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The vitamin A and mortality paradigm: past, present, and future

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ABSTRACT

Vitamin A deficiency contributes to the morbidity and mortality from some infectious diseases. Empirical observations and trials from the early twentieth century led to the paradigm that improvement of vitamin A status could reduce morbidity and mortality among women and children. Many seminal observations of vitamin A deficiency and infection were made in Scandinavia. International organizations in the 1930s and 1940s emphasized adequate vitamin A status to prevent morbidity and mortality. With improvement of nutrition and hygiene in Europe and the United States, vitamin A deficiency largely disappeared, and attention later turned towards developing countries. Over one hundred clinical trials have addressed the impact of vitamin A on infectious disease morbidity and mortality and show that adequate vitamin A status is important in measles and diarrheal disease but not in non-measles pneumonia. Current studies extend investigations of the role of vitamin A to malaria, tuberculosis, and human immunodeficiency virus infection.

Key words: Immunity, infection, morbidity, mortality, vitamin A

Introduction

Vitamin A deficiency is a major public health problem in at least sixty developing countries worldwide, and an estimated 253 million preschool children are affected by vitamin A deficiency (1). Pregnant women and women of childbearing age also constitute a high risk group for vitamin A deficiency in developing countries. Vitamin A plays an important role in immune function, growth, reproduction, and vision. Clinical trials in the last fifteen years showed that improving vitamin A status of preschool children through supplementation or fortification can reduce morbidity and mortality, specifically of diarrheal diseases but not acute lower respiratory disease (2,3). Vitamin A supplementation also reduced morbidity and mortality in children with acute measles (4) and seems to reduce mortality related to pregnancy (5). Empirical observations and clinical trials conducted as early as the 1920s and 1930s suggested that vitamin A could reduce infectious disease morbidity and mortality, and the origins of these ideas and earlier clinical practice have largely gone unacknowledged during the last fifteen years (6). Recent trials from developing countries have further reinforced the idea that vitamin A reduces morbidity and mortality from infectious diseases – a paradigm that was established by the early part of the twentieth century.

Early uses of vitamin A as "anti-infective" therapy

In the nineteenth century, physicians at Brompton Hospital in London found that vitamin A – in the form of cod-liver oil – could reduce morbidity and mortality in patients with tuberculosis (7). At the time, it was not known that the active agent in cod-liver oil was vitamin A, but it was widely concluded from clinical experience and comparison with historical controls that this extremely potent source of vitamin A was an effective therapy. As is not uncommon in the history of medicine, the intrinsic value of certain therapies was established early through trial and error, without evaluation through a randomized, controlled clinical trial. Cod-liver oil was widely used as "anti-infective" therapy against tuberculosis, like foxglove was used for heart failure, even though the active agents were not named, isolated, and synthesized until hundreds of years later. Other parallels can be made with the early use of lemons and oranges for scurvy in the centuries prior to the vitamin hypothesis. Several physicians claimed to have "discovered" that cod-liver oil reduced mortality, and many disputes arose about the priority of this claim. However, the use of fish liver oils for infectious diseases had already been practiced for hundreds of years, as is evident in Arabic, Roman, and Greek medical texts.

Towards the characterization of vitamin A

The existence of vitamin A was demonstrated through a long series of steps that spanned a period of over one hundred and thirty years. In 1816, François Magendie found that dogs raised on sugar and water alone developed corneal ulcers and died (8). In the late nineteenth century at the University of Dorpat, Nicolai Lunin (9) and C. A. Socin (10) showed that mice could not survive on purified protein, fat, carbohydrate, and mineral salts alone, but were able to survive for extended periods if supplemented with milk or egg yolk. Cornelis Pekelharing (11) and Frederick Hopkins (12) both conducted studies that also suggested there was something essential in milk that supported growth and survival, and Hopkins believed these "accessory factors" were necessary for life. In 1911, Wilhelm Stepp extracted lipids from milk with alcohol-ether that appeared to contain the active substance (13,14) and in 1913 at the University of Wisconsin, Elmer McCollum and Marguerite Davis extracted the lipids with ether from cod-liver oil, concluding "our observation ...strongly supports the belief that there are certain accessory articles in certain food-stuffs which are essential for normal growth for extended periods" (15). At Yale University, Thomas Osborne and Lafayette Mendel made the seminal observation that infectious diseases in vitamin A-deficient animals were quickly alleviated by introduction of butter-fat in the diet (16,17). In 1916, this growth-promoting and anti-infectious substance was termed "fat-soluble A" (18).

Harry Steenbock and colleagues proposed in 1919 that there was a connection between yellow plant pigments ("carotin") and vitamin A, an observation suggested by the appearance of vitamin A deficiency in a rat colony when white corn was substituted

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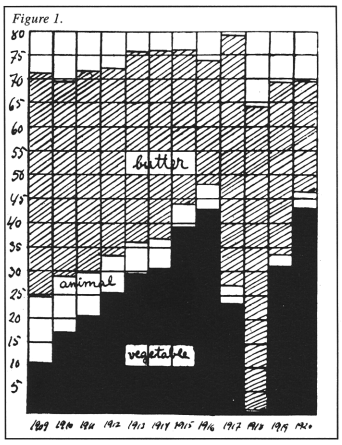
for yellow corn in the regular animal feed (19). Carotin had growth-promoting (20) and "anti-infective" (21) properties similar to vitamin A. Thomas Moore found that purified carotin restored growth and cured ophthalmia and concluded that carotin was a precursor to vitamin A (22,23). The structure of vitamin A was deduced in 1931 by Paul Karrer and colleagues (24,25) and vitamin A was finally crystallized in 1937 (26). During this long period leading to the biochemical characterization of vitamin A, important clinical observations were being made among children.

Observations from Denmark

From 1909 to 1920, the Danish ophthalmologist, Olaf Blegvad documented cases of xerophthalmia, or clinical vitamin A deficiency, among children in Denmark (28). From 1911 to 1917, there was a strong, gradual increase in the number of cases of keratomalacia, the most severe eye lesion of vitamin A deficiency, followed by a decline in 1918 and 1919 and then an increase in 1920. During the same period in Sweden, there was no epidemic of xerophthalmia. Blegvad showed that the export of butter and cheese from Denmark and increased consumption of margarine within the country were linked with the increase in vitamin A deficiency. The manufacture of margarine ceased in 1917 after a German submarine blockade halted importation of raw materials, and butter, which was produced in Denmark at an expensive price, was then rationed at a more affordable cost for the poor after December 21, 1917. On May 1, 1919, butter rationing ceased (Figure 1) (28). The mortality rate observed among 434 children with xerophthalmia was about 21%, with the highest mortality noted among younger infants. The high mortality of children was attributed to infections and the lack of vitamin A, and it resembled the infections and mortality found in animals experimentally raised on a vitamin A-deficient diet (28).

Carl Edvard Bloch (1872-1952), a pediatrician in Copenhagen, also dealt with the epidemic of xerophthalmia and provided important descriptions of the epidemiology of vitamin A deficiency (29). Bloch observed that the number of cases of children admitted with xerophthalmia at the State Hospital in Copenhagen rose from 1912 to 1917, then dropped dramatically in 1918 (Figure 2) (30). The abrupt decline in cases of xerophthalmia in 1918 coincides with butter rationing for the poor in 1918 (Figure 1). Bloch noted that xerophthalmia was associated with lack of milk and green vegetables in the diet, and that children with xerophthalmia had retarded growth. He concluded that vitamin A deficiency was characterized by a decline in immunity, increased severity of infections, and a higher risk of death. Child mortality was reduced by providing foods containing vitamin A. Bloch advocated the provision of milk, cream, and butter to reduce eye disease, promote growth and development, and reduce infectious diseases of children (29).

The concerns about vitamin A deficiency clearly extended beyond children who had xerophthalmia, or clinical vitamin A deficiency. The concept of subclinical vitamin A deficiency was widely discussed. Based upon the observations in Denmark and animal studies, Erik Widmark (1889-1945), Professor of Medical and Physiological Chemistry at the University of Lund, concluded in *The Lancet* "...there must be in a population in which xerophthalmia occurs a much larger number of cases in which the deficiency in vitamin A, without producing the eye disease, is the cause of a diminished resistance to infections, of general debility, and of malnutrition" (31). A state of subclinical vitamin A deficiency was acknowledged as "the borderline between health and disease" where a child would appear healthy, but in the face of an infection would do less well because of an underlying vitamin deficiency (32). The emphasis shifted from targeting children with xerophthalmia to ensuring adequate vitamin A status of children in populations.



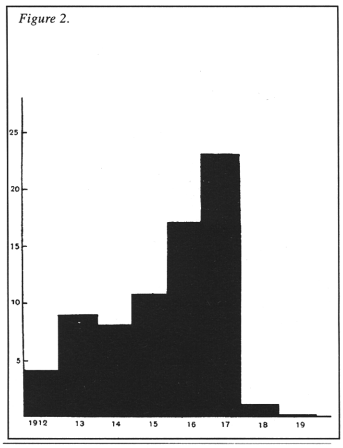


Figure 1. Original figure from Olaf Blegvad's study in 1924 showing butter and margarine consumption from 1909 to 1920. Relative amount of butter used each year (oblique lines); substitutes made from animal fats (white spaces); and vegetable fat substitutes (black spaces) (28).

Figure 2. Original figure from Carl Bloch's study in 1921, showing the number of cases of xerophthalmia admitted to the State Hospital, Copenhagen, 1912-1919 (30).

Vitamin A as the "anti-infective" vitamin

Vitamin A became known as the "anti-infective" vitamin, and from 1920 through 1940, vitamin A underwent considerable evaluation through at least thirty therapeutic trials, from dental caries and pneumonia to puerperal sepsis and measles. These studies were conducted during a period when there was an increased awareness of the problem of infant and child mortality in Europe and the United States (6). These trials were conducted in places such as England, Sweden, Spain, France, the United States, and South Africa. Among the notable findings of these trials was that vitamin A supplementation reduced mortality from measles in children (33) and reduced the morbidity of puerperal sepsis (34,35). With the introduction of antibiotics in the mid-1930s, greater attention was paid to sulfa antibiotics and later penicillin, and there was an accompanying decline in the number of vitamin A trials. Vitamin A became a mainstream preventive measure: cod-liver oil was part of the morning routine for millions of children – a practice promoted by physicians and popularized by the pharmaceutical industry (6). Much of the world's supply of cod-liver oil, and hence, vitamins A and D, came from the commercial fisheries of Norway and Newfoundland. Other public health measures that were taken to improve vitamin A status of children were institution of school milk programs, fortification of milk and margarine with vitamin A, and the promotion of home gardening (6,36,37).

The idea that vitamin A deficiency could increase susceptibility to infection and increase morbidity and mortality was widely accepted and influenced public health efforts in the first five decades of the twentieth century. Major health organizations, including the League of Nations Health Committee, the Women's Foundation for Health, the Council of British Societies for Relief Abroad, and the Medical Research Council of Great Britain, emphasized the importance of ensuring adequate vitamin A intake in populations in order to increase resistance to infectious diseases (38-41). These concerns were also echoed in nutrition textbooks and research monographs at the time by such influential nutritionists, physicians, and public health leaders such as Robert McCarrison (42). Jack Cecil Drummond (43) and Edward Mellanby (44) in England, Georges Mouriquand (45) in France, Giambattista Bietti (46) in Italy, Robert Ammon (47) in Germany, and Henry Clapp Sherman (48) Mary Swartz Rose (49) and Wilson Smillie (50) in the United States.

Table 1. Some important trials of vitamin A and infectious diseases.

Location	Date	Subjects	Observation	Ref
England	1871	adults	cod-liver oil reduces tuberculosis mortality	(7)
England	1931	women	vitamin A reduces morbidity of puerperal sepsis	(34,35)
England	1932	children	vitamin A reduces measles mortality	(33)
Indonesia	1986	children	vitamin A reduces diarrheal mortality	(2,3, 65)
S Africa	1990	children	vitamin A reduces measles mortality	(4)
S Africa	1995	children	vitamin A reduces morbidity in children born to HIV+ mothers	(72)
Tanzania	1999	children	vitamin A reduces mortality in HIV + children	(74)
PNG[1]	1999	children	vitamin A reduces malaria morbidity	(71)
Nepal	1999	women	vitamin A or β-carotene reduce mortality related to pregnancy	(5)

[1]Papua New Guinea

Attention turns towards developing countries

With improvements in nutrition, hygiene, and living standards, vitamin A deficiency gradually disappeared from Europe and the United States. The Joint Food and Agricultural Organization/ World Health Organization Expert Committee on Nutrition focused on vitamin A deficiency as a public health problem in developing countries in the 1950s, and in 1962 a world-wide survey of xerophthalmia was organized by the World Health Organization (51). The main investigators of the global survey, H.A.P.C. Oomen, Donald S. McLaren, and Humberto Escapini, showed that vitamin A deficiency remained a major health problem in many parts of the world, especially in south Asia, southeast Asia, sub-Saharan Africa, and Central America. These investigators recognized a vicious cycle of vitamin A deficiency and infection: "Not only may deficiency of vitamin A itself play an important role in lowering the resistance to infection... but infectious diseases themselves predispose to and actually precipitate xerophthalmia." In their influential work, *Interactions of Nutrition and Infection*, Nevin S. Scrimshaw, Carl E. Taylor, and John E. Gordon reviewed the large body of clinical and experimental evidence that had accumulated by 1968 and concluded: "One of the first recognized features of avitaminosis A, increased susceptibility to infection, has had strong confirmation" (52).

Nutrition surveys by the Interdepartmental Committee on Nutrition for National Defense of the U.S. National Institutes of Health, also conducted during the late 1950s and early 1960s, assessed vitamin A deficiency in many populations around the world. Vitamin A deficiency was considered a major health problem in Jordan (53) Ethiopia (54) Vietnam (55) Thailand (56) Lebanon (57) and East Pakistan (Bangladesh) (58). These surveys defined vitamin A deficiency as a public health problem if more than 5% of the population had plasma or serum vitamin A concentration <0.35 μmol/L or more than 15% had concentrations <0.70 μmol/L (59). Nutritional surveys conducted in Central America and Panama from 1965 to 1967 showed that vitamin A deficiency was widespread (60). In 1974, vitamin A fortification of sugar was implemented in Guatemala after strong advocacy by Guillermo Arroyave of the Institute of Nutrition of Central America and Panama (INCAP). The underlying rationale for such a far-reaching program was that vitamin A fortification would improve growth and resistance to infectious diseases in children (61).

During the late 1960s, Johanna ten Doesschate conducted epidemiological investigations in Indonesia that identified risk factors for xerophthalmia, including inadequate dietary intake of vitamin A and carotenoids, Ascaris infection, diarrheal disease, tuberculosis, measles, artificial feeding, prematurity, and lower socioeconomic status (62). The main cause of blindness among infants and young children in Indonesia was vitamin A deficiency, and follow-up of small children who had become blind showed that about 30% had subsequently died (62). In the late 1970s, the Indonesian government began to consider vitamin A fortification of either wheat flour, sugar, or monosodium glutamate (MSG) (63). After further deliberation, of the three, only monosodium glutamate was considered a suitable carrier. Concern was raised by Indonesian government officials that fortification of MSG would appear to be government endorsement of a commercial product. An analysis by Carl Fritz at Helen Keller International in 1982 showed that fortification of monosodium glutamate, even if only 10% effective, would be cost effective in reducing mortality of an estimated 20,000 Indonesian children each year (63).

Further clinical trials of vitamin A

Through a national survey conducted in 1977-1978 in Indonesia, children with Bitot's spots and night blindness were noted to have a higher risk of mortality in 1983 (64) sparking further vitamin A clinical trials in the 1980s and 1990s (2,65). There have been at least seventy clinical trials conducted in the last fifteen years that have evaluated the potential effect of improving vitamin A status on morbidity and mortality from infectious diseases. These trials were conducted in such places as Indonesia, India, Nepal, Sudan, Ghana, Chile, Guatemala, Bangladesh, Peru, and Brazil (2,66). The contemporary trials revisit many of the same issues that were addressed in vitamin A trials conducted in the 1920s and 1930s (6). Recently, trials have been conducted to investigate the impact of vitamin A on measles, diarrheal disease, acute lower respiratory infection, respiratory syncytial virus infection, malaria, tuberculosis, human immunodeficiency virus (HIV) infection, maternal mortality, infant mortality, and infections in older adults. The types of interventions with vitamin A include community-based high dose supplementation, disease-targeted high dose supplementation, low dose daily supplementation, weekly supplementation, and fortification of monosodium glutamate (2,66). The hospital and community-based trials have shown that supplementation or fortification reduces the morbidity and mortality of diarrheal disease and measles, but has no apparent impact upon acute lower respiratory infections (Table 1) (2,3,66).

It is not clear why vitamin A supplementation does not improve morbidity and mortality from acute lower respiratory infections, and the lack of effect may be related to the type of immune responses involved (67) the age of the children, and other co-existing micronutrient problems, such as zinc deficiency. There is new evidence that vitamin A supplementation may reduce mortality for infants under the age of six months (68,69). Vitamin A supplementation appears to reduce the morbidity of malaria and improve some clinical outcomes among adults and children with HIV infection (66,70,71-74). Other studies have focused on the impact of vitamin A supplementation upon growth (75,76).

The World Health Organization currently recommends high dose vitamin A supplementation for children with xerophthalmia, acute measles, and diarrheal disease in developing countries where vitamin A deficiency is a public health problem (1). Some developing countries have adopted programs of intermittent, high dose vitamin A capsule distribution for infants and children, a measure that may reduce diarrheal morbidity and mortality and is largely considered a temporary solution until other remedies

can be found (66). In a sense, the contemporary distribution of vitamin A capsules to children in the community in developing countries resembles the widespread home use of cod-liver oil by the teaspoon or capsule for children in the early half of the twentieth century in Europe and the United States. Nowadays, a return to cod-liver oil is no longer a viable option: the cod fisheries have nearly been depleted in the North Atlantic, and synthetic vitamin A is a relatively inexpensive source for supplements or fortification.

The vitamin A gap

In developed countries there is a high consumption of preformed vitamin A in meat, dairy, and vitamin A-fortified foods, whereas in developing countries there is a high consumption of pro-vitamin A carotenoids in fruits and vegetables (77). Recent evidence suggests that dark green leafy vegetables may not be as good a source of vitamin A as previously believed, due to low bioavailability (78,79). In the 1980s, conventional wisdom held that green leafy vegetables, and hence vitamin A, were everywhere in tropical environments: the rural poor only needed some dietary education and to increase their consumption of these plant sources of vitamin A. This concept has recently been uprooted, so to speak, based upon recent studies from Indonesia that have challenged this assumption (78). Although changes in dietary and horticultural practices may be expected to improve nutrition in women and children, these reforms may not completely close the gap. Efforts are also being made to fortify food products with vitamin A, such as sugar in Zambia, Guatemala and other Central American countries, margarine in the Philippines (80) instant noodles in Indonesia, and wheat flour in various countries (77,80). These measures may help to overcome insufficient dietary intake of vitamin A in populations where consumption of meat and dairy products is low. Treatment for intestinal parasites such as *Ascaris lumbricoides* may also help improve the vitamin A status of children who consume a diet high in pro-vitamin A carotenoids (81).

Too much of a good thing?

Recent studies suggest that high dose vitamin A supplementation may have adverse consequences for some children who are not malnourished (82,83). In a study conducted in Dar Es Salaam, Tanzania, children hospitalized with pneumonia received high dose vitamin A supplementation, and after discharge, they were monitored for diarrheal and respiratory disease. Vitamin A supplementation was associated with a higher rate of diarrheal disease among children who were better nourished, whereas a reduction in diarrheal morbidity was noted among wasted children. In an accompanying editorial, Jeffrey Griffiths has termed this effect the vitamin A paradox (57). A recent controlled clinical trial conducted in Quito, Ecuador also suggested that weekly vitamin A supplementation to children, aged 6-36 months, significantly reduced the incidence of acute lower respiratory infections in underweight (weight-for-age Z score < -2) children but significantly increased the incidence of acute lower respiratory infections in normal weight children (weight-for-age Z score >-1) compared with placebo (83). These observations suggest that more cautious monitoring of high dose vitamin A capsule distribution programs is needed, especially in countries that are undergoing rapid demographic change and a nutrition transition towards that of developed countries.

Future directions

Future studies are addressing some of the final gaps in knowledge regarding the potential for vitamin A supplementation to reduce morbidity and mortality from infectious diseases. Ongoing trials will help to determine whether vitamin A supplementation can reduce morbidity and mortality in individuals with tuberculosis and in those with HIV infection. Other studies are attempting to replicate the finding that weekly vitamin A or β-carotene supplementation can reduce pregnancy-related mortality (5). Further investigation is needed to address the impact of vitamin A supplementation on the morbidity and mortality of *Plasmodium falciparum* malaria (71). The biological mechanisms by which vitamin A enhances immunity to infection are being studied mostly through experimental animal models (85). Taking clues from the field of cancer research (86,87) various synthetic retinoids may eventually find application as primary or adjunct treatment for infectious diseases.

Given that multiple deficiencies of micronutrients often occur simultaneously and that many micronutrients act synergistically, clinical trials with daily, multi-micronutrient supplements can be expected to largely supplant single micronutrient interventions with vitamin A in developing countries.88 An area that begs much further investigation is the impact of home gardening on nutritional status and resistance to infection, as in the long run, food-based approaches will likely be more sustainable than vertical programs of supplement distribution. Much activity is now being focused on food-based approaches, such as community home gardening projects (89,90) and complementary programs for deworming (81). If the historical record provides any guidance, a variety of approaches will be needed to combat vitamin A deficiency in developing countries, and improved vitamin A status will likely be accompanied by reduced morbidity and mortality from diarrheal disease, measles, and other infections.

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