiency states (if they exist) which can be used in community surveys.

It is plausible that, in some settings, diarrhoea may precipitate or exacerbate xerophthalmia, although the evidence for this is weak. Studies of this relationship may have a lower priority because the findings would not greatly influence policies towards the control of either diarrhoea or xerophthalmia.

The evidence suggests that, despite lowered absorption, clinically significant amounts of vitamin A can be absorbed when administered to patients during acute diarrhoea. There are 4 possible reasons for administering vitamin A to children with diarrhoea: to contribute to the community-wide control of vitamin A deficiency; to avert subsequent xerophthalmia in the children under treatment; to influence the course of the current diarrhoea episode; or to reduce the risk of subsequent diarrhoea in the children under treatment. More evidence is required on each of these possible justifications.

If, for any or all of the above reasons, it is decided to administer vitamin A to children with diarrhoea, the method of administration must be carefully researched. The various options have different implications for targeting, as well as for minimizing the risk of administering over-doses or under-doses. Further, if ORS fortification is selected as the method of administration, important practical issues will require resolution.

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