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THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE AND PUBLIC HEALTH
INSTITUTE FOR INTERNATIONAL PROGRAMS

Vitamin A Deficiency and Childhood Morbidity and Mortality:

Scientific Background and Implications for Child Survival

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Preface

The **Occasional Papers Series** of the Johns Hopkins Institute for International Programs was established as a means of disseminating information on advances in international health. The Institute is currently conducting research and providing technical support to child survival programs throughout the world, in cooperation with the United States Agency for International Development.

The Institute for International Programs, as part of the Johns Hopkins School of Public Health, brings together leading Hopkins experts in biomedical, environmental, social science, and health management fields. When the Institute was founded in 1985, it identified three key child survival activities -- immunization, vitamin A supplementation, and program evaluation -- and established a faculty working group to focus on each.

This distinguished group of Hopkins professionals, together with collaborators from established research centers and other major academic institutions throughout the world, provides a comprehensive approach to international development.

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Vitamin A Deficiency and Childhood Morbidity and Mortality: Scientific Background and Policy Implications

I. INTRODUCTION

Vitamin A is an essential nutrient for normal physiologic functions, including cellular differentiation, membrane integrity, vision, immunologic responses and growth. Vitamin A deficiency has recently received much attention, generated largely by results of studies done in Indonesia that linked vitamin A deficiency with childhood morbidity and mortality. In a prospective field study done in Java, more vitamin A deficient children died than non-vitamin A deficient children after adjustment for several covariates[1]. In the same study population, vitamin A deficient children had an increased relative risk of diarrheal (RR=2.7) and of respiratory disease (RR=1.8) compared to non-deficient children[2]. Results from a field trial in Sumatra indicate that mortality rates are reduced among children in the communities that received supplemental vitamin A[3]. Cancer and dermatology literature have also recently focused attention on the importance of vitamin A (and its precursor beta-carotene), due to its potential anticarcinogenic and antikeratogenic effects.

Because scientific evidence on vitamin A is being generated from diverse sources, and because there is a paucity of results strictly relevant to childhood survival in developing countries, the implications of these and other findings have been difficult to translate into specific policies and programmatic recommendations. In addition, there have been conflicting interpretations of the existing scientific results. For example, while the Indonesian studies have uncovered an association between vitamin A deficiency and morbidity, the degree and direction (causality) of this relationship have been debated without consensus or the benefit of confirmatory studies. The scarcity of definitive scientific data on vitamin A severely limits the policy making process. This review attempts to delineate the strengths and weakness of the current scientific evidence as it relates to the relationship between vitamin A deficiency and childhood morbidity and mortality in developing countries. Interrelationships between vitamin A and xerophthalmia, growth, and carcinogenesis are not within the scope of this review.

The scientific community has had little time to evaluate the many existing vitamin A supplementation programs. Despite this, policy recommendations continue to appear for expanded applications of vitamin A, beyond its well established use to prevent nutritional blindness. Recommendations have been generated by various sources[4,5] for the use of vitamin A in childhood infections, in pregnancy, and in disasters. Most of these recommendations are designed to prevent the development of xerophthalmia that is frequently associated with these conditions. Implicit in some of these recommendations is the

expectation that vitamin A can reduce childhood morbidity or mortality, as well as prevent blindness. This expectation has been particularly reinforced by the results reported by Sommer, et. al. and others from Indonesia as well as by other studies noting positive associations between vitamin A deficiency and childhood morbidity. The role of vitamin A in childhood infection has not been explicitly presented in terms of adjunctive therapy, i.e. that administration of vitamin A will prevent the deterioration of vitamin A status during infection. Moreover, the expectation has arisen that vitamin A dosing during a specific episode will have a therapeutic effect on childhood infections. While prevention of nutritional blindness by vitamin A programs has been better established, the impact of vitamin A on childhood morbidity and mortality remains an open question. Recommendations targeted at the prevention of blindness then would appear to be indicated, but those targeted at the larger question of morbidity and mortality would appear to be premature.

While the recommendations and expectations for vitamin A are growing, the practical considerations of implementing vitamin A programs receive little attention. There is a great need to consider the operational and cost aspects of vitamin A interventions. Expanding the role of vitamin A to morbidity and mortality reduction may compete for funding of other programs targeted for the same goal. Therefore the cost effectiveness of a vitamin A intervention relative to other interventions will need to be determined. With regard to the recommendations under consideration for the treatment of childhood diarrhea and acute respiratory infections (ARI) with vitamin A, the following questions arise from a programmatic standpoint: What specific episodes of diarrhea or ARI should be treated and at what dosing schedule? What might be the expected effects? Given the frequency of these episodes in certain settings, what is the likelihood of toxicity if all episodes were to be treated with vitamin A? How generalizable are the results of the studies in Indonesia to other parts of the world where vitamin A deficiency appears to be less prevalent? How would distribution of vitamin A capsules or fortification of foods with vitamin A compare with interventions aimed specifically at infectious disease control? Which of the possible interventions will be more cost effective given a specific region? Instead of creating another vertical program for vitamin A deficiency, how could the interventions be incorporated into existing programs? Because of these unanswered questions, current recommendations for use of vitamin A in infection are vague, and for these reasons will be difficult to interpret and implement in the field.

In addition to the ambiguity surrounding these programmatic aspects of vitamin A interventions, there are difficulties associated with the definition and assessment of vitamin A deficiency that have complicated the planning, implementation and evaluation of vitamin A programs. High cost and technical problems make it difficult to determine whether vitamin A deficiency is a public health problem of significant proportions

in most developing countries. This may be a deterrent in program initiation. This review will address the difficulties encountered in past determinations of the prevalence of vitamin A deficiency as well as current developments in the assessment of vitamin A status.

II. BACKGROUND AND LITERATURE REVIEW

What is known about the relationship between vitamin A deficiency and the risk of infection and mortality?

A. Vitamin A and Infection

Studies dating back to the 1920's have consistently demonstrated that vitamin A deficiency is frequently associated with the presence of infection. Animal studies have documented, 1) the difficulty of isolating vitamin A deficiency from other nutritional deficiencies, 2) that in vitamin A deficient animals, keratinization occurred in several epithelial sites, including the respiratory and gastrointestinal tracts, and 3) that infection frequently accompanied this keratinization, making it difficult to discern whether the keratinization was due to the infection or whether the infection occurred secondary to the breakdown of epithelial integrity. The interested reader is referred to a review that traces these developments in the early literature, titled "Vitamin A and Infection" by Howard, West and Sommer, 1986[6].

Recent animal studies have demonstrated the preferential effect of vitamin A deficiency on mucous secreting cells, i.e. goblet cells[7,8] as well as drying, keratinization and atrophy of the surrounding epithelium. In rabbits made progressively vitamin A deficient (VAD), serial examinations of the ocular surface of the eye revealed that the density of goblet cells decreased with increasing vitamin A deficiency and that these changes preceded the development of clinical signs of xerophthalmia by several weeks[7]. Therefore, it appears that a breakdown of one barrier to infection, i.e. epithelial integrity, may predispose several sites in the body to an increased risk of infection that could be directly attributable to vitamin A deficiency. In the process of keratinization, secretory antibodies (sIgA) and other protective factors from the epithelial surface are probably also lost.

B. Interactions of Vitamin A and the Immune System

In addition to its effects on epithelial barriers to infection, vitamin A deficiency may also impair the body's immune defenses. As early as the 1930's, Bloch attributed the more frequent and severe infections in xerophthalmic children to a "decline in immunity"[9]. However, his observations were limited to states of severe vitamin A deficiency that were confounded by other nutritional deficiencies that could likewise depress the immune system. This remains a critical problem in the study of vitamin A and the immune system because it is difficult to create isolated vitamin A deficiency, even in experimental animal models. Since vitamin A deficiency affects appetite and growth

as well, the dietary intake of VAD animals is less than non-deficient animals, thereby confounding the vitamin A deficiency with at least some degree of protein calorie malnutrition. One way to avoid this is to use pair-fed controls as was done by Nauss[10]. However, in this experiment, even though the controls were fed whatever their VAD partner ate, the weight gain of VAD rats still progressively fell off when compared to the pair-fed controls. This weight plateau is attributed to vitamin A deficiency. Additionally, investigators have had difficulty keeping vitamin A deficient animals alive. For example, fatality rates among vitamin A deficient rabbits was reported as 52% compared to 12% in one study[11].

Another way to produce isolated vitamin A deficiency is to cycle experimental animals on and off diets containing retinoic acid. In one such experiment, growing VAD rats demonstrated decreased food intake, decrease in intestinal goblet cells and a weight plateau within 1-3 days of removal of retinoic acid from the diet[12]. Because of these early changes due to vitamin A deficiency, these animals were subsequently force fed to try and overcome the potential confounding effect of other nutrient deficiencies.

Determining the effect of vitamin A deficiency or the effect of vitamin A administration on the immune system is also obfuscated by the complexity of a system whose components (i.e. cellular, humoral and complement) are so interactive. For example, certain components of cell-mediated immunity regulate the activity of humoral immunity, thereby affecting the production of antibodies in response to antigens or what the body recognizes as foreign. Given the extensive interactions of the immune system, it becomes difficult to tease out exactly what the effect of vitamin A deficiency, or the retinoids, have on the immune system.

Aside from these experimental considerations, vitamin A deficiency rarely occurs as an isolated nutritional deficiency in developing countries. Study of the immune status of children in these settings can be confounded by protein energy malnutrition, parasitic infestation, increased incidence of infectious diseases, and the synergy of the malnutrition-infection cycle [13,14]. Also, the breakdown in epithelial integrity that is secondary to vitamin A deficiency potentially exposes the child to a larger spectrum of antigens that, depending on the intensity or duration of the exposure, could independently depress or stimulate the immune system.

Apart from these limitations, animal studies have demonstrated varied effects of vitamin A deficiency on the immune system depending on the degree of deficiency, the species under study, and component of the immune system examined. For example, severe deficiency led to lymphoid organ atrophy in rats as reported by Wolbach and Howe in 1925[15] whereas a more recent, well-controlled study demonstrated no effect on spleen or thymus

weight among mildly VAD rats[10]. Decreased numbers of lymphocytes were observed in VAD rats[10] but not in VAD chickens[16]. Adjuvant effects of vitamin A administered with tetanus toxoid have been described in several animal models[17] but not in children[18,19]. For a detailed review of this subject, the reader is referred to a chapter titled "Influence of Vitamin A Status on the Immune System" by K. Nauss[13]. The highlights of the experimental animal studies as they pertain to this review include, 1) VAD rats survive longer in a germfree environment [20] which supports the link between vitamin A deficiency and increased risk of infection and mortality, 2) the severity of experimental infection is greater in VAD animals compared to controls[21], 3) the beneficial effect of vitamin A supplementation among both vitamin A deficient and replete animals on the immune system or on the outcome of experimental infection was frequently observed only at very high doses of vitamin A supplementation[14], and 4) there is evidence for the stimulatory effect of vitamin A and its analogues on cell mediated immunity, particularly related to cell-mediated cytotoxicity and natural killer cells[14]. The implications of these animal studies are that more research is needed to determine what impact vitamin A supplementation might have on the immune status of VAD children. However, since such research will be confounded by all of the factors mentioned above, studies of the immune system may not be the most direct way of assessing a potential impact of vitamin A supplementation on childhood morbidity and mortality.

C. Respiratory Infection and Vitamin A Deficiency

Early animal studies described keratinization of the larynx and trachea in several species that were made vitamin A deficient [15]. Certain viral infections produce keratinization of nasal mucous epithelium in vitamin A deficient chicks but not in normal chicks[22]. Recent animal studies of tracheal tissue have demonstrated preferential depletion in mucous secreting cells due to decreased mitotic rate[8]. Additionally, it has been shown that the ciliary cells that line the respiratory tract and "sweep" debris up and out of this tract, are derived from mucous cell precursors[23]. Impairment of this mucociliary escalator by vitamin A deficiency could be one way to specifically link respiratory infection and vitamin A deficiency in the causal chain. Again, the extent or degree of vitamin A deficiency necessary to precipitate this respiratory dysfunction remains in question and has yet to be documented in humans.

Many associations between vitamin A deficiency and respiratory disease have been reported. The results are difficult to compare, however, given the varying definitions of both vitamin A deficiency and respiratory disease and the differing study designs. An increased risk of respiratory disease (RR=1.8) was reported for children with mild vitamin A deficiency (defined as XN and XIB) in a longitudinal observational study in Indonesia[2]. Respiratory disease in this study was defined as the presence of cough, rhonchi, or rales that led to the diagnosis by an examining pediatrician of

bronchitis or pneumonia. In a similarly designed study of 1500 children in India, mild vitamin A deficiency was associated with a comparably increased risk of respiratory disease (RR=2.0)[24]. In a prevalence survey conducted in Cebu, in the Philippines, active xerophthalmia was positively correlated with having had pulmonary tuberculosis (diagnosed by x-ray) or recent whooping cough[25]. In a more recent prevalence survey of xerophthalmia in Malawi, children with active xerophthalmia were more likely to have had a prior week history of cough and fever (33% more) than those without xerophthalmia[26]. In a case control study done in the context of a xerophthalmia prevalence survey of southern Ethiopia, 165 children with severe xerophthalmia or Bitot spots were found to have a higher prevalence of respiratory disease (27/165) over the preceding year compared to age and sex matched controls (13/165)[27]. Respiratory disease was defined as fever and cough that made the child unable to walk and play for a minimum of five days. Even though this definition of respiratory disease is fairly dramatic, making it more likely to be remembered, the long duration of recall (one year) would make this data less reliable.

There is less current information on the use of vitamin A in the treatment of respiratory disease. In the 1930's, several clinical trials of vitamin A use in pneumonia, pertussis, scarlet fever, measles, and the common cold were attempted, although most of these were poorly controlled and no assessment of vitamin A status of the participants was made. These older studies are described by S.W. Clausen in a review titled "The Pharmacology and Therapeutics of Vitamin A"[28]. In the conclusion of his discussion on vitamin A and infection, Clausen summarized the 'state of the art' in the 1930's as follows:

The evidence reviewed indicates that severe deficiency of vitamin A lowers resistance to infection in man and that the administration of vitamin A during the course of an infection probably has no beneficial effect on the outcome unless severe deficiency is present. There is evidence that moderate deficiency of vitamin A may also increase the duration and severity of respiratory infections in man; that an adequate intake may lessen the severity and duration of infection in persons moderately deficient. It is also evident that many other factors are of equal or greater influence on infection, and no justification exists for calling vitamin A "the anti-infective vitamin".

Given that interesting historical perspective, there are two recent clinical trials of vitamin A in respiratory disease to consider, one done among vitamin A replete Australian children [29] and the other among preterm US infants with respiratory distress syndrome[30]. In the former, 147 1-4 year olds with a three month history of greater than 15 days of cough or three different episodes of respiratory disease (not defined) were randomized into a vitamin A (dose = US RDA 1160ug RE given by parents three times weekly) and placebo group. Whether the respiratory disease

was strictly infectious in origin or whether there was an allergic component to the respiratory disease in these children is unclear. Over the ensuing 11 months, the supplemented group had 19% ($p<0.05$) fewer episodes of acute respiratory infection (ARI) symptomatology (diary recorded by parents) compared to placebo group. Extrapolation of these results to other populations is limited given the replete vitamin A status of the participants, no change in mean serum vitamin A level between the two groups and the study's methodological problems (e.g. no validation of parents' ARI assessment). The later clinical trial involved 40 very low birth weight (LBW) infants with premature lungs (presumably a noninfectious condition) and the need for mechanical ventilation. Over the 28 days of supplementation, the vitamin A supplemented group demonstrated higher mean retinol levels, less bronchopulmonary dysplasia (BPD, lung scarring) and shorter required ventilation time than the placebo group. This study is limited by the small number of study subjects, a very selective study population, a short interval of follow-up, the difficulty discerning vitamin A toxicity in preterms[31] and the uncertain reliability of diagnosing BPD.

As neither of the above trials specifically addresses issues of childhood morbidity and mortality in the developing world (the former study deals with vitamin A replete children in a developed country setting and the latter deals with respiratory disease secondary to prematurity and mechanical ventilation), trials to assess the therapeutic and prophylactic impact of vitamin A on lower respiratory infection (LRI) are indicated both in inpatient and in community settings in vitamin A deficient areas. The implications of the clinical trial of vitamin A in LBW infants for LRI management and control programs in developing countries is unclear because LRI among LBW infants in these settings is compounded by infectious etiologies as well as prematurity[32]. Although what is currently known about associations between vitamin A deficiency and ARI and about the effect of vitamin A on respiratory disease should encourage other clinical trials, not enough is presently known to recommend vitamin A specifically for therapy of LRI.

D. Diarrheal disease and vitamin A deficiency

Various researchers have looked at the relationship between vitamin A deficiency and diarrhea. Sommer and co-workers have done extensive work in Indonesia that has focused interest on the possible degree and direction of this relationship. In a prospective study of 4600 rural Indonesian children, an increased risk of diarrheal disease (RR=2.7) was noted among those children with preexisting vitamin A deficiency[2]. From the same data set it was reported that there was an increased risk of xerophthalmia following diarrhea[33]. The interpretation of this work has generated much debate. The association between diarrheal disease and vitamin A deficiency does not imply the causality of either condition. A common underlying factor, for instance poverty, may predispose children to both more diarrheal disease and less vitamin A intake independently.

Numerous other studies, some much less rigorous than the above, have found associations between vitamin A deficiency and diarrhea. A study from Bangladesh suggested that malnutrition (low weight for length) is a determining factor in the duration of diarrhea[34]. These investigators noted that children with low weight for length had longer durations of episodes but they also noted that the incidence of diarrhea was independent of nutritional status as determined by anthropometric status. Khan et al noted that 86% of the cases of xerophthalmia in their study in Matlab gave a history (past 30 days) of diarrhea or dysentery [35], however there was no control group. Among 2971 Bangladeshi children in another study who were aged 1-10 years and hospitalized for diarrheal disease, those with night blindness were more likely to have dysentery (especially Shigella and E. hystolytica) (RR=1.68)[36]. Another study conducted in Bangladesh demonstrated that "protracted" diarrhea, defined as three or more stools per day for greater than 14 days, was also found to be associated with mild vitamin A deficiency defined as X1A and/or X1B[37]. Two reports from Nepal suggest an association between vitamin A deficiency and diarrhea. The three cases of corneal disease (1=X3, 2=XS) from Upadhyay's work[38] were all reported to be preceded by diarrhea. This is anecdotal information. Among 50 matched pairs from the Nepal Blindness Survey[39], the authors report that diarrhea preceded xerophthalmia in a high proportion of cases. It is not clear from their methods how they established that sequence, however. From Ethiopia there is confirmation of an association between diarrhea and vitamin A deficiency but their use of a one year recall time frame is rather unconventional[27].

Some research efforts have discovered no association between vitamin A deficiency and diarrhea. In an attempt to replicate the Indonesian findings, Milton et al., could not show an association between mild xerophthalmia and incidence of diarrhea (n=1544)[24]. In the Philippines, diarrhea was not positively correlated with xerophthalmia (n=1715)[25]. From the prevalence survey in southern Malawi among children 2-5 years old, a history of diarrhea was not found to be associated with xerophthalmia (n=5436)[26].

The reader is referred to Feachem's recent publication[39] which deals with most of the issues under debate concerning the relationship between vitamin A deficiency and diarrhea. Dr. Feachem addresses these issues in a critical manner. He suggests models for the relationship between vitamin A deficiency and diarrhea, introducing an element of confounding by "unspecified poverty-related factors" that might provide a possible explanation for some of the confusion. While he does not give the answers to resolve the debate, Feachem suggests the following research needs: 1) placebo-controlled, randomized trials of the impact of vitamin A supplementation on specific morbidity and mortality rates, 2) studies to establish the association between vitamin A status and diarrhea of varying severity and etiology,

and 3) studies to establish the utility of giving vitamin A to children under treatment for a current episode of diarrhea as it might impact on subsequent diarrhea and xerophthalmia.

One of the issues surrounding treatment of diarrhea with vitamin A is absorption of vitamin A during an acute or chronic diarrheal episode. Various studies have demonstrated that the absorption of vitamin A depends on dose and type of preparation [41]. The use of combined vitamin A oral rehydration solution was recently assessed in India, and it was found that 70% of administered dose of 100,000 IU of vitamin A (water-miscible) in 500 ml was absorbed in 19 children with acute diarrhea[42]. If treatment of diarrhea with vitamin A is to be recommended, further studies of the absorption of vitamin A, particularly the oil-based vitamin A capsules that are more readily available, will be necessary.

E. Measles and Vitamin A Deficiency:

A recent joint WHO/UNICEF recommendation[4] advocates the following:

> High-dose vitamin A supplementation should be provided to all children diagnosed with measles in communities in which vitamin A deficiency is a recognized problem. In countries where the fatality rate of measles is 1% or higher, it is sensible on the basis of current evidence to provide vitamin A supplements to all children diagnosed with measles.

The implied intention of this recommendation appears to be not only prevention of vitamin A deficiency related measles blindness but also to prevent measles mortality. The evidence cited to support this recommendation was several older studies describing the well known association between vitamin A deficiency and measles, the morbidity and mortality studies done by Sommer in Indonesia as well as a recent clinical trial of vitamin A done during a measles season in Tanzania[43]. In this clinical trial, measles admissions to hospital were randomized to receive 200,000 IU of vitamin A in oil orally on the day of admission and the following day or to receive just the standard treatment for measles without placebo. Measles mortality in the supplemented group was 6/88 (7%) compared to 12/92 (13%) among the controls, a difference that did not reach statistical significance. The recommendation for the treatment of measles may lead to as yet scientifically unfounded expectations that vitamin A will decrease measles mortality. Even the use of vitamin A to prevent measles blindness is not so straight forward as other etiologic agents have been implicated. On this topic, the interested reader is referred to a review titled "Severe Measles and Measles Blindness" by Koblinsky, that discusses the etiologies of measles blindness and the role of vitamin A deficiency[44].

Another excellent and more recent review of measles by the EPI Global Advisory Group has examined relationship between

vitamin A deficiency and measles. In this review, the point is made that the outcome of measles is dependent on several factors, for instance general nutritional status, and is not a function solely of vitamin A status. However, the relationship between measles outcome and vitamin A deficiency was felt to be one that required much more research. This review concluded with the following areas for further research 1) what is the extent of measles mortality, morbidity and eye lesions relative to vitamin A status preceding infection, 2) how do measles virus and vitamin A deficiency interact to produce morbidity and mortality, 3) to what degree does measles precipitate vitamin A deficiency, and 4) if vitamin A deficiency is causally related to the measles mortality, what is the effect of vitamin A supplementation on this outcome. Additionally, the review called for studies to evaluate and confirm the joint WHO/UNICEF recommendation that all children with measles in countries with a high case fatality rate be given 200,000 I.U. of vitamin A upon being diagnosed with measles.

Several issues regarding vitamin A and measles were neither addressed by this review nor elsewhere. To the above list should be added concerns about the operational issues that arise if and when vitamin A supplementation is added to EPI activities as was recently proposed at the IVACG meetings in Ethiopia. Also to be determined is the dose or doses that are most effective in the prevention of vitamin A related measles blindness and (if shown to be useful) in the prevention of measles mortality.

In summary, the use of vitamin A to reduce measles mortality requires more research in the areas listed above before it is considered a mainstay of measles treatment and competes with limited resources in child survival. However, from an ethical perspective, the recent recommendations make furthur research into this area difficult. From a policy standpoint, it would be preferable to stress a primary intervention, i.e. measles immunization, whereas treatment of measles with vitamin A to prevent measles mortality falls into the realm of secondary prevention. This may be a mute point because, even though there is controversy over the extent to which measles blindness can be attributed to vitamin A deficiency, the treatment of severe measles with vitamin A in an attempt to reduce measles blindness has already been advocated. Vitamin A may become a mainstay of measles treatment for this other reason.

F. Other Childhood Morbidities and Vitamin A Deficiency

Vitamin A deficiency occurs as a complication of cystic fibrosis, short bowel syndromes and malabsorption in the USA, but the specific pathophysiology of these diseases makes them less relevant to childhood morbidity and mortality in developing countries. There may be more relevance to less prevalent diseases such as tropical enteropathy, sprue and other malabsorption syndromes, which fall outside the realm of this review.

In a study where children with protein calorie malnutrition (PCM) complicated by xerophthalmia were compared to children with PCM alone, 78% of the xerophthalmics had bacteriuria (bacteria in the urine that normally is sterile) versus 17% in their matched controls[45]. The authors speculated that altered urinary tract epithelium may have provided a focus or nidus for infection. Since the children with xerophthalmia also had lower plasma total protein (5.2 gm/dl) compared to their controls (6.0 gm/dl), the authors also speculate that the severity of PCM in the xerophthalmia group may have also influenced the rate of positive urine cultures in the xerophthalmia group.

At the recent IVACG meeting in Ethiopia, the cytology of epithelial cells excreted in the urine of xerophthalmic children was examined as reported by Dr. Gopa Kothari. Although there was some relationship between the presence of clinical signs of vitamin A deficiency and the presence of keratinized cells in the urine, urinalysis still was not a sensitive indicator of vitamin A deficiency (see section on assessment of vitamin A status).

It seems reasonable to expect that other epithelial sites (skin, uro-genital, rectal, exocrine glands) in the body may be more susceptible to infection in the presence of vitamin A deficiency. Follicular keratosis has been noted in severe vitamin A deficient states, however since it can also be a result of vitamin C and/or nicotinic acid deficiency, it is not a specific sign of vitamin A deficiency[12] and is not believed to be related to infection per se.

G. Vitamin A and Childhood Mortality

In the introduction to this review, the studies done in Indonesia by Sommer et al.[2,33,3] were mentioned as one of the chief reasons that so much interest has been generated in the potential role of vitamin A in childhood survival. Given that the Aceh study[3] has attracted so much attention and that it is at present the only field trial of vitamin A supplementation with mortality as the outcome, it is worthwhile focusing attention on some of the details of that study.

The Aceh study reported a 34% decrease in mortality rate of 1-5 year olds in 229 vitamin A supplemented "programme" villages compared to 221 control villages that received no supplement or placebo. The difference in mortality is more striking when the results are stratified by sex: for males in the programme villages the mortality rate was 7.2/1000 versus the rate of 12.2/1000 in the control villages. For females, the mortality rate was 8.2/1000 in the programme villages versus 8.9/1000 in the control villages.

While encouraging, the Aceh study has been criticized by several sources[46,47,48] on issues pertaining to study design and methods, demographic inconsistencies and analysis of the results. Some of the concerns raised in these critiques have been that

since randomization was done on the village as opposed to household or child level, aspects of the village as a whole may have led to confounding of the results. The following baseline inequalities between the control and programme villages were raised by one of the critics[46] and may have independently influenced the difference in mortality:

	Control > Programme
-xerophthalmia	24%
-recent hx of diarrhea	23%
-stunting	14%
-wgt for hgt <80%	23%

It has been pointed out that, although sex specific mortality rates were similar between control and programme for the first two months, in such a short period of time too few deaths would be likely to occur to show a difference[47]. Besides baseline differences between control and programme villages, xerophthalmia decreased in the control villages 48% during the study period, which suggests that other variables were changing[46]. Finally, the absence of baseline mortality data prior to the intervention as well as absence of causes of death during the intervention detract from attributing the difference in mortality solely to vitamin A during the trial.

The demographic inconsistencies that have been noted occur within the age specific mortality rates from the Aceh study as follows:

REPORTED AGE SPECIFIC MORTALITY DURING FOLLOW-UP
RATE per 1000

Baseline Age in months	Programme	Control	RR
0-12	23.1	27.8	1.21
12-23	9.6	11.3	1.17
24-35	6.7	12.1	1.81
36-47	4.8	4.0	0.83
48-59	2.6	4.1	1.58
60-71	1.5	5.3	3.53
TOTAL	7.8	10.6	1.36

The age specific mortality rates in control villages appear to rise with age among the oldest two age groups. There is also a greater proportion of 60-71 month olds in both programme and control villages. Both of these findings run counter to the usual demographic situation of greater numbers and mortality in the younger age groups. It has been suggested that this inconsistency may have arisen from enumeration errors and the

recall method of assessing mortality that could lead to under-reporting[47]. Under-reporting or better conditions in general are suggested by the following comparison of the Aceh study areas mortality rates with that of Indonesia as a whole[46]:

CONVENTIONAL INFANT (<1yr) AND CHILDHOOD (1-4yrs) MORTALITY RATE per 10000

	Programme	Control	Indonesia
INFANT	23.1	27.8	101
CHILD	5.96	7.99	13

In response to critiques, Sommer and West indicated that inaccuracies in recorded age may have arisen due to use of a local events calendar and under-reporting of young infants may have occurred for cultural reasons[49].

A re-analysis of the Aceh data, particularly noting participation, was recently reported[50] and the authors concluded that the impact of vitamin A on mortality in certain groups may be even greater than previously reported. The mortality rates of control village children aged 3-11 months (ie. 6.0/1000) and aged >=12 months (ie. 1.8/1000) were higher than the respective rates for program village children who received a capsule (ie. 0.9/1000 and 0.2/1000). A comparison of similar age specific mortality rates between program village children who did (above) and did not (ie. 12.0/1000 and 5.4/1000, respectively) receive a capsule revealed a significant difference leading to the authors' conclusions. From this report, the group most likely to benefit from vitamin A supplementation would appear to be those who did not receive it. While this may seem obvious, the message to those involved in implementing programs is clear; those children often most difficult to reach are perhaps those who might benefit most. This fits well within the framework proposed by Mosley and Chen[51].

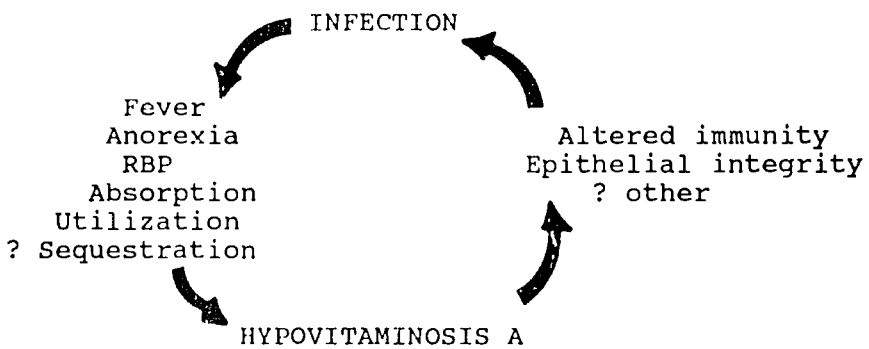
In summary, the landmark Aceh study has contributed greatly to the understanding of the relationship between vitamin A deficiency and childhood mortality in developing countries. However, until confirmatory studies that overcome some of the limitations of the Aceh study are conducted, it appears premature to recommend vitamin A universally as way of preventing childhood mortality to the degree suggested.

H. A Model for the Relationship Between Vitamin A Deficiency and Infection

The study of this relationship has always been complicated by the fact that vitamin A status changes in the presence of acute infection. For example, the levels of serum retinol and retinol binding protein (the carrier protein for retinol) are depressed in children with infections[52,53]. Histories obtained from the caregivers of xerophthalmic children often reveal a

preceding infection, and many of the studies reviewed here have reported associations between vitamin A deficiency and preceding or concurrent infection. It is difficult at the time of infection to ascertain if vitamin A deficiency preceded the infection or the infection precipitated vitamin A deficiency. The best way to determine the causality of this relationship is to study it in a prospective fashion.

MODEL FOR THE RELATIONSHIP
BETWEEN CHILDHOOD INFECTION AND VITAMIN A DEFICIENCY



In summary, the relationship between vitamin A deficiency and infection may be circular, (see model), with the weight of the evidence in animals supporting infection leading to vitamin A deficiency. A recent study of Brazilian children with chicken pox demonstrated that this infection does deplete liver stores of retinol as reflected by sequential RDR studies pre and post infection[54]. Therefore, preventing recurrent and frequent infections may help prevent vitamin A deficiency, and in this sense, other public health efforts such as diarrheal disease control, EPI and ARI management may contribute greatly to the control of vitamin A deficiency.

The cause and effect relationship between vitamin A deficiency and infection can be approached via a clinical trial of vitamin A with morbidity as the outcome. If vitamin A impacts significantly on childhood morbidity, inferences could be made from the morbidity specific results as to what the impact on childhood mortality might be. The extent to which vitamin A deficiency is merely a marker for other risk factors that lead to the increased incidence and severity of infection in children in developing countries, has yet to be fully elucidated.

Whether or not vitamin A has greater impact on the incidence versus the severity of an infection will depend on the degree of exposure to infectious pathogens and the host's immune status. The role of exposure to infectious disease pathogens may outweigh any of the advantages of a vitamin A replete state. A good example of this is measles. It is unlikely that vitamin A can

prevent the incidence of measles in a susceptible child exposed to measles, but it may moderate the severity of the disease.

At this point, not enough is known about the potential impact of vitamin A on childhood morbidity in non-deficient populations to make any policy recommendations. Recent cancer research has been designed to measure the impact of vitamin A and/or beta-carotene in cancer patients or patients at high risk of developing cancer. Presumably, these patients will not be vitamin A deficient (unless they are cachectic), and these studies may provide clues about the effect of vitamin A in non-deficient populations. However, the inferences that can be made from such studies of adult populations in developed countries with outcomes that pertain to cancer reduction, will be limited relative to the potential impact of vitamin A on the other end of the age spectrum in developing countries. It seems prudent to establish the impact of vitamin A on childhood morbidity in deficient populations before moving to clinical trials of vitamin A in non-deficient populations.

III. ASSESSMENT OF VITAMIN A STATUS

A. Clinical Signs and Symptoms:

Clinical signs have long been used to diagnose vitamin A deficiency. The WHO classification[55] lists these signs in order of severity, as follows:

Nightblindness	XN
Conjunctival xerosis	X1A
Bitot's Spots	X1B
Corneal Xerosis	X2
Corneal Ulceration	X3

In its severest form, Vitamin A deficiency causes corneal xerosis and ulceration and subsequent blindness, while milder forms are reversible, both spontaneously and with dietary or pharmocologic vitamin A treatment. Relying on the clinical signs of xerophthalmia is unsatisfactory given that the severe stages of xerophthalmia are irreversible, that Bitot's spots in older children (>5 years old) are sometimes unresponsive to treatment with vitamin A and thus thought not to reflect current vitamin A deficiency, and given the late appearance of these signs. This latter point is of particular concern in that the immune system demonstrates changes before any ocular signs of vitamin A deficiency appear[10]. Additionally problematic is that large sample sizes are needed in order to obtain enough cases of clinical xerophthalmia to yield a reliable estimate of the prevalence of vitamin A deficiency in a given population.

B. Biochemical Assessments

The best standard for assessing vitamin A status is liver biopsy and analysis for vitamin A content because 90% of total body vitamin A is stored in the liver. For obvious reasons, this is not an acceptable assessment method in field settings. In

hospital settings however, liver biopsies have been used to evaluate other methods of vitamin A status assessment[56,57].

The relative dose response (RDR) technique provides an estimate of hepatic reserves of vitamin A in experimental animals. This technique is based on the release of apo-retinol binding protein from the liver in response to a small dose of retinyl palmitate when hepatic reserves of vitamin A are low[58]. Severe protein malnutrition and alcoholic cirrhosis in adult inpatients appear to confound the results of RDR, thus RDR may not be reliable in these cases[59]. The test has been recently validated in a small inpatient study of children with liver disease and has shown good correlation with liver biopsy results despite varying levels of protein[56]. It does require two specimens of blood separated by 5 hours, when no vitamin A other than the test dose is ingested. A simplified method of RDR requiring only one blood sample is being developed (personal communication from JA Olson).

Serum retinol levels have been used by numerous researchers for decades to estimate the vitamin A status of subjects. Assessing the vitamin A status of a population in the past has been fraught with the cultural, technical and analytic problems associated with obtaining and measuring serum levels of vitamin A. Except at the extremes of deficiency (<10 ug/dl) and excess, serum retinol levels cannot be reliably used to assess vitamin A status in individuals[60]. However, frequency distribution curves of serum retinol levels may be used to assess the status of vitamin A in a population as was done by Arroyave in evaluating the fortification of sugar in Guatemala in 1975-77[61]. At least one published study[62] has shown that serum retinol levels are correlated with the RDR at the level of the individual.

C. Cytologic Methods of Assessment

1. Conjunctival impression cytology- ICEPO Technique

Conjunctival impression cytology (CIC) has been proposed as a method of detecting early xerophthalmia[63] and even subclinical vitamin A deficiency[64]. In rabbits that were progressively depleted of vitamin A, this technique demonstrated a gradual reduction of conjunctival goblet cells with increasing vitamin A deficiency[7]. These cytologic changes occurred before clinical signs of deficiency appeared, thus the technique showed promise as a means of detecting subclinical vitamin A deficiency.

Prior field trials of CIC involved application of CIC to highly selected populations in India and Indonesia, i.e. those who had clinical signs of xerophthalmia were compared to those without clinical signs[63,65]. In India, 32 children with mild xerophthalmia (night blindness, conjunctival xerosis or Bitot's spots) had baseline CIC taken followed by vitamin A treatment and 18 of the 32 had follow up CIC three and eight weeks later[63]. In the follow up group of 13 children with xerophthalmia, of these, 12 had abnormal CIC at baseline and normal CIC posttreatment. In a larger study in Indonesia, the CIC of 75 children with night

blindness or conjunctival xerosis with Bitot's spots were compared with 74 age matched controls[65]. CIC was obtained in hospital using papoose board and lid retractor. The results of CIC were compared to mean serum retinol levels, clinical xerophthalmia and response to vitamin A, two doses 25,000 and 200,000, given in a randomized fashion. The mean serum retinol levels decreased with increasingly abnormal CIC stages from 23 umol/L to 11 umol/L in cases and from 23 umol/L to 17 umol/L in controls. Following vitamin A treatment, 50 children out of the 53 who had abnormal cytology and had received vitamin A initially had normal cytology at some point during the six month follow up. CIC was felt to be closely correlated with vitamin A status and "more sensitive than a clinical ocular exam". In a prior abstract of this work, the sensitivity and specificity of CIC compared to clinical findings was cited as 88% and 93% respectively. CIC compared to serum vitamin A levels yielded a sensitivity of 60% and a specificity of 80%.[66].

The authors of this review conducted a field trial of CIC in Guatemala to assess its validity and feasibility (in press, AM J Clin Nutr). CIC was performed in varied field settings much as it would be applied by a ministry of health or private voluntary organization attempting to assess the extent of the problem of vitamin A deficiency in a given population. 236 Guatemalan children aged 2 to 14 years were examined for subclinical vitamin A deficiency using CIC. One impression was taken from the temporal bulbar aspect of each eye. The feasibility of the technique was assessed. The CIC technique was easily performed on children greater than 3 years of age, but was more difficult among those 3 or less years. However, neither lid speculum nor physical restraint in the form of a papoose board was necessary. Laboratory processing of specimens is uncomplicated, but microscopic interpretation may be problematic and requires clearly defined criteria of normal and abnormal cytology as well as careful standardization of readers.

CIC results were compared with fasting serum retinol levels and RDR of study children to assess how CIC may detect marginal or subclinical vitamin A deficiency in various field settings. Fasting serum vitamin A levels were drawn following CIC, and a follow-up vitamin A level was drawn five hours after 480 retinol equivalents of retinyl palmitate was given (standard RDR procedure). Using a 20% RDR cut-off to define vitamin A deficiency, the sensitivity of CIC was 23%, with a specificity of 80% and a positive predictive value 9% (n=213 children). Compared to fasting vitamin A levels alone (using <20 ug/dl as abnormal), the sensitivity of CIC was 26%, specificity was 81% and positive predictive value was 22% (n=221 children). There was no significant difference in the mean serum retinol level between those with abnormal CIC and those with normal CIC. These results challenge the utility of CIC as a field test for detecting subclinical vitamin A deficiency in individuals and in populations with a low prevalence of clinical vitamin A deficiency. This study should be replicated in an area of higher

prevalence of vitamin A deficiency to determine if CIC can be used in those settings. Although this technique has been recommended as a screening tool for vitamin A deficiency, more research is required to determine how co-morbidities affect its validity as a screening test for vitamin A deficiency, how better specimens can be more reliably obtained, and whether or not the use of anesthetic drops alters the epithelial cell cytology.

Recently CIC has been applied to a population of refugee children in Sudan by Helen Keller International, to Tanzanian children by ministry of health personnel, and in India by Dr. Vinodini Reddy. Results of these efforts have yet to be published, but comments made at the recent IVACG meeting in Ethiopia (1987) indicate mixed reviews. Some problems were encountered in the field application in Tanzania. The problem of co-morbidities confounding results was noted in the Sudanese evaluation. In India, a response to therapy was noted among subjects who initially had abnormal CIC, but who, after treatment with vitamin A, had normal CIC. In this very preliminary but promising report, numerous unclear or "unreadable" specimens were excluded.

2. Conjunctival impression cytology- Amedee-Manesme technique

A variation on the above-mentioned CIC technique has been studied by Amedee-Manesme in Paris[64]. His technique departs from the previously described CIC technique in that the filter paper, after it has been applied to the conjunctiva, is then pressed onto a glass slide. The goblet cells are transferred in this way, so that the glass slide can then be dipped into a single staining solution, dried and read directly. This technique would seem to save time and expense. However, other researchers reported at the recent IVACG meetings that the transfer of goblet cells was incomplete, and there was little to no reliable transfer of mucin spots. It has been suggested that this shorter technique be used as a quick screen followed by the technique developed at ICEPO for all children initially read as abnormal. How practical this may be remains to de determined. The ICEPO technique appears to be more reliable in picking up normal cytology (personal communication with Barbara Underwood). Both techniques may have problems in reliably picking up abnormals.

3. Urinalysis

Given the effect of Vitamin A deficiency on epithelial integrity (animals), sites other than the conjunctiva have been considered for sampling. The increase in positive urine cultures in children with xerophthalmia and the hypothesis that keratinization and sloughing of ureteral epithelial cells may provide a nidus for infection[45] have been previously mentioned. At the 1987 IVACG meeting in Ethiopia, results of a small study of urinary and buccal (inside surface of the cheek) epithelia in 56 xerophthalmic children compared to 58 non-xerophthalmic children were presented by Dr. Gopa Kothari (from Bombay). When stained in the same fashion as CIC, there was a correlation between abnormal cytology and clinical signs of xerophthalmia.

There was, however, low sensitivity and specificity of these buccal and urinary sediment smears. Both methods, but particularly the buccal smear, were noted to be very feasible.

D. Dietary Assessment

Measuring dietary intake of vitamin A is fraught with the usual measurement difficulties that limit other types of dietary assessments. Block, et al., developed a self-administered diet history which had excellent correlation with a one-day diet record but which is limited by a requirement for a population based data set to construct the questionnaire[67]. Additionally, it is unclear the degree to which a single assessment accurately reflects an individual's vitamin A status over time. It has been estimated that 5 to 26 independent measurements of dietary data (24 hour recalls) may be necessary to reduce the error introduced by intraindividual variation[64]. Interindividual variation presents another limitation of dietary history. Because individuals within certain cultures may share dietary habits, there often is little difference between individuals in terms of dietary intake[69], particularly in monocrop cultures. This lack of dietary heterogeneity within in a culture "results in a statistical inability to differentiate individuals by nutritional factors"[69]. Therefore, dietary intake tends to be a poor indicator of an individual's current vitamin A status.

The methods of measurement of intake measurement face problems of reliability and validity that require further research, development and correlation with other methods of assessment of vitamin A status. Some comparisons between dietary questionnaire results and plasma carotenoid levels were poorly correlated[70] while other comparisons between intake of vitamin A and plasma vitamin A levels had good correlation ($p<0.001$)[71]. Quantitative dietary histories combined with food frequencies demonstrated in Indonesia that children with corneal disease and those with Bitot's spots consumed vitamin A and provitamin A foods less frequently than normal children[72]. Seasonal availability of foods can be important in many areas of the world making the timing of such an assessment crucial.

Dietary intake would appear to be a better indicator for identifying populations at risk for vitamin A deficiency who, for instance, have intakes below Food and Agriculture Organization of the United Nations (FAO) standards. Efforts are underway to standardize a dietary history that might be used for assessment of populations at risk for vitamin A deficiency. A standarized methodolgy for obtaining combined food frequency, recall and semi-quantitative intakes of vitamin A foods was presented at the IVACG meetings in Ethiopia and is currently being field tested. Although less helpful in assessing individual vitamin A status, the information gained from a valid and reliable dietary assessment may be key to effective nutrition education and horticultural planning.

E. Summary and Controversies

In the past, vitamin A deficiency has often been dichotomized as the presence or absence of clinical signs. From a biochemical standpoint, the spectrum of vitamin A deficiency, as measured by liver vitamin A concentrations, includes the categories of adequate (>=20 ug/g), marginal (10 to 20 ug/g), poor (5 to 10 ug/g) and critical or deficient (< 5 ug/g)[67].

Serum retinol levels < 10 ug/dl correspond to liver concentrations < 20 ug/g[67]. Commonly, one hears reference to "subclinical" vitamin A deficiency, particularly in the ophthalmologic literature[64,65], and while this term implies the absence of clinical signs of xerophthalmia, it is unclear how the distinction between subclinical and normal (both being the absence of clinical signs) can be made. The different terminologies are displayed below in relative order of severity, although at this point it is not clear how the various categories relate. For example, does subclinical indicate a biochemical state that is marginal, poor or critical? In one inpatient study, two of 24 children with cholestasis and liver vitamin A concentrations <20 ug/g had clinical signs of xerophthalmia[73].

Spectrum of Vitamin A Status
A Comparison of Terminology

	True Status	Ophthalmologic Assessment	Biochemical Assessment
Normal Vitamin A Status			
↕	Replete	Normal Exam	Adequate
			Marginal
	Less VAD	Subclinical	
			Poor
Deficient Vitamin A Status	More VAD	Clinical signs	Deficient

The area of marginal or subclinical vitamin A status is currently the focus of research because of the physiologic and immunologic changes that occur preceding the appearance of clinical signs of vitamin A deficiency[10]. Ways of detecting marginal vitamin A deficiency are being sought so that interventions can be made well before the child develops clinical signs. Presumably the subclinical state corresponds to depleting or depleted stores of vitamin A. However, there is disagreement as to the exact nature of the relationship between ophthalmologic and biochemical parameters, and between end organ physiology and

liver stores of vitamin A. Because of the poor correlation between clinical signs and serum retinol levels, some feel that all biochemical measures are poor indicators of vitamin A status since vitamin A metabolism is homeostatically controlled, i.e. kept constant. While this may be true of serum retinol levels, it may not be true of other biochemical parameters. It has been theorized that serum retinol levels are maintained to meet physiologic needs until the concentration of vitamin A in the liver falls below a certain critical level[74]. One recent study of vitamin A metabolism in rats supports these findings and also demonstrated that below this critical level, the utilization of retinol is decreased at the tissue level[75]. In short, it appears at this time that there is a direct relationship between depleted or depleting liver stores of retinol and retinol utilization and concentrations at the tissue level at least in rats.

Aside from the technical aspects of assessment techniques that are currently under debate and research, there are other questions that relate to assessment that require attention. For instance, what are the programmatic implications of the different stages of vitamin A status? What are the relative risks of morbidity or mortality for a child with eye signs versus a child with reduced liver stores (estimated via RDR) versus a child with less than the recommended daily dietary intake of vitamin A? Should each one of these be targeted with the same intervention (given limited resources) and yet be expected to demonstrate the same impact?

IV. THE GLOBAL PROBLEM: ESTIMATING PREVALENCE

A. Use of Prevalence Criteria

Vitamin A deficiency has been identified as a public health problem in many areas of the world[76]. The full extent to which children in the developing world suffer from this deficiency is not accurately known, although attempts to estimate the global problem have been made. WHO has published prevalence criteria for determining the public health significance of vitamin A deficiency that use clinical signs and serum retinol levels[53].

Prevalence Criteria for Determining
the Public Health Significance
of Xerophthalmia and Vitamin A Deficiency
Among Pre-school Children

Night blindness (XN) in >1%
Bitot's spot (X1B) in >0.5%
Active corneal disease (X2/X3A/X3B) in >0.01%
Corneal scar (XS) in >0.05%
Plasma vitamin A of <0.35 umol/l (10 ug/dl) in >5%

These criteria have been applied to individual country situations to help establish needs for interventions. Dr. E. M. DeMaeyer of the WHO, using secondary data from a variety of

sources, has placed countries into three classes: a) Class 1, those with a public health problem in part or the whole of the country, b) Class 2, those where information is insufficient but where there is a high probability of a significant public health problem in part or the whole of the country, and c) Class 3, those countries from which sporadic cases are reported but where the prevalence of vitamin A deficiency is not believed to be a significant problem. This was reported at the IVACG meeting in Ethiopia, 1987. While this classification was not done to reflect true prevalence, it could be misinterpreted. For instance, the absence of Guatemala for which there is some biochemical data indicating vitamin A deficiency and the listing of Thailand as Class 3 when historically it has harbored significant populations of deficient children may lead to an underestimation of the extent of the problem in these countries. Additionally, changing conditions such as drought or war may precipitate more epidemic proportions of vitamin A deficiency in populations with little vitamin A reserve, such as occurred in Denmark during the first World War[77]. It must be recognized that such a classification is limited by the difficulties associated with assessing vitamin A status, the cost of such assessments (surveys), as well as, probable under recognition and under-reporting. This listing is likely to be quite fluid as additional information is available.

B. Problems in Prevalence Ascertainment

The true prevalence of vitamin A deficiency is very difficult to ascertain[76]. Case definitions must be consistent in order to compare rates both within and among countries and sampling methods must consider some of the epidemiological problems associated with vitamin A deficiency, eg. clustering and seasonality. Clearly, one must weigh the costs both in time and in monetary terms of attempts to establish rates of vitamin A deficiency against the returns of specific, local information versus other sources of data suggesting the extent of the problem of vitamin A deficiency. This is perhaps particularly true for private voluntary organizations and others who may not have the expertise or the resources for the assessment of vitamin A status or in conducting such surveys.

Guidelines for assessing vitamin A status have been outlined by IVACG[78] but given the various ways that rates of vitamin A deficiency are measured, ie. by clinical signs, biochemical indicators, dietary intake and now cytologically, these rates may differ. Various means of assessment may describe different portions of the vitamin A deficiency spectrum which makes comparisons difficult. Certain methods of assessment may also imply particular routes for intervention. For example, capsule administration may be indicated for areas where clinical exams found eye signs to be prevalent. An agricultural/health education approach, however, may be more appropriate for a population that may not have such an alarming clinical picture but that, by dietary history, has inadequate intake.

In addition to problems of definition, survey methods can present obstacles. Since vitamin A deficiency is a relatively rare occurrence, the sampled population must be quite large to ensure the accuracy of the estimate of the rate of deficiency. Using figures from an heroic effort to determine the extent of the problem in the country of Indonesia as an example[79], 4 cases were discovered among 4147 children in one zone where children were examined for active corneal xerophthalmia. This gives a rate of about 10 per 10,000. In spite of the large (from a logistic standpoint) sample size, the 95% confidence limits for the prevalence in the sampled zone were 0-21, meaning that one could be 95% certain that the true prevalence fell into this range. It is also known that vitamin A deficiency clusters in neighborhoods which makes getting an accurate estimate even more difficult[80]. The seasonality of vitamin A deficiency[81,82,83] and the spontaneous resolution of some clinical signs add to the difficulty in establishing the true prevalence of this condition. Cross-sectional and cluster surveys must take these facts into account when attempting to assess the extent of the problem.

C. Recent Prevalence Surveys

Numerous surveys have been conducted in several countries or regions that have added to the body of knowledge of vitamin A deficiency. The effort by Sommer et al.[79] to establish the extent of the problem of vitamin A deficiency in Indonesia was a massive undertaking. These researchers found an annual incidence rate for corneal xerophthalmia of 0.27% and a prevalence of 0.064% in rural Indonesia. The prevalence data for rural Indonesia were based on 20 cases of corneal xerophthalmia. While the relevance of these findings is diminished over time and the use of disaggregated data is fraught with problems of validity[80], much useful information can still be obtained from this survey done over a decade ago. The results of this survey have been the basis for the often cited extent of the problem in four of the most populated countries in Asia[84]. Extrapolation of the Indonesian findings to these neighboring Asian countries may be done but with an attendant increase in the margin of error, ie. there is a greater range for both over- and underestimating the extent of the problem. Fortunately, there are reports from these countries to support the conclusion drawn from the Indonesian data.

The island of Cebu in the Philippines was the site of a study that initially used a survey to determine the prevalence of vitamin A deficiency. Solon et al.[25] assessed 1715 children from 626 families from three areas in each of four ecological zones. There were about 100 1-6 year olds and about 50 7-16 year olds in each of the 12 areas. The prevalence of all clinical signs (except X1A) was 4.5%, of low or deficient serum retinol levels was 57%, and of both was 2.9%. The validity of these rates when using more than one child per family could be questioned on the basis of the clustering of vitamin A deficiency[85]. There are, however, little published data from other equally rigorous surveys in the Philippines with which to compare these findings.

India has a reported prevalence rate of corneal disease of 0.24% and of non-corneal xerophthalmia of 8.0% among children 1-5 years old[76,86]. The rates are particulary high in the south of India where hospitals report hundreds of cases of keratomalacia each year. While there is variation between states and over time, many areas of India report rates which exceed WHO criteria for a public health problem.

Reported rates in Bangladesh are similar to those in Indonesia[76]. From the Matlab research area a prevalence rate of 0.47% is reported for all forms of xerophthalmia among children aged six years and less[35].

Additional information has recently become available from Nepal[38]. In a point prevalence survey using a multistage sampling design with consideration for geographic representation and proportionate population samples, 6118 children 1-14 years old were evaluated (96.9% of those eligible from the sampling frame). The prevalence rates were 0.03% for corneal ulcers among preschoolers (one case), 1.3% for Bitot's spots among preschoolers (39 cases), and 1.1% for night blindness among all children (66 cases).

The extent of the problem of vitamin A deficiency in Africa is not accurately known[76]. Few sound surveys have been recently done on the continent, although many case reports and hospital or clinic based data are available[87,26]. One country-wide survey was noted in Kenya that looked at the prevalence rates among children under age six and found no significant problem as defined by the WHO prevalence criteria[87]. In one region of Malawi, a probability-based cluster sampling technique was used to assess blindness in children under six years[26]. Signs of xerophthalmia and history of night blindness were sought from the 5436 children (99% of those eligible from the sampling frame). A total prevalence rate of 3.9% for all signs of active xerophthalmia is reported suggesting that this region has a problem of public health significance. The specific rates were 0.06% for corneal disease (3 cases), 0.33% for Bitot's spots (18 cases), and 5.39% for night blindness (184 cases). De Sole et al[27] assessed 2647 Ethiopian children aged 6 months to 6 years. They utilized a cluster sample technique with systematic selection of households. They discovered prevalence rates of 0.6% for active corneal disease (16 cases), 0.4% for corneal scar (11 cases), and 3.89% for Bitot's spots (103 cases). In a subset of their population, where monocrop grain farming was the rule, the rates were 0.8%, 0.5%, and 5.0% respectively.

The extent of the problem of vitamin A deficiency in the Americas is not well known due to a lack of current data. Extensive surveys showing significant levels of vitamin A deficiency were conducted in Haiti and El Salvador over a decade ago[76,88]. While these are outdated, the situation now in those countries is sufficiently similar to suspect that the problem remains. Guatemala had had a now discontinued program of

remains. Guatemala had had a now discontinued program of fortification to deal with hypovitaminosis A but it is possible that this intervention may be reinstituted. In Brazil, 4991 children were examined in several areas in the northeastern state of Paraiba[83]. In one area the observed prevalence rate of Bitot's spots among preschoolers was as high as 1.9% (n=570). The presence of clinical signs of xerophthalmia was noted to a lesser extent in other areas. There is little survey information from other regions in the Americas.

D. Summary

Knowing the true extent of the problem of vitamin A deficiency in any given situation is difficult. There are problems in establishing the prevalence of vitamin A deficiency which include as yet inconsistent case definitions, the rarity, clustering and seasonality of the condition, and the expertise and resources required for the determining of vitamin A status. The problem has been best studied in Asia, though even there and certainly elsewhere in the world, surveys are becoming outdated. In many countries which have had or potentially could have a significant problem of vitamin A deficiency, there have been climatologic, political and economic changes which could dramatically change the situation.

V. INTERVENTIONS AND PROGRAMS

A. Determining the Need for an Intervention

Establishing the need for an intervention to deal with vitamin A deficiency means assessing vitamin A status and invokes the problems associated with assessment that have been covered proviously. The first line of investigation is usually an examination of hospital or clinic records for cases of xerophthalmia, although misdiagnosis may make this an unreliable source. As previously indicated, prevalence surveys are difficult and costly due to the sample size needed for a reliable estimate. Current research efforts are focused on field applicable means for assessing vitamin A status reliably and rapidly. If a word exists in the local language, this helps in case-finding and indicates that at least the local population has recognized the problem. Once a need for a program has been determined, the data or evidence must be strong enough to persuade public health officials or a Ministry of Health that vitamin A deficiency should be a priority.

B. Targeting Vitamin A Programs

Vitamin A interventions have usually targeted preschool children given that this appears to be a high risk group for vitamin A deficiency particularly as manifest as blindness. The risk factors that were significantly associated with vitamin A deficiency in urban Bangladesh after controlling for demographic factors, included lack of maternal knowledge about vitamin A, poor dietary vitamin A intake, and cessation of breast-feeding [37]. This study concluded that programs should focus on dietary approaches such as support of breast feeding and provision of food

supplements "targeted at slum dwelling families, particularly those with large numbers of children."

While associated with vitamin A deficiency[37], low SES and lack of maternal education have not been specifically targeted for vitamin A interventions. As suggested above, vitamin A deficiency may be a marker for these common findings. Low SES and lack of maternal education are also associated with increased childhood morbidity[51], so that targeting ill children for capsule delivery, for instance, is one way to cover these other risk factors. Other perhaps more sustainable and development oriented interventions, such as income generating projects, home gardens, nutrition education programs and women's education, may also have an impact on vitamin A deficiency.

Targeting on the basis of acute illness and malnutrition has been considered given the association of vitamin A deficiency with various childhood morbidities, ie. diarrhea (particularly prolonged diarrhea), acute respiratory illness, urinary tract infection, measles and protein energy malnutrition. The clinical setting would be the most logical place for such targeting and in some areas of the world, Tanzania for example, all hospital admissions of measles are treated with vitamin A. Clearly, targeting all families with children treated for malnutrition for dietary education may prove efficacious.

Recommendations for treating diarrhea and measles with vitamin A were discussed at the 1987 IVACG meeting in Addis Ababa. Administration of vitamin A to children with diarrhea was presented as a prophylactic intervention to prevent vitamin A deficiency that is associated with diarrhea, and as a way to extend coverage of children at risk[89]. The expectation that vitamin A administration might also reduce the incidence and severity of subsequent episodes of diarrhea was mentioned but the need for further research to confirm this was underscored. It is not clear which type of diarrhea responds best to vitamin A administration, so it is difficult to construct unambiguous operational recommendations for what episodes to treat, with what dose and how frequently. Assuming that the question of the absorption of vitamin A is answered, the effect, if any, that vitamin A has on an ongoing episode of diarrhea needs to be determined. Is this effect greater for dysenteric syndromes or secretory types of diarrhea? If the effect of vitamin A is on prevention of subsequent episodes, does this effect apply to all types of diarrhea or to specific pathogens? What is the effect of vitamin A administration on the duration of diarrheal episodes? What is the effect of vitamin A on the growth of the child recuperating from a diarrheal episode? More applied research in this area is needed.

The expectation that reaching the high risk groups will be facilitated by targeting acute illnesses, such as diarrhea, through clinics may not be valid. Targeting morbidity is dependent on contact with a health worker or clinic. A maximum

of 5-10% of diarrheal illnesses reach the health clinic, and often the ones that reach the clinic are not the poorest, least educated families most at risk for vitamin A deficiency (personal communication with Kenneth Brown MD, JHU SHPH, Div of Nutrition). Health seeking behavior, distance from the home to the health center and availability of health centers and of vitamin A interventions in health centers will also modify the hoped for increase in coverage.

One could argue that delivering vitamin A, for instance as a capsule, to ill children perhaps reaches these children too late. This may be especially true of hospital admissions who, depending on the disease in question, are frequently quite moribund by the time they reach the hospital. Even as adjunctive therapy, it would seem overly optimistic to expect reversal of advanced pathology by vitamin A in hospital settings. It may be more effective to try to reach the high risk groups in community based, preventive effort before infection precipitates a more acute situation for the high risk child. However, at present the data to support one mode of targeting versus another are inconclusive.

C. Preventive Interventions

Until recently, the objective of intervention programs has been to prevent clinical xerophthalmia and the ensuing blindness. Thus far, vitamin A intervention programs have not been specifically geared at reducing childhood mortality and morbidity, although this is what is currently being considered. When either objective is discussed, the same means of dealing with vitamin A deficiency are usually considered. There are three well described preventive strategies for improving vitamin A status; these include: 1) periodic large dose vitamin A distribution, 2) fortification of a widely available and consumed food, and 3) agricultural and horticultural programs with a large dietary education component[78]. That treatment programs for acute xerophthalmia are important goes without saying but these efforts will not be discussed here.

The use of vitamin A capsule distribution is generally regarded as an interim (temporary) measure for the control and prevention of vitamin A deficiency. The recommended dosing schedule for a vitamin A capsule distribution program is 200,000 international units given twice a year. The dose for children less than one year of age or who are significantly underweight is 100,000 I.U. twice a year. While the capsule is relatively inexpensive, as might be expected, the costs of distribution are significant unless a well developed infrastructure exists and can absorb the expense. It may be more cost effective to tie the distribution of capsules to some other health intervention already in operation, such as vaccination programs or other regularly occurring events. A recent WHO report of an EPI Global Advisory Group Meeting (11/9-13/87) proposed that the addition of iodine and vitamin A administration to the EPI program would be feasible and cost effective in that these nutritional supplements

separate distribution system. Field trials of this proposal are being discussed for Rwanda and Pakistan as reported by Nicholas Cohen from WHO at the recent IVACG meetings.

Coordination between clinic and community based distribution is necessary to prevent potential overdosage, particularly if multiple criteria for dosing are used, eg. biannual prophylaxis and dosing during diarrhea. This unfortunately underscores the need for good record keeping. In Indonesia, the growth monitoring and immunization card that is given to the child's family to keep has an area devoted to recording of vitamin A receipt. Unfortunately, it is not universally used. However, given proper training and supervision, the use of these cards can be reinforced and the monitoring of vitamin A receipt made much easier. The issue of monitoring capsule distribution in areas where there are multiple channels for distributing vitamin A is important and requires operational research to answer the question of how potential overdosage can be avoided.

While capsule administration fits into a medical/ pharmaceutical model for the control of vitamin A deficiency, the more long term measures of fortification and dietary/ horticultural interventions are more appealing to those who ascribe to a broader development approach. These long term approaches may face the limitations of increased costs, and of the need for education, resources and the political will required to implement them. Fortification with vitamin A of a food that is widely consumed, e.g. tea, sugar, or monosodium glutamate (MSG), will only be effective if the high risk groups can buy and will consume the fortified product. Fortification of a food is usually a large scale undertaking, eg. done on a national level. Research efforts are now underway in several settings which would clarify many questions about this promising method of intervention.

Dietary education and horticultural interventions are more easily implemented on a smaller scale. Some approaches to this method of intervention have been suggested by previous epidemiologic surveys. A case control study conducted with a xerophthalmia prevalence survey in Malawi also found a strong association between early cessation of breast-feeding and poor weaning practices and xerophthalmia[90]. Given these findings, the focus on prolonging breast-feeding and improving weaning practices that many nutrition programs already advocate, may have an impact on vitamin A deficiency. Dietary education is, however, a formidable undertaking given how rigidly dietary habits are often held. Agricultural programs in turn must overcome cultural preferences as well as region specific obstacles, e.g. cultivation of vitamin A rich foods in poorly arable land (the altiplano of Bolivia, drought prone areas).

D. Comparison of Various Interventions

Three intervention programs, capsule distribution, MSG fortification and dietary education, have been compared in Cebu in the Philippines[91] in a pre- and post-intervention evaluation design. Over the two year period of the study MSG fortification was the only intervention that significantly decreased clinical signs and resulted in a rise in serum levels of vitamin A. Capsule distribution, 200,000 I.U. every six months, reduced the prevalence of clinical signs significantly but did not change serum retinol levels. A cost-benefit analysis was performed as well, which indicated a high benefit-cost ratio for both MSG fortification and capsule distribution. A low benefit-cost ratio for the public health/horticultural intervention was calculated, although the "non-vitamin A related benefits" were not included in the calculation. The estimated annual costs of the interventions, implemented between 1973 and 1975, were $63 per barrio (300 households) for capsules, $173 for MSG fortification, and $2840 for public health/horticultural program. The authors projected that, if done on a national level that would allow for economy of scale, fortification would cost less.

This technically difficult and yet informative study has certain limitations that bear attention. There was insufficient time for the longer term, public health interventions (provision of a community health worker, environmental sanitation, deworming, immunization, and nutrition and health education) or horticultural development to demonstrate an impact. Certainly, this program's non-vitamin A related benefits are important and should be accounted for as well. The impact of capsule distribution on serum retinol levels may not have been demonstrated because these levels were drawn six months after the capsules were given. (Data from Brazil have shown that serum retinol levels return to baseline 3-4 months after capsule administration[92].) There were no comparison groups and time and inter-village differences could have influenced the results independent of the interventions. For example, the lowest mean per capita incomes and the lowest levels of maternal education were found in the public health/horticultural villages, while the highest mean per capita incomes were in the capsule villages, and the highest level of maternal education was found in the fortification villages.

These interventions differ with regard to sustainability as well. Fortification is purportedly more sustainable than capsule administration, once the costs get passed onto the consumer. It remains to be seen whether those passed-on costs put the fortified product out of the reach of those who need it most, i.e. low SES group. The sustainability of nutrition education/horticultural efforts depends to a great extent on the agricultural potential of the terrain available to the target population, the mechanisms available for transferring the information and the resources available to implement any changes. An income generating component added to horticultural efforts may increase sustainability. Multiple factors may influence the

success or failure, the sustainability of any particular program. For example, harsher terrains like the altiplano in Bolivia, may be suitable sites for fortification of commonly consumed item than the more costly alternative of constructing and maintaining glass enclosed greenhouses. On the other hand, the political will (or lack thereof) necessary to actualize fortification may overwhelm such attempts if the problem of vitamin A deficiency is region specific (e.g the altiplano) and does not affect the entire country.

A cost effectiveness model for interventions aimed at the reduction of vitamin A deficiency in developing countries has recently been developed by Robert Tilden and Robert Grosse of the University of Michigan[93]. The interventions selected for this computer model were diet modification, fortification and capsule administration (200.000 I.U.). The model is designed to help the user chose the intervention that achieves the desired impact at the lowest cost given the particulars of the user's developing country setting.

Based on data generated by Sommer in 1976 in West Java, as applied to the Indonesian situation at various levels of expenditure per capita, diet modification was found to be the least cost-effective when the outcome of death reduction among 0-6 year olds was used. Fortification and capsule distribution were determined to be more cost-effective than diet modification. When the outcome of vitamin A deficiency reduction (an index comprised of health savings, deaths avoided, days lost and blindness avoided) was considered, fortification far out led the other interventions in terms of cost-effectiveness. When crude death rate reduction was used as an outcome, again fortification was the winner in terms of cost-effectiveness. However, these results were based on Sommer's findings of a reduction in childhood mortality of about 30%; results which may not be as generalizable or as conclusive as has been discussed in a previous section. Additionally, the spillover effects of diet modification into other areas of health were not be factored in, so the model may underestimate the effectiveness of this intervention in terms of crude death rate reduction.

Nevertheless, the model is a valiant effort at instilling more objectivity into the decision making process of policy makers. It is a flexible model that can accommodate several different kinds of input. Database inputs that are necessary to run the program are: 1) a disease profile, which includes the prevalence of vitamin A deficiency and the health damages due to vitamin A deficiency, 2) program components, including costs of training, materials equipment, salaries, assessment and evaluation, 3) projected success of the program which will include projected coverage, utilization of health care, quality of the program inputs, etc., and 4) ecological factors such as incidence of diarrhea and prevalence of protein energy malnutrition (PEM) in the community. Thus, the input requirements for this model are extensive, yet well balanced and

contemplated.

One must keep in mind, however, that the quality of the results generated by such a computer analysis can only be as good as the quality of the input variables used in the program. A prior section of this review has dealt with the cost, difficulties, and sources of error in estimating prevalence data on vitamin A deficiency. Prevalence is just one of the many input variables needed. In order to generate the above cost effectiveness conclusions, 'data' were input that originated from secondary sources, or were best guesses. The uncertainty of the inputs, however, is not reflected in anyway by the presentation of the output, the results. The definitive appearance of the results displayed on the computer screen could mislead policymakers unaware of the relative strength or weakness of some of the inputs used to generate the results. Therefore, given the controversy over the impact of vitamin A on childhood morbidity and mortality, the inputs into this cost effectiveness model must be considered carefully to avoid unrealistic and overly optimistic predictions.

E. Reported Program Evaluations

A brief mention of a clinical trial of Red Palm Oil in Central Java is included here for historic interest[94]. Four milliliters of red palm oil was administered to 1-5 year olds by their parents in two treatment villages, a third village received skim milk fortified with vitamin A and D, another village received a placebo and the last received no treatment. The outcomes examined were serum retinol levels and clinical signs. All intervention villages demonstrated a significant increase in mean serum retinol levels compared to the placebo and no treatment villages. The results on clinical signs are not interpretable on account of the small numbers employed. Both the red palm oil and the fortified skim milk were reportedly well received. Use of locally available sources of vitamin A, such as red palm oil, "elephant ears", and other greens, could obviate the need for importing and distributing capsules as well as fortification. In NE Brazil, a beta-carotene rich fruit, named "buriti", is used as a natural food supplement to reverse RDR defined marginal vitamin A deficiency in 21 days (personal communication with Barbara Underwood, PhD, National Eye Institute, NIH).

In the 1970's, several capsule distribution programs were evaluated via a pre- and post-intervention comparison of clinical eye signs. This pre- and post-intervention evaluation procedure has been the one recommended by IVACG (78,95). This method involves baseline and follow-up xerophthalmia prevalence surveys, the results of which may be confounded by insufficient sample sizes for the prevalence surveys, the seasonality of vitamin A deficiency, other interventions that may affect the availability of vitamin A and/or the prevalence of vitamin A deficiency, and socioeconomic changes that occur over the same time period.

The fortification of sugar with vitamin A in Guatemala was evaluated by cross-sectional sampling of serum retinol levels, which allowed for smaller sample sizes (n=500-700). When serum levels pre-intervention were compared to levels post-intervention, the distribution of serum retinol levels was shifted higher after the fortification[61]. Whether and how this improvement in biochemical status affected rates of childhood morbidity and mortality is unknown, but it did establish the efficacy of sugar fortification when measured biochemically.

An interesting method of evaluating of vitamin A programs that does not require baseline data is based upon the simple linear regression relationship that usually exists between the prevalence of Bitot's spots and age between one and five years [96]. Under the influence of an effective intervention, this linear relationship changes over time and the slope of the regression line decreases thereby reflecting an impact and degree of coverage. The advantages of this technique, sometimes referred to as " the slope test", are that it requires no baseline data, requires a relatively reliable measure (clinical exam for Bitot's spots) and the age of the child. The disadvantages of this approach are that the sample sizes required for surveying Bitot's spots are large, that there is a dependence on a strong relationship between age and Bitot's spots (apparently not universal), and that there is seasonality of Bitot's spots. Such evaluations were conducted in Indonesia and India with various degrees of success[97], and again were focused upon measuring the impact of vitamin A on xerophthalmia as opposed to morbidity and mortality.

A very extensive evaluation of the impact of a nationwide capsule distribution program on xerophthalmia was recently reported from Bangladesh[98]. While again the outcome of interest was clinical xerophthalmia, the results have operational implications for any on-going or future vitamin A programs. 22,335 children were examined for clinical signs and histories of night blindness and of vitamin A capsule receipt were obtained from clusters of 150 households selected within a stratified random sampling scheme that included the whole country. The coverage of the rural population was approximately 50% whereas that of urban populations was <20%. Interestingly, larger households with better socioeconomic status and better sources of drinking water had better coverage than poorer households. Despite the fact that the vitamin A program in Bangladesh is 10 years old, 83% of rural householders did not know that vitamin A "had anything to do with the eyes"[98]. There was no relationship found between xerophthalmia prevalence and vitamin A distribution, except for nightblindness where the mean rate of 43.4/1000 was observed for areas with coverage of 0-24% as opposed to a rate of 27.5/1000 for areas with >75% coverage. The above mentioned "slope test" revealed no change in prevalence of Bitot's spot relative to age, indicating no effect of the program on Bitot's spots.

In the discussion of the results of this evaluation, the authors identify the following problems with capsule distribution that may explain the low impact on mild xerophthalmia: 1) low coverage rate, (it is estimated that coverage rate should be >65% in order to demonstrate an impact[95]), 2) the children most at risk were not reached, for unstated reasons there is better coverage of children less at risk (that the groups most at risk were not reached is supported by the Aceh study[50]), 3) depleted initial vitamin A status accompanied by poor nutritional status in general dilutes the effect that one 200,000 I.U. capsule can have. The authors suggest that alternative methods are needed to improve the efficacy of the vitamin A capsule program. These efforts include targeting high prevalence seasons for capsule administration, fostering home gardens, improved weaning practices and fortification of wheat with vitamin A.

Evaluation of India's capsule distribution program in the later 1970's was a similar large scale effort, involving examination of 69,000 children in 8 states in India[99]. The above mentioned slope test was utilized to assess the impact of capsule distribution on Bitot's spot prevalence. From an operational standpoint, however it was discovered that poor maintenance of records, lack of community nutrition education, little awareness in the community of the role of vitamin A (80% knew nothing of the program), and poor supervision were the main problems encountered with capsule distribution. The recommendations that were made subsequent to this evaluation were for better training of the supervisors and the distributors, with an emphasis on education and record keeping, shorter and more precise recording forms, and nutrition education in the community.

These evaluations underscore the interim nature of capsule distribution and the vagaries of reaching those children most at risk. Operationally, it would have been helpful to know what factors specifically impeded capsule distribution in the low coverage areas, and conversely what contributed to the high coverage achieved in other areas. For instance, at the village level, was the level of capsule coverage a function of a particular type of distributor, capsule supplier, the accessibility of the target population, the demand for capsules, etc.?

Additionally, these evaluations indicate a need for nutrition education and social marketing. Nutrition education has been favorably evaluated to a limited extent with regard to its effect on knowledge, attitude and practices of participants[100], however, more research is necessary. The role of social marketing should be to create demand, thus increasing coverage and thereby increasing efficacy of the program. Trials of social marketing approaches are underway in Indonesia and Thailand. Operationally, the social marketing component has been viewed as an interim measure until the vitamin A intervention becomes established, but it may well need to be a sustained effort, with messages cycled through at regular intervals, and renewed

periodically to avoid message burnout. It has yet to be determined how cost-effective social marketing will be.

The interested reader is referred to C. Fischman's AED review[101] which summarizes the experience of current programs with social marketing efforts and nutrition education.

In summary, it is unrealistic for private voluntary organizations or smaller scale MOH programs to attempt to measure the impact of vitamin A on morbidity or mortality. The numbers required to demonstrate the impact of any vitamin A intervention are very high, perhaps larger than the target population of the program. Sophisticated tracking and recording systems would be necessary in addition to a control group in order to attribute solely to vitamin A any effects seen. Even if it were possible to catalogue all deaths in a sufficiently large population or to keep track of all diarrheal episodes in a smaller population, it would be impossible to isolate the effect of vitamin A from the effect of other interventions that a PVO or MOH is most likely concurrently implementing. It is more realistic that the focus of private voluntary or smaller MOH projects should be the evaluation of process as opposed to impact indicators, switching the emphasis from evaluation of efficacy to evaluation of delivery and sustainability.

VI. CURRENT PROGRAMMATIC ACTIVITIES

All current US Agency for International Development funded projects are nicely summarized in "Evaluation of Vitamin A Intervention Programs: Focus on IEC/Social Marketing" by Claudia Fischman of the Academy for Educational Development (AED)[101]. This document also highlights the potential for social marketing and nutritional education components in these projects.

VII. RECOMMENDATIONS

A. Research Efforts

Besides more specific suggestions made in the text as to areas needing additional research, continued support and/or funding for research efforts are also necessary to establish:

1. the magnitude of effect of vitamin A on childhood morbidity and mortality.
2. prevalence of vitamin A deficiency in suspected vitamin A deficient areas.
3. field applicable, reliable, valid, inexpensive methods of vitamin A assessment.
4. means of improving distribution of vitamin A capsules to high risk, difficult to access populations.
5. means of reaching difficult to access groups with various fortified foods.
6. means of optimizing results with dietary education and horticultural training efforts applied to high risk groups.

7. cost effectiveness of vitamin A programs recognizing the differences in vitamin A epidemiology in different areas of the world.
8. identification of indigenous food sources of carotene rich foods for child feeding.

B. Program Efforts

Programs aimed at the eradication of vitamin A deficiency must take into account several points. Limitations of the data suggesting the need for a program (both over- and under-estimations) must be taken into account. Program design should target high risk populations if possible. These efforts must consider sustainability and the ability to be integrated into other health care activities in the area when apropriate. Additionally, any effort must include a means of evaluation which is realistic for the situation. This will in many cases, especially for small efforts, not involve the measurement of changes in morbidity and mortality rates.

Support for programmatic efforts could include:

1. facilitating fortification where appropriate.
2. increasing capsule coverage where appropriate.
3. collection of other information that would allow for the compilation of a profile of demographic, socioeconomic and geographic factors describing those who have received the capsules versus those who have not recieved capsules. (This information could be fed back into the system on the next round of distribution in order to increase total coverage but specifically to increase coverage of those at high risk.)
4. exploration of ways that vitamin A interventions can be incorporated into ongoing programmatic activities, especially growth monitoring, nutrition education, food supplementation programs and primary care.
5. more long term solutions, ie. dietary and horticultural programs, with particular examination of their sustainablity.
6. insisting on realistic program evaluation for each effort, emphasizing process indicators as opposed to impact indicators until further research elucidates the proper impact indicators. (This could best be accomplished by convening a meeting of vitamin A consultants who have been involved personally in the evaluation of vitamin A programs. The objective of the meeting would be to derive a list of indicators for program implementation, monitoring and evaluation.)
7. the review of results of current social marketing trials to decide whether this is a cost-effective addition to current programatic activities.
8. the evaluation of different modes of distribution to determine which mode reaches the high risk

groups most effectively.

9. the development of operational guidelines for field staff for identifying those children to treat with vitamin A if research efforts demonstrate that vitamin A supplementation of children with diarrhea or LRI is effective.
10. the development of modes of monitoring capsule distribution from multiple sources that would safeguard against overdosage.
11. incorporation of indigenous and culturally acceptable carotene rich food sources into child feeding programs and nutrition education.

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