

Serum retinol concentrations for determining the prevalence of vitamin A deficiency in populations

WHO/NMH/NHD/MNM/11.3

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Background

Retinol is the predominant circulating form of vitamin A in the blood. In response to tissue demand, it is released from the liver in a 1:1 ratio with its carrier protein, retinol-binding protein (1). In the blood, this complex combines with transthyretin (2). Specific receptors on target cell surfaces or nuclei bind this complex or its active metabolites, thereby regulating many critical functions in the body, including vision, epithelial tissue integrity, and the expression of several hundred genes (2). Serum retinol levels reflect liver vitamin A stores only when they are severely depleted ($< 0.07 \mu\text{mol/g}$ liver) or extremely high ($> 1.05 \mu\text{mol/g}$ liver) (1). Between these extremes, serum retinol is homeostatically controlled and thus not always correlated with vitamin A intake or clinical signs of deficiency. Consequently, serum retinol is not useful for assessing the vitamin A status of individuals and may not respond to interventions. Rather, the distribution of serum retinol values in a population and the prevalence of individuals with serum retinol values below a given cut-off can provide important information on the vitamin A status of a population and may reflect the severity of vitamin A deficiency as a public health problem (3), especially when the degree of underlying infection or inflammation is taken into account. Serum retinol values are most often measured in young children, a group highly vulnerable to deficiency (3).

Deficiency of vitamin A is associated with significant morbidity and mortality from common childhood infections and is the world's leading preventable cause of childhood blindness (3).

Scope and Purpose

This document aims to provide users of the Vitamin and Mineral Nutrition Information System (VMNIS) with information about the use of serum retinol for assessing the prevalence of vitamin A deficiency in populations. It is a compilation of the current World Health Organization (WHO) recommendations on the topic and summarizes, from the three documents

described below, the cut-offs for defining vitamin A deficiency and its severity at the population level, and the chronology of their establishment.

The cut-offs included in this summary are essential for identifying populations most at risk of deficiency and in need of intervention. Assessment of serum retinol permits both the monitoring of trends of vitamin A deficiency as well as the evaluation of the impact of interventions. Such assessments allow for the measurement of progress towards international goals of micronutrient deficiency control.

Description of Technical Consultation

This document compiles current WHO recommendations from the following publications:

Vitamin A deficiency and xerophthalmia: Report of a joint WHO/USAID meeting (4). This document was published in 1976 following a meeting on vitamin A deficiency and xerophthalmia that was convened jointly by WHO and USAID in Jakarta, Indonesia, 25-29 November 1974. The purpose of the meeting was to discuss priorities for research and vitamin A programmes. Meeting attendees made several recommendations concerning the assessment of vitamin A status and discussed the feasibility of vitamin A deficiency prevention measures. A protocol for the treatment of emergency cases of xerophthalmia was also developed.

Control of vitamin A deficiency and xerophthalmia: Report of a joint WHO/UNICEF/USAID/Helen Keller

International/IVACG meeting (5). This document was published in 1982 following a meeting also held in Jakarta, Indonesia, 13-17 October 1980, to review progress that had been made in the establishment of measures to control vitamin A deficiency and xerophthalmia that had been instituted since the preceding meeting held in 1974.

Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes (3). This document was published in 1996 following a technical consultation held in Geneva, Switzerland, 9-11 November 1992. The consultation was attended by academic and governmental experts in vitamin A deficiency. The stated objectives of the consultation were: 1) to identify indicators and establish cut-off points for assessing subclinical vitamin A deficiency in populations; 2) to determine which indicator, or combinations of indicators, may be useful in populations with vitamin A deficiency at levels that pose an important public health problem; 3) to discuss, according to age and/or sex, which groups are most appropriate for assessment using different indicators; and 4) to consider the characteristics of the indicators and their usefulness given different surveillance objectives.

Recommendations

The prevalence in the population with low serum retinol (0.70 µmol/l or below) can be used to assess the severity of vitamin A deficiency in most age groups as a public health problem, as shown in Table 1.

Table 1

Prevalence of low serum retinol (0.70 µmol/l or below) to define a public health problem and its level of importance among children 6-71 months of age^a

	Degree of public health problem ^b		
	Mild	Moderate	Severe
Prevalence of low serum retinol (0.70 µmol/l or below)	2-9%	10-19%	20 % or more

^a Source: reference (3)

^b These cut-offs do not apply in infants younger than 6 months of age

Prior to the 1996 publication, a 5% or higher prevalence of serum retinol values of 0.35 $\mu\text{mol/l}$ or lower among children younger than six years of age had been used to define a deficient population and served to corroborate xerophthalmic findings (4,5). Serum retinol values below this cut-off were associated with low liver vitamin A stores and an increased prevalence of clinical signs of deficiency (4). However, members of the 1992 consultation concluded that this cut-off was likely too low to identify individuals who have suboptimal vitamin A status and were at risk of the subclinical consequences of vitamin A deficiency, but had not yet developed the clinical signs associated with severe deficiency (3). Further consideration of new evidence of increased mortality risk among populations without clinical signs of deficiency, consultation members raised the cut-off to 0.70 $\mu\text{mol/l}$ and proposed the ranking of mild, moderate, and severe public health significance, as presented in Table 1.

More specifically, the consultation designated vitamin A deficiency as a public health problem requiring intervention when at least one of two specifications is met:

1) The prevalence of low serum retinol is within the range specified and another biological indicator of vitamin A status (including night blindness, breast milk retinol, relative dose response, modified dose response, or conjunctival impression cytology) also indicates widespread deficiency; and/or

2) The prevalence of low serum retinol indicates widespread deficiency and at least four demographic and ecologic risk factors are met, including:

- infant mortality rate higher than 75/1000 live births and under-5-year mortality rate of higher than 100/1000 live births;
- full immunization coverage in less than 50% of children at 12-23 months of age;
- less than 50% prevalence of breastfeeding in 6-month-old infants;
- median dietary intake lower than 50% of recommended safe level of intake among 75% of children 1-6 years of age;
- two-week period prevalence of diarrhoea 20% or higher;
- measles case fatality rate 1% or higher;
- no formal schooling for 50% or more of women 15-44 years of age;
- less than 50% of households with a safe water source.

Serum retinol concentrations, particularly in deficient populations, may not be normally distributed. Ideally, the full serum retinol distribution should be presented, along with a measure of central tendency (mean, median) and cut-offs to describe the upper and lower range of the distribution (3). Haemodilution associated with later stages of pregnancy may alter interpretation of serum retinol values in pregnant women (3). Clinical and subclinical infections may also lower serum retinol concentrations by as much as 25%, making knowledge of the infection burden of the population critical for accurately interpreting the serum retinol distribution (7). Additionally, other micronutrient deficiencies can depress serum retinol values (3). Zinc, in particular, is required for the synthesis of retinol-binding protein (6). Zinc deficiency thus reduces the amount of retinol that can circulate, causing a functional vitamin A deficiency even when liver stores may be sufficient. Severely malnourished children or those with protein-energy malnutrition similarly produce retinol-binding protein at a diminished rate and have lower serum retinol concentrations (2). The seasonality of vitamin A-rich foods in some populations may also cause small shifts in serum retinol distributions, complicating comparison of distributions between populations or even within populations during different times of the year (3).

Serum retinol can be measured in either a venous or free-flowing capillary blood sample. Blood should be protected from light and chilled until centrifugation, which should occur within 12 hours of blood collection (3). Serum retinol can be measured by high-pressure liquid chromatography (HPLC), by fluorescence, or by ultraviolet (UV) spectrophotometry. Although most expensive, HPLC is the method of choice, due to its high sensitivity and specificity (3). Serum retinol can also be measured in dried blood spots (1).

Summary Development

This summary contains information primarily from three WHO publications. The first, *Vitamin A deficiency and xerophthalmia: Report of a joint WHO/USAID meeting* (4), was published in 1976 and first presented serum retinol cut-offs to designate low (10-20 µg/100 ml, 0.35-0.70 µmol/l) and deficient (< 10 µg/100 ml, < 0.35 µmol/l) serum concentrations. These values were first recommended by the United States Interdepartmental Committee on Nutrition for National Defense in 1963. The 1982 publication, *Control of vitamin A deficiency and xerophthalmia. Report of a joint WHO/UNICEF/USAID/Helen Keller International/IVACG meeting* (5) built on these cut-offs by proposing the prevalence criteria of no more than 5% of children 6 months – 6 years of age having a serum retinol concentration < 0.35 µmol/l for determining the public health significance of vitamin A deficiency in a population. *Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes* (3), published in 1996, raised the serum retinol cut-off to < 0.70 µmol/l and devised a classification system using the prevalence of values below this level among children 6-71 months of age to determine whether vitamin A deficiency is a problem of mild, moderate, or severe public health significance in a population.

Plans for Update

The Micronutrients Unit in the Department of Nutrition for Health and Development at WHO Headquarters in Geneva is responsible for reviewing this document and updating it, if needed, by January 2013, following the newly adopted *WHO Handbook for guideline development* (8) procedures.

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