

## **GLOBAL IMPORTANCE OF VITAMIN A DEFICIENCY IN HUMANS AND ITS RELATIONSHIP TO MALNUTRITION**

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## Summary

Vitamin A deficiency (VAD), including the clinical and sub-clinical forms of severe and moderate degrees of public health significance, is currently believed to exist in 60 countries, and may be a problem in at least 13 others. An estimated 3 million pre-school children are clinically affected, more than 250 million at the sub-clinical level. This article discusses the methods of assessing vitamin A status and how the global assessments are derived. VAD is especially important, since it synergistically interacts with infection, thus its consequences are magnified where poverty and disease are endemic. Mechanistically, the vulnerability of epithelial tissues to VAD may be important in the pathology of some diseases, and measles, HIV, malaria and diarrheal disease are discussed as specific examples.

General improvements in vitamin A status reduce the risk of morbidity and mortality. Respiratory disease appears to be the main exception, but the recent demonstration that administration of vitamin A by aerosol improved status should provide a stimulus to further work to determine whether the resistance of respiratory disease to treatment is connected to impaired mobilization or absorption of vitamin A. VAD and infection are also implicated in the etiology of anemia.

Maternal VAD is also a continuing problem and is particularly so in South Asia, where night blindness may occur in 15-20 % of all first pregnancies. The importance of breastfeeding to supply the growing infant with adequate vitamin A and to reducing the incidence of infection is highlighted. The paper ends with a discussion of the problems and methods to improve vitamin A status. Enrichment and fortification of foods are short-term solutions in some places, but sustainable improvement will only be achieved by increasing consumption of vitamin A. To achieve the latter, changes in social structure to reduce poverty and infection have to be implemented, not just the provision of more vitamin A rich foods.

## 1. Definitions

### 1. 1. Vitamin A

Vitamin A is a general term for a group of related compounds that have the biological activity of all-trans retinol and includes retinol, its esters and retinoic acid. Chemically, the subgroup of retinoids, which include vitamin A, is derived from a monocyclic parent compound with a five carbon-carbon conjugated double bond and a functional group at the end of the acyclic portion (Figure 1).

The richest food source of vitamin A is liver, with other animal and fish sources providing substantial amounts of pre-formed vitamin A. However, in global terms, vitamin A is obtained by most people from plants in the form of the pro-vitamin A compound,  $\beta$ -carotene.

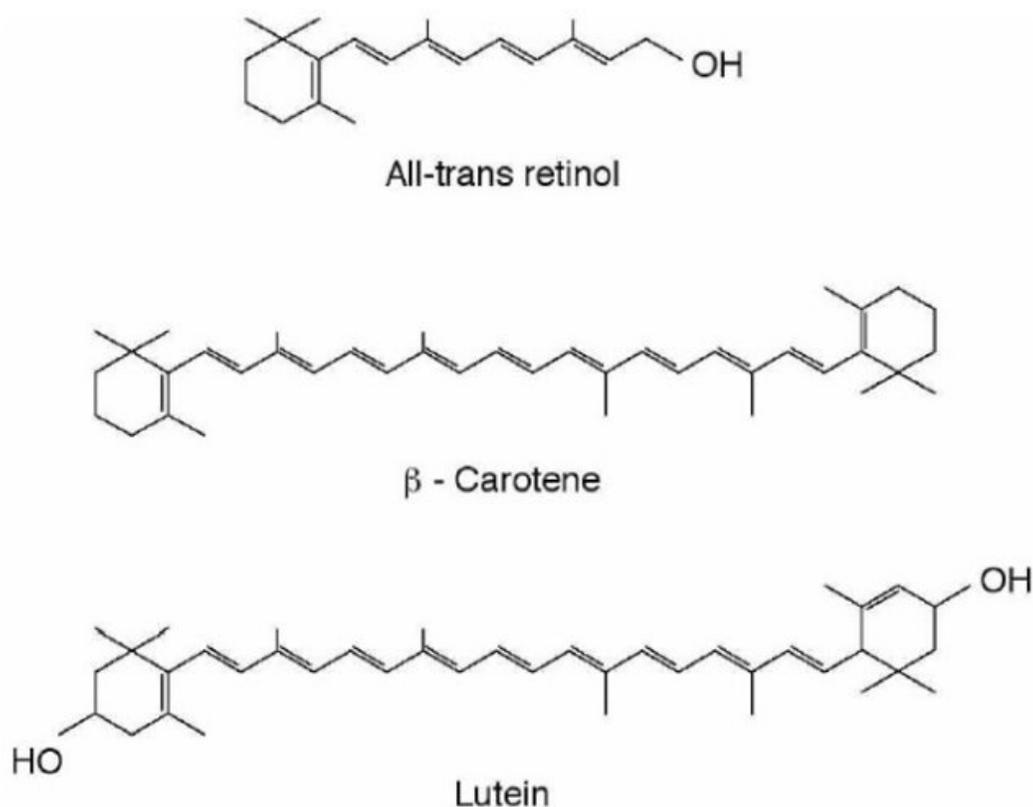


Figure 1. The structures of retinal, beta-carotene and lutein.

## 1.2. Carotenoids

$\beta$ -Carotene is one of a group of compounds known as carotenoids. Carotenoids are the most widespread of all groups of naturally occurring pigments (see *Classical Breeding to Improve Vegetable Vitamin and Provitamin Content*). More than 600 carotenoids have been identified, most of which are xanthophylls, that is, they contain an oxygen-containing functional group, usually on one or both of the terminal ring structures. Five or six carotenoids are found regularly in blood, including:  $\beta$ -carotene,  $\alpha$ -carotene, lutein, lycopene and  $\beta$ -cryptoxanthin. Animals are not able to synthesize carotenoids, so they must be obtained from dietary sources. All vitamin A is ultimately derived from a subset of the carotenoids which can be metabolized to vitamin A, the provitamin A carotenoids. Rich sources of provitamin A carotenoids are green leaves, most yellow and orange fruits and vegetables and red palm oil. The efficiency of conversion and bioavailability of the provitamin A carotenoids is very variable and dependent on many different factors, such as dietary fat content and accessibility of the dietary carotenoids within the plant structure. Provitamin A carotenoids can be metabolized by enzymes in the gut to retinal.  $\beta$ -Carotene is the main dietary provitamin A carotenoid, more minor contributors are  $\alpha$ -carotene and  $\beta$ -cryptoxanthin. Lutein, (Figure 1) one of the most important xanthophylls, is found in green leaves in similar amounts to  $\beta$ -carotene, but is not a pro-vitamin A carotenoid, and very little is probably

metabolized; some evidence suggests it may be a useful marker of vegetable intake (see *Classical Breeding to Improve Vegetable Vitamin and Provitamin Content* and *Molecular Breeding of Vegetable Crops for Improved Provitamin A Carotenoid Content*).

### 1.3. Units of Measurement

Vitamin A levels in the diet are expressed as retinol equivalents (RE), i.e., 6 µg β-carotene or 1 µg retinol or 3.33 international units (IU) retinyl palmitate equals 1 µg RE. Currently, there is much discussion about the bioavailability and convertibility of β-carotene to retinol with some workers suggesting that the equivalence of the two compounds is much poorer, particularly when the source is green vegetables, than the current officially recognized equivalences reflect (see section 8.2).

## 2. Vitamin A Deficiency (VAD)

In the 1920s, Bloch recognized that VAD arose from 3 basic causes: an inadequate diet, mal-absorption and infection. The association with infection is the most common and complex, and despite the many reports of the associations between indices of VAD and infection, it is not always clear which comes first. VAD clearly increases the risk of morbidity, however, on the other hand, the association is sometimes better explained by the impact of infection on vitamin A status.

VAD occurs when body stores of vitamin A are depleted, to the extent that physiological functions are impaired. A pathological process known as xerosis occurs in which keratin-producing cells replace mucous-secreting cells in many epithelial tissues of the body. One example of xerosis is the drying of the conjunctiva and cornea of the eye. However, even before xerosis of the eye is evident, changes may occur, even though vitamin A stores may not be depleted. During such early changes, the integrity of epithelial barriers and the immune system are compromised, and there is increased severity of some infections, and increased risk of death, especially among children. Thus, it is now recognized that the health of pre-school and perhaps older children, pregnant and lactating women, is compromised by VAD, even at moderate and possibly mild sub-clinical levels.

### 2.1. Clinical Deficiency

As a clinical sign of VAD, the presence of severe xerophthalmia classically served as a surrogate for "vitamin A status" and biochemical criteria were of secondary value. The clinical classification of xerophthalmia is described in Table 1. Where VAD was a serious problem, xerophthalmia prevalence rates were high and in such communities, poor vitamin A status was recognized to be a public health problem.

Criteria	Xerophthalmia classification		Abnormal appearance	Minimum prevalence*
Subclinical			Abnormal epithelial & goblet cells	
		XN	Impairment of vision	1.0

			in low	
Clinical	Night blindness		light intensity	
		XIA	Dryness	
	Conjunctival xerosis Bitot's spots			
		XIB	Foamy, cheesy heaping up of	0.5
			keratinised epithelial cells in	
			interpalpebral fissure	
	Corneal xerosis	X2	Hazy cornea	0.01
	Keratomalacia	X3	Liquefaction of part or all cornea.	
	Corneal scar	XS		0.05
	Xerophthalmic fundus	XF		
Biochemical (supportive)	Serum retinol < 0.35 qmol/l			5.0

\* Minimum prevalence in community surveys to suggest a problem of public health significance.

Table 1. Xerophthalmia classification by ocular signs and criteria for assessing the public health significance of xerophthalmia and VAD, based on prevalence among children less than 6 years old in the community (based on data from WHO Expert Group 1982)

As xerophthalmia was, and still is, the most common cause of blindness in young children, much effort was put into controlling it throughout the 1960s. However, in the 1980s, it became evident that sub-clinical deficiency was also associated with a high prevalence of child mortality, and therefore more sensitive indices of status than xerophthalmia were required to identify the children at risk.

## 2.2. Sub-Clinical Deficiency.

### 2.2.1. Functional Indicator

Night blindness or poor adaptation to dim light, is the first functional manifestation of clinical VAD that can be measured, and prevalence of night blindness can be used to map areas where interventions should be targeted. Assessment of night-blindness for subjects able to co-operate is by direct observation and a standardized interview. In addition, a good indicator that clinical VAD was and still is a public health concern in an area, is the existence in the local language, of specific terms for night blindness or poor vision in dim light, e.g., "chicken eyes". Symptoms of night-blindness in children who are at least 24 months old are usually noticed by mothers. Children less than 24 months are not very mobile at night, so symptoms would probably go unnoticed.

In a hospital setting, other tests of eye function can be used, such as vision restoration time and scotopic-vision testing and, although non-invasive, the methods are too sophisticated for the field setting.

### **2.2.2. Liver Stores**

Where there is no xerophthalmia, sub-clinical or marginal deficiency is difficult to assess quantitatively because there is no simple, specific and sensitive indicator that will measure body stores. Ideally liver vitamin A concentration is the best indicator of status and using methods such as the relative dose response (RDR) or modified dose response (MRDR), some measure of its adequacy can be obtained. However, the necessity to take at least one blood sample means that in many populations, these methods may not be acceptable and the influence of infection on the outcome of these tests has not been properly evaluated.

### **2.2.3. Serum/Plasma Retinol**

Homeostatic controls on circulating retinol concentrations limit the interpretation of plasma levels of vitamin A as measures of status. In adequately-nourished individuals, dietary vitamin A does not influence plasma concentration. Therefore, when an increase in plasma retinol occurs in response to a seasonal increase in dietary vitamin A, this is indicative of marginal vitamin A status. However, retinol concentrations are decreased by acute, sub-clinical or underlying chronic infections and by starvation, and are increased by sex hormones e.g., treatment with oral contraceptives. Seasonal changes in disease patterns may occur, which are unrelated to intake of vitamin A-rich foods, for example, the presence of malaria might depress plasma retinol values at a time when adequate food sources of vitamin A are available and plasma values should be normal.

As indicated above, plasma vitamin A levels over a broad range, i.e., 1.05-2.45  $\mu\text{mol/L}$  remain relatively unresponsive to changes in body stores. However, in 1996 WHO recommended that a plasma vitamin A value of  $< 0.7 \mu\text{mol l}^{-1}$  was consistent with the presence of a sub-clinical deficiency state. Nevertheless, a cut-off value of  $0.7 \mu\text{mol l}^{-1}$  should still be used cautiously, unless infection can be excluded, because even the British Pre-School Child survey showed 10% of the children had plasma retinol values of  $< 0.7 \mu\text{mol l}^{-1}$ . In developing countries, the numbers with evidence of sub-clinical infection may be considerable even among apparently-healthy children. It was recently shown in a regional survey in Pakistan that 45 % of pre-school children had levels of the acute phase protein,  $\alpha$ -1-acid glycoprotein (AGP) compatible with sub-clinical infection.

### **2.2.4. Breast Milk**

The vitamin A concentration of breast milk is a unique indicator because it provides information about the status of both the mother and (indirectly) her infant. In cultures where breast-feeding is the predominant mode of infant feeding, the collection of breast milk for vitamin A assessment is generally acceptable.

The average retinol concentrations in breast milk in a vitamin A-sufficient population range from 1.75 to 2.45  $\mu\text{mol l}^{-1}$ , however in lactating undernourished mothers, the

concentration is lower ( $< 1.4 \mu\text{mol l}^{-1}$ ). For an infant who is exclusively breast-fed from 0 to 6 months and partially breast-fed from 6 to 12 months, a milk concentration of  $1.05 \mu\text{mol l}^{-1}$  provides enough vitamin A to meet metabolic needs, but little or none for liver storage. It has been suggested that a value of  $< 1.05 \mu\text{mol}$  vitamin A per liter of milk or  $< 27.9 \text{ nmol g}^{-1}$  milk fat ( $\leq 8 \mu\text{g g}^{-1}$  milk fat) is used as an indicator of borderline deficiency in a population.

### 2.2.5. Histology

VAD generally means that the integrity of epithelial cells is compromised. By examining the morphology of epithelial cells obtained from the conjunctival surface of the eye on a piece of filter paper, it is possible to assess whether changes have occurred associated with VAD (conjunctival impression cytology (CIC)). Variability of results is, however, a problem and may be due to inter- and intra-observer differences, and the relatively low sensitivity and specificity relative to other non-ocular indicators of vitamin A status highlight the importance of using more than one indicator to assess sub-clinical vitamin A status to determine if a public health problem exists.

### 2.2.6. Ecological Factors

A WHO report in 1996 introduced the concept of "ecological and related indicators associated with risk of VAD". These indirect indicators do not replace biological indicators and cannot be used alone for determining the vitamin A status of populations, or to define whether a population has a VAD problem of public health significance. However, a composite picture based on them can be used to corroborate biological criteria to determine if there is a public health problem. Table 2 summarizes the nutrition and diet-related indicators, however there are also illness-related (e.g., immunisation coverage, disease prevalence and diarrheal episode rates) and socio-economic related indicators (e.g., maternal education, income, sanitation, water supply, access to health services) that can be used to indicate the potential risk of VAD in a community.

Indicator	Suggested prevalence
Breast-feeding pattern	
< 6 months of age	< 50 % receiving breast milk
$\geq 6$ -18 months of age	< 75 % receiving vitamin A-containing foods in addition to breast milk, 3 times/week.
Nutritional status	
(< -2 SD from WHO/NCHS reference for children < 5 years of age)	
stunting	$\geq 30$
wasting	$\geq 10$
Low birth weight (< 2.5 kg)	$\geq 15\%$
Food availability	
Market	DGLV unavailable $>_ 6$ months/year
Household	< 75 % households consume vitamin A-rich foods 3 times /week.

Dietary patterns	
children aged 6 - 71 months	< 75 % consume vitamin A-rich
pregnant/lactating women	foods at least 3 times/week.
Semi-quantitative/qualitative food frequency	foods of high vitamin A content eaten < 3 times/week by $\geq$ 75 % vulnerable groups.

Table 2. Ecological indicators of populations at risk of VAD (WHO 1996).

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### **Biographical Sketches**

**Dr Northrop-Clewes** began her career in 1974 at the Agriculture Food Research Council, Institute of Animal Physiology Genetics, Babraham, Cambridge, then moved to the Medical Research Council, Dunn Nutrition Centre, Cambridge in 1984. She has been working at NICHE since 1994. She has 38 peer-reviewed papers and has recently written several book chapters, including one on 'Parasites' for the millennium edition of the British Medical Bulletin on 'Food Safety' (2000) and three others on 'Vitamin supplementation in developing countries', 'Mass Nutritional supplementation' and 'Formula feeds: attributes and disadvantages' in "Nutrition in the Infant" (2001). She has presented work at five International Vitamin A Consultative Group Meetings (IVACG) and has acted as a reporter for Sight and Life Newsletter for four of these meetings. She is at present a correspondent for Task Force Sight and Life. Dr Northrop-Clewes is a Member of the Nutrition Society, a Member of the Royal Institute of Biology and a Fellow of the Royal Society for Tropical Medicine and Hygiene (RSTMH). She is the Local Secretary for the RSTMH for Northern Ireland and The Republic of Ireland.

Her research interests in vitamin A began in 1995 when she received a Charles Wallace Award, which enabled her to carry out studies in North West Frontier Province in Pakistan on controlling iron deficiency by improving the vitamin A status of infants. Dr Clewes has also worked in India, Bangladesh, Thailand, Nigeria, Nepal and Indonesia and is currently collaborating with other workers in The Gambia on a study on the role of vitamin A in preventing growth faltering during infancy.

**Professor Thurnham** trained as a biochemist at Liverpool University under Professor RA Morton and as a result developed an early interest in vitamin A and nutrition generally. However, he moved from biochemistry into malaria research for his PhD. These two basic interests set the scene for much of his later work, as the malaria parasite became a useful focus to pursue studies on the interactions between infection and nutrition. After leaving Liverpool, he spent three formative years in Thailand at the Faculty of Tropical Medicine, Bangkok. Here, he began a more formal interest in nutrition that culminated in his joining the Department of Nutrition at the London School of Tropical Medicine. Through the students, he taught at the 'London School' where his research interests maintained an international dimension, which helped him to develop many fruitful collaborations with colleagues in Africa and Asia. In London, he also worked with the Department of Health and assisted in the National Nutritional Surveys of the Elderly (1970-80) and later in collecting similar data for the Adult (1990) and Pre-school Child (1995) Surveys. In 1983, he moved to the Wolfson Research Unit in Birmingham, and five years later to the Dunn Nutrition Laboratories in Cambridge where his research centred on the antioxidant nutrients and particularly vitamin A; interests which have remained ever since. In 1993, he became the Howard Professor of Human Nutrition at the University of Ulster. Professor Thurnham has served as a consultant for both Government and Commerce, at both National and International levels. He was a member of the working parties for the UK Panel on Recommended Dietary Allowances and at the most recent FAO/WHO committee. He is a member of the Nutrition Society and the Biochemical Society in the UK.

He has written over 150 peer-reviewed publications and has contributed chapters to several important textbooks.

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