Vitamin A supplements

A guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia

Second edition

Prepared by a WHO/UNICEF/IVACG Task Force

World Health Organization
Geneva

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Preface

In 1984 the Thirty-seventh World Health Assembly adopted a resolution requesting the Director-General of the World Health Organization (WHO) to give all possible support to Member States in the prevention and control of vitamin A deficiency and xerophthalmia and to coordinate with other intergovernmental and nongovernmental organizations the launching and management of programmes for this purpose.

In 1985, WHO proposed a coordinated 10-year plan of action for the prevention and control of vitamin A deficiency and xerophthalmia. The overall strategy included a mixture of long-, medium-, and short-term measures. Long-term measures are those designed primarily to increase the availability and consumption of foods rich in vitamin A, which may include vitamin-A-fortified foods. Medium- and short-term measures are employed until dietary changes or food fortification have checked the problem, and include the administration of vitamin A supplements, most often in high doses.

Considerable impetus for this plan of action was provided by the World Summit for Children, held at the United Nations in New York during September 1990, where 71 heads of state and government and 88 other senior governmental officials committed their governments to overcoming the worst forms of malnutrition, including the virtual elimination of vitamin A deficiency and its consequences, by the year 2000. This commitment was further strengthened by the International Conference on Nutrition (Rome, December 1992), attended by senior representatives of 159 states and the European Economic Community. The resulting Plan of Action for Nutrition recognized that the control of vitamin A deficiency is one of the most cost-effective child health and child survival strategies governments can pursue. It was agreed that governments, in collaboration with international agencies, nongovernmental organizations, the private sector and industry, expert groups, and local communities, should support a combination of strategies—including dietary diversification, food fortification, breast-feeding promotion, and vitamin A supplementation—to achieve the virtual elimination of vitamin A deficiency.

Recent years have seen a steady increase in the number of programmes distributing high-dose vitamin A supplements to treat or prevent vitamin A deficiency and its consequences. Health care workers are sometimes in doubt about how much vitamin A should be given to different age and population groups, how often, and in what form.

WHO, UNICEF, and the International Vitamin A Consultative Group (IVACG) have therefore prepared the guidelines contained in this publication, which update and extend those published by WHO in 1988. Members of the WHO/UNICEF/IVACG Task Force are listed in Annex 1.

New information deriving from scientific investigations and practical experience have warranted this revision, whose recommendations are based on the best current evidence. Easy-to-follow treatment and prevention schedules are given, and suggestions are made for the integration of vitamin A distribution into a variety of primary health care services. Those concerned with the prevention and treatment of vitamin A deficiency and its consequences are invited to consider these guidelines, adapt them as necessary to local conditions, and carefully monitor their application and impact.

Contents

1. Introduction

Vitamin A supplements are used in two principal situations: to treat those with acute xerophthalmia and other high-risk individuals in immediate need of improved vitamin A status, and to prevent vitamin A deficiency where the periodic administration of supplements is determined to be the most feasible and cost-effective means of improving vitamin A status. In some areas, it may be possible to increase the dietary consumption of vitamin A to adequate levels among all population groups relatively quickly. In other regions and populations, for example those affected by periodic drought, chronic poverty, and food shortages, vitamin A supplementation may be required for many years.[1]

High-dose vitamin A supplementation[2] is a proven means of controlling xerophthalmia, preventing nutritional blindness, and, among deficient populations, reducing the severity and case-fatality rate of certain childhood infections, particularly measles and diarrhoea. High-dose supplementation is also an effective means of rapidly improving the vitamin A status of deficient mothers and their nursing infants following delivery. Refugees and other populations cut off from their usual sources of food and dependent on relief rations also often need high-dose supplementation.

Vitamin A supplementation can be organized relatively quickly and at reasonable cost and has the effect of immediately improving the bodily reserves of vitamin A among deficient populations. In areas where vitamin A deficiency and xerophthalmia are known to constitute a significant public health problem (see Annex 2), a sufficient and regular supply of appropriate vitamin A preparations should be available for distribution at the peripheral level to the local high-risk populations. In addition, all primary health care personnel, and community health workers in particular, should be trained in the prevention, recognition, and treatment of vitamin A deficiency and xerophthalmia as part of their regular duties.

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[1] Even in the United Kingdom, daily low-dose supplements are recommended for children 1–5 years of age, unless adequate intake from dietary sources can be assured. In addition, vitamin A supplements are made available at no cost for pregnant and lactating women and for young children in low-income households.

[2] This book focuses primarily on high-dose vitamin A supplementation (i.e. ≥ 25 000 IU per dose). However, more frequent low-dose supplementation can, and in some cases should, be substituted as indicated.

Ensuring that a population achieves and maintains adequate nutritional intake of vitamin A requires comprehensive, long-term measures that can include nutritional education; vitamin A fortification of condiments and foods consumed by the target population, such as sugar, monosodium glutamate (MSG), wheat flour, oil, or margarine; and promotion of a diet containing foods rich in vitamin A such as eggs, fish-liver oil, red palm oil, green leafy vegetables, and dark-orange fruits and vegetables.

The protection, promotion, and support of breast-feeding should also be an integral part of any strategy to combat vitamin A deficiency; among its many benefits, breast-feeding helps ensure an adequate intake of vitamin A by infants and young children. Mothers whose vitamin A status is adequate—either as a result of dietary intake or supplementation—produce breast milk with a vitamin A concentration that meets their infants' needs for at least the first 6 months of life.

2. Prevention of vitamin A deficiency, xerophthalmia, and nutritional blindness in children

Rationale

Vitamin A (retinol) is a fat-soluble substance stored in body organs, principally the liver. It is released as needed into the bloodstream, becoming available for use by cells throughout the body, including those of the eye. Periodic high-dose supplementation is intended to protect against vitamin A deficiency and its consequences by building up a reserve of the vitamin for periods of reduced dietary intake or increased need. For individuals 1 year of age and older, administration of 200 000 International Units (IU) of vitamin A will provide adequate protection for 4–6 months, the exact interval depending on the vitamin A content of the diet and the rate of utilization by the body. Adequate protection can also be achieved by means of smaller, more frequent doses, for example 10 000 IU once a week or 50 000 IU once a month.

Safety

Vitamin A supplementation programmes are known to be effective and safe. When vitamin A is administered in recommended doses, there are no serious or permanent adverse effects; such side-effects as may occasionally occur (e.g. for infants, a tense or bulging fontanelle or vomiting) are minor and transitory and do not require specific treatment. As adequate vitamin A status is achieved through other means, supplementation becomes less necessary, although its continuation is not harmful. Moreover, continued targeted supplementation may be required to ensure adequate vitamin A status among groups with a persistent deficiency.

Universal distribution

Universal vitamin A distribution involves the periodic administration of supplemental doses to all preschool-age children, with priority given to age groups (usually 6 months–3 years) or regions at greatest risk (Table 1). All mothers in high-risk regions should also receive a high dose of vitamin A within 8 weeks of delivery. The earlier the dose, the sooner the mother's vitamin A status is raised, likewise the vitamin A concentration of her breast milk and the vitamin A status of her breast-fed child. For pregnant women, smaller doses (e.g. 5000–10 000 IU) can be given more frequently throughout pregnancy, even daily (see p. 5).

Table 1: High-dose universal-distribution schedule for prevention of vitamin A deficiency

Infants < 6 months of age [a]	
Non-breast-fed infants	50 000 IU orally
Breast-fed infants whose mothers have not received supplemental vitamin A	50 000 IU orally
Infants 6–12 months of age	100 000 IU orally, every 4–6 months [b]
Children > 12 months of age	200 000 IU orally, every 4–6 months [b]
Mothers	200 000 IU orally, within 8 weeks of delivery

[a] Programmes should ensure that infants < 6 months of age do not receive the larger dose intended for mothers. It may therefore be preferable to dose infants with a liquid dispenser to avoid possible confusion between capsules of different dosages.

[b] Evidence suggests vitamin A reserves in deficient individuals can fall below optimal levels 3–6 months following a high dose; however, dosing at 4–6 month intervals should be sufficient to prevent serious consequences of vitamin A deficiency.

The timing of vitamin A distribution depends on a variety of factors, including the size of the dose, the season, logistic constraints (e.g. opportunities for contact with the target population) and available resources. Universal-distribution schemes should make vitamin A available before a season of special risk—for instance, a season when diarrhoea or measles is common or when foods rich in vitamin A are scarce.

Refugees and others cut off from their usual food sources or afflicted by famine constitute very-high-risk groups in special need of periodic supplementation; their access to natural sources of vitamin A is usually extremely poor and their risk of infectious diseases and other complicating factors quite high. The dosage schedules used for routine supplementation (Tables 1–3) should also be used for such groups.

Targeted distribution to high-risk children

Infants and children with severe protein–energy malnutrition or infections such as measles, diarrhoea, respiratory disease, and chickenpox have an increased risk of vitamin A deficiency. In view of strong evidence indicating that vitamin A deficiency occurs in clusters, siblings and children living in the same home or community as children with xerophthalmia are also at increased risk. All such children are high-risk children; prevention of vitamin A deficiency among these groups can be achieved by targeted distribution programmes.

Vitamin A supplementation in targeted distribution helps re-establish body reserves drained by chronic or repeated infectious disease

(e.g. diarrhoea), protecting the high-risk child against vitamin A deficiency and also against the severity of subsequent infections. High-risk children with subclinical vitamin A deficiency are also protected. Although vitamin A supplementation does not appear to influence the outcome of a bout of diarrhoea or a respiratory infection already in progress, it does reduce the complications of an existing measles infection and dramatically lowers measles morbidity and mortality.

The prevention schedule for high-risk children is shown in Table 2. Where it is absolutely certain that a high-risk child has regularly received supplements every 4–6 months, additional dosing is not necessary. However, if a high-dose supplement has been administered more than 1 month previously, an additional dose is not harmful. In contrast, a child who has received a routine high-dose supplement within the past month should not receive an additional targeted dose.

Table 2: High-dose prevention schedule for children at high risk [a] of vitamin A deficiency

Infants < 6 months of age	50 000 IU orally [b]
Infants 6–12 months of age	100 000 IU orally [b]
Children > 12 months of age	200 000 IU orally [b]

[a] High-risk children are children with measles, diarrhoea, respiratory disease, chickenpox, other severe infections, or severe protein–energy malnutrition, or who live in the vicinity of children with clinical vitamin A deficiency.

[b] Those known to have received a routine high-dose vitamin A supplement within the last 30 days should not receive an additional dose.

Targeted distribution to pregnant women

Numerous studies have shown that pregnant women have an increased risk of vitamin A deficiency, particularly in populations where such deficiency is endemic. A significant proportion of pregnant women develop night blindness, especially during the third trimester. To improve the vitamin A status of both mother and fetus, the mother should consume a diet containing adequate amounts of vitamin A and/or receive frequent *small* doses not exceeding 10 000 IU daily or 25 000 IU weekly, unless severe signs of active xerophthalmia (i.e. acute corneal lesions) are present (see Table 3 and p. 7).[1,2]

[1] Teratology Society position paper: recommendations for vitamin A use during pregnancy. *Teratology*, 1987, **35**: 269–275.

[2] *Safe vitamin A dosage during pregnancy and the first 6 months postpartum. Report of a consultation, Geneva, 19–21 June 1996.* Geneva, World Health Organization, 1997 (unpublished document WHO/NUT/97.2, available on request from Programme of Nutrition, World Health Organization, 1211 Geneva 27, Switzerland).

3. Treatment of xerophthalmia

With the exception of women of reproductive age (see p. 7) the treatment schedule in Table 3 applies to individuals with all stages of active xerophthalmia, including those with night blindness, conjunctival xerosis with Bitot's spots, corneal xerosis, corneal ulceration, and keratomalacia. Doses should be administered orally, the first dose *immediately* upon diagnosis of xerophthalmia. Immediately thereafter, individuals with acute corneal lesions should be referred to a hospital on an emergency basis, as they present complex treatment problems.

Table 3: Treatment schedule for xerophthalmia for all age groups except women of reproductive age [a]

Timing	Vitamin A dosage [b]
Immediately on diagnosis:	
< 6 months of age	50 000 IU
6–12 months of age	100 000 IU
> 12 months of age [a]	200 000 IU
Next day	Same age-specific dose [c]
At least 2 weeks later	Same age-specific dose [d]

[a] *Caution:* Women of reproductive age with night blindness or Bitot's spots should receive daily doses ≤ 10 000 IU, or weekly doses ≤ 25 000 IU (see p. 7). However, all women of childbearing age, whether or not pregnant, who exhibit severe signs of active xerophthalmia (i.e. acute corneal lesions) should be treated as above (see p. 7).
[b] For oral administration, preferably in an oil-based preparation.
[c] The mother or other responsible person can administer the next-day dose at home.
[d] To be administered at a subsequent health-service contact with the individual.

Young children

Children with diarrhoea may have reduced vitamin A absorption, but they will still absorb more than enough to treat their deficiency if the recommended doses are administered. However, xerophthalmic children with severe protein-energy malnutrition need to be carefully monitored. Their vitamin A status is unstable and may rapidly worsen, even when they are treated with the recommended doses. Additional doses may be required for this vulnerable group.

Corneal xerophthalmia is a medical emergency. Vitamin A must be administered immediately according to the schedule shown in Table 3. In order to treat or prevent a secondary bacterial infection, which

would compound corneal damage, topical application of an antibiotic eye ointment, e.g. tetracycline or chloramphenicol, is recommended. *Ophthalmic ointments containing steroids should never be used in these circumstances.* To prevent trauma to a cornea weakened by ulceration, the eye should also be protected by a shield, and in the case of young children, it may be necessary to restrain arm movements.

Women of reproductive age

Women of reproductive age with night blindness or Bitot's spots should be treated with a daily oral dose of 5000–10 000 IU of vitamin A for at least 4 weeks. Such a daily dose should never exceed 10 000 IU, although a weekly dose not exceeding 25 000 IU may be substituted.

When *severe signs of active xerophthalmia* (i.e. acute corneal lesions) occur in a woman of reproductive age, *whether or not pregnant,* it is necessary to balance the possible teratogenic effect or other risks of a high dose of vitamin A to the fetus (should she be pregnant) against the serious consequences (for her and the fetus) of vitamin A deficiency. In these circumstances, the high-dose treatment for corneal xerophthalmia as described in Table 3 can be administered.[1]

[1] *Safe vitamin A dosage during pregnancy and the first 6 months postpartum. Report of a consultation, Geneva, 19–21 June 1996.* Geneva, World Health Organization, 1997 (unpublished document WHO/NUT/97.2, available on request from Programme of Nutrition, World Health Organization, 1211 Geneva 27, Switzerland).

4. Treatment during measles

Children with concurrent vitamin A deficiency and measles can suffer serious complications, and immediate vitamin A therapy significantly reduces the risk of excessive measles case fatality. It is therefore recommended to treat children with high-dose vitamin A supplements during episodes of measles, and all published trials to date suggest that optimal therapy is the same as that for xerophthalmia (see Table 3).[1]

[1] Although WHO and UNICEF originally recommended a single 100 000-IU dose for children with measles in populations with known vitamin A deficiency or where measles case fatality exceeds 1%, all treatment trials to date have used the 200 000-IU (x2) dose. Moreover, a number of countries without known xerophthalmia have achieved reductions in excess measles case fatality by means of vitamin A administration. WHO and UNICEF recommendations for high-dose supplementation (200 000-IU, x2) therefore now include all children older than 1 year of age with measles in populations where vitamin A deficiency may be present. The American Academy of Pediatrics (USA) also recommends this approach.

5. Operational issues

Vitamin A preparations

For the population groups and dosages given in sections 2, 3, and 4, some combination of the dosage forms of vitamin A shown in Table 4 will typically be required.

Oil-based preparations are preferred for *oral* administration of vitamin A, but water-miscible preparations may be used if an oil-based solution is not available. As an alternative, a similar oral dose of vitamin A can be given in other forms, e.g. fish-liver oil. Oil-based preparations are normally well absorbed when administered orally, but since oil-based vitamin A is liberated extremely slowly from an intramuscular injection site they should *never* be injected. The only preparation suitable for intramuscular injection is water-miscible vitamin A, but injection should rarely be required. Except in instances of severe malabsorption, such as in patients suffering from severe cystic fibrosis, it is preferable to administer vitamin A orally.

Table 4: Typical population groups, dosages, and dosage forms in vitamin A administration

Population group	Dosage	Dosage form
Women of reproductive age with night blindness or Bitot's spots	10 000 IU, daily (p. 7)	10 000-IU tablet, or appropriate amount of oil-based solution
Non-breast-fed infants < 6 months of age	50 000 IU, once (p. 4)	Contents of 50 000-IU capsule, or one plunger stroke of oil-based solution [a]
Infants 6–12 months of age	100 000 IU, every 4–6 months (p. 4)	Contents of 100 000-IU capsule, or two plunger strokes of oil-based solution [a]
Children > 12 months of age	200 000 IU, every 4–6 months (p. 4)	Contents of 200 000-IU capsule, or four plunger strokes of oil-based solution [a]
or	10 000 IU, weekly (p. 3)	10 000-IU tablet, or appropriate amount of oil-based solution [a]
or	50 000 IU, monthly (p. 3)	Contents of 50 000-IU capsule, or one plunger stroke of oil-based solution [a]

[a] Assumes a dispenser delivering 50 000 IU with each plunger stroke, e.g. 0.5 ml of solution containing 100 000 IU per ml. Children older than 36 months of age are usually able to swallow capsules; tablets are harder to swallow and should be dissolved in liquid before being administered to young children.

Gelatin capsules can usually be swallowed whole by adults, or by children at least 36 months of age. For younger and even some older children, the nipple on the capsule should be cut off, or the capsule pricked with a pin, and the contents squeezed into the child's mouth. For children 6–12 months of age, if no better means are available, a dose of approximately 100 000 IU can be obtained by squeezing out half the contents of a 200 000-IU capsule. However, this is wasteful and may be inaccurate, so 100 000-IU capsules, or a measured dose from a multidose liquid dispenser is preferable.

WHO and UNICEF have developed and tested a robust dispenser for oil-based vitamin A solution that can be used repeatedly provided it is periodically cleaned. The dispenser delivers 0.5 ml with each stroke of the plunger. The solution is available in sealed 100-ml bottles containing 100 000 IU of vitamin A per ml.

The dispenser has proven particularly effective for delivering vitamin A supplements to children under 12 months of age in the context of immunization programmes. Health workers can quickly and easily provide a 50 000-IU (1 stroke) or 100 000-IU (2 strokes) dose of vitamin A to children receiving measles immunizations. For children 12–36 months of age, 200 000 IU can be administered from a dispenser (4 strokes) or by squeezing out the contents of a 200 000-IU capsule. Children older than 36 months of age can usually swallow capsules.

Vitamin A units

Although the International Unit (IU) for vitamin A—which expresses biological activity and not chemical quantity—was officially discontinued in 1954, vitamin A preparations are still conventionally labelled in IU (with equivalence in mg or μg of retinol or its esters also indicated). Preparations of vitamin A can be supplied as retinyl palmitate, retinyl acetate, or retinol, although retinyl palmitate is the form most widely available from commercial sources. A dose of 200 000 IU is equivalent to 110 mg of retinyl palmitate, 69 mg of retinyl acetate, or 60 mg of retinol. As long as the recommended doses are administered, the chemical form is not important. Typically, these preparations are diluted with a high quality vegetable oil, usually peanut oil, with vitamin E (40 mg/200 000 IU) included as an antioxidant and to promote the absorption and retention of vitamin A by the body.

Storage considerations

The chemical stability and therefore the biological activity of vitamin A is affected by temperature and exposure to sunlight and other sources of ultraviolet light; however, it is sufficiently stable that a cold chain is not required in the distribution system. The useful shelf-life of an

oil-based solution of vitamin A in a properly stored, unopened, opaque container is estimated to be at least 2 years.

However, once a container has been opened, potency is gradually reduced. Partial protection against this loss of potency is afforded when the oil-based solution is formulated in capsules. All vitamin A preparations should be stored in opaque containers—aluminium containers are frequently used—for protection against light. Liquid vitamin A preparations from properly stored containers should be used within 6–8 weeks of opening. It is therefore recommended that containers of liquid vitamin A for use in the field or by peripheral health units should be limited in size (e.g. 200 doses) to minimize the amount of vitamin A supplies at risk once the containers are opened. Detailed information on the stability of various vitamin A preparations is given in Annex 4. Although preparations stored beyond the designated periods are less potent, they are nevertheless safe and often contain enough vitamin A for therapeutic use.

Sources of vitamin A supplies

UNICEF

UNICEF has established a worldwide programme of cooperation with national governments for the elimination of vitamin A deficiency. This programme is active in almost every country where vitamin A deficiency is a public health problem. In 1994, for example, UNICEF supplied more than 180 million 200 000-IU capsules to over 70 countries. In addition to provision of vitamin A supplements, often to nongovernmental organizations for use in their own programmes, UNICEF's programme includes support of projects for the elimination of vitamin A deficiency.

UNICEF purchases and ships vitamin A supplies to governments, international agencies, and nongovernmental organizations under an arrangement known as "procurement services". Advance payment (normally in a convertible currency) covering the cost of supplies, a handling charge (normally 6% of cost), freight charges, and a "buffer" fee against price increases is required. The minimum order size for standard 200 000-IU gelatin capsules is usually one carton containing 20 bottles of 500 capsules each; however, UNICEF may waive minimum order size requirements. Information about the vitamin A preparations stocked by UNICEF is shown in Table 5. Prices are reviewed every 6 months; current price information can be obtained from the most recent UNICEF *Essential drugs: price list.*