Summary

- Vitamin A deficiency (VAD) can be caused by insufficient intake through food or by increased need in case of infection
- Leading cause of preventable childhood blindness
- Causes xeropthalmia: dryness of conjunctiva and cornea, Bitot spots, keratomalacia and night blindness
- Is associated with excess mortality
- Treatment with large and repeated doses, lower doses in pregnancy
- Prevention can be achieved with diet change, periodic supplementation and fortification

Epidemiology

Vitamin A deficiency (VAD) or hypovitaminosis A is a shortage of vitamin A in blood and tissues. It is the leading cause of preventable childhood blindness and is related with child mortality. VAD affects about one-third of children under five worldwide and claims the live of more than 500.000 children annually, mainly in Southeast Asia and Africa. An estimated 250.000 to 500.000 children go blind each year due to vitamin A deficiency and half of them die within a year of becoming blind. VAD prevalence in high among pregnant women in many developing countries and contributes to maternal mortality. VAD affects the immune system and infectious diseases such as measles have higher fatality rates. Even subclinical deficiency can be a problem as it may increase child's risk of developing respiratory and diarrhoeal infections, decrease growth rate (stunting), slow bone development and decrease likelihood of survival from serious illness. Periodic, high-dose vitamin A supplementation is a proven, low-cost intervention which has been shown to reduce all-cause mortality by 12 to 24 percent. Globally, around 65% of all children aged 6 to 59 months received two doses of vitamin A, fully protecting them against VAD.

However between 2015 and 2016 vitamin A supplementation coverage dropped by more than half in countries with the highest under-five mortality rates, the countries where it is needed most. This caused an increase of children aged 6 to 59 months left unprotected from 19 to 62 million. Two-thirds of at risk countries have no VAD data of use data that are > 10 years old, challenging vitamin A supplementation programs.

Vitamin A metabolism and pathophysiology

The term vitamin A should be used as the generic descriptor for retinoids exhibiting the qualitative biological activity of retinol. The main molecular structure contains a cyclic part and a non-cyclic chain with 5 double bonds in the all-trans position. A functional group is found at the end of the non-cyclic part which can be an alcohol (retinol), an aldehyde (retinaldehyde), a palmitate (retinolpalmitate), etc. The term *provitamin A carotenoid* should be used as the generic descriptor for all carotenoids exhibiting qualitatively the biological activity of beta-carotene.

Vitamin A is fat soluble and is absorbed in the gut in the chylomicron fraction and then transported via the lymphatics, to the liver. The availability of fats in the intestine will influence the fraction of the available vitamin that will be absorbed. Vitamin A (retinol) is ingested as either retinyl esters or carotenoids and metabolized to active compounds such as 11-cis-retinal, which is important for vision, and all-trans-retinoic acid, which is the primary mediator of biological actions of vitamin A. Once stored in the liver as retinolpalmitate it will be transported to the target organs bound to a protein, the retinol binding protein (RBP). Zinc and an adequate intake of proteins are required for normal production of RBP. Transthyretin (TTR= transports thyroxine and retinol) is a transport protein in the serum and cerebrospinal fluid that carries the thyroid hormone thyroxine (T_4) and retinol-binding protein bound to retinol. The liver secretes transthyretin into the blood, and the choroid plexus secretes TTR into the cerebrospinal fluid. If retinol is not needed, it is instead stored in liver stellate cells in the form of retinyl esters.

Rhodopsin, the light-sensitive pigment in rods of the eye, is formed when 11-cis-retinal combines with the protein opsin. Absorption of light energy causes rhodopsin to decompose by a series of photochemical reactions to all-trans-retinal and opsin. As this occurs, a visual signal is transmitted to the central nervous system. Night blindness is an early symptom of vitamin A deficiency. In night blindness, the small amount of light at night does not elicit an adequate response because the amounts of 11-cis-retinal and rhodopsin that can be formed are depressed. Another important function of vitamin A is regulation of growth and differentiation of cells. In the absence of vitamin A: 1) proper stem cell differentiation does not occur; 2) growth and development of embryos are altered; 3) epithelial cellular development with ciliary function is deficient, and the barrier to infection is decreased; 4)

cells involved in innate and acquired immune function are decreased; 5) xerophthalmia develops because of abnormalities in corneal and conjunctiva development; 6) normal bone growth and tooth development do not occur, contributing to stunting.

Vitamin A in skin creams

Companies that produce skin creams often juggle with terms as '*Pro-retinol A',...* The creams contain pro-retinols (precursors to retinols) that break down to retinol on exposure to the skin. Vitamin A itself is what does all the work. As well as being the precursor to retinal, it is also a chemical messenger, one function of which is to instruct cells to begin multiplying more uniformly, and to produce more elastin and collagen, two protein building materials essential in healthy, young-looking skin cells.

Causes of vitamin A deficiency

Both an insufficient input and an increased need can result in the deficiency. Insufficient intake is seen when following food items are lacking the diet:

- Animal sources of vit A: milk – butter – fish oils – liver – meat – egg yolk
- Vegetables: green leafy vegetables – carrots
- Fruits: mango – papaya
- Oils: palm oil

Infections of the gut, malabsorption, worm infestations and particularly giardiasis that provokes steatorrhea decrease vitamin A absorption. Infections can increase vitamin A demands dramatically. Some investigators even calculated the increase during infections in the order of 3000 IU per day. Particularly children with measles are very likely to develop a very fast progressing keratomalacia.

Recommended daily intake

Adult:	750 µg
Pregnancy:	750 µg

Breastfeeding:	1200 µg
Children:	
< 1 yr:	300 µg
1-4 yr:	250 µg
4-6 yr:	300 µg
7-9 yr:	400 µg
10-12 yr:	575 µg
13-15 yr:	725 µg

Note: 1 IU = 0,3 mcg retinol

There is a very strong association of vitamin A deficiency with malnutrition (PEM). Both are diseases of the poorer people of the population and of the deprived. They will have an overall lower food intake but particularly of meats and milk products, sources rich in vitamin A and of oils and fats, which are necessary for the vitamin A absorption. These children will also have more frequent infections, increasing their demands and interfering with the absorption at the level of the gut. Once their serum protein levels decrease like in severe malnutrition the necessary enzymes for absorption and transportation to the target organs will diminish further aggravating the deficiency.

Clinical aspects

VAD is an important contributing factor in mortality which is still very high in the majority of the third world countries. This can for a large extend be explained by the role vitamin A has in maintaining the immunological response and the differentiation and maintenance of epithelial surfaces, like the skin, bronchi, gut and genito-urinal tract, which are more prone to invasion by bacteria in a vitamin deficiency state. A higher frequency of diarrhoea, ARTI (acute respiratory tract infection) and otitis media have been noted. These effects are present well before there are overt clinical signs at the level of the eye.

Xerophthalmia

Although xerophtalmia literally means (xeros= dry ; ophthalmos = eye) dryness of the eye and is used as such by the ophthalmologists, it is used in a broader sense in the public health context of vitamin A deficiency. Here it means all lesions, internal and external, attributable to the deficit of vitamin A: dryness of conjunctiva and cornea, Bitot spots, keratomalacia and night blindness. Xeroderma is another expression of xerosis.

The natural course of the disease progresses from night blindness to dryness of the cornea, sometimes with Bitot spots, to keratomalacia, although many children will not pass through this sequence. In a community where children have eye signs, there will be many other children who are vitamin A deficient but who have completely normal eyes and vision. Children with eye signs due to VAD are only the 'tip of the iceberg' explaining why community approaches to control VAD are important. Some eye signs reflect long-standing VAD, whereas other eye signs reflect severe, acute, sudden-onset VAD. A child who is vitamin A deficient, but who does not have eye signs, may develop immediately corneal ulcers as a result of infections or diarrhoea. Children with any of the eye signs of VAD are at high risk of dying.

Grade of xerophthalmia		Peak age group (years)	Type of deficiency	Risk of death
XN	Night blindness	2–6; adult women	Long standing. Not blinding	+
X1A	Conjunctival xerosis	3–6	Long standing. Not blinding	+
X1B	Bitot's spot	3–6	Long standing. Not blinding	+
X2	Corneal xerosis	1–4	Acute deficiency. Can be blinding	++
X3A	Corneal ulcer/ <1/3 cornea	1–4	Severe acute deficiency. Blinding	+++
X3B	Corneal ulcer/keratomalacia ≥1/3	1–4	Severe acute deficiency. Blinding	++++
XS	Corneal scarring (from X3)	>2	Consequence of corneal ulceration	+/–
XF	Xerophthalmic fundus	Adults	Long standing. Not blinding. Rare	–

Table: WHO classification of vitamin A deficiency and the age groups most affected

Night blindness

- Nyctalopia or night blindness is not always perceived because it is a subjective sign; on

the one hand and because its perception is very much influenced by the availability of electricity on the other hand. The child has an inability to see in poor lighting conditions like those which prevail at the end of the day when the evening is setting. A longer adaptation of vision to the dark is needed, like when one is getting from a light to a darker environment. Children will usually not complain and mothers should be asked if they stumble over objects in the house in the evening or that their children can't find the parents anymore in the house in the evening. The child might become less active and may be fearful of moving around. Night blindness is quantifiable through a dark adaptation test, but it is difficult to evaluate objectively in children.

Historical note: Xeropthalmia and Vitamin A

The Eber's Papyrus describes night blindness in ancient Egypt. Physicians treated the condition by squeezing the ''juices'' of a grilled lamb's liver into the eyes of afflicted patients. In 1971, George Wolff speculated that these topically applied ''drops,'' rich in retinol, probably drained into the lachrymal sac, where they were absorbed into the systemic circulation and thereby reached the retinal cells. Perhaps that was the case, but Alfred Sommer observed the treatment of a young boy in rural Indonesia that was described in exactly the same fashion, but provided a more direct explanation for the way in which ''liver juices,'' applied topically, could reach the back of the eye. At the conclusion of the ceremony, after juice from a goat liver had been squeezed onto the boy's eyes, the traditional healer fed the child the remaining liver! The healer did not consider eating the liver part of the treatment; he fed the child the liver so as not to waste precious food.

Modern concepts of xeropthalmia date from the early 1800s, when dogs that were "starved" on sugar and distilled water developed perforating corneal ulcers resembling those in "ill-nourished infants". One hundred years elapsed before investigators realized that these changes were caused by lack of a specific nutrient "fat soluble A", present in the lipid fraction of milk, eggs, butter and cod-liver oil, and -as provitamin A carotenoids- in dark-green leafy vegetables and certain coloured fruits. Bloc -studying the growth and development of children in a Danish orphanage, noted that vitamin A-deficient children were far more likely to develop urinary tract infections, grew less and were less likely to develop xeropthalmia, and that vitamin A treatment cured the condition. By 1928, Green

and Mellanby dubbed vitamin A the “anti-infective factor”.

In 1932 Ellison administered daily vitamin A to one-half of the cases of measles admitted to the Grove fever hospital outside London. Those given vitamin A had only half the case-fatality rate of those restricted to standard therapy. Vitamin A was finally crystallized in 1937.

Conjunctival- and corneal xerosis

VAD causes squamous metaplasia and keratinization in the eye. Conjunctival xerosis can be difficult to detect. One can see a slight wrinkling of the conjunctiva. In corneal xerosis glands in the conjunctiva no longer function normally, leading to loss of tears and mucous with an increased risk for infections. The light reflex of the cornea loses its well-defined appearance and becomes mottled and hazy. The cornea becomes dry, less translucent and more opaque.

Bitot spots are unpainful, triangular, whitish, pearly coloured spots, usually found on the lateral side of the conjunctiva, which are pathognomonic for VAD. They consisting of keratin accumulations, often intermixed with an overgrowth of Corynebacterium xerosis, which result from epithelial (squamous) metaplasia: the conjunctival cells become more like skin than a mucous membrane. The white foamy deposits can be wiped away partially, but they don’t disappear completely, even when the deficiency is reversed.

Corneal ulcer and keratomalacia

If the acute VAD is not treated promptly, the cornea can become ulcerated and melt away. The liquefaction necrosis of the cornea varies from small ulcerations to softening and rupture of the cornea, with resulting loss of anterior chamber fluid and collapse of the eye. Keratomalacia indicates that more than one-third of the cornea is affected. In just a few days the cornea can be completely destroyed and secondary infection is common. As long as there is no superinfection, there is no pain or redness. The end result is corneal scarring, staphylomas (bulging of a badly damaged cornea) or phthisis bulbi (a shrivelled up eye). Children with keratomalacia are often malnourished, but previously healthy appearing children can develop keratomalacia following measles infection or diarrhoea. It is important

to screen young children from the same family and community.

Diagnosis

Clinical

In low resource settings the diagnosis of individual patients is usually made clinically. Fundus examination can be useful to detect xerophthalmic fundus, which is more present in adults. Small white spots are found on the retina. This moderate form of VAD (night blindness, conjunctival dryness) will disappear after 2-4 days of treatment without leaving any lesions or sequelae.

Plasma levels and Hepatic reserves

The problem with measuring plasma retinol levels is that they only change after a prolonged period of vitamin deficit, due to the buffering action of the liver. Their use is limited to research evaluations of vitamin A deficiency and of very little practical use in real life situations. Hepatic reserves can be determined with a liver biopsy, which is only done on an experimental and research basis. The reserves can be estimated: after administration of a small dose of retinol (1.800 IU) the plasma retinol levels are measured again and compared with the retinol concentrations before the administration. If the concentration increases by more than 20 % then this indicates reserves are low.

Plasma retinol	
>= 30 mcg/100 ml	Normal
30-20 mcg/100 ml	Mild deficiency
20- 10 mcg/100 ml	Associated with night blindness, Bitot spots Moderate deficiency
< 10 mcg/100 ml	Severe deficiency

Impression cytology

Impression cytology is a technique to detect the degree of metaplasia of the conjunctiva. The lack of differentiation and the decrease or absence of goblet cells is looked for. It is not a routine diagnostic test.

Vital staining

Vital staining detects the degree of conjunctival metaplasia by putting dye (Lissamon green or Bengal rose) on the conjunctiva. This method lacks specificity.

Treatment

The presence of clinical signs of vitamin a deficiency should be considered an emergency. The most urgent are those infants with corneal signs. Large and repeated doses are therefore given. Associated illnesses should always be treated.

In an endemic zone, all children with PEM and measles need vitamin A treatment.

Treatment dosage

Children < 1 yr	Children > 1 yr and adults except pregnant women
100.000 IU immediately 100.000 IU after 24 hrs 100.000 IU after 14 days	200.000 IU immediately 200.000 IU after 24 hrs 200.000 IU after 14 days

Below one year or below 8 kg the dose is half of the dose delivered in the vitamin A high dosage capsules. These contain 6 drops; to administer throw away tree drops and give the remainder.

Although teratogenic in animals, a clear correlation between ingestion of large doses of

vitamin A and congenital malformations has not been established. As a precautious measure, **pregnant women** should not receive large doses of vitamin A due to the possible teratogenic effect. Smaller doses up to 10.000 IU per day are safe. A total dose of 200.000 IU should be aimed at. **Lactating women** should receive 200.000 IU in the first month postpartum. One month after delivery again smaller doses up to 10.000 IU per day are preferred. This because one month after delivery there is the possibility of recurrent pregnancy.

Xerophthalmia is treated with topical antibiotics and padding of the eye. Topical steroids should be used with caution. Corneal grafting and conjunctival reconstruction using a flap are out of scope for most settings where VAD is prevalent.

Prevention

“Appropriateness” is a basic premise for vitamin A intervention. Two conditions dictate whether a program, designed to prevent vitamin A deficiency, is appropriate:

- A substantial segment of the population is “at risk” of developing clinical or biochemical vitamin A deficiency of sufficient severity to be considered of Public Health importance.
- The problem is serious enough to warrant the diversion of scarce resources toward a program to control vitamin A deficiency versus other preventable diseases or community projects within the country.

Currently vitamin A prophylaxis is approached through one of the three major intervention strategies:

1. A change in diet directed toward achieving a continuous intake of vitamin A rich foods.
2. Administration of a single, large dose of vitamin A administered on a periodic basis.
3. Fortification of an appropriate dietary vehicle with vitamin A.

Change in dietary intake

Different strategies have been applied to increase dietary intake. Promotion of breastfeeding is effective in entirely breastfed children, provided the mother has adequate daily intakes of

vitamin A. They have a lower prevalence of mild and severe xerophthalmia during early childhood. Nutritional education, kitchen gardening programs, larger scale agricultural programs and income generating programs are possibilities to achieve a higher vitamin A intake. Diet adaptation is the most sustainable solution and avoids the risk of hypervitaminosis. This approach de-medicalizes a food related condition. Challenges can be the availability of vitamin A rich products. These products must also be culturally accepted and land suitable.

Distribution of large dose vitamin A capsules

Large doses of 200.000 IU are distributed at regular intervals, most frequently every six months. The seasonal distribution approach is used to protect children in the higher prevalence seasons, reduces cost while maintaining the same impact. There are three possible delivery strategies: the ‘medical’ or ‘therapeutic’ approach, which offers treatment to children who present to a health facility with an illness episode. They will be given a dose of vitamin A according to a set of pre-set criteria of high risk of developing vitamin A deficiency. The ‘targeted’ distribution covers groups within the larger general target population; e.g., residents of a high prevalence neighbourhood, those attending mother and child health clinics, etc. The ‘universal’ distribution in which all pre-school children and not pregnant lactating mothers in a prescribed region are dosed at prescribed intervals by single or multipurpose workers in the community.

Vitamin A fortification

Fortification of Mono-sodium Glutamate in the Philippines and of sugar in Guatemala has been highly successful. Other possible vehicles are wheat and milk. Vitamin A is light- and heat sensitive so it must be protected from light and stored in a cooler environment. The success of this type of program depends on the identification of a suitable vehicle, which has to be consumed by all and particularly the population at risk, and in a continuous and constant fashion. Fluctuations between people and in time should be as small as possible. The cost of the program on a national scale is usually high enough to raise the question as to who is going to bear it; the government, the industry or the consumer. Disagreement over this last point has led to the discontinuation of some

fortification programs.

Vitamin A toxicity

Acute hypervitaminosis

Ingestion of large dose can give rise to transient signs and symptoms of toxicity, which are self-limiting and completely reversible. No deaths have been reported after the ingestion of the doses used in treatment and prevention. Intracranial pressure rises giving rise causing headaches and a bulging fontanel in young children. Nausea, vomiting, dizziness, headaches have been described in adults. Desquamation of the skin, bone pains and hair loss can occur in the following days.

Chronic hypervitaminosis

Ingestion of large doses on a regular basis can lead to hepatitis, cirrhosis, hair loss, dry scaling skin, hyperpigmentation, hyperostosis and bone pains, hepato-splenomegaly and anaemia. It is therefore recommended not to exceed a daily intake of 3000 µg (10.000 IU) in children and 7500 µg (20.000 IU) in adults. Why does the liver get damaged in chronic hypervitaminosis A? The liver gets a double blood supply: arterial via the arteria hepatica and venous via the portal vein. The blood vessels branch until they form a capillary-like network, the so-called liver sinusoids. These vessels are rather different from ordinary capillaries and containing large fenestrations. They do not rest upon a basal membrane but are surrounded by reticuline fibers. The sinusoids contain, apart from vascular endothelial cells, also Kupffer cells, monocyte-derived phagocytes. Outside the sinusoids is the space of Disse (German anatomist, Joseph Disse; 1852–1912). This space contains the microvilli of hepatocytes as well as Ito cells (syn. stellate cells; Japanese physician Toshio Ito: 1904–1991). Ito cells store fat and fat soluble vitamins, like vitamin A. Excessive intake of vitamin A leads to pathologically enlarged Ito cells. When damaged, Ito cells can change into an activated state. These are responsible for secreting collagen scar tissue. This leads to fibrosis, cirrhosis and portal hypertension.