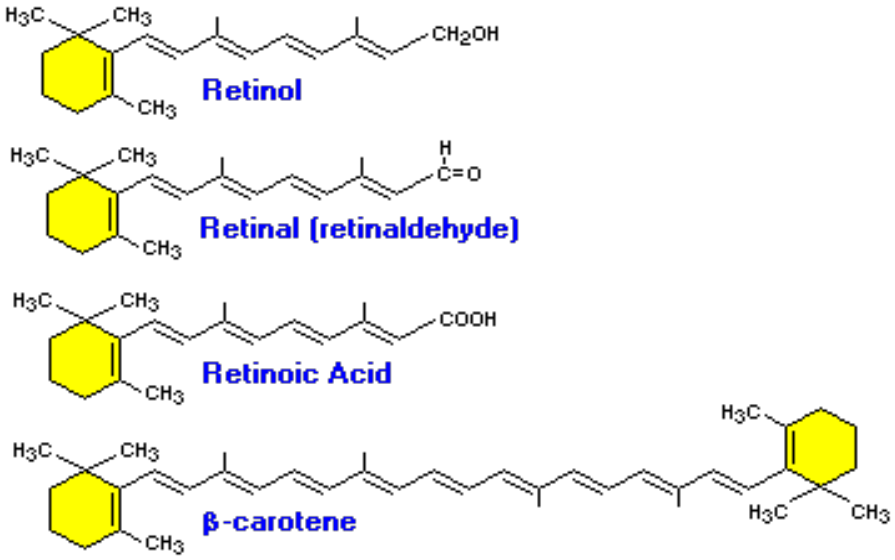
PHC
PROJECT HEALTHY CHILDREN

Overview of Vitamin A



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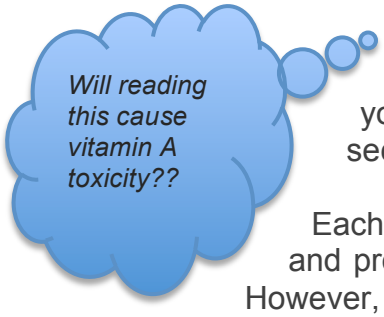
Acknowledgements

The creation of this vitamin A training module would not have been possible without the contribution of numerous sites and organizations. Specifically, the Linus Pauling Institute; the National Institutes of Health's Office of Dietary Supplements (NIH / ODS); Wardlaw, Hampl, and DiSilvestro's 2004 sixth edition of *Perspectives in Nutrition*; and Tufts University's Friedman School of Nutrition Science and Policy 'Introduction to Human Nutrition' course (McKay, Fall 2004). Special thanks to the Flour Fortification Initiative (FFI) for their willingness to share the material on their website.

This vitamin A module is the first in a series of micronutrient modules adapted from an internal organizational training program developed by Project Healthy Children (PHC). The material is intended to provide the reader with an in-depth look at the major micronutrients generally targeted in nutrition interventions to ensure a detailed understanding of how the nutrients work and why they are important. Subsequent modules include iron, folic acid, iodine, and zinc.

For any questions regarding the material, please contact Project Healthy Children's Director of Nutrition Programming, Laura Rowe, at lrowe@projecthealthychildren.org.

Document guide: suggestions on how to tackle this module



Warning: reading through this entire document in one day *may* cause vitamin A toxicity! Divide up the document and the time you have to read it so that you are only going through a few sections at a time.

Each section is followed by a 'quick recap' to summarize main points and provide a convenient way of returning to each section for review. However, reading through the entire document would be of benefit as several diagrams attempt to make potentially confusing points clearer and explain the 'why' behind much of the statistics we already know about vitamin A.

If you understand the content included in the 'take home points: vitamin A summary chart' and the 'quick recaps' you will have retained the nuts and bolts of this module. If you would like further explanation, any of the module's cited sources are good to review.

Please note this information is not intended to be used as individual nutritional guidance. It is meant only to be used as education material.

Take home points: vitamin A summary chart	
Forms	- Preformed retinoids (active form; from animal products) - Provitamin A carotenoids (precursor to vitamin A; must be converted by body into the active form; from plants)

Functions and functional explanation	- Vision
	  o Required by the retina to absorb light and communicate it to the brain.
	  o Required by the cornea to produce mucus and tears, which in turn protect the eye from bacteria, infection, and deterioration and prevent the development of blindness.
	- Immune function
	  o Ensures working mucosal cells, membranes, and epithelial layers that function as the body's first line of defense against bacteria and viruses.
	  o Aids in the development of lymphocytes and white blood cells (required for proper immune responses) and improves their fighting capabilities.
	- Cellular health and maintenance; growth, reproduction, gene expression, skin health
	  o Required for cells to grow and divide, particularly the cells of the eye, lungs, and skin.
	  o Required to mobilize iron from the liver and produce red blood cells.
	- Fetal development
	  o Required for proper fetal development including bones, lungs, heart, eyes, ears, and growth hormone.
	- Antioxidant activity
	  o Carotenoids oxidize free radicals found in the body and prevent cellular damage that can lead to cancer, aging, and a variety of diseases.

Sources	- Preformed vitamin A: liver, fish oils, dairy, eggs - Provitamin A: red, orange, yellow and dark green vegetables, orange fruits such as carrots, cantaloupe, mango, sweet potato, squash, pumpkin, spinach, kale, broccoli, collards - Retinol from animal sources is more bioavailable (i.e. usable by the body) than beta-carotene. - Supplements are an important source for weaning infants and pregnant and lactating women to improve breast milk content (risk of retinol toxicity to fetus if upper limit (UL) is exceeded).
Absorption, transport, storage	- Absorption is dependent on fat in the diet; absorbed in small intestine, packaged with other fats, sent to blood for circulation, delivered to liver if it is being stored or to specialized tissues if being used.
Recommended Daily Allowance	- RDA is based on amount needed to ensure adequate stores to support the functions it is responsible for (thought to be ~4

(RDA)	months worth). Infant stores only last a few days after birth regardless of maternal vitamin A status. - Infants and children: 400-600 µg RAE (1,333 -2,000 IU) - Adolescents (14-18), adults 19+: 700 µg RAE (2,333 IU) for females; 900 (3,000 IU) for males - Pregnant women: 750-770 µg RAE (2,333-2,567 IU); the Upper Limit (UL) for pregnant women is 3,000 µg RAE or 10,000 IU - Lactating women: 1,200-1,300 µg RAE (4,000-4,333 IU) - RAE is the vitamin A measurement of choice. 1 µg RAE and 1 µg RE are equivalent. 1 µg RAE = 3.33 IU. 12 µg of beta-carotene from food is required to provide the body with 1 µg of retinol demonstrating the greater bioavailability of retinol.
People most at risk	- Pregnant women - Young children
Deficiency symptoms	- Poor growth - Night blindness - Xerophthalmia, permanent blindness (leading cause of preventable blindness in children) - Increased susceptibility to infection and subsequently death
Toxicity symptoms	- Too much beta-carotene will make your skin turn orange. - Too much retinol can, in severe cases, lead to birth defects (teratogenic) and spontaneous abortions if pregnant women consume >3,000 µg or 10,000 IU/day. Long-term consumption in excess of 10X RDA has potential* to lead to hip fractures due to vitamin A's link with vitamin D. - Symptoms: headache, vomiting, double vision, hair loss, joint pain
Measurement indicators / biomarkers	- Functional: maternal night blindness - Clinical: xerophthalmia - Histological (i.e. requiring tissue samples): conjunctival impression cytology - Biochemical: serum retinol, relative dose response, retinol binding protein - Numerous demographic and ecological proxy measures (e.g. measles rate, IMR, immunization rate, to name a few)
Nutrient-nutrient interactions	- Vitamin A deficiency can cause anemia. - Zinc & protein deficiency can cause vitamin A deficiency. - Vitamin A may decrease the extent to which phytates prevent iron absorption.
Stability	- Very sensitive to light and oxidizing agents (e.g. iron); moderately sensitive to heat; fine in humidity. - Stability in fortified products is good unless stored in temps above 45°C. Frying does away with most vitamin A.

* Scientific consensus on the link between excessive vitamin A intake and hip fractures and osteoporosis has not yet been established.

A Fat-Soluble Vitamin[1]

Vitamin A is a fat-soluble vitamin, which, as you may recall, means it holds the following properties of all fat-soluble vitamins:

Fat-Soluble Vitamin General Properties

1. Not properly absorbed when there is not enough fat available in the diet
2. Intake in excess of daily needs causes storage in the body as opposed to excretion in urine
3. Small amounts are excreted in the bile
4. Deficiency symptoms are generally slow to develop
5. Have precursors or pro-vitamins
6. Some are toxic at relatively low levels (6-10 times the RDA)

Historical perspective[2,3,4,5]

Long before vitamins were "discovered", certain foods were known to cure illnesses. For example, the ingestion of liver and the topical application of juice were long recommended as remedies for night blindness in ancient Egypt and Greece, indicating a known connection between vision and the nutrients found in juices and liver. Vitamin A is believed to have been discovered in 1913, stemming from research by McCollum and Davis when they found that factors other than macronutrients (carbohydrates, proteins, and fats) were necessary to keep cattle healthy. They successfully isolated a fat-soluble growth factor later found to be vitamin A. In 1917, it was discovered that a deficiency in vitamin A caused rats to develop eye lesions, known as xerophthalmia. And, research from Germany at the same time found rats fed lard as their only fat source failed to grow, but butter, cod liver oil, or egg yolk (all containing vitamin A) allowed growth. In 1919, Steenbock from the University of Wisconsin proposed a relationship between yellow plant pigments (beta-carotene) and vitamin A and, in 1947, vitamin A was synthesized for the first time by two Dutch chemists. Vitamin A is thought to be the first recognized fat-soluble vitamin.

Vitamin A forms[6,7,8]

Vitamin A is a broad term for a number of similar compounds. In general, there are two categories, depending on whether the food source is from an animal or a plant: *preformed retinoids* (from animals) and *provitamin A carotenoids (predominately beta-carotene)* (from plants).

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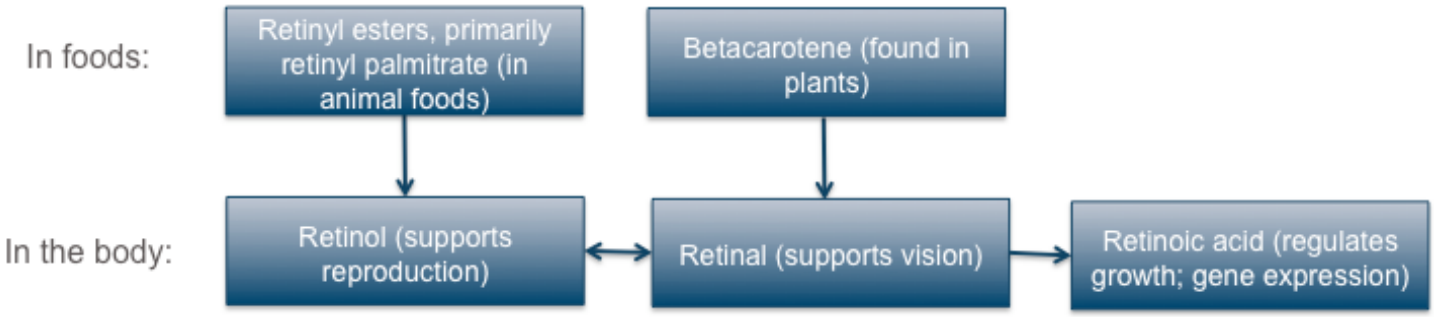
[1] Wardlaw, Hampl, DiSilvestro. 2004. Perspective in Nutrition. Sixth edition.
[2] United Nations Administrative Committee on Coordination – Subcommittee on Nutrition (ACC/SCN). Epidemiology of vitamin A deficiency. http://www.unsystem.org/scn/archives/npp13/ch08.htm
[3] Wardlaw, Hampl, DiSilvestro. 2004. Perspective in Nutrition. Sixth edition.
[4] McKay, D. Friedman School of Nutrition Science and Policy. Introduction to Human Nutrition. Fall semester 2004 slides.
[5] National Institutes of Health. Office of Dietary Supplements. Vitamin A and Carotenoids Fact Sheet. http://ods.od.nih.gov/factsheets/vitamina/
[6] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/
[7] National Institutes of Health. Office of Dietary Supplements. Vitamin A and Carotenoids Fact Sheet. http://ods.od.nih.gov/factsheets/vitamina/
[8] Wardlaw, Hampl, DiSilvestro. 2004. Perspective in Nutrition. Sixth edition.

Preformed vitamin A: Retinoids (these are considered active or usable forms)

- There are four different categories of retinoids: retinal, retinol, retinoic acid, and retinyl esters (retinyl esters are primarily in the form of retinyl palmitate, which turn into retinol in the intestinal tract).
- All retinoids are absorbed as retinol.
- Retinol must then be converted in the body to required forms. For example, retinol needs to convert to retinal to aid in vision and into retinoic acid to aid in skin and bone growth and gene expression.
- Found in animal products (liver, fish, fish oils, whole milk, eggs).

Provitamin A carotenoid (predominately as beta-carotene)

- Provitamin A is a precursor of vitamin A; in other words, the body has to convert it into active vitamin A after consumption.
- Found in plant products (dark green, yellow-orange vegetables and some fruits). Ever wonder why carrots are orange? It's because of beta-carotene!
- Although beta-carotene is the most predominant provitamin A carotenoid, other forms include alpha-carotene and beta-cryptoxanthin.
- Interesting fact: There are actually 563 different carotenoids (only about 10% can be made into vitamin A). Lycopene, lutein, and zeaxanthin are carotenoids that you may have heard of before that do not have vitamin A activity but have other health promoting properties. Lutein and zeaxanthin are the yellow pigments in corn and, like beta-carotene, play a key role in the health of the eye. Lycopene is the red pigment in tomatoes.



Quick recap (i.e. what I should take away from this section): Vitamin A comes in two general forms: preformed as retinol (this is active vitamin A found in animal products) or provitamin A carotenoids (this form must be converted by the body into active vitamin A; found in plants).

Functions and deficiencies[9,10,11,12]

[9] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/
[10] Institutes of Health. Office of Dietary Supplements. Vitamin A and Carotenoids Fact Sheet. http://ods.od.nih.gov/factsheets/vitamina/
[11] Wardlaw, Hampl, DiSilvestro. 2004. Perspective in Nutrition. Sixth edition.
[12] McKay, D. Friedman School of Nutrition Science and Policy. Introduction to Human Nutrition. Fall semester 2004 slides.

Vitamin A compounds play a vital role in numerous biological functions. As a result, a lack of this nutrient can lead to severe malfunctioning of key systems and processes throughout the body.

Functions of vitamin A

1. Vision
2. Immune response
3. Cell production, division and differentiation (cell differentiation is when a cell becomes part of specialized tissue, such as that of the brain, muscle, lungs, blood, or other); regulation of gene expression; cellular skin health
4. Embryonic development and reproduction
5. Antioxidant activity

Consequences of deficiency

If the body does not receive adequate vitamin A, the consequences can be severe:

Consequences of vitamin A deficiency[13]
• 1.1 million premature child deaths a year • Leading cause of visual damage and preventable blindness among children; ~350,000 children become blind each year due to vitamin A deficiency • Compromises immune systems of 40-60% of children under 5 in the developing world; even mildly deficient children have a higher incidence of respiratory disease, diarrhea, and rate of mortality from infectious disease • Absence during critical periods of fetal development can lead to central nervous system defects

What is the connection?

Vision

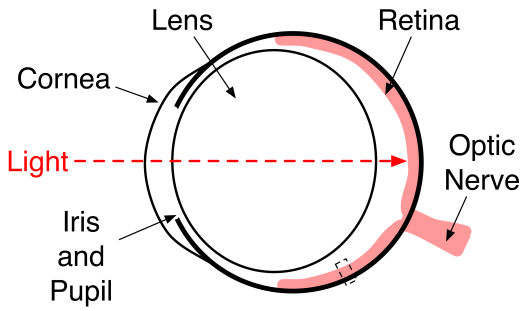
There are two reasons why vitamin A is needed for vision:

1. *The retina of the eye needs A to absorb light and communicate it to the brain.*
2. *The eye's cornea needs A to keep its cells healthy. Damage to the cornea due to a lack of vitamin A causes dryness, xerophthalmia, scarring, and eventually blindness.*

Let's looks at the connection between vitamin A and the eye's retina first: Vitamin A, as retinal (remember retinal is an active form of vitamin A found in animal foods and what plant sources of beta-carotene are converted into once consumed), is *needed in the retina of the eye to absorb visual light and communicate it to the brain*. OK, but *why* is vitamin A needed to absorb and communicate visual light?

[13] *Investing in the future: A united call to action on vitamin and mineral deficiencies.* Micronutrient Initiative, 2009; UNICEF and MI's Vitamin and Mineral Deficiency: A damage report

A bit of eye anatomy (take a look at the image below): the retina is located at the back of the eye and contains the eye's rods and cones (rods and cones are specialized cells in the eye; rod cells allow for vision in dim light and cone cells allow for vision under bright light). As light enters the eye, pigments within the rod cells of the retina absorb the light and convert it to a nerve impulse for interpretation by the brain. This is possible because of a light-sensitive pigment in the rod cells called *rhodopsin*. *Rhodopsin requires vitamin A for synthesis.* (Rhodopsin is composed of opsin [a protein] and *cis*-retinal [vitamin A]).



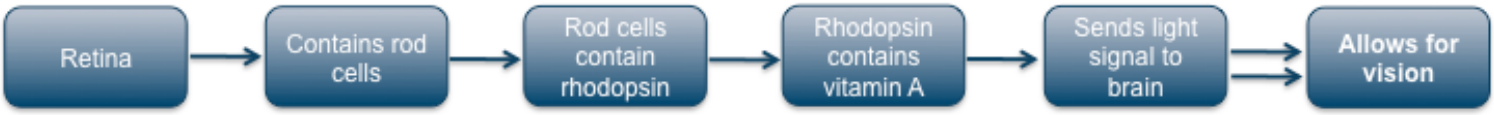
Rods in the retina:

- Responsible for vision in dim light
- Translate objects to black and white vision
- Can detect very small amounts of light, making them important for night vision

Cones in the retina:

- Responsible for vision under bright lights
- Translates objects to color vision

So, going back to the question, "why is vitamin A needed to absorb and communicate visual light?" the answer is: because rhodopsin, the light-sensitive pigment in rod cells that is responsible for absorbing light and converting it to a nerve impulse for the brain, is partially made up of vitamin A. No vitamin A means no rhodopsin. Therefore, without vitamin A, the retina cannot do its job: absorb light, communicate it to the brain, and allow one to see properly. The flow diagrams below reinforce this point.

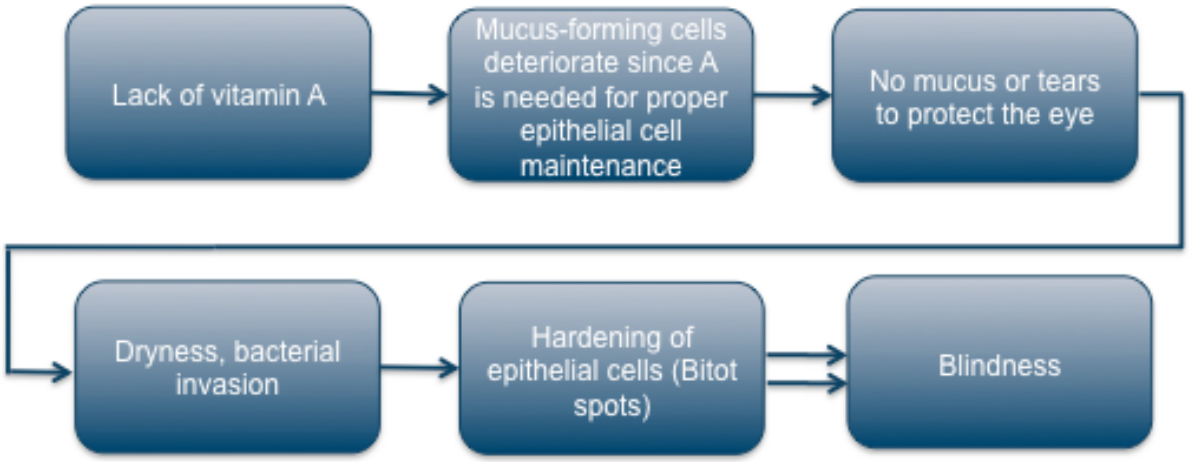


Imagine this scenario: Under adequate vitamin A conditions, in dim light, you can make out the details in a room through the use of rod cells within the retina. This is called 'dark adaptation' or the process by which the rhodopsin concentration in the eye increases in dark conditions allowing for improved vision in the dark. Suddenly, a flash of bright light momentarily blinds you as the pigment in the rods is "bleached". This is called the 'bleaching process' or the process by which light depletes the rhodopsin concentration in the eye. This fall in rhodopsin allows the eye to become adapted to bright light. A signal is then sent to the brain to use up available retinal and reform rhodopsin cells causing a bit of vitamin A to be lost in the process (this occurs each time light hits your eye). You quickly recover and can see the details of the room again in a few seconds. With inadequate vitamin A, you do not have the ability to recover from the bright flash and remain blinded for many seconds since rhodopsin levels cannot be restored. This is considered a form of 'night blindness', often a precursor to overt blindness.

Now, moving away from the effects of vitamin A on the retina to the effects on the cornea. The retinoic acid form of vitamin A is needed *to maintain normal functioning of the cells that make up the cornea of the eye*. Vitamin A is critical here to keep the cornea from drying out, scarring, and causing xerophthalmia. Night blindness is usually a precursor to xerophthalmia. But again, how does all this work?

Xerophthalmia is a Greek word meaning 'dry eyes'. It refers collectively to the sequence of changes that occur as the eye deteriorates as a result of vitamin A deficiency. *Without vitamin A, mucus-forming cells in the cornea deteriorate and are no longer able to synthesize mucus*. As will be explained later, this is a problem throughout the entire body but within the eye, the cornea is most affected. The eye can no longer produce enough tears or mucus needed to lubricate the eye and wash away bacteria leaving the eye vulnerable to bacterial infections. As a result, the cornea and conjunctiva become inflamed and dry out. (The conjunctiva is the mucous membrane that covers the white part of the eye and lines the inside of the eyelids helping to lubricate the eyes and produce tears). Deterioration of the eye results from bacterial invasion. The cornea becomes cloudy and spots (Bitot's spots, which is the hardening of epithelial or surface layer cells on the eye) and ulcers form on the surface. If untreated, it can lead to corneal ulceration, scarring, and ultimately blindness due to corneal damage. This is mainly seen in young children. In the picture above, the white portion in the eye is scarring as a result of the cells drying out and hardening.

Xerophthalmia tends to follow a particular disease progression: night blindness, decreased mucus production causing dryness and bacterial invasion, development of Bitot's spots indicating abnormal dryness of the eye, keratomalacia or a softening of the cornea, scarring, and eventually blindness. Because the fatality rates from advanced xerophthalmia are high, relatively few blind children survive in the community, which can often reduce the visibility of the problem.



Although a low intake of vitamin A over an extended period is the most common cause of xerophthalmia, the condition may be influenced by other factors such as intestinal parasitic infections and malabsorption preventing the body from absorbing any vitamin A that is ingested (examples include Celiac and Crohn's disease). Protein energy malnutrition (PEM) is also an important cause of or accompaniment to xerophthalmia with data suggesting that corneal involvement in xerophthalmia seldom occurs except in children who have moderate or severe PEM.

Quick re-cap: Vitamin A and vision:

1. *Needed by the rods cells of the retina to absorb light and communicate to the brain.*
2. *Needed by the cells of the cornea to form mucus and tears to prevent dryness and to ward off bacteria and infection.*

Immune response

Vitamin A plays an important role in ensuring proper functioning of surface linings and mucous membranes throughout the body; the body's first line of defense against bacteria, viruses, and disease. These include linings and mucosal cells of the eyes, skin, and respiratory, urinary and intestinal tracts. Vitamin A also plays a central role in directly regulating the immune system. Retinoic acid is important in the development and differentiation of white blood cells such as lymphocytes that influence immune response and may help lymphocytes fight infection more effectively. Activation of T-lymphocytes, the major regulatory cells of the immune system, appears to require retinoic acid. And, finally, blood retinol levels decrease rapidly during the onset of infection. So a vicious cycle of vitamin A deficiency is stimulated: the body is extra vulnerable to infection AND once infected, retinol levels decrease even further, increasing the susceptibility to infection.

So, it's not all that surprising that a lack of vitamin A greatly increases the chances of disease and infection since the immune system is so dependent on it to function properly. In fact, vitamin A deficiency can be considered a "nutritionally acquired immunodeficiency disease", according to the Linus Pauling Institute, with children being the most affected. "Even only mildly deficient children have a higher incidence of respiratory disease, measles, diarrhea, and mortality from infectious diseases compared to children with sufficient vitamin A levels"[14].

Quick recap: vitamin A is required for proper immune functioning for the following reasons:

1. *Ensures working mucosal cells and mucous membranes that are the body's first line of defense against bacteria and viruses.*
2. *Aids in the development of lymphocytes and white blood cells (required for proper immune responses) and improves their fighting capabilities.*

Cell growth, development, division and differentiation; regulation of gene expression; red blood cell production; skin health

Vitamin A's role under this category reviews what has already been discussed regarding vision and immunity but from a slightly different angle. Different cell types in the retina,

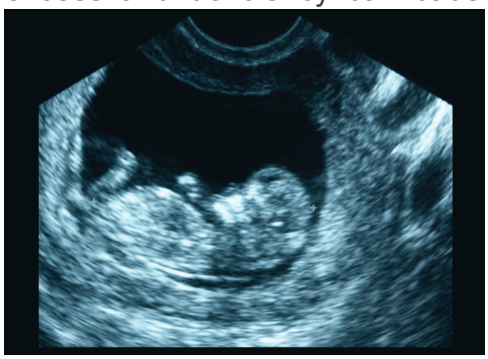
[14] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/

cornea, and epithelium of the eye depend on retinoic acid for maintaining structural integrity including gene expression and cell differentiation. Without vitamin A, cells will deteriorate leading to xerophthalmia, as mentioned above, and follicular hyperkeratosis (a skin disorder that manifests as bumpy, rough skin) can result. In vitamin A deficiency, the epithelial cells of the skin secrete the protein keratin in a process known as keratinization (this can be seen as roughness on the skin). Retinoic acid is also required for cell maintenance in the mucous membranes of the lungs, trachea, skin, and GI tract. Finally, vitamin A influences red blood cell production by helping to mobilize iron stores from the liver and due to the fact that stem cells require retinoids to turn into red blood cells.

Quick recap: Cells need vitamin A to grow and divide, particularly the cells that line major organs and systems such as the lungs, trachea, GI tract and skin. Vitamin A is required to mobilize iron from the liver and produce red blood cells.

Embryonic development and reproduction

Retinol and retinoic acid are essential for embryonic development. However, both an excess and deficiency can cause birth defects. During fetal development, retinoic acid allows for limb development and formation of the lungs, heart, eyes, and ears and regulates expression of the growth hormone gene.



The importance of vitamin A in the functioning of a newborn's lungs has been a topic of recent discussion. Vitamin A's role in lung maturation in late stages of embryonic development has been found to be crucial. Evidence suggests that newborns with low vitamin A stores are at increased risk of respiratory diseases and frequent infections in early childhood. Where maternal vitamin A is deficient, fetal lung development might be seriously impaired with consequences for postnatal function.[15] This goes back to the key role of vitamin A in cell growth and division.

Quick recap: Vitamin A is required for proper fetal development including that of the lungs, heart, eyes, ears, and growth hormone.

Antioxidant activity

Epidemiological studies have consistently shown that people who eat a diet high in fruits and vegetables have a lower risk of developing certain cancers due to the antioxidant activity of carotenoids found in these foods. How does this work? Carotenoids (and all antioxidants for that matter including vitamins C and E) work to oxidize free radicals (free radicals are molecules with unpaired electrons found in the body) and prevent free radical cellular damage that can lead to cancer, aging, and a variety of other diseases. Where do these free radicals come from? Our bodies can produce them naturally and we can absorb

[15] Sight and Life. Vol. 25 (1). 2011

them from our environment. Micronutrients are considered 'scavengers of free radicals' making their consumption a preventative measure for degenerative diseases and cancers.

Absorption, transport, and storage in the body[16]

The cells of the small intestine absorb 90% of retinol. After absorption, retinol is packaged up with other lipids (fats) and enters the lymph system and then the blood for circulation throughout the body. Since carotenoids are absorbed intact, their absorption rate is much lower than that of retinol (i.e. they are less bioavailable). The retinol-fat "packages" then deliver vitamin A to tissues for use or for storage.

If storage occurs, vitamin A is delivered to the liver. Under normal conditions, 90% of all vitamin A is stored in the liver with a reserve that is adequate for several months. When released from storage, retinol is transported from the liver to other sites in the body by retinol binding protein (RBP), a specific carrier protein. Since protein deficiency reduces the creation of RBP, it may also have an adverse effect on vitamin A status.

At birth, liver stores of vitamin A in infants are sufficient only to supply adequate requirements for a few days, even if the mother is well nourished during pregnancy. This makes breast milk with a sufficient amount of vitamin A and other sources such as supplements critical during this period.

Storage of vitamin A in the liver has been important in understanding the patterns of deficiency. For example, in countries that face seasonal changes in vitamin A intake, liver storage accumulated in the harvest season may be important in avoiding deficiency in the dry or lean season. Due to this cyclical intake, however, it is difficult to examine the relationship between estimated vitamin A intake and evidence of deficiency in a population. In other words, no intake of vitamin A foods during a specific time period does not necessarily mean individuals don't have liver stores of vitamin A that are sufficient to carry them through the season and into another season where intake can occur. Therefore, the choice of appropriate biochemical indicators (i.e. ones that take into account liver stores of vitamin A or allow for the control of seasonal intake) is critical for measuring deficiency. This will be described in detail in the section on deficiency measurements.

Quick re-cap: Vitamin A is absorbed in the small intestine. After being packaged up with other fats, it can take one of two routes: 1) it can be circulated throughout the body via the blood system and delivered to specialized tissues or 2) it can go to the liver for storage until needed. Normal storage levels in the liver can last several months. However, infants at birth only have enough vitamin A stored for a few days.

Food sources[17]

The potency of vitamin A will depend on the dietary source from which it is obtained. Retinol will have an easier time being absorbed when compared to beta-carotene.

[16] Wardlaw, Hampl, DiSilvestro. 2004. Perspective in Nutrition. Sixth edition.
[17] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/

Retinoids are found in liver, fish and fish oils, some dairy products, and eggs. Provitamin A carotenoids, are found in dark, green vegetables (the carotenoid pigment is masked by the green pigment of chlorophyll) and yellow-orange vegetables and fruits.

Example food sources of vitamin A are listed in the table below along with their vitamin A content in micrograms (µg) of retinol activity equivalents (RAE) and International Units (IU). In foods where retinol activity comes mainly from carotenoids, the retinol activity equivalents are presented. To convert RAEs to IUs, the RAE is roughly multiplied by 3.33. Before you get overwhelmed, the next section will explain what RAE and IU are all about. For now, just focus on what foods contain vitamin A.

Not to be overlooked, breast milk is a very important source of vitamin A for infants.

Food	Serving	Vit A, µg RAE	Vit A, IU
Cod liver oil	1 teaspoon	1,350 µg	4,500 IU
Egg	1 large	91 µg	303 IU
Butter	1 tablespoon	97 µg	323 IU
Whole milk	1 cup (8 fl oz.)	68 µg	227 IU
Sweet potato, baked	1/2 cup	961 µg	3,203 IU
Pumpkin, canned	1/2 cup	953 µg	3,177 IU
Carrot (raw)	1/2 cup, chopped	538 µg	1,793 IU
Cantaloupe	1/2 medium	467 µg	1,555 IU
Mango	1 fruit	79 µg	263 IU
Spinach	1/2 cup, cooked	472 µg	1,572 IU
Broccoli	1/2 cup, cooked	60 µg	200 IU
Kale	1/2 cup, cooked	443 µg	1,475 IU
Collards	1/2 cup, cooked	386 µg	1,285 IU
Squash, butternut	1/2 cup, cooked	572 µg	1,907 IU

Source: Linus Pauling Institute

Vitamin A supplements[18,19]

Supplemental vitamin A provides what is sometimes the primary source of this vitamin for individuals in the developing world and so is included in this section. As mentioned earlier, liver stores of vitamin A at birth are sufficient to supply an infant's requirements for only a few days, even if the mother is well nourished during pregnancy. Two options have been universally accepted as means of improving the vitamin A status of breastfed infants: 1) improve the vitamin A status of mothers and thus the vitamin A content of breast milk (assuming the mother will breast feed) or 2) supplement the infant. For breast fed infants, supplementation is important during the weaning process, as they no longer have access to vitamin A through the mother's breast milk, assuming there is not an alternative dietary source being consumed that is rich in vitamin A.

[18] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/
[19] Food and Nutrition Bulletin. Vol. 22. No. 3. 2001

Non-breastfeeding women will also benefit from post-partum doses of vitamin A to replenish their own liver stores in order to decrease rates of morbidity. Additionally, there is well-established evidence for a beneficial effect of vitamin A supplementation in the treatment of measles and the management of severe acute malnutrition.

Retinyl palmitate and acetate are the common forms of vitamin A found in supplements. Some supplements, such as those found in the US that are bought over-the-counter, contain a combination of retinol and beta-carotene. Interestingly, most multivitamin supplements available in the US provide 1,500 µg (5,000 IU) of vitamin A, which is substantially more than the current RDA for vitamin A. This is because the Daily Values (DV) used by the FDA are based on the RDA established in 1968 rather than the most recent RDA. Because retinol intakes of 5,000 IU/day may be associated with an increased risk of osteoporosis in older adults, some companies have reduced the retinol content in their multivitamin supplements to 750 µg (2,500 IU).

It should be noted that vitamin A supplementation among smokers and those exposed to asbestos has been linked with increased rates of lung cancer.

WHO and IVACG (International Vitamin A Consultative Group) supplementation guidelines

Group	Vitamin A dosage and timing
Pregnant and / or fertile women (independent of their vitamin A status)	Up to 10,000 IU daily at any time during pregnancy or a weekly supplement of up to 25,000 IU (this is the max that pregnant women should receive)
Breastfeeding / non-breastfeeding postpartum women	Two doses of 200,000 IU*. An alternative to large-dose supplementation, mothers can receive vitamin A at any time post-partum, given as a low dose not exceeding 10,000 IU / day or 25,000 IU / week.
Children up to 6 months	Three 50,000 IU doses within the first six months of life at an interval of one month between doses.
Children 6-11 months	Single dose of 100,000 IU every 4-6 months to maintain stores throughout the first year of life.
Children 12+ months	Single dose of 200,000 IU given every 4-6 months.
*To be given to breastfeeding and non-breastfeeding mothers as soon after delivery as possible and not more than six weeks later. The first dose should be given immediately after delivery and the second dose at least one day (24 hours) later. **Supplements are also recommended as treatment for measles and severe malnutrition.	

Source: WHO Vitamin A supplementation guidelines; IVACG Statement 2002 – The Annecy Accords to Assess and Control Vitamin A Deficiency: Summary of Recommendations and Clarifications

Quick re-cap: Retinol from animal sources is more bioavailable (usable by the body) than beta-carotene. Liver, eggs, dairy, and fish oils provide retinoids; red / orange fruits and vegetables and some greens provide beta-carotene (cantaloupe, carrots, pumpkin, squash, sweet potato, spinach, kale). Supplements are an important source for weaning infants and pregnant and lactating women to improve breast milk content (note: there is a risk of toxicity to the fetus if the upper limit of 3,000 µg or 10,000 IU / day is exceeded; this is outlined under the toxicity section).

Units of measurement[20,21,22]

This section is meant to outline the different units used to measure vitamin A and their conversion ratios. You will often see three different units of measurement used for vitamin A: 1) International Units (IU); 2) Retinol Equivalents (RE) measured in micrograms (µg); and 3) Retinol Activity Equivalents (RAE) also measured in micrograms (µg).

To simplify things, the Institute of Medicine decided that vitamin A should be expressed as RAE rather than RE or IU taking into account new research on the activity of vitamin A. However, you will often see all three units expressed depending on what you are reading so it's good to know how they relate to one another.

Retinol Activity Equivalent (RAE)	Commonly used units
1 µg RAE =	1 µg RE of retinol (so RE and RAE measurements are equivalent) 1 µg retinol (again, equivalent measurements) 3.33 IU of retinol (or, 1 IU = 0.3 µg of retinol) 2 µg beta-carotene in oil 12 µg beta-carotene plant foods

It was outlined earlier how retinol is more bioavailable than beta-carotene. The conversion ratio above, however, shows just how much more: *12 µg of beta-carotene from food is required to provide the body with 1 µg of retinol, giving dietary beta-carotene a 12:1 RAE ratio.*

Quick re-cap: RAE is now the measurement of choice. 1 µg RAE and 1 µg RE are equivalent. 1 µg RAE = 3.33 IU. 12 µg of beta-carotene from food is required to provide the body with 1 µg of retinol.

Variability of requirements across populations and recommended dosage[23]

Although all individuals need sufficient intakes and stores of vitamin A, young children and pregnant women are the most at risk. Since infants' vitamin A stores only last a few days after birth, there is need to ensure the child (and therefore the mother) maintains sufficient levels. However, deficiencies in infants occur most often after the baby has been weaned (weaning refers to the time when breastfeeding ends and complementary feeding begins, ideally at the age of 6 months).

The Food and Nutrition Board (FNB) revised the RDA for vitamin A in 2001. This RDA is based on the amount needed to ensure adequate stores of vitamin A in the body to support normal reproductive function, immune function, gene expression, and vision. It is estimated that about *four months of vitamin A storage is adequate for these purposes*.

Recommended Dietary Allowance (RDA) for Vitamin A			
Life Stage	**Age**	**Males: µg /day**	**Females: µg /day (IU/day)**

[20] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/
[21] Wardlaw, Hampl, DiSilvestro. 2004. Perspective in Nutrition. Sixth edition.
[22] International Vitamin A Consultative Group (IVACG). 2002.
[23] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/

		(IU/day)	
Infants	0-6 months	400 (1,333 IU)	400 (1,333 IU)
Infants	7-12 months	500 (1,667 IU)	500 (1,667 IU)
Children	1-3 years	300 (1,000 IU)	300 (1,000 IU)
Children	4-8 years	400 (1,333 IU)	400 (1,333 IU)
Children	9-13 years	600 (2,000 IU)	600 (2,000 IU)
Adolescents	14-18 years	900 (3,000 IU)	700 (2,333 IU)
Adults	19 years +	900 (3,000 IU)	700 (2,333 IU)
Pregnancy	≤18 years	-	750 (2,500 IU)
Pregnancy	≥19 years	-	770 (2,567 IU)
Breast-feeding	≤18 years	-	1,200 (4,000 IU)
Breast-feeding	≥19 years	-	1,300 (4,333 IU)

Source: Linus Pauling Institute

Quick re-cap: The RDA for vitamin A is based on the amount needed to ensure adequate stores to support the functions it is responsible for (thought to be ~4 months worth). Infant vitamin A stores only last a few days after birth regardless of maternal vitamin A status, however, deficiency most often occurs during the weaning period. Needs are greatest for breastfeeding women: 1,200-1,300µg/day or ~4,000 IU.

Toxicity[24,25,26]

Being a fat-soluble vitamin that is rapidly absorbed and slowly cleared from the body, too much vitamin A does pose a toxicity risk. This is only the case for preformed retinol, however. Beta-carotene from plant sources is not toxic even at high levels of intake. If one does consume a high level of beta-carotene, excessive levels of carotenoids in the blood manifest as hypercarotenemia. This causes the skin to turn a yellow-orange color. (In other words, too many carrots will make you look like a carrot)!

Vitamin A toxicity from retinol is called hypervitaminosis A and can pose a number of risks more serious than turning your skin orange. Most notably, sustained intake above the RDA for pregnant women can be teratogenic (i.e. it can cause birth defects and spontaneous abortions). Toxicity can be acute or chronic:

Acute vitamin A toxicity:

- Ingestion of 100X RDA within a short period (days)
- Relatively rare; symptoms include nausea, headache, fatigue, loss of appetite, dizziness, blurred vision, dry / scaly skin, cerebral edema, poor muscle coordination
- Severe cases may result in liver damage, hemorrhage, and coma

Chronic vitamin A toxicity

- Long-term consumption in excess of 10X the RDA

[24] Wardlaw, Hampl, DiSilvestro. 2004. Perspective in Nutrition. Sixth edition.
[25] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/
[26] Harvard School of Public Health. The Nutrition Source. http://www.hsph.harvard.edu/nutritionsource/what-should-you-eat/vitamin-a/index.html

- Symptoms include dry itchy / scaly skin, loss of appetite, headache, double vision, cerebral edema, bone and joint pain, increased liver size, and some studies indicate increased risk of osteoporosis and hip fractures (this is likely due to the fact that vitamin A can interfere with the beneficial effects of vitamin D, which is connected to the beneficial effects of calcium, critical for healthy bones, however these studies are not conclusive)
- Severe cases may result in liver damage, hemorrhage, and coma

Toxicity in pregnant women

- To avoid teratogenic effects pregnant women should limit intake of vitamin A from fortified foods / supplements to <3,000 µg / day and avoid vitamin A analog medications (e.g. Accutane, Retin-A).

Toxicity in infants

- Manifests as bulging fontanel (the soft spot on top of the baby's head)

Signs of toxicity are usually associated with long-term consumption in excess of 10X the RDA. However, according to the Linus Pauling Institute, there is evidence that some populations may be more susceptible to toxicity at lower doses, including the elderly, chronic alcohol users, those exposed to asbestos, smokers (high-dose single supplements have been linked with increased lung cancer risk among smokers) and some with a genetic predisposition to high cholesterol. In 2001, the Food and Nutrition Board set the UL of intake for adults at 3,000 µg (10,000 IU/day) of preformed vitamin A.

Tolerable Upper Level of Intake (UL) for Preformed Vitamin A (Retinol)	
Age Group	**UL in µg /day (IU/day)**
Infants 0-12 months	600 (2,000 IU)
Children 1-3 years	600 (2,000 IU)
Children 4-8 years	900 (3,000 IU)
Children 9-13 years	1,700 (5,667 IU)
Adolescents 14-18 years	2,800 (9,333 IU)
Adults 19 years and older	3,000 (10,000 IU)

Source: Linus Pauling Institute

Quick re-cap: Too much vitamin A as beta-carotene will make your skin turn orange. Too much vitamin A as retinol is more serious and can, in severe cases, lead to birth defects and spontaneous abortions (teratogenic) if pregnant women consume >3,000 µg or 10,000 IU/day (also considered the UL for all adults). Long-term consumption in excess of 10X RDA has the potential to lead to hip fractures due to vitamin A's link with vitamin D.

Vitamin A's interconnectedness with other micronutrients (and protein)[27,28,29]

[27] Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/

[28] IVAG Statement. The Annecy Accords to Assess and Control Vitamin A Deficiency. Summary of Recommendations and Clarifications. 2002.

Iron / anemia

- Vitamin A affects hemoglobin levels by helping to mobilize iron stores from the liver influencing red blood cell production; additionally, stem cells require retinoids to turn into red blood cells.
- Vitamin A helps increase absorption of iron from the intestine.
- Supplementation or fortification with vitamin A can reduce the risk of mild to moderate anemia in vitamin A deficient and anemic populations. However, benefits associated with anemia are more likely when anemia is not due to infections such as hookworm, malaria, and HIV.

Zinc

- Zinc is required for the synthesis of retinol-binding protein (RBP) (recall this is needed to transport retinol from the liver to other sites in need). Therefore zinc deficiency can reduce the amount of retinol that can circulate, causing a functional vitamin A deficiency even when liver stores are sufficient.
- Zinc is needed by the enzyme that releases retinol from storage in the liver (similar to the role of iron).
- Zinc is required for the enzyme that converts retinol into retinal.

Protein

- Since protein deficiency reduces the creation of RBP, it may also result in low vitamin A status.

Seasonality can also affect vitamin A concentrations. The seasonality of vitamin A-rich foods in some populations may cause shifts in vitamin A levels in the blood, complicating comparisons between and within populations.

Quick-recap: Vitamin A deficiency can cause anemia; zinc and protein deficiency can cause vitamin A deficiency. Why?

- *Vitamin A is needed to move iron from the liver, to produce red blood cells, and to increase absorption of iron from the intestine.*
- *Zinc and protein deficiency can cause vitamin A deficiency since retinol-binding protein (RBP) needs zinc and protein to be made. Without RBP, vitamin A can't be transported to tissues in need.*
- *Retinol needs zinc to leave the liver (just like iron needs vitamin A to leave the liver).*
- *Zinc is required to convert retinol to retinal.*

Absorption inhibitors / promoters[30,31]

Although few to no absorption inhibitors have been identified for vitamin A, it is worth noting that several studies have found that the addition of vitamin A to iron fortified

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[29] Sandstrom B. Micronutrient interactions: effects on absorption and bioavailability. *British Journal of Nutrition*. Vol. 85. Suppl. 2. S181-S185. 2001.

[30] Garcia-Casal MN. Beta-carotene and inhibitors of iron absorption modify iron uptake by Caco-2 cells. J Nutr. 2000;130:5-9.http://jn.nutrition.org/content/130/1/5.full

[31] Layrisse M. et al. New property of vitamin A and beta-carotene on human iron absorption: effect on phytate and polyphenols as inhibitors of iron absorption. Arch Latinoam Nutr. 2000. Sept; 50(3):243-8. http://www.ncbi.nlm.nih.gov/pubmed/11347293

mixtures (using ferrous fumarate) actually inhibits the adverse effect that polyphenols and phytates have on iron absorption (recall that polyphenols and phytates prevent absorption of iron and are found in foods such as coffee, tea, beans, and maize flour). Findings from two different studies indicate that beta-carotene allows for increased absorption of iron in the presence of phytates (one of these studies actually found positive evidence for both active vitamin A and beta-carotene). A portion of the study's findings is quoted below.

"The presence of vitamin A increased iron absorption up to 3 times for rice, 2.4 times for wheat and 1.8 times for corn. Beta-carotene increased absorption almost 3 times for the three cereals tested, showing that both compounds were capable of preventing the inhibitory effect of phytates on iron absorption. This information suggest that vitamin A and beta-carotene form a complex with iron keeping it soluble in the intestinal lumen and preventing the inhibitory effect of phytates and polyphenols on iron absorption."[32]

Quick re-cap: Vit A may decrease the extent to which phytates prevent iron absorption.

Stability[33]

Vitamin A is highly sensitive to light and oxidizing agents such as iron and copper. It is moderately sensitive to heat and acids, but not very sensitive to humidity and alkalis. The stability of vitamin A in fortified wheat and corn flour is excellent. Studies show that, when stored under normal conditions, these flours retain over 95% of vitamin A after six months. However, the stability of vitamin A under high temperatures (at or above 45°C) is not as good. Wheat flour stored for three months at 45°C retained only 72%.

Baking causes limited losses, while frying has a significantly adverse effect on stability. After an initial use of vitamin A fortified soybean oil for frying, ~65% of the original vitamin remained; after four repeated uses, less than 40% of the original level was retained.

Quick re-cap: Very sensitive to light and oxidizing agents; moderately sensitive to heat; fine in humidity. Stability in fortified products is great unless stored in temps above 45°C. Frying does away with a good portion of vitamin A.

[32] Layrisse M. et al. New property of vitamin A and beta-carotene on human iron absorption: effect on phytate and polyphenols as inhibitors of iron absorption. Arch Latinoam Nutr. 2000. Sept; 50(3):243-8. http://www.ncbi.nlm.nih.gov/pubmed/11347293

[33] Fortification Basics: Stability. MOST Project.

Indicators / biomarkers of vitamin A deficiency (functional, clinical, histological, and biochemical)[34,35,36]

So how does one determine the vitamin A status of a population? Although there is no one perfect indicator at this point that accurately measures current / circulating vitamin A in the blood, vitamin A stores in the liver, *and* is practical to conduct in a field setting, there are a few that come close and that can be combined with other measurements to provide a fairly accurate picture. The table below outlines the pros and cons of each measurement with serum retinol and retinal binding protein starred (*) as the recommended forms of biochemical measurements when combined with measurements of C-reactive protein (a blood protein that is elevated during infection / inflammation; therefore, by measuring it, you can control for disease status). The drawback of these two indicators is their inability to measure liver stores, therefore studies using these indicators should measure or control for seasonality and consumption.

Indicator	Pros	Cons
Maternal night blindness (functional) – defined as a woman experiencing difficulty seeing at night at some point during her last live-birth pregnancy.	- May initially serve as a useful indicator due the existence of these words in local languages that describe the condition - A minimum prevalence of 5% among mothers is considered indication of deficiency in a population	- Difficult to standardize under field conditions - Limited effectiveness in detecting and monitoring populations with mild to moderate levels of vitamin A deficiency
Xerophthalmia (clinical)	- Visual indication of vitamin A deficiency	- Conjunctival xerosis and Bitot's spots (indicators of xerophthalmia) are variable and subjective so heath workers must be carefully trained for accurate diagnosis - Low prevalence of findings means large samples are required to establish the disorder with any certainty, particularly if mild to moderate levels are present
Conjunctival impression cytology (histological – meaning it requires tissue samples)	- Filter paper is applied to conjunctiva of the eye to remove epithelial cells, which are then classified as positive or negative; simple and minimally invasive	- Results do not provide continuous scale of deficiency (only yes or no indication like an iron or iodine spot test) - Interpreting samples requires careful training and standardization
Serum retinol (biochemical)*	- Widely used and validated to measure vitamin A status at the *population level*	- *Does not reflect liver stores of vitamin A* *- May be affected by other factors such as infection and*

	(not the individual level); it can be measured in a small sample of blood serum - Not always correlated with vitamin A intake or signs of deficiency and is therefore NOT a useful way of measuring an individual's vitamin A status. HOWEVER, the distribution of serum retinol values in a population and the prevalence of individuals with low serum retinol levels below a certain cut-off CAN provide important information about a population's vitamin A status. - Can be measured in venous blood, free-flowing capillary blood samples, *or* dried blood spots	*protein-energy malnutrition therefore C-reactive protein should be measured when using serum retinol as an indicator to control for infection* - Requires proper storage, transport, and sophisticated lab analyses (high-performance liquid chromatography [HPLC] is considered the only reliable lab technique), therefore may not always be practical in the field - For supplementation, measuring serum retinol is not an effective measure of program impact since serum retinol does not maintain its level. Elevated serum retinol levels will only last 16 weeks. Therefore, supplementation programs should not use this as an indicator of vitamin A status. An alternative indicator is yet to come from the WHO. Achieving adequate coverage is emphasized as an important measurement and measuring vitamin A status in breast milk is suggested when appropriate
Relative dose response (biochemical)	- A dose-response test based on retinol's response to an administered dose of vitamin A; measures vitamin A status more accurately than serum retinol - *Significant advantage of reflecting liver stores of vitamin A*	- Acceptability is limited because it requires two blood sampled to be drawn for the test - The modified relative dose-response test requires only a single venous sample, but it is complex for field application and its use as an indicator in continuing ongoing surveillance may be limited
Retinol binding protein (biochemical)*	- Highly correlated with serum retinol since it's the carrier protein for retinol in circulation - Can potentially be measured in a dried blood spot sample - This indicator must be developed further, but appears to have substantial potential for field application	- Has many of the limitations of serum retinol, including low levels in response to infections and inability to reflect liver stores

What is considered a low level of vitamin A?[37]
According to the WHO, the prevalence of serum retinol levels ≤ 0.70 micromoles / liter can be used to assess the severity of vitamin A deficiency as a public health problem in most age groups in a population.

Degree of public health problem			
Prevalence of low serum retinol (≤ 0.70 micromols / l or < 20 micrograms / dL)	Mild	Moderate	Severe
	2-9%	10-19%	20% or more

Other demographic and ecologic risk factors, along with low serum retinol levels or other identified biomarkers, can be used as proxy measures to strengthen the case for vitamin A deficiency in a population. According to the WHO, widespread deficiency is considered established when low serum retinol levels are coupled with another biological indicator of vitamin A status (indicated above) OR at least four of the following risk factors:

- Infant mortality rate > 75 / 1,000 live births or an under-five mortality rate of higher than 50 / 1,000 live births;
- For children 12-23 months of age, full immunization coverage lower than 50%;
- Prevalence of breastfeeding in children 6 months of age lower than 50%;
- Median dietary intake lower than 50% of the recommended safe level of intake among 75% of children 1-6 years;
- Cases of diarrhea for two-weeks is 20% or higher;
- A measles case fatality rate of 1% or higher;
- No formal schooling for 50% or more of women 15-44 years of age;
- Less than 50% of households have indicated they have a safe water source

Quick re-cap: Measurement indicators include: maternal night blindness (functional); xerophthalmia (clinical); conjunctival impression cytology (histological, meaning it's a tissue sample); and three biochemical indicators including serum retinol (≤0.70 micromols/liter), retinol binding protein (these two are universally used but the biggest drawback is that they don't measure liver stores of vitamin A and require the measurement of C-reactive protein to control for infection), and relative dose response, which does measure liver stores but is complex for use in the field. IMR, immunization coverage, and measles case fatality rate are a few (of many) indicators that can be used as proxy measures in conjunction with low retinol levels.

[37] Serum retinol concentrations for determining the prevalence of vitamin A deficiency in populations. 2001. World Health Organization.