INTRODUCTION & BACKGROUND

VITAMIN A DEFICIENCY (VAD)

Vitamin A is an essential nutrient needed in small amounts for the normal functioning of the visual system, growth and development, maintenance of epithelial cellular integrity, immune function, and reproduction. VAD occurs when body stores are depleted to the extent that physiological functions are impaired even though clinical eye signs may not be evident. Because the vitamin is fat-soluble it is stored in the body when intake is in excess of physiological need. Nearly 90% of that which is stored is found in the liver. Depletion of stored vitamin A occurs over time when the diet contains too little to replace the amount used by tissues or reduced by breast-feeding. The level of depletion at which physiological functions begin to be impaired is not entirely clear. What is known, however, is that the vitamin is actively recycled through the liver and among tissues, and it appears that rates of utilization by specific tissues can at least partially adapt to diminishing availability. This adaptation and recycling serves to maintain relatively constant blood levels until body stores become depleted below a critical point for which adaptation can no longer compensate (1).

The integrity of epithelial barriers and the immune system are compromised before the visual system is impaired. This leads to increased severity of some infections and risk of death, especially among children (2). When vitamin A depletion is sufficient to affect the visual system, nightblindness occurs first due to the body's decreased ability to generate rhodopsin, which is essential for vision in dim light. This is accompanied by a loss of goblet cells from the epithelial tissue of the eye and results in xerophthalmia ("dry eye") which can affect both the conjunctiva (conjunctival xerosis and Bitot's spot) and cornea (corneal xerosis), and may lead to corneal ulceration, invasion by microorganisms, and irreversible partial or total blindness (keratomalacia) (3).

Ocular symptoms and signs resulting from VAD—xerophthalmia—have a long, well-recognized history, and have until recently been the basis for estimating the global burden from the disease. However, it is now recognized that the health of far larger numbers of preschool-age children (4), and perhaps older children and pregnant or lactating women as well, is compromised by VAD, even at moderate, and possibly mild, sub-clinical levels.

Figure 1 illustrates the relation between age and basal requirements for vitamin A on the basis of body weight and recommended safe levels of intake. Required intake during pregnancy and lactation are included in Table 1. The estimated

![Recommended intake of Vitamin A (FAO/WHO, 1988)](image)

Fig. 1 Estimated basal requirements for vitamin A by age
basal requirements and safe level of intake for vitamin A by age group and sex are also given in Table 1. When weighted by a typical age-sex distribution in a population, the basal vitamin A requirement for planning purposes is 250 \( \mu g \) daily and the recommended safe intake level is 550 \( \mu g \).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Basal requirement</th>
<th>Safe intake level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( \mu g/day )</td>
<td>( \mu g/kg )</td>
</tr>
<tr>
<td>Both sexes</td>
<td>0-1</td>
<td>180</td>
<td>40-20</td>
</tr>
<tr>
<td></td>
<td>1-6</td>
<td>200</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>6-10</td>
<td>250</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>10-12</td>
<td>300</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>12-15</td>
<td>350</td>
<td>7.8</td>
</tr>
<tr>
<td>Girls</td>
<td>15-18</td>
<td>330</td>
<td>6.1</td>
</tr>
<tr>
<td>Women</td>
<td>18+</td>
<td>270</td>
<td>4.8</td>
</tr>
<tr>
<td>Pregnant women</td>
<td></td>
<td>370</td>
<td></td>
</tr>
<tr>
<td>Lactating women</td>
<td></td>
<td>450</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>15-18</td>
<td>400</td>
<td>6.1</td>
</tr>
<tr>
<td>Men</td>
<td>18+</td>
<td>300</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Vitamin A deficiency before, and 4 days after, receiving a single high-dose (200 000 IU) of vitamin A.*

Photo: B. Underwood
A 1989 estimation of the global supply of vitamin A is summarized in Table 2 according to WHO and UNICEF regions (6). In recent years a slight increase in total supply has occurred in all regions of the world except in parts of Africa where supplies, apart from North Africa, have remained unchanged or declined. The increase has occurred mainly in vegetable rather than animal sources of vitamin A with the exception of China where per capita intakes from animal sources have increased. Although the available global vitamin A per capita is above basal requirements, safe levels of intake are not met in South and South-East Asia, or in East and Southern Africa.

Table 2. Available supply of vitamin A by WHO region (μg RE/day)*

<table>
<thead>
<tr>
<th>Region</th>
<th>Total</th>
<th>Animal</th>
<th>Vegetable</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>776</td>
<td>122</td>
<td>654</td>
</tr>
<tr>
<td>AMR</td>
<td>814</td>
<td>295</td>
<td>519</td>
</tr>
<tr>
<td>SEAR</td>
<td>431</td>
<td>53</td>
<td>378</td>
</tr>
<tr>
<td>EUR</td>
<td>738</td>
<td>271</td>
<td>467</td>
</tr>
<tr>
<td>EMR</td>
<td>936</td>
<td>345</td>
<td>591</td>
</tr>
<tr>
<td>WPR</td>
<td>997</td>
<td>216</td>
<td>781</td>
</tr>
</tbody>
</table>

Available supply of vitamin A by UNICEF region (μg RE/day)*

<table>
<thead>
<tr>
<th>Region</th>
<th>Total</th>
<th>Animal</th>
<th>Vegetable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern &amp; Southern Africa</td>
<td>453</td>
<td>137</td>
<td>316</td>
</tr>
<tr>
<td>Central &amp; West Africa</td>
<td>1035</td>
<td>105</td>
<td>926</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>951</td>
<td>336</td>
<td>615</td>
</tr>
<tr>
<td>East Asia &amp; the Pacific</td>
<td>850</td>
<td>168</td>
<td>682</td>
</tr>
<tr>
<td>Americas &amp; the Caribbean</td>
<td>814</td>
<td>295</td>
<td>519</td>
</tr>
<tr>
<td>Devl./Indus. countries</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>South Asia</td>
<td>435</td>
<td>71</td>
<td>364</td>
</tr>
</tbody>
</table>

* Source: ACC/SCN

Per capita availability data must be viewed with caution. For example, the highest per capita availability of vitamin A-activity in foods is found in the Sahelian belt and West Africa, most of which is from vegetable sources of provitamin A. In these African regions, clinical VAD is endemic just as it is in South Asia where the available per capita supply, also largely from vegetable sources, is two-fifths as great. Clearly per capita data can

Some vegetable sources of vitamin A.
Photo: B. Underwood
Table 3. Type of data available by WHO region

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of countries</th>
<th>No data or data prior to 1980</th>
<th>Data since 1980</th>
<th>National sample</th>
<th>Sub-national sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>46</td>
<td>19</td>
<td>27</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>AMR</td>
<td>36</td>
<td>22</td>
<td>14</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>SEAR</td>
<td>11</td>
<td>3</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>EUR</td>
<td>50</td>
<td>47</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>EMR</td>
<td>22</td>
<td>13</td>
<td>9</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>WPR</td>
<td>26</td>
<td>14</td>
<td>12</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Country data presented in this document are not all based on representative national sampling. A listing of the type of data available by region and used to derive the summary tables is given in Table 3. A country-by-country evaluation of the available data is provided in the notes for each country to assist readers in interpreting the prevalence data. In several countries, current information is not available and judgements were made based on projections as to how recent events would likely influence earlier prevalence data. Attention is drawn to the fact that data are not available or current for a large number of countries in those regions where VAD is widespread. Thus, the estimates in Table 4 reflect only available data and should not be interpreted as the total population "at risk" either regionally or globally. Based on the available data projected to reflect conditions in 1994, the global estimates of the numbers of children 0-4 years of age clinically affected is 2.8 million, and severely and moderately subclinically affected (taken as one category), is 251 million. These estimates are provided by country in the summary tables and are summarized by WHO region in Table 4.

Table 4. Estimates of affected and at-risk populations

<table>
<thead>
<tr>
<th>Region</th>
<th>Clinical (x10^6)</th>
<th>Subclinical severe &amp; moderate (x10^6)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>1.04</td>
<td>52</td>
<td>49.0</td>
</tr>
<tr>
<td>AMR</td>
<td>0.06</td>
<td>16</td>
<td>20.0</td>
</tr>
<tr>
<td>SEAR</td>
<td>1.45</td>
<td>125</td>
<td>69.0</td>
</tr>
<tr>
<td>EUR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>EMR</td>
<td>0.12</td>
<td>16</td>
<td>22.0</td>
</tr>
<tr>
<td>WPR</td>
<td>0.13</td>
<td>42</td>
<td>27.0</td>
</tr>
<tr>
<td>Sub-Totals</td>
<td>2.80</td>
<td>251</td>
<td></td>
</tr>
</tbody>
</table>

| TOTAL | 254 |

*Based only on a projection for 1994 from those countries in each region where data were available. See Table 3 for numbers of countries without data.

**Epidemiology of VAD**

VAD as a public health problem occurs within an ambience of ecological, economical and social deprivations in the macro-environment in which populations are found (i.e. regions and countries), and in the micro-environments in which families live (i.e. communities and households). The rela-
tive influence of causal factors at both the macro-
and micro-level will vary among countries, and
even regions within countries, necessitating a
situation analysis to understand and subsequently
design appropriate and effective intervention pro-
grammes to change specific undesirable situations.
It is, therefore, with considerable reservation that
national and global projections are made that could
be inappropriately applied to local situations.
Nevertheless, there are some underlying
epidemiological traits that tend to characterize
most situations where VAD occurs as a public
health problem (8). These are described below.

Ecological factors

At the macro-level, hostile environments, e.g. arid,
infertile land, or the periodicity of excessive rain
and humidity, in part determine the variety and
amount of foods rich in vitamin A-activity that can
be grown, and the duration of their availability.
This applies particularly to vegetables (e.g. green
leafy vegetables), and fruits that require abundant
water supplies and/or moderate temperature to
grow. Where the necessary favourable growing
conditions occur in food-scarce countries, even if
only seasonally, national agricultural policies
generally favour production of staples as food for
local populations. From a national perspective,
vegetable and fruit crops are of less importance
and thus do not compete for land use. Crops rich
in vitamin A-activity for local consumption,
therefore, are more often provided through
horticultural activities at the micro-level. Even at
community and household levels, however, the
characteristics of a hostile environment,
particularly where water is in short supply, limit
home and community gardening activities and, as
a consequence, the availability of inexpensive
sources of vitamin A. Thus, countries or parts of
countries with long periods of water shortage and
relatively constant hot temperatures are more
likely to have a VAD problem than those with
stable water supplies.

The seasonality of VAD is only partially related to
ecologic factors that influence food availability.
The pattern of disease frequency is also important.
VAD tends to reach its apex following the peak
prevalence of diarrhoeal and respiratory diseases.
Overcrowded housing and contaminated
environments associated with poor living condi-
tions contribute to the problem. Measles
epidemics that occur under these conditions are
especially devastating and often precipitate VAD,
frequently resulting in blindness and death for
many children.

Social factors

Social underdevelopment within a country limits
accessibility to health and social services, including
education. Under-educated, impoverished women
tend to follow traditional ideas and practices, and
are less confident in engaging in social interactions
where more modern concepts and practices are
promoted. Due to under-education, they are less
likely to learn from educational materials typically
displayed at health centres and used in health-
related community educational activities, including
those concerned with appropriate child care and
feeding practices. Under-educated males also are
less likely to adopt within their households new
ideas and practices related to family care and
feeding. A socially backward, impoverished
environment also favours large families with
consequent overcrowding that is associated with
poor environmental sanitation and personal
hygiene. As noted above, these are prime
conditioning factors for VAD and malnutrition.

Economic factors

Poverty is a root, though not invariable, cause of
VAD in public health terms. Because only foods
of animal origin contain preformed sources of
vitamin A, which are generally relatively expen-
sive, VAD is confined largely to impoverished
countries, neighbourhoods and families which rely on less expensive provitamin A sources to meet their requirements. Provitamin A sources must be converted to retinol before they can provide protection from VAD. The series of events between consumption of provitamin A and its conversion to retinol include several steps that are dependent on normal physiological functions. For reasons discussed below under Host factors, it is more difficult to satisfy vitamin A-activity needs of infants and young children from foods of vegetable origin than from other food sources.

Poverty contributes in other ways, some already noted, to inadequate living conditions that are associated with high death rates among infants and young children. Unemployment and low-wage jobs are major obstacles to overcoming VAD in depressed environments.

Clustering

As already mentioned, the occurrence of clinical VAD tends to cluster rather than to be evenly distributed. Clustering within countries at the macro-level is related to ecological factors noted above exacerbated by poorly developed infrastructures to distribute vitamin A-containing foods from excess-to deficient-areas. Because vitamin A-rich foods tend to be quite perishable, they are especially susceptible to inadequate intra-country distribution.

Clustering has been described primarily based on the occurrence of clinical eye signs. It is likely to reflect the convergence of several risk factors that lead to depletion of vitamin A stores in the surrounding child population among which a few individuals who have been exposed to additional causal factors have developed clinical deficiency. For this reason severely subclinically deficient populations of children up to 5 years of age, based on the distribution of serum retinol levels, are considered to be as much at risk of severe morbidity and mortality as those populations experiencing clinical deficiency. Moderately subclinically affected populations are also likely to be at higher risk but the magnitude of risk is unknown.

Host factors

Age. Varying levels of VAD can occur at any age, from subclinical effects that increase risk of morbidity and mortality to blinding malnutrition (keratomalacia). As a public health problem, however, VAD affects children of preschool age because of their great susceptibility to infections and due to an increased demand for the micronutrient by the body to support their rapid growth. The potentially blinding corneal disease is most prevalent among children under 3 years of age and is usually associated with PEM. An increased risk of death of at least 60% is associated with severe, potentially blinding VAD malnutrition (9). The mortality risk associated with VAD of lesser severity extends at least from 6 months to 5 years of age, and perhaps beyond. The elevated risk of death among those less severely clinically affected, and severe to moderately subclinically affected, is estimated to be about 23% (4).

There is little information regarding the health consequences of VAD among school-age children. The prevalence of mild xerophthalmia, notably Bitot's spots, may be highest in the school-age group, although this may be more a reflection of past rather than current vitamin A status (10).

Sex. No consistent sex difference in vulnerability is demonstrated based on physiological parameters. Differences have been reported from some cultures, which are more likely to be related to sex differences in cultural practices of feeding and care rather than to physiological differences.
**Feeding practices.** Breast milk provides retinol in a readily absorbable form. Clinically apparent VAD is rare among populations where breastfeeding prevails. Even though clinical deficiency rarely occurs as long as a child is receiving breast milk, depletion of an infant's body stores, leading to subclinical deficiency and consequent health risks, may occur by six months of age when maternal vitamin A status is inadequate and thus, breast milk vitamin A content is low (11). In general, the problem of subclinical depletion increases in significance between 6 months and 3 years of age during which complementary foods and later the family diet, represents a large proportion of the infants diet. These foods often do not contain vitamin A in amounts that adequately replace that provided from the diminishing contribution of breast milk. The diet of the newly weaned child frequently has very little vitamin A and often contains less fat than at any other period in the life cycle. Dietary fat is especially important for the absorption of vegetable sources of provitamin A. The post-weaning period, until a child has begun receiving a diversified family diet, is therefore one of great vulnerability to VAD.

**Disease patterns.** The frequency, duration and severity of infections contribute directly and indirectly to vulnerability. Infections influence appetite and are especially devastating for the weaned child. Infections lessen efficiency of absorption, conservation and utilization of vitamin A. Frequent acute bacterial infections damage mucosal surfaces required for absorption. Furthermore, intestinal worm infections may directly compete for uptake of vitamin A in addition to their more general impact on health by suppressing appetite. The frequency of diarrhoeal and respiratory infections is associated with VAD vulnerability (12). For diarrhoeal disease, restoring vitamin A status decreases the severity of subsequent episodes and the risk of death (13). Curiously, no such link has yet been established with respiratory illness, except for pneumonia associated with measles (14).
fact be responsive to improved vitamin A status (15). There is only limited information to determine if increased morbidity or mortality risks are associated with Bitot's spots in school-age children.

Other periods of increased physiological need are gestation and lactation. Women are vulnerable to VAD in these periods because of the increased need to provide for the developing fetus and, following parturition, to replace vitamin A transferred from maternal stores via breast milk to the nursing infant. Pregnant and lactating women in underprivileged populations often report night blindness and studies have found that their breast milk frequently is low in vitamin A (breast milk vitamin A content reflects that of maternal diet and maternal vitamin A status) (11,16). Few data are available to determine if there is an increase in morbidity or mortality risk to the mother that is associated with mild depletion of vitamin A stores. For this reason, pregnant and lactating women are not included in the global estimates of the at-risk population. This will be corrected as the MDIS databank receives more specific information about the vitamin A status of pregnant and lactating women, e.g. data on breast milk vitamin A levels.

INDICATORS OF VAD

Clinical eye signs are rare events. Therefore, when examinations are performed to determine prevalence of severe, potentially blinding VAD, large representative samples are required. Eye signs are, however, the most specific and sensitive of the VAD indicators. Biological indicators of subclinical VAD below selected cut-off points are more common, thus requiring a smaller sample size for estimating prevalence. Regrettably, however, all the subclinical indicators available to date lack specificity and/or sensitivity. Furthermore, when these indicators are used as the basis for cut-off points in determining the severity of vitamin A deficiency, additional population-based validation is required.

Clinical indicators

There is a standard classification system for ocular indicators of VAD, and minimum prevalence criteria for interpretation to identify a public health problem have been widely accepted and applied (Table 5). These criteria have been used to identify countries in the database with a significant public health problem of xerophthalmia and hence risk of VAD-related blindness.

Serum retinol

Distribution curves for serum or plasma retinol levels are useful for identifying populations likely to be at risk of VAD. The prevalence of values below selected cut-off points is useful for estimating the relative risk and prevalence of severity and its magnitude as a subclinical problem. A prevalence of values ≤0.35 μmol/l above 5% has been used globally to define a deficient population as corroborative evidence of clinical eye signs for risk of blinding malnutrition. However, this cut-off is insufficient to identify the prevalence of risk to those likely to have inadequate vitamin A status, i.e. who are subclinically deficient and suffering health consequences. For this purpose, <0.70 μmol/l was suggested earlier as a cut-off for inadequate vitamin A status, but the prevalence criteria to define a public health problem was not generally applied except in the Latin America and Caribbean region (AMR). In the Region of the Americas a prevalence of >15% below 0.70μmol/l has been generally applied to identify an unacceptable situation (18). New evidence substantiating increased mortality risk among populations without clinical signs has necessitated a reevaluation of cut-off points and criteria for interpreting serum retinol distributions. A WHO consultation (19) held to address this question recommend that
Table 5. Classification of xerophthalmia and prevalence criteria constituting a public health problem (17)

<table>
<thead>
<tr>
<th>Criteria*</th>
<th>Minimum prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night blindness (XN)</td>
<td>&gt;1.0%</td>
</tr>
<tr>
<td>Bitot's spot (X1B)</td>
<td>&gt;0.5%</td>
</tr>
<tr>
<td>Corneal xerosis and/or ulceration (X2,X3A,X3B)</td>
<td>&gt;0.01%</td>
</tr>
<tr>
<td>Xerophthalmia-related corneal scars (XS)</td>
<td>&gt;0.05%</td>
</tr>
</tbody>
</table>

(A serum retinol level <0.35 μmol/l in >5% of the population is corroborative evidence)

* See reference 3 for detailed definitions and illustrations of the clinical classification and diagnosis of xerophthalmia.

A cut-off level of ≤0.70 μmol/l be used and that the prevalence of values below the cut-off be ranked to indicate the degree of public health importance as shown in Table 6. The consultation recommended that a severe public health problem be defined as existing when 20% or more of a surveyed preschool-age child population has values ≤0.70 μmol/l, and a minimum prevalence of ≥10% to identify a moderately severe public health problem. It was also recognized that among well-nourished, healthy populations of preschool-age children, and even those still living in poverty but whose vitamin A status is adequate, fewer than 5% have values ≤0.70 μmol/l (20). Therefore, a category is included to identify a mild problem worthy of consideration even when the prevalence is <10% of the surveyed preschool-age population having serum levels ≤0.70 μmol/l.

Unilateral blindness before 6 months of age due to vitamin A deficiency in a non-breast-fed Thai child given an unfortified condensed milk product. Photo: E. Wasanwisut
Table 6. Prevalence of VAD in children ≥ 1 year of age of serum values ≤ 0.70 μmol/l

<table>
<thead>
<tr>
<th>Level of public health problem</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≥2 - &lt;10%</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥10 - &lt;20%</td>
</tr>
<tr>
<td>Severe</td>
<td>≥ 20%</td>
</tr>
</tbody>
</table>

The prevalences in Table 6 for severe and moderate subclinical VAD have been used in this document to classify countries and to estimate the at-risk population. The "mild" category was not included in calculating the at-risk estimates. These prevalences need further verification under field conditions using other indicators of VAD. Several factors common to deprived populations can lower serum values of vitamin A or status independently of intake, e.g. acute and chronic infections (21). The variable prevalence of these confounders among populations may in future necessitate using different criteria for different situations.

Other biological indicators

As noted above, additional supporting evidence is needed because no single biological indicator of subclinical VAD by itself, is of sufficient specificity and sensitivity to identify a public health problem. Other indicators of subclinical VAD include dose response tests and CIC. These measures of VAD also have limitations both due to confounders and in terms of reliability of interpretation. In addition, they have had very limited application in field surveys. Data using these indicators are entered into the database as they accumulate. However, data collected on the basis of these new assessment techniques, have not been included here for determining prevalence of at-risk populations. They are used only as corroborative information. The prevalence of VAD can be determined only by using biological indicators. Once again, the root cause of VAD in a public health context is habitual inadequate dietary intake of foods containing vitamin A-activity, i.e. preformed vitamin A and provitamin carotenoids. Reliable quantitative assessment of habitual dietary intake is problematic, however. Newer approaches to solving this problem use qualitative or semi-quantitative measures of intake frequency of vitamin A-containing foods. The information obtained is useful in corroborating biological indicators, which is how it has been used in this document.

A fuller discussion of the use of other nutritional, ecological and demographic indicators for surveillance purposes other than determining prevalence is presented in a separate WHO document.1


Young girl with xerophthalmia consuming a low-vitamin A meal. Photo: International Center for Eye Health, London
REFERENCES


