

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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WHO Library Cataloguing in Publication Data

Vitamin A supplements : a guide to their use in the treatment of vitamin A deficiency and xerophthalmia / prepared by a WHO/UNICEF/IVACG Task Force. — 2nd ed.

1.Vitamin A — administration and dosage 2.Vitamin A — therapeutic use 3.Xerophthalmia — drug therapy 4.Xerophthalmia — prevention and control 5.Vitamin A deficiency — drug therapy 6.Vitamin A deficiency — prevention and control 7.Guidelines I.WHO/UNICEF/IVACG Task Force

ISBN 92 4 154506 2

(NLM Classification: QU 167)

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Printed in Switzerland
97/11381—Strategic—12500

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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.

VITAMIN A SUPPLEMENTS

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.

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 supplementation² 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.

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. $\geq 25\,000$ IU per dose). However, more frequent low-dose supplementation can, and in some cases should, be substituted as indicated.

VITAMIN A SUPPLEMENTS

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 $\leq 10\,000$ IU, or weekly doses $\leq 25\,000$ 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
<i>or</i>	10 000 IU, weekly (p. 3)	10 000-IU tablet, or appropriate amount of oil-based solution ^a
<i>or</i>	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.

VITAMIN A SUPPLEMENTS

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 multi-dose 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*.

Table 5: Vitamin A supplies available from UNICEF

Product	Description	Price ^a
Retinol, 3 mg (10 000 IU) ^b	White compressed powder tablets	—
Retinyl palmitate, 27.5 mg (50 000 IU) ^c	White opaque soft-gelatin capsules with nipple (pack of 500)	7.00 per pack
Retinyl palmitate, 55 mg (100 000 IU)	Blue opaque soft-gelatin capsules with nipple (pack of 500)	8.00 per pack
Retinyl palmitate, 110 mg (200 000 IU)	Red opaque soft-gelatin capsules with nipple (pack of 500) ^d	10.12 per pack
Retinyl palmitate in vegetable oil (100 000 IU/ml)	Sealed opaque bottle (100-ml capacity)	2.05 per bottle
Dispenser for oil-based solution (delivers 0.5 ml/plunger stroke)	Reusable heavy-duty plastic plunger	1.80 each

^a Prices in US\$ for estimation purposes only; contact UNICEF (see below) for current prices.

^b These low-dose tablets are not a routinely stocked item; UNICEF will fill specific orders within about 10 weeks.

^c Dosage equivalence: 1.83 mg retinyl palmitate = 1 mg retinol (see p. 10)

^d Stock No. 15 830 05; also available in packs of 100 capsules, for approximately US\$ 2.12 per pack (Stock No. 15 830 00).

Further information can be obtained from any of UNICEF's 156 country offices, or from:

Procurement Services
UNICEF Supply Division
UNICEF Plads
Freeport, DK 2100
Copenhagen Ø, Denmark
telephone: 45-35-273527
fax: 45-35-269421
e-mail: crambert@unicef.dk

International Dispensary Association

The International Dispensary Association (IDA) supports health care in developing countries on a non-commercial basis by supplying high-quality medicines and medical supplies at the lowest possible price. Information about the vitamin A preparations stocked by IDA is shown in Table 6.

Table 6: Vitamin A supplies available from the International Dispensary Association (IDA)

Product	Stock No.	Description	Price ^a
Retinol, 25 000 IU	6217	Pack of 1000 capsules	\$9.40
Retinol, 50 000 IU	6218	Pack of 1000 capsules	\$12.70
Retinol, 200 000 IU	6219	Pack of 1000 capsules	\$22.50
Multivitamin tablets, 2500 IU retinol each	6206	Pack of 5000 tablets ^b	\$11.35
Multivitamin powder sachets ^c	6211	10 sachets	\$61.20

^a Prices in US\$ for estimation purposes only; contact IDA for current prices.

^b Also available in packs of 1000 tablets, for approximately US\$ 2.35 per pack.

^c The contents of each sachet, when added to 500 ml of water, yields an elixir containing 5000 IU of vitamin A per 5 ml.

IDA has no minimum order size. Further information may be obtained by contacting:

IDA
P.O. Box 37098
1030 AB Amsterdam
Netherlands
telephone: 31-20-4033051
fax: 31-20-4031854
e-mail: ida_sale@euronet.nl

Commercial sources

There are no commercial suppliers routinely delivering small orders of 200 000-IU capsules of vitamin A, as high-dose capsules are not a registered pharmaceutical preparation in many countries. Such capsules are almost always manufactured for specific orders. UNICEF and IDA purchase their stock in large quantities through competitive bidding from companies conforming to internationally accepted standards and Good Manufacturing Practices.

Logistics

The coverage and continuity of vitamin A supplementation depend on the availability of supplies when and where they are needed. Procurement and distribution effectively determine such availability.

¹ A list of such commercial suppliers is available upon request from UNICEF (see p. 12).

Procurement

Procurement involves the timely purchase of appropriate quantities of supplies, according to the size of the population, its age distribution, and the conditions to be treated. For instance, in a country where xerophthalmia is a significant public health problem, vitamin A supplements should be provided to all preschool children and lactating women (universal distribution), as well as to those with active xerophthalmia and other forms of vitamin A deficiency (targeted distribution). In the calculations that follow, a universal distribution programme, with a targeted distribution component, is taken as an example to illustrate the steps involved in procurement planning for such a country. Yearly procurement requirements are calculated for each 1000 of population.

Example

Assume a population with the following characteristics per 1000:

3% infants under 1 year of age	→ 30 infants
5% children 1–3 years of age	→ 50 children
9% children 3–6 years of age	→ 90 children
3% lactating women	→ 30 women
25% women of reproductive age (250 women), 4% of whom have night blindness or Bitot's spots	→ 10 women
5% of the 140 children between 1 and 6 years of age have one episode of xerophthalmia per year	→ 7 children

Assume the following vitamin A preparations are available:

- Capsules containing 200 000-IU vitamin A (oil-based solution)
- Liquid vitamin A preparation containing 100 000 IU/ml (oil-based solution)
- Tablets containing 10 000-IU vitamin A (compressed powder)

Assume infants and children under 3 years of age will receive liquid preparation from a dispenser and those older will receive capsules.

The supplies necessary for each group (per 1000 of population) are:

Infants 6–12 months of age: Max. two 100 000-IU doses each	→ 2 ml x 30 infants
Children 1–3 years of age: Three 200 000-IU doses each	→ 6 ml x 50 children
Children 3–6 years of age: Three 200 000-IU capsules each	→ 3 capsules x 90 children
Children with xerophthalmia: Three 200 000-IU capsules each	→ 3 capsules x 7 children
Lactating women: One 200 000-IU capsule each	→ 1 capsule x 30 women
Women of reproductive age with night blindness or Bitot's spots: One 10 000-IU tablet per woman per day for 28 days	→ 28 tablets x 10 women

Yearly procurement requirements (per 1000 of population) are:

Liquid preparation:	$(2 \text{ ml} \times 30) + (6 \text{ ml} \times 50) = 360 \text{ ml}$
Capsules:	$(3 \times 90) + (3 \times 7) + (1 \times 30) = 321 \text{ capsules}$
Tablets:	$28 \times 10 = 280 \text{ tablets}$

Distribution

The target groups requiring vitamin A supplementation most urgently are children with xerophthalmia and measles. Other vulnerable groups in need of immediate attention include children with persistent diarrhoea, acute lower respiratory infections, and severe protein-energy malnutrition, and apparently healthy children living in the same household or community as children with xerophthalmia. Any distribution strategy should give priority to the treatment of sick children, whether treatment is administered in a hospital or medical centre or in the community. However, such target groups represent only a small proportion of those who would benefit from preventive supplementation with vitamin A.

The timely distribution of vitamin A preparations to clinics in the field depends on a well functioning supply system. It also depends on the perceived need for a vitamin A supplementation programme and on the available resources and infrastructure for implementing it. When universal vitamin A distribution programmes were first developed, special teams were formed, often solely for that purpose. Today's strategies stress the integration of vitamin A distribution into existing primary health care systems, such as immunization programmes. Although special teams may still be used in certain circumstances, integration promotes widespread and timely vitamin A delivery as well as cost-efficiency and sustainability.

It is not possible to set out in detail how measures for distributing vitamin A preparations can be incorporated into specific programmes in the health systems of different countries. Nevertheless, those responsible may wish to consider some of the following possibilities, bearing in mind their own unique opportunities as well.

Primary health care and maternal and child health care services

Since the adoption in 1978 of the Declaration of Alma-Ata emphasizing the importance of community outreach in meeting the demand for health care, increased emphasis has been placed on strengthening and upgrading primary health care and maternal and child health care services. The community health worker is a critical link between the individual and health care services. As the primary health care system is responsible for both treating sick children and monitoring those who are healthy, it is an effective vehicle for vitamin A supplementation. Some countries have included vitamin A preparations in their essential drugs programmes, and consequently in the essential drugs kits supplied to health care workers and health centres at primary and other levels.

Programmes for the prevention of blindness

Programmes for the prevention of blindness are being implemented in increasing numbers of developing countries and focus on taking action against the major causes of avoidable blindness, including xerophthalmia. These programmes are usually linked to, or are a part of, the primary health care system. Where programmes for the prevention of blindness exist, they can facilitate the regular delivery of vitamin A to children and mothers, particularly as these groups are at greatest risk for trachoma, another major blinding disorder.

Immunization programmes

In many countries immunization programmes offer more consistent contact with young children and their mothers than any other public health programme. In areas of vitamin A deficiency, an immunization programme can provide a particularly efficient channel for the distribution of vitamin A to children under 2 years of age, the most vulnerable age group. As older children and children at particularly high risk, e.g. severely malnourished children, can still be missed, vitamin A supplementation needs also to be linked to other primary health care activities to ensure that adequate vitamin A status is maintained throughout the preschool years.¹ Immunization efforts linked to emergency relief programmes and refugee services can be a particularly valuable and practical opportunity for providing vitamin A to high-risk populations of children and should be utilized to the fullest extent possible. However, as the efficacy of combining high-dose vitamin A supplements with live, attenuated virus vaccine, e.g. measles and polio vaccine, has not been fully demonstrated and is under investigation, alternatives for contact with target populations should also be explored. Nevertheless, where such options are limited, combining vitamin A supplementation with immunization is likely to be justifiable.

National immunization days

A number of countries, for example Bangladesh, the Philippines, and Viet Nam, have recently organized "national immunization days" (NID) during which polio and measles vaccines are administered to all eligible children during one or two days each year. The administration of a high-dose vitamin A supplement has been successfully combined with

¹ Discussed further in *Using immunization contacts as the gateway to eliminating vitamin A deficiency: a policy document*. Geneva, World Health Organization, 1994 (unpublished document WHO/EPI/GEN/94.9, available on request from either the Global Programme on Vaccines and Immunization or the Programme of Nutrition, World Health Organization, 1211 Geneva 27, Switzerland).

these programmes, and has resulted in very high coverage with vitamin A supplementation. The main disadvantage of a NID is that it usually takes place only once a year, and high-dose vitamin A supplements need to be administered at least twice a year. Some countries are considering organizing a supplementary “vitamin A day” 4–6 months after the NID, during which vitamin A supplements can be provided, perhaps along with activities such as education on the management of diarrhoea.

Diarrhoea control activities

The child suffering from acute or persistent diarrhoea has an increased risk of vitamin A deficiency. Accordingly, consultations for diarrhoeal illness at health centres or other points of primary health care can be used to identify children in need of supplemental vitamin A. In areas of known or suspected deficiency, routinely determining whether and when vitamin A supplements have been received by children with diarrhoea is an effective means of identifying individuals at risk. Supplemental vitamin A should be administered if it has not already been given within the past month, or has not been given at regular 4–6 month intervals (see Table 2, p. 5).

Other distribution channels

Channels outside the health care system have occasionally been used for vitamin A supplementation. Examples are the school system, agricultural extension programmes, mothers' groups, and nongovernmental organizations and voluntary agencies. Several nongovernmental organizations have been actively supporting vitamin A supplementation schemes as a part of their routine contribution to development work.

Training

In order to ensure the maximum coverage of vulnerable population groups, the entire health system must be involved. Moreover, all its personnel must be proficient in recognizing the signs and symptoms of vitamin A deficiency and its complications, and be familiar with appropriate treatment, prevention, and referral protocols. Community health workers in particular need clear instruction in the identification, prevention, treatment, and referral of vitamin A deficiency. Staff at all levels of the health system as well as others involved in the control of vitamin A deficiency and its consequences should know the treatment and prevention schedules (Tables 1–3).

The most efficient way to ensure regular training is to integrate instruction modules into the existing curricula for health workers at all levels. Teaching materials that can easily be included in formal training

sessions have been developed by WHO and other organizations such as Helen Keller International and IVACG.¹

Monitoring and evaluation

Monitoring is essential for determining whether or not vitamin A is delivered to those who need it, when and where they need it. It is a useful tool for programme management and invaluable for identifying problems of supply and logistics as they arise. It is therefore recommended that a record of vitamin A administration be included in existing record systems, such as growth charts, home-based health records ("mothers' cards"), immunization records, and health centre records. This is particularly important if several channels are used for the delivery of vitamin A, as record-keeping will help avoid the potential side-effects of dose duplication, as well as help ensure full coverage.

The simplest form of evaluation is to measure the coverage of the supplementation programme. To do this, a population and its intended level of coverage should first be identified, then the degree to which this coverage was achieved should be determined. Existing record systems can be used, but population surveys that determine for each mother sampled whether she and her children received their scheduled doses offer stronger proof. Impact evaluation (i.e. evaluation of whether the incidence and prevalence of vitamin A deficiency have declined) requires a greater commitment of resources than coverage determination but can be invaluable for motivating politicians, health administrators, and the public to support vitamin A distribution. Operational research can help reveal why a distribution programme is not having its intended impact. Disease-targeted distribution programmes, which may deal with a number of pathological conditions whose frequency and severity can vary from place to place, are likely to require still more sophisticated evaluation tools.

¹ For more information contact: Programme of Nutrition, World Health Organization, 1211 Geneva 27, Switzerland; or Helen Keller International, 90 Washington Street, 15th Floor, New York, NY 10006, USA; or IVACG Secretariat, International Life Sciences Institute, Human Nutrition Institute, 1126 16th Street NW, Washington, DC 20036, USA.

Selected further reading

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ANNEX 1

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ANNEX 2

Countries categorized by degree of public health importance of vitamin A deficiency, by WHO region^a

WHO Region	Clinical	Subclinical			No data available	No known problem
		Severe	Moderate	Mild		
African Region	Angola	Burundi	Botswana	Madagascar	Algeria	
	Benin	Cape Verde	Eritrea		Central African Republic	
	Burkina Faso	Congo	Namibia		Equatorial Guinea	
	Cameroon	Côte d'Ivoire	Sierra Leone		Gabon	
	Chad	Gambia			Guinea	
	Comoros	Lesotho			Guinea-Bissau	
	Ethiopia	Senegal			Liberia	
	Ghana				Mauritius	
	Kenya				Sao Tome & Principe	
	Malawi				Seychelles	
	Mali				Swaziland	
	Mauritania				Zaire	
	Mozambique					
	Niger					
	Nigeria					
	Rwanda					
	South Africa					
	Togo					
	Uganda					
	United Republic of Tanzania					
	Zambia					
	Zimbabwe					
Region of the Americas	Dominican Republic	Brazil	Belize	Guyana	Argentina	Antigua & Barbuda
	Haiti	Colombia	Bolivia	Panama	Cuba	Barbados
		El Salvador	Ecuador		Dominica	Canada
		Mexico	Guatemala		Paraguay	Chile
		Nicaragua	Honduras		Puerto Rico	Costa Rica
		Peru			Suriname	Grenada
					Uruguay	Jamaica
					Venezuela	St Kitts & Nevis
						St Lucia
						St Vincent & the Grenadines
South-East Asia Region	Bangladesh	Indonesia	Thailand		Maldives	Trinidad & Tobago
	Bhutan	Myanmar				United States of America
	India					
	Nepal					
	Sri Lanka					
						Democratic People's Republic of Korea

^a From information available to WHO as of April 1996.

WHO Region	Clinical	Subclinical			No data available	No known problem
		Severe	Moderate	Mild		
European Region				Israel	Albania	Austria
				Romania	Armenia	Belgium
				Turkey	Azerbaijan	Denmark
				Uzbekistan	Belarus	Finland
					Bosnia & Herzegovina	France
					Bulgaria	Germany
					Croatia	Greece
					Czech Republic	Iceland
					Estonia	Ireland
					Georgia	Italy
					Hungary	Luxembourg
					Kazakhstan	Monaco
					Kyrgyzstan	Netherlands
					Latvia	Norway
					Lithuania	Poland
					Malta	Portugal
					Republic of Moldova	Russian Federation
					San Marino	Spain
					Slovakia	Sweden
					Slovenia	Switzerland
					Tajikistan	United Kingdom of Great Britain & Northern Ireland
					The Former Yugoslav Republic of Macedonia	
					Turkmenistan	
					Ukraine	
					Yugoslavia	
Eastern Mediterranean Region	Iraq	Afghanistan	Djibouti	Jordan	Kuwait	Bahrain
	Somalia	Pakistan	Egypt	Lebanon	Morocco	Cyprus
	Sudan		Islamic Republic of Iran	Libyan Arab Jamahiriya	Qatar	
	Yemen		Oman	Saudi Arabia		
				Syrian Arab Republic		
				Tunisia		
				United Arab Emirates		
Western Pacific Region	Cambodia	Lao People's Democratic Republic	China		Cook Islands	Australia
	Kiribati		Malaysia		Mongolia	Brunei
	Marshall Islands				Nauru	Darussalam
	Micronesia (Fed. States of)				New Zealand	Fiji
	Papua New Guinea				Niue	Japan
	Philippines				Palau	Republic of Korea
	Solomon Islands				Tonga	Samoa
	Vanuatu				Tokelau	Singapore
	Viet Nam				Tuvalu	

ANNEX 3

Scientific rationale for vitamin A supplementation

Infants under 6 months of age

There is considerable evidence that newborn infants, particularly in developing countries where vitamin A deficiency is endemic, are born with limited reserves of vitamin A. An adequate supply of vitamin A in early life is normally provided by means of the breast milk of a well nourished mother. Non-breast-fed infants, therefore, are particularly at risk for deficiency, and should receive supplementation if the breast-milk substitute is not fortified with vitamin A. While there is little evidence indicating that early vitamin A supplementation of breast-fed infants decreases their morbidity and mortality during the first few months of life, the evidence is growing that better vitamin A status in early life improves later vitamin A reserves and status. There are, moreover, abundant data indicating the importance of adequate vitamin A status to health, sight, and survival from 6 months of age onward. Increased vitamin A reserves in early life should enhance these benefits.

Mothers

There are two possible approaches to improving the vitamin A status of infants under 6 months of age: providing a high-dose of vitamin A to the breast-feeding mother, or one or more doses to the infant. However, it is considered safest to ensure that all mothers in areas of potential vitamin A deficiency receive a high-dose vitamin A supplement (200 000 IU) shortly after delivery. This not only improves the mother's vitamin A status as reflected by increased vitamin A levels in her serum and breast milk, but also increases the serum vitamin A levels of her breast-fed child(1). Mothers from high-risk areas who do not breast-feed should also be supplemented, because of the benefits both to their health and to that of any future children.

It is considered both safe and feasible to provide a high-dose vitamin A supplement to mothers during the 8 weeks following delivery.¹ It is extraordinarily rare for a woman to become pregnant within 4 weeks of delivery. In addition, the potential teratogenic effects of high-dose vitamin A do not occur until at least 2 weeks after fertilization. There is thus a 6-week window of nearly absolute safety after delivery for the

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).

administration of vitamin A. Breast-feeding women are furthermore extremely unlikely to regain fertility during the first 6 weeks following delivery, which extends the window of safety to at least 8 weeks. Since most women in developing countries breast-feed, and while the risk of teratogenicity is possible it is far from certain, the 8-week interval is recommended in developing countries under normal circumstances.

Infants 6–12 months of age

The recommended high doses for periodic vitamin A supplementation result in transient side-effects from benign increased intracranial pressure in 2–3% of recipients in almost all age groups. Carefully conducted studies in children over 1 year of age revealed transient side-effects following a dose of 200 000 IU (2); such side-effects were also seen in children 6–11 months of age who received 100 000 IU (3 & P. Arthur, unpublished data, 1995), and in infants receiving 50 000 IU at birth, whether alone or with diphtheria–tetanus–pertussis (DTP) immunization (4). The most common side-effects are mild vomiting in children with a closed fontanelle, and an elevated fontanelle in children in whom it is still open. In a carefully conducted study in Indonesia (5), ultrasound measurement of vascular resistance suggested little if any elevation of intracranial pressure in neonates with elevated fontanelles. In virtually all instances these minor side-effects resolved within 24–48 hours with no lasting sequelae, as demonstrated in studies conducting comprehensive growth and development examinations of children receiving vitamin A supplementation at birth (J.H. Humphrey, unpublished data, 1996) or during DTP immunization (6).

In some populations, 50 000 IU administered at birth reduced neonatal mortality, particularly during the second, third, and fourth month of life (7).

Programmes providing one or more high doses (25 000 IU) to infants under 6 months of age and one high dose (200 000 IU) to mothers are also being evaluated. It is highly unlikely that breast-feeding infants receiving both direct and indirect supplementation will experience any unfavourable consequences.

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ANNEX 4

Stability of common vitamin A preparations

Stability of retinyl palmitate ^a in oil-based solution ^b

Storage temperature	Potency retention in unopened container after:		
	6 months	12 months	24 months
5°C	99%	98%	97%
23°C	99%	95%	92%
35°C	97%	92%	76%

^a 1 000 000 IU/g.

^b Stabilized with (±)-α tocopherol.

Source: Hoffmann La Roche, Basel, Switzerland.

Stability of retinyl palmitate solution in soft gelatin capsules ^a

Capsulation run	Initial potency/capsule	Potency retention
1	214 000 IU	99% (after 20 months)
2	209 000 IU	99% (after 29 months)
3	214 000 IU	97% (after 31 months)

^a Stored at 23 °C in closed containers.

Source: Hoffmann La Roche, Nutley, NJ, USA.

Stability of “Sight and Life” vitamin A capsules ^a

Storage temperature	Vitamin A content/capsule after:			
	6 months	12 months	24 months	40 months
4 °C	—	—	—	202 500 IU
25 °C	209 000 IU	199 000 IU	187 000 IU	—
35 °C	200 000 IU	167 000 IU	—	—
45 °C	167 000 IU	—	—	—

^a Nominal content, 200 000 IU/capsule; initial content, 210 000 IU/capsule; each capsule stabilized with 36 mg (±)-α tocopherol; capsules packaged in white polyvinyl chloride containers (500 capsules each) sealed with a metal cap; containers stored closed at 60–65% relative humidity.

Source: Hoffmann La Roche, Basel, Switzerland.

VITAMIN A SUPPLEMENTS

Stability of retinyl palmitate in peroxide-free peanut oil ^a

Storage temperature	Vitamin A content/ml after:			
	6 months	12 months	24 months	40 months
4 °C	107 000 IU	—	—	—
25 °C	106 000 IU	105 000 IU	104 000 IU	97 200 IU
30 °C	—	—	93 800 IU	91 300 IU
35 °C	102 000 IU	101 000 IU	—	—
45 °C	96 300 IU	—	—	—

^a Nominal content, 100 000 IU/ml; initial content, 110 000 IU/ml; each ml stabilized with 18.1 mg (±)- α tocopherol; solution packaged in brown polyethylene terephthalate (PET) containers (150 ml each) sealed with a screw cap; containers protected from light and stored at 60% relative humidity.

Source: Hoffmann La Roche, Basel, Switzerland.

Stability of high-dose vitamin A preparations^a used in universal distribution programmes

Country	Preparation	Temperature range	Potency retention after:	
			1 year	2 years
Nepal ^b	High-dose capsules	10–25 °C	89%	—
Ghana ^c	Oil-based solution and high-dose capsules	20–30 °C	~90%	—
Sudan ^d	High-dose capsules	20–30 °C	—	85%
India ^e	Low-dose liquid	20–30 °C	~80%	—

^a Stored under field conditions in unopened opaque bottles.

^b West KP Jr et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet*, 1991, **338**: 67–71.

^c D. Ross, personal communication, 1996.

^d Herrera MG et al. Vitamin supplementation and child survival. *Lancet*, 1992, **340**: 267–271.

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