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Vitamin A deficiency as a public health problem & assessment methods

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INTRODUCTION

A conservative estimate according to WHO is that today there are 1.5 million children under 16 years of age who are blind, that 0.5 million new cases occur annually, and that 70% of these new cases are due to vitamin A deficiency (VAD 1). With this incidence of VAD blindness, why does it account for only 4-5% of the total number of blind people in the world (27-35 million)? Tragically it is because 60-70% of those children who become blind die within a year, and therefore are not present to be counted as blind adults. As a result, VAD blindness does not appear to be competitive for public concern with other causes of blindness. But this estimate based on blindness does not reflect the true consequences for child health and survival of the problem of VAD. There are 5-10 million additional children with milder clinical ocular signs of VAD, night blindness and Bitot's spots, who die from infections at least twice the rate of those non-deficient, and another 40-50 million without eye symptoms or signs whose body supply is depleted to a point where their health, survival, and development may also be compromised (2).

Based largely on the occurrence of ocular signs, the WHO in 1987 mapped the global occurrence of VAD as a public health problem. Some 34 countries were identified and these were largely found in Asia and Africa. Clinical VAD is not commonly reported in Latin America and the Caribbean and WHO only identified suspect areas that require continued monitoring. But subclinical VAD may be wide spread in the region and possibly in some areas a contributing factor to high young child mortality and morbidity. Only now are studies underway to reassess the problem on this continent.

REVIEW OF RECENT STUDIES OF VAD AND CHILD HEALTH AND SURVIVAL

Using newer techniques for assessing marginal vitamin A deficiency (3), data indicate that in some developing countries with documented inadequate dietary intakes of vitamin A, 40-50% of the preschool-aged children may be subclinically deficient. Recent surveys conducted in Belize by Dr. Makdani and colleagues revealed over 60% with inadequate liver stores as indicated by the RDR. Gadomski and the group at CeSSIAM report 11-18% deficiency using a variety of assessment techniques. Dr. Flores used the RDR to assess vitamin A status among underprivileged urban children in NE Brazil and found nearly one-third sub-clinically deficient. An earlier study that was done among similar children in Recife who developed chickenpox, a common childhood infection, demonstrated how such infections deplete body supplies of vitamin A and that such a depletion can be detected using the RDR methodology before serum levels are substantially lowered. This early detection is important because the survival of depleted children is at risk when they contract common, and normally not life-threatening, childhood infections such as measles, diarrhea, and acute respiratory infections. The remarkable effect on case fatality from these infections,

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however, has not been conclusively linked to the incidence of infections. As with blinding malnutrition, those children under 3 years of age are at greatest health and survival risk. Although it is well recognized that the health effects of VAD are especially pronounced when associated with severe protein-energy malnutrition (PEM), recent data suggest that its most devastating effect on mortality risk occurs among chronically undernourished (stunted) children (4). These are the children who generally come from the most socially and economically deprived homes, the ones least likely to be reached by the usual government health programs.

Since the landmark study reported from Aceh, Indonesia claiming more than a 34% reduced risk of mortality by providing a high-dose vitamin A supplement 6-monthly (5), a series of clinical trials has been carried out in several countries to test the replicability and universality of these findings. The results have been variable. Some studies have provided a continuous supply of the vitamin at near physiologic levels through low-dose supplementation (4) or fortified foods, as with fortified MSG (6), to populations of children, where the prevalence of chronic undernutrition and xerophthalmia is high to moderate, and have reported mortality risk-reductions of 30-50%. Other trials have distributed high-dose supplements at 4-6 month intervals and the results range from no significant impact (7-8) to a 30% or greater risk-reduction (9,10). Some trials using high-dose supplements in Asia, Africa, and Latin America are still in progress and their results are eagerly awaited (11).

The variable experiences from completed mortality-risk trials emphasize the importance of identifying the existing mix of physiological and socio-economic conditions that appear to be most responsive to vitamin A interventions for the betterment of child health and survival. The end of May, a meeting at WHO drew together the principal investigators from the 10 studies listed on the last two slides to discuss these issues (11). After careful review of baseline characteristics and outcomes, the group agreed that some of the reasons that may explain the variable impacts of vitamin A supplementation on mortality among populations studied include differences in:

a) severity of the underlying VAD;
b) severity of the underlying malnutrition and its characteristics, i.e., acute and/or chronic;
c) exposure to illness and causes of death;
d) access to health facilities, including immunization coverage;
e) socioeconomic status, particularly literacy, affecting mothers and their children.
f) it was acknowledged that presupplementation mortality rates are also likely to be important because where these rates are quite high, such as was the case in Jumla, Nepal, any health and/or nutrition intervention is likely to impact on mortality.
g) it was also conceded that differences in study design and implementation could also contribute to the variable results.

Again, I would emphasize that where VAD has been associated directly with a reduced mortality risk from infections such as diarrhea, as in the Tamil Nadu study, it is more difficult to unambiguously link the problem with morbidity incidence. Controlled clinical trials in field-based settings have failed to make this linkage using the currently available methodologies for determining incidence and severity of illnesses (12,13). A linkage probably exists and is most likely related to severity and lethality, i.e., case fatality, rather than incidence. Institutionally based studies of severe measles in Africa, clearly link the vitamin to at 50% reduced measles mortality (14) and to reduction in the duration and severity of measles-related morbidities (15). This suggests that the immune system is more critically altered than are the mucosal barriers to pathogen penetration. It clearly indicates that vitamin A is no "magic bullet" to child health. Public health programs that address underlying causes of illness are of critical and concurrent importance. Vitamin A interventions, therefore, should not be introduced at the expense of proven effective public health interventions.

VAD has health-related effects for children beyond those of ocular health and mortality risk. Studies have also shown that among certain populations an adequate vitamin A status improves iron utilization and thus reduces the prevalence of iron deficiency (6). Iron deficiency is likely to be even more prevalent and detrimental to child health than that of VAD and the two problems frequently occur together. Programmatic attacks on these two micronutrient deficiencies, therefore, should be considered concurrently.

Some, but not all studies, claim that child growth is enhanced by improved vitamin A status (6,12,16). Growth, of course, is influenced by many factors, including frequency of illnesses and diet. In some circumstances, PEM rather than vitamin A may be more limiting to growth, and in still other situations additional micronutrients, such as zinc, may also be pivotal. Our studies in Tamil Nadu, India failed to show any beneficial effect on growth of the continuous supply of an adequate level of dietary vitamin A. It may be that in this setting, PEM was more limiting than vitamin A, or that because we did not influence the incidence of morbidity, particularly diarrhea, this was the more influential factor limiting growth.

In March 1990 the Steering Committee of IVACG released a statement summarizing the consensus view as to where we stood in relationship to determining whether vitamin A deficiency could substantially reduce childhood mortality. The recently completed meeting among the PIs

of the major trials has only slightly modified that statement but has extended it to note the most likely factors that are causing variation in outcomes. These factors I noted earlier.

a. vitamin A status between communities, including diet;
b. anthropometric (nutritional status) indices;
c. exposure to illness and causes of death;
d. access to health facilities, including immunization coverage;
e. socioeconomic status, particularly literacy, affecting mothers and their children; and,
f. study design and implementation.

Even though we await completion of studies still in progress with much eagerness, there is no doubt that VAD has an adverse effect on child health and development. For this reason there is no justification for not proceeding with efforts to improve vitamin A status where it has been shown to be inadequate. The group of investigators at the Geneva meeting reached consensus that of the several programs available it is the prerogative of governments to decide what best suits their situation. This should be based on an adequate assessment of the severity and magnitude of the problem and the national and local resources available to solve it.

ASSESSMENT OF VITAMIN A STATUS

Vitamin A nutriture exists as a continuum between clinically evident deficiency and toxicity. For most non-diseased individuals, their place on the continuum is determined by their habitual quantitative dietary intake of the vitamin. Intake is more or less directly related to liver stores. When liver stores become notably deficient or excessive, the signs and symptoms and the corresponding biochemical alterations in blood are well described. However, at intermediate levels of habitual intake covering a broad range of liver stores, blood levels are not sensitive to different levels of dietary intake, i.e., to different levels of body stores. This makes blood levels inappropriate for assessing where an individual is on the vitamin A status continuum, and insensitive also at the population level. Because of the implications for child health, development, and survival, assessing unsatisfactory vitamin A status (marginal) has assumed increased importance. Yet, a single, field-applicable, specific and sensitive methodology for assessing marginal status that is simple, rapid, and reasonably non-invasive is not available. There are several assessment methodologies, dietary, biochemical, and histological, but each has its limitations and used alone is not adequate. The best currently available means of determining prevalence and identifying at risk populations is to use a combination of two of more methodologies appropriately applied on a randomly selected population because the sample size, hence the resources required, to do prevalence studies based on rarely encountered clinical signs are prohibitive for most country budgets.

I will now discuss some of the newer methodologies for assessment of marginal vitamin A status.

DIETARY INTAKE METHODOLOGIES

The difficulty in obtaining representative quantitative historical dietary information, particularly on young children, through interviewing adult caretakers using the usual questioning techniques, are well recognized. Techniques that require weighing of foods eaten for one or more days provide quantitative information, but are impractical under most field survey conditions, and often are not representative of the usual intake pattern over a longer time span. A semi-quantitative dietary approach may be all that is required to place populations of children into risk categories for inadequate vitamin A status, especially if combined with a simple biologically-oriented parameter such as a history of nightblindness, an RDR, or a CIC assessment. For example, a simple dietary-nightblindness history approach, if predictive of prevalence, would narrow the population that might require additional confirmation of status through the use of more time consuming and costly physiological measurements, or who might be targeted to receive an intervention program.

In assessing vitamin A nutriture among children where 80-90% of the intake is from carotenoids contained in a limited number of food groups, the major determinant of vitamin A status will be the frequency and the portion sizes usually consumed of foods of high, moderate or low vitamin A activity. IVACG® recently has produced guidelines founded on the premise that a simplified dietary assessment questionnaire based on a food composition table adapted to the locally available foods and portion sizes fed children, can be developed that will categorize populations into "at risk" groups for vitamin A inadequacy. This semi-quantitative approach has been tried in several countries and currently experiences using it are being evaluated. It has been found useful for nutrition education and once developed is easily used by non-professionals. An even simpler version of the IVACG guideline that omits attempts to determine portion sizes is being developed and tested by HKI. Thus far the approach is useful for assessment but may be more limited in its use as an educational tool.

BIOCHEMICAL MEASURES

Marginal vitamin A status has been arbitrarily defined biochemically by assigning distinguishing cut-off concentrations to levels in blood, breast milk, or tissues. Usually the cut-off value is chosen to reflect the lower range of the usual distribution curve of populations where clinical malnutrition and vitamin A deficiency are rare. Or,

as in the case for liver reserves, the cut-off concentrations are selected to provide a calculated protective period before deficiency symptoms would be expected to appear. These are static biochemical measures that can only suggest the risk that physiological functions might be compromised in populations; they fail to indicate whether physiological functions in fact are compromised in individuals. As already discussed, blood levels are insensitive to relative vitamin A status in the marginal range in individuals although population-based distribution curves are useful. These have been discussed extensively in the past and are the topic of an article by Dr. Flores that will appear in the October issue of AJCN. In this article Dr. Flores suggests that a cut-off value of 30 μg/dl (1.05 μmol/L) is a more appropriate figure than the traditionally used 20 μg/ dl and he provides data to substantiate his claim from children from low income families in and around Recife, Brazil. Using this cut-off, the frequency distribution among low income preschool aged children from North and Northeast Thailand shows that more than 55% have lower values.

We do have other sophisticated techniques available, such as isotope dilution, which is the most accurate measure of status along the entire continuum spectrum, but this methodology is not practical in population-based surveys, and liver biopsy is not an option for surveys in living populations.

There are dynamic ways of using biochemical measurements, however, some of which are applicable both for individual and population assessment. These dynamic measures are based on a response to dosing. In most instances, two samples are required, one before dosing and at a specified time post-dosing. Dr. Flores has applied this approach at a population level using serum distribution curves at baseline and 30 days following dosing with a large dose of the vitamin on a randomly obtained population sample. A shift to the right in the 30-day post-dosing distribution curve indicates that a certain portion of the population were marginally deficient before dosing..

The similar concept, dose-response, was the basis for the relative dose response test (RDR) developed earlier to be applied at an individual level. In this case a small physiological dose of the vitamin is given and the serum response after 5-hours is determined. The RDR is an appropriate test to screen at the individual level for inadequate liver reserves. This approach lends itself to many survey situations also where one cannot return after 30-days, if it is done on a randomly selected subsample of the population surveyed. But it also is problematic because two samples from the same individual must be obtained in a brief period making compliance a potential problem particularly with children.

Recently, a modification of the procedure that uses dehydroretinol (vitamin A2, [DR]) and requires a single blood sample at 5-hours post-dosing, has been tested in children suspected of being vitamin A (retinol, [R]) deficient. The 5-hour post-dosing ratio of DR/R provides a measure of adequacy of liver reserves. The advantage of a single blood sample are partially offset by the fact that a relatively larger sample is required (venous), the analysis requires an HPLC, and the dehydroretinol currently is not commercially available.

The vitamin A carrier protein, RBP, has been used as a surrogate measure for retinol in the RDR procedure and in some serum surveys. Currently there is an effort to use it for assessment on a dried blood spot collected on filter paper and useful for other micronutrient assays as well. There are several factors that influence the level of RBP in blood in addition to vitamin A nutriture, and therefore, this approach requires additional evaluation before it can be recommended as a valid assessment approach.

FUNCTIONAL MEASURES OF VITAMIN A STATUS

Functional tests reflect whether the vitamin is sufficiently available for normal participation in its known metabolic activities. The recognized physiological functions of vitamin A that are useful for assessment purposes are: 1) generation of the visual pigment rhodopsin and, 2) maintenance of the differentiation of cells originating from the epithelium, including the production of goblet cells. The response in circulating holo-RBP (retinol bound to its specific binding protein [RBP]), after providing an additional exogenous source of vitamin A, the RDR test described above which is a measure of whether the vitamin is available in the circulation from liver reserves at its appropriate homeostatic level, could also be considered a functional test.

IMPAIRED DARK ADAPTATION

Night blindness.

Rhodopsin is generated when the protein opsin in the rods of the retina combines with a cis-isomer of retinol. The complex is split in response to light, yielding opsin and a trans-isomer of retinol and generating the visual response signal. After isomerization of the trans- to the cis-isomer, recycling of the process occurs at a rate that normally maintains the level of rhodopsin so that visual accommodation is not prolonged when going from brightly to dimly lighted conditions. When the retinol supply is limited, the rate of regeneration of rhodopsin after bleaching by exposure to bright light is impaired. The final dark adaptation threshold can be quantitatively measured. In practical terms, individuals who are deficient in vitamin A have difficulty seeing when going from bright to dimly lighted situations, i.e. they are "night blind".

Measuring nightblindness *objectively and reliably* among preschool aged children under survey conditions has not been successful. In the latter situation, a history of night

blindness elicited from the mother or responsible adult has been the most successful approach. This is true, however, only in cultures where a specific word or words exist that characterize the condition. Such a word usually, but not always, exists in areas with endemic vitamin A inadequacy. For example, in Bangladesh the Bengali term is 'rat kana', the Indonesian and Sundanese terms are 'buta ayam' or 'kotokeun' (chicken blindness) respectively. In Tamil Nadu, South India the term is 'malai ken' (evening eyes) and in Zambia it is 'kafifi'. Investigators must carefully determine under each local situation whether an appropriate term exists and can be reliably used in an historical interview.

Where local terms are not used, alternate strategies to indirectly test dark adaptation may be useful. For example, a child taken from the bright outdoor sun into a darkened room may be asked to find the waiting mother or sibling or to locate a favorite toy placed at a defined distance away. The time required to achieve this task relative to that needed for a similarly aged child known to not be deficient is compared.

Among school aged children, an instrument is currently being evaluated that measures the time required to restore vision after brief exposure to a bright light. This instrument requires the cooperation and response of the subject who is strapped to a fixed goggle for a period of several minutes. Currently the evaluation suggests that a delayed VRT is associated with other measures of inadequate vitamin A status but further testing is required. Attempts are also in progress to adapt the procedure to younger aged groups.

DIFFERENTIATION AND MORPHOLOGY OF EPITHELIAL TISSUES

The principle underlying this methodology is that when mucus-secreting epithelial tissues receive too little vitamin A, they develop a metaplasia which in some cases is characterized by keratinization (e.g. skin). In other epithelium, keratinization is minimal or does not occur (e.g. intestinal mucosa, lungs and conjunctive), but the number of goblet cells decline and, in deficiency, may be absent. In addition, the morphology of the epithelial cells may be altered to take on a squamous or flattened appearance with small nuclei and an expanded proportion of cytoplasm. Various modifications of a test in humans to evaluate the morphology of conjunctival epithelial cells are referred to in the literature as conjunctival impression cytology (CIC), or ocular impression cytology (OIC), and impression cytology with transfer (ICT).

The technique is relatively non-invasive when compared to obtaining blood, but experience in many cultures have found considerable resistance among children under 3 years in its application. Patients and care are required and a great deal of practice before one can be assured of obtaining reproducible results. It looks simple but this can be deceptive. Pitfalls in obtaining samples and in their appropriate interpretation if not recognized by investigators, can yield very unreliable data. A disk-applicator has been developed which is said to improve the consistency in obtaining reliable samples, but again, practice has shown that this can be even more frightening to children is some cultures and that, with practice, equal reproducible results are obtainable by the touch technique.

PROGRAMMATIC IMPLICATIONS FOR LATIN AMERICA AND THE CARIBBEAN.

Because of the complex interactions of the social, ecologic, and economic circumstances that contribute to the problem of malnutrition generally including VAD, simple solutions that are sustainable and can be universally applied are unlikely. Where clinical VAD is evident, there is no question but that vitamin A supplements are required, this is a medical emergency. But, where a clinical problem is rare, as is the case in much of this areas of the world, other more locally appropriate, affordable, and sustainable strategies should be considered that address not only the lack of vitamin A in the diet, but also the factors contributing to its inefficient utilization and conservation (17). These factors may include the incidence of infectious diseases, some of which could be prevented through broader immunization coverage and access to health care, and others through programs to improve environmental sanitation and personal hygiene. Programs that generate income for women and decrease the prevalence of illiteracy among them can contribute significantly, though indirectly, toward improved nutritional status and child health generally. Such measures will in turn reduce the problem of VAD.

One intervention that has proven effectiveness in this region is the sugar fortification program. Whereas this strategy, fortification, has not worked well for operational reasons in areas of the world lacking an adequate level of infrastructure development, this is not the case for most of Latin America. Because of the demonstrated potential, there may be other food vehicles that also reach the vulnerable populations that can be fortified. I am aware, for example, of the efforts of Dr. Dutra de Oliviera and his colleagues to fortify a cooking oil, and of others to fortify an atole variation of INCAPARINA.

However, I am also aware that there are under utilized food resources within the region that deserve more consideration. To increase their utilization in child diets will require behavioral change through appropriate nutrition education programs. Such programs where successful will improve the entire family diet. For example, Dr. Santos and her colleagues demonstrated in Paraiba, Brazil that the under utilized palm fruit, Buriti, found in the Amazonia when prepared as a candy at the community level was well

accepted by children and effective in improving their vitamin A status.

CONCLUSIONS

The recently held meeting in Geneva among principal investigators of large, population-based trials with vitamin A concluded the following:

"There are several possible strategies to ensure and sustain an adequate vitamin A status in all population groups, especially in young children. The choice of intervention is the prerogative of governments and should depend on specific country factors including the severity of the vitamin A problem, the resources available, and national priorities for their utilization (11)."

Countries of Latin America and The Caribbean are likely to house many children with subclinical VAD. It is imperative to determine if subclinical depletion exists and to identify where it occurs and the magnitude of the problem. The importance of this problem to child health should be acknowledged and sustainable, regionally and locally appropriate strategies for its alleviation be undertaken. Under all circumstances, attention should be given to effective nutrition and health education to achieve changed behaviors to improve the diets of children and improve their health. The technology is available to eliminate VAD as a public health problem and the political will has never been greater, as evidenced in the expressed goals of the UN Agencies' 10-year plans, UNICEF's Summit for Children, the Bellagio Declaration, and other documents that seek to achieve health for all by the years 2000 and the virtual elimination of VAD as a public health problem. The proclamations have been made; it is up to the people, including those of us working with our governments and constituencies, to make it happen.

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