IAEA FACTSHEET

Human Health

How the Retinol Isotope Dilution Test Can Help Assess Vitamin A Status in Public Health Programmes

What should I know?

Vitamin A is an essential nutrient for normal vision, cellular growth and development, proper functioning of the immune system and synthesis of red blood cells. It is mostly stored in the liver. Vitamin A deficiency (VAD) remains a leading cause of childhood blindness and is a major contributor to anaemia and infectious disease morbidity and mortality among pre-school children.

The current global prevalence of VAD among children aged 6–59 months is approximately 29%, with the highest prevalence occurring in sub-Saharan Africa (48%) and South Asia (44%)[1]. Worldwide, more than 150 000 children die each year owing to the effects of VAD[2] [Figure 1].

The IAEA is raising awareness of, and building capacity on, the use of an isotopic technique to help assess vitamin A status from deficiency to excess.

What foods contain vitamin A?

Vitamin A, provided either in the form of provitamin A in plant-based products or preformed vitamin A

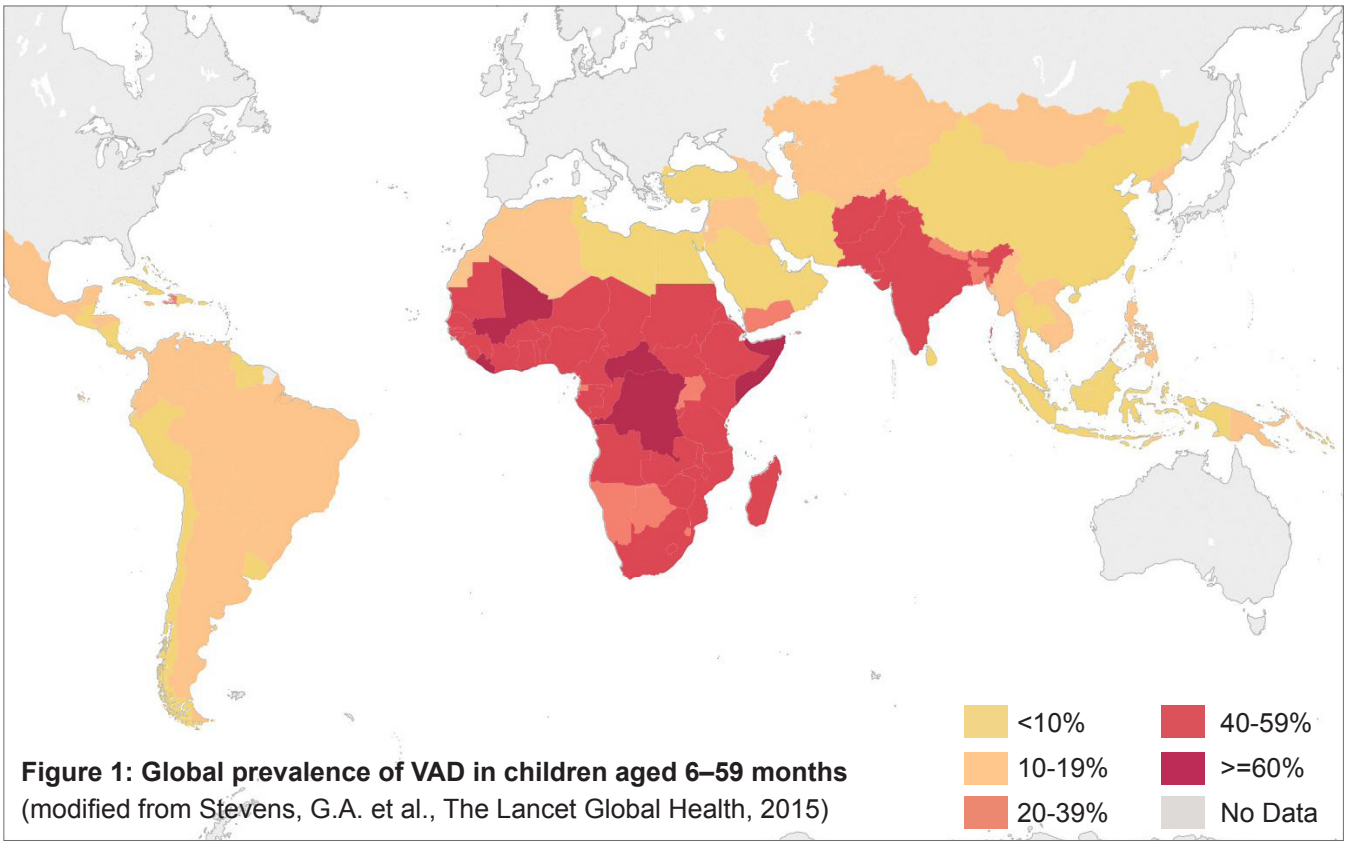

Figure 1: Global prevalence of VAD in children aged 6–59 months
(modified from Stevens, G.A. et al., The Lancet Global Health, 2015)

[1]Stevens, G.A. et al. (2015). Trends and mortality effects of vitamin A deficiency in children in 138 low-income and middle-income countries between 1991 and 2013: a pooled analysis of population-based surveys. The Lancet Global Health 3(9):e528-36.
[2]Black, R.E. et al. (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 382(9890):427-451.

in animal products, is present in a relatively small number of foods such as green leafy vegetables, yellow and orange fruits and vegetables, organ meats, dairy products, and breast milk.

How to address VAD?

Fruits and vegetables are usually available seasonally and animal products are relatively expensive, so eliminating VAD through dietary counselling alone has not been successful on a large scale.

Accordingly, public health programmes have been implemented in low and middle income countries to provide additional vitamin A through the periodic delivery of high dose vitamin A supplements to pre-school children and by fortifying commonly consumed foods with vitamin A, including edible oils, cereal flour and sugar.

These programmes have reduced the global prevalence of VAD (from 39% in 1991 to 29% in 2013[4]). However, concerns are now being raised that the increased intake of vitamin A achieved through combined programmes, along with self-administered vitamin supplements and vitamin A-rich food sources, may place some individuals at risk of excessive intake, resulting in high vitamin A status (hypervitaminosis A) and possibly vitamin A toxicity (i.e. hypervitaminosis A accompanied by clinical signs of adverse health effects). Vitamin A toxicity can result in fetal malformations during pregnancy and can have deleterious effects on bone structure and liver function at other stages of life. Both VAD and vitamin A toxicity therefore need to be considered in public health programmes. These programmes should be carefully designed to deliver adequate amounts of vitamin A to populations at risk of VAD and to modify or cancel these interventions when the risk of deficiency has diminished, or when a risk of excessive intake has been identified. These kinds of decisions require accurate information concerning the population's vitamin A status.

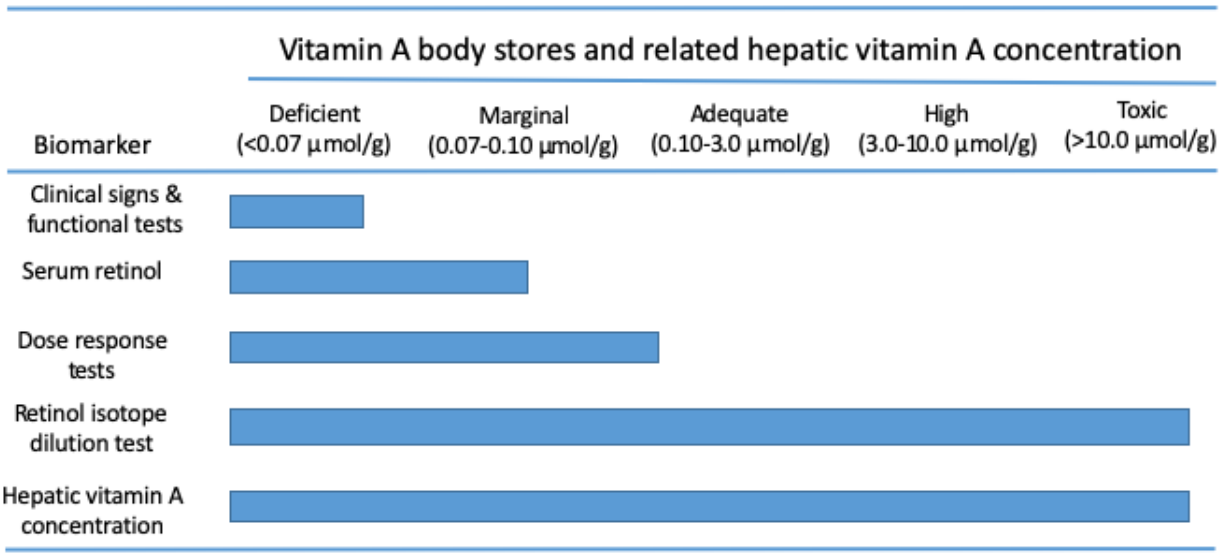

Figure 2: Biomarkers showing Vitamin A status and its range, as well as hepatic Vitamin A concentration (modified from Tanumihardjo, S.A. et al., J Nutr, 2016[3])

Note: the precise cutoff point when hepatic vitamin A concentration indicates the excessive (toxic) status associated with specific health risks is still uncertain. There is a growing consensus that a hepatic vitamin A concentration of >10.0 µmol/g liver may be associated with adverse (toxic) clinical effects. If the prevalence of high stores (>3.0 µmol/g liver) is increasing in a population then modifications to the programme should be considered.

[3]Tanumihardjo, S.A. et al. (2016). Biomarkers of Nutrition for Development (BOND)-Vitamin A Review. The Journal of Nutrition 146(9):1816S-48S.

[4]This is the latest year for which data is available.

What are the methods used to assess vitamin A status in individuals and the population as a whole?

There are several methods available to assess vitamin A status and/or risk of VAD, including:

- Measurement of vitamin A intake from diet and supplements;
- Clinical examination of eye function and tissue structure;
- Laboratory analysis of vitamin A biomarkers in blood or breast milk; and
- Liver biopsy samples (too invasive to be applied routinely).

The methods most commonly used to provide information on a population's vitamin A status (such as the concentration of vitamin A in serum) only detect VAD; they are not useful for assessing the risk of excessive vitamin A status due to high intake [Figure 2].

The only practical assessment method that can be applied across the entire spectrum of vitamin A status is the retinol isotope dilution (RID) test. It provides a quantitative estimate of the body's total stores of vitamin A, both in individuals and within a given population. The results can also be used to estimate the concentration of vitamin A in the liver to classify individuals as having deficient, adequate or excessive stores.

How does the RID test work?

To assess vitamin A status using the RID test, the following steps must be taken [Figure 3]:

- The study participant consumes a small dose of 'labelled' vitamin A using a stable (non-radioactive) marker isotope of hydrogen or carbon;
- The labelled vitamin A mixes with the unlabelled vitamin A in the participant's body;
- After a period of equilibration (usually 4 to 14 days), the ratio of labelled to unlabelled vitamin A in plasma is measured using mass spectrometry;
- The calculation of the total amount of vitamin A present in the participant's body is based on the amount of labelled vitamin A that was administered and the ratio of labelled to unlabelled vitamin A in the blood.

The procedure is safe for the participants and only requires one or two blood samples to be collected.

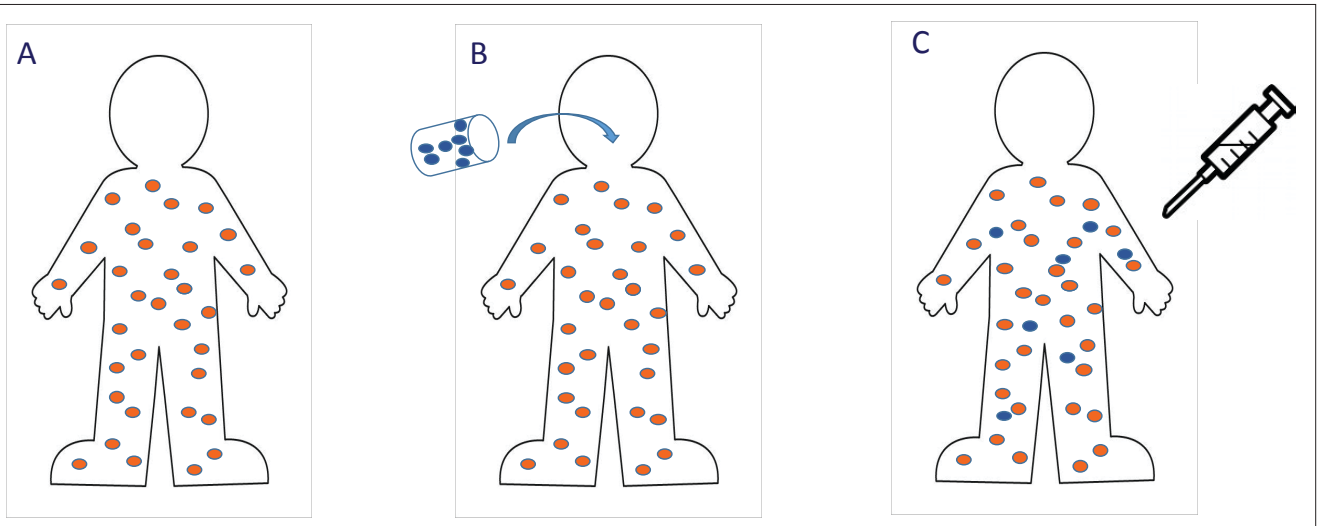

Figure 3: Illustration of the RID test

Panel A – Orange dots represent the unlabelled retinol present in the body

Panel B – Blue dots represent the consumption of labelled retinol

Panel C – A blood sample is collected after the period of equilibration to measure the ratio of labelled retinol to unlabelled retinol

How does the RID test help to assess the vitamin A status of a population?

The RID test can be applied to achieve three major objectives:

1. Determine the prevalence of VAD and high or excessive vitamin A status in a population or selected subgroups;
2. Assess the response of a population's vitamin A status (or prevalence of VAD) following an intervention; and
3. Decide when it is appropriate to modify or withdraw the intervention, based on the prevalence of a high or excessive vitamin A status.

For population assessments, the RID test must be carried out with a representative sample of the population in question, possibly subdivided by geographic region or urban versus rural residence. The methods used to select a representative sample of the population and to calculate sample size are the same as those routinely applied for health and nutrition surveys.

The RID test can also be applied to answer specific research questions, such as to evaluate the efficacy of a novel intervention for improving the vitamin A status of the recipients, and to estimate the vitamin A requirements of humans.

What does it cost to use the RID test?

Providing a single estimate of the cost of applying the RID test is difficult, as it depends on local personnel costs and on whether it is necessary to ship the specimens abroad for laboratory analysis. Although it is likely that the cost per test will be greater than conventional methods, only the RID test can provide information on both excessive vitamin A status and deficiency. The information derived from the RID test may indicate a need to curtail certain programme activities or the amount of vitamin A provided. Therefore, the assessment results could ultimately lead to substantial programme savings in addition to greater programme safety.

IAEA support for Member States

The RID test can be considered an additional tool to support decision-making processes in health programmes. The IAEA seeks to build capacity in the use of the test by helping to increase the number of scientists able to conduct it and by expanding the number of laboratories available to analyse the resulting clinical specimens.

In addition, IAEA-supported research projects have generated new data on both the extent of VAD and on the risks of excessive intake of vitamin A. Recent studies have shown that high exposure to multiple vitamin A programmes and other available sources of vitamin A intake in some settings contribute to high vitamin A body stores[5].

The IAEA is supporting countries to better their understanding of the RID test and how it can be used to improve the assessment of vitamin A status in public health programmes.

[5]Ford, J.L. et al. (2019). Use of Model-Based Compartmental Analysis and a Super-Child Design to Study Whole-Body Retinol Kinetics and Vitamin A Total Body Stores in Children from 3 Lower-Income Countries. The Journal of Nutrition 150(2):411-418.
Van Stuijvenberg, M.E. et al. (2019). South African preschool children habitually consuming sheep liver and exposed to vitamin A supplementation and fortification have hypervitaminotic A liver stores: a cohort study. American Journal of Clinical Nutrition 110(1):91–101.

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