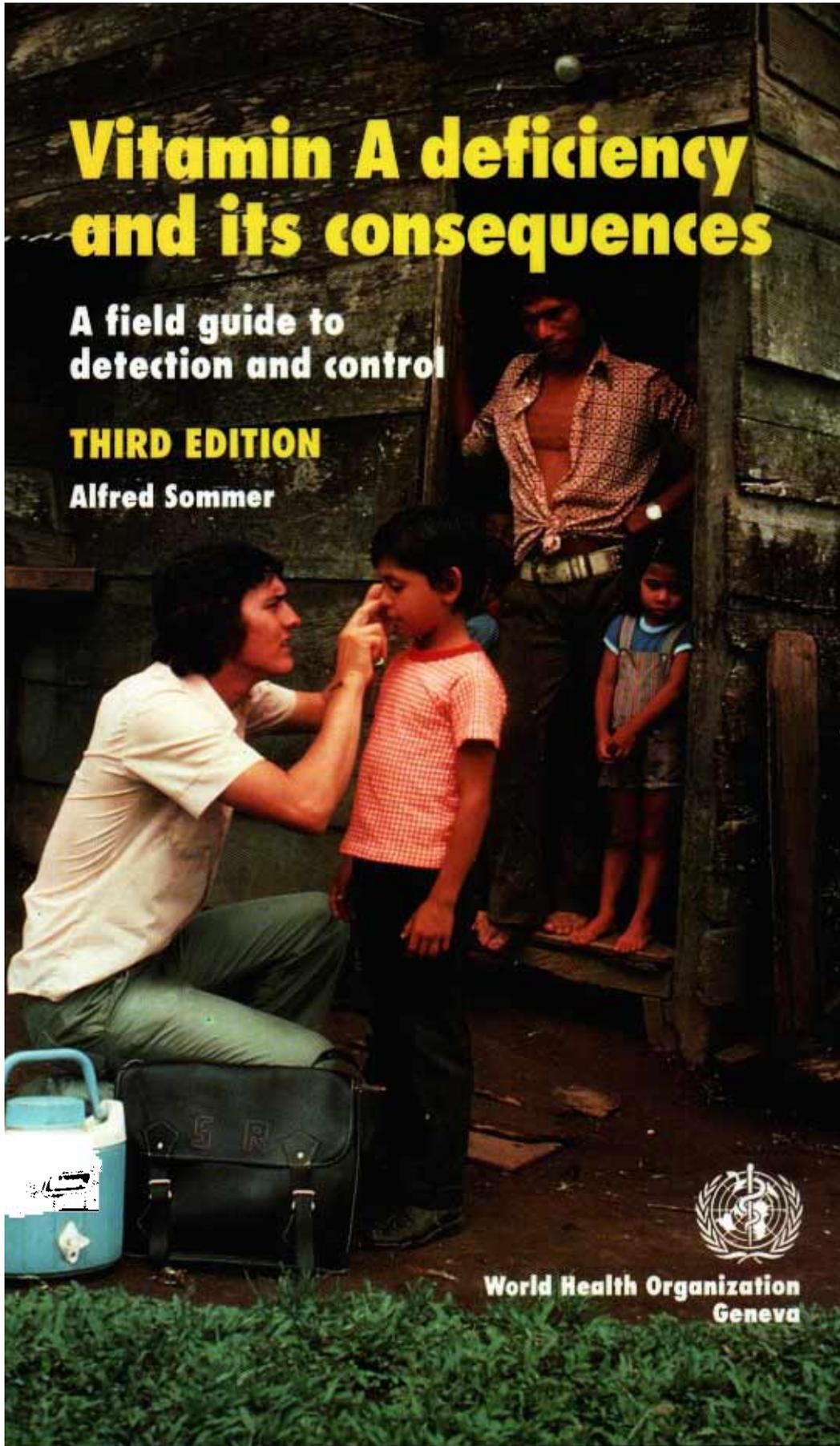# Vitamin A deficiency and its consequences

A field guide to detection and control

THIRD EDITION

Alfred Sommer

World Health Organization
Geneva

The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 190 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of human resources for health, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care-that reach the whole population of Member countries, promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases including tuberculosis and leprosy; coordinating the global strategy for the prevention and control of AIDS; having achieved the eradication of smallpox, promoting mass immunization against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Statistical Classification of Diseases and Related Health Problems; and collecting and disseminating health statistical information.

Reflecting the concerns and priorities of the Organization and its Members States, WHO publications provide authoritative information and guidance aimed at promoting and protecting health and preventing and controlling disease.

VITAMIN A DEFICIENCY AND ITS CONSEQUENCES
A field guide to detection and control

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CONTENTS

PREFACE

The first edition of this manual was published in 1978 under the title *Field guide to the detection and control of xerophthalmia,* to meet the need for a practical guide for use by clinicians, nurses, and public health officials concerned with preventing xerophthalmia This was in accord with a resolution of the Twenty-fifth World Health Assembly (1972), which urged an intensification of activities to prevent needless loss of sight from one of the three most important causes of preventable blindness

A second edition of the manual was published in 1982 to reflect advances in understanding of the clinical manifestations, pathogenesis, epidemiology, and treatment of xerophthalmia (*1*), it included revisions to the clinical classification of the disease, prevalence criteria for establishing a public health problem, and treatment recommendations (*2*)

Since 1982, new information has increasingly pointed to the importance of vitamin A in the broader realm of child health and survival (*3–7*) This was recognized by the Thirty-seventh (1984) and Forty-fifth (1992) World Health Assemblies, which directed the World Health Organization to intensify its efforts to control the impact of vitamin A deficiency on child health, blindness, and survival With extension and further refinement of this knowledge, growing commitment by governments to control and eliminate the problem — embodied notably in the World Declaration on the Survival, Protection and Development of Children (*8*) and the World Declaration and Plan of Action for Nutrition (*9*) — and programmatic momentum and leadership provided by WHO and UNICEF (*10, 11*), it has again become necessary to revise and expand the scope of the original manual

ACKNOWLEDGEMENTS

INTRODUCTION

Ocular manifestations of vitamin A deficiency, particularly night blindness, have been recognized since antiquity Animal research and clinical observations early in the twentieth century indicated that vitamin A was important for numerous bodily functions animals and humans deficient in vitamin A grew poorly, suffered more persistent or severe infections, and subsequently developed characteristic ocular manifestations termed "xerophthalmia" or "dry eye" Vitamin A-deficient animals died prematurely of overwhelming sepsis, usually before developing xerophthalmia

Interest soon focused on the readily apparent, and devastating, ocular manifestations of vitamin A deficiency By the early 1940s, these had been eliminated from wealthier countries through a variety of dietary interventions Surveys subsequently revealed that vitamin A deficiency and xerophthalmia were largely limited to developing countries, especially in Africa, Asia, and the Western Pacific, with isolated foci in the Caribbean, Central and South America, and the Eastern Mediterranean (1, 2) The World Health Organization now classifies countries according to evidence of subclinical as well as clinical deficiency in all or part of the territory Accordingly, there are 39 countries in which vitamin A deficiency is a clinically significant public health problem, and 11 countries where, subclinically, it is sufficiently prevalent and severe as to constitute a serious public health problem, 27 countries where this is the case in at least some regions, and 18 other countries where there is likely to be a problem but where data are lacking and careful monitoring is called for At least 5–10 million children develop xerophthalmia every year, of whom between a quarter and half a million go blind (12, 13)

Modern concepts of xerophthalmia date from the early 1800s, when dogs that were "starved" on sugar and distilled water developed perforating corneal ulcers resembling those in "ill-nourished infants" (14) One hundred years elapsed before investigators realized that these changes were caused by lack of a specific nutrient (15–17) "fat soluble A", present in the lipid fraction of milk, eggs, butter, and cod-liver oil, and — as provitamin A carotenoids — in dark-green leafy vegetables and certain coloured fruits Block noted that vitamin-A-deficient children were far more likely to develop urinary tract infections, and that vitamin A treatment cured the condition (18), and Mellanby dubbed vitamin A the "anti-infection vitamin" (19) Histopathological observations soon demonstrated the importance of vitamin A for maintenance of normal epithelial integrity (20), thus providing one possible explanation for its role in

resistance to infection More recently, it has been suggested that vitamin A also affects immune competence (21)

Recent data indicate that mortality rates are increased among children with mild vitamin A deficiency (22) and that, in many areas, improvement in vitamin A status can reduce the risk of mortality from childhood infections by as much as 19–54% (7, 23–29) The reduction in mortality that results from improvements in vitamin A status exceeds what would be expected solely from reducing the numbers of deaths associated with xerophthalmia vitamin A deficiency appears to increase the risk of death even before xerophthalmia is clinically apparent Vitamin A therapy reduces the severity of complications and the mortality rates associated with measles (5, 30–32), and improvement in community vitamin A status reduces the subsequent risk of measles mortality (26, 28, 29) Thus, WHO and UNICEF recommend vitamin A supplementation as part of the case management of measles in populations among whom vitamin A deficiency is known to be a problem or measles case-fatality rates exceed 1% (33)

It is estimated that at least one million child deaths would be prevented each year if vitamin A nutriture were improved (34) The impact of improved vitamin A status on preschool mortality varies from one population to another and depends on a wide variety of factors These include severity and prevalence of pre-existing vitamin A deficiency, concomitant nutritional and related disorders, and the type, intensity, and frequency of prevailing infections and related factors (7, 24, 35, 36)

VITAMIN A METABOLISM

Vitamin A, or retinol, is a fat-soluble substance found in liver (particularly fish liver) and in egg yolk and dairy products Carotenoids — potential provitamin A precursors that can be converted to retinol in the wall of the gut — are present in green leafy vegetables, red palm oil, yellow fruits, and the like The relative biological values of these various substances were formerly expressed in international units (IU) of vitamin A activity,[1] 1 IU being equivalent to 0 3 µg of retinol, 0 55 µg of retinyl palmitate, 0 6 µg of β-carotene, and 1 2 µg of other provitamin A carotenoids Not only are carotenoids biologically less active than retinol, but their dietary sources are also less efficiently processed and absorbed from the gut Thus, approximately six times as much provitamin A β-carotene (by mass) as retinol must be ingested for there to be a similar effect

Some 50–90% of ingested retinol is absorbed in the small intestine and transported, in association with chylomicra, to the liver, where it is stored primarily as retinyl palmitate When needed, it is released into the bloodstream as retinol in combination with retinol-binding protein (RBP), a specific carrier protein elaborated by the liver, this 1 1 complex is referred to as holo-RBP In the serum, the RBP–retinol complex combines with transthyretin, a large protein also synthesized in the liver The retinol is then removed from the serum and utilized by target cells, such as retinal photoreceptors and epithelial linings throughout the body, whose metabolism it influences Specific receptors exist on the cell surface and nucleus for the vitamin A complex or its active metabolites, particularly retinoic acid Vitamin A affects the expression of several hundred different genes, and that number is rising as scientific understanding grows Alterations in gene expression presumably explain resultant changes in cellular differentiation, immunity, and many other vitamin-A-dependent functions A simplified schematic outline of these main metabolic pathways is shown in Fig 1

Liver stores form an important buffer against variations in the intake of vitamin A and provitamin A carotenoids When intake surpasses requirements, which range from 180 to 450 µg/day of retinol or its equivalent, depending on age, sex and physiological status, the excess is stored and liver reserves increase When vitamin A intake

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[1] The international units for vitamin A and provitamin A were discontinued in 1954 and 1956 respectively However, since their use persists, particularly in the labelling of capsules and injectable preparations, all intakes and dosages mentioned in this book are expressed both in micrograms (µg) or milligrams (mg) and in international units (IU)

Vitamin A deficiency and its consequences

Dietary source

RETINOL   RETINYL PALMITATE   BETA-CAROTENE

Hydrolase
(pancreatic juice)   Dioxygenase
                                      (intestinal
                                      mucosa)

RETINAL

Intestine

metabolism &
absorption   Aldehyde reductase

RETINOL

Emulsification and absorption
Re-esterification with palmitic acid

(RETINOL + ESTER)

Liver

storage

WHO 94409

Blood

transport

RBP RETINOL
RBP RETINOL TRANSTHYRETIN

Periphery   Epithelial   Other target   Photoreceptors
utilization   cells   cells

Fig 1 Schema of vitamin A metabolism

is less than this amount, liver stores are drained to maintain serum
retinol at a normal level (well above 0 7 μmol/litre or 200 μg/litre)
If intake remains low for prolonged periods, liver stores become
depleted, serum retinol levels drop, and cellular function is impaired,
resulting in abnormal differentiation (e g xerophthalmia) and other
physiological consequences and clinical manifestations of deficiency
(e g anaemia, impaired resistance to infection). The duration of

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inadequate intake required for this to occur depends on the amount of vitamin A (or precursor) ingested, the extent of pre-existing liver stores, and the rate at which vitamin A is being utilized by the body

A child with borderline, marginal intake to begin with will have very limited stores Any sudden drop in intake, either as a result of a change in diet or because of impaired absorption (as in gastroenteritis), or a sudden increase in metabolic demand (febrile state — notably measles — or growth spurt) will cause rapid depletion of limited reserves This can precipitate blinding xerophthalmia (even in a child whose eyes had previously appeared entirely normal) or overwhelming sepsis and death When liver retinol stores are very high, however, an individual may go for months without vitamin A and not suffer serious consequences

The availability of stored vitamin A also depends on a child's general nutritional status Severely malnourished, protein-deficient children synthesize RBP at a much reduced rate Serum retinol levels may therefore be subnormal, even if liver stores are high Moreover, a diseased liver cannot store as much retinol, or make as much RBP, as a normal one

VITAMIN A STATUS

Normal vitamin A status implies that an individual is free of physiological or pathological consequences of vitamin A deficiency and has sufficient liver stores to provide protection against the increased metabolic demands in disease, reduced absorption as a result of diarrhoea or parasitic infection, or significant variations in dietary intake

A normal, well nourished child in a developed country will commonly have adequate liver stores of vitamin A to maintain serum retinol levels of 1 0 to 1 4 μmol/litre or more Lesser stores may fail to maintain normal serum levels or physiological function (37) Liver stores can be measured directly on liver specimens obtained at surgery or autopsy, but opportunities for such measurements are uncommon and not representative of the child population as a whole A new test, that of relative dose-response (RDR), provides an indirect estimate of the adequacy of liver stores by measuring the degree to which the liver releases holo-RBP in response to a small priming dose of vitamin A (38)

As liver stores decline, serum vitamin A levels will eventually fall as well Under carefully controlled conditions of depletion, physiological consequences of vitamin A deficiency, such as impaired dark adaptation or abnormal conjunctival epithelial differentiation (determined by impression cytology), generally begin to occur at levels below 1 0 μmol/litre, and especially below
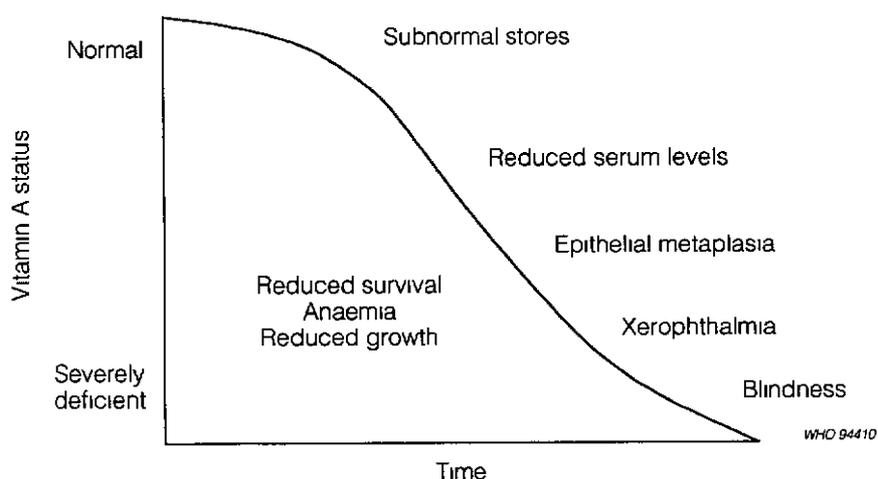
Fig 2 Manifestations of vitamin A deficiency

0 7 μmol/litre (200 μg/litre) (*39*) Frank xerophthalmia may be manifest at levels below approximately 0 7 μmol/litre, but becomes far more frequent and severe at levels below 0 35 μmol/litre (*1*) The risks of interference with iron utilization and of death probably begin to increase even before the appearance of xerophthalmia, but become progressively greater as vitamin A status declines further (*36, 40*, see Fig 2)

Xerophthalmia remains the most specific and readily recognized clinical manifestation of vitamin A deficiency, and has served as *the* definitive criterion for assessing vitamin A status However, it is now recognized that other serious consequences, including increased mortality, result from milder degrees of vitamin A deficiency, before xerophthalmia is apparent or prevalent in the population It is thus important, even in the absence of obvious xerophthalmia, that vitamin A deficiency be carefully investigated as a potential public health problem in any area of high child morbidity and mortality

XEROPHTHALMIA: CLINICAL CLASSIFICATION AND DIAGNOSIS

Vitamin A deficiency is a systemic disease that affects cells and organs throughout the body, the resultant changes in epithelial architecture are termed "keratinizing mataplasis" Keratinizing metaplasia of the respiratory and urinary tracts and related changes in intestinal epithelia probably occur relatively early in the disease, even before the appearance of clinically detectable changes in the eyes However, since these non-ocular changes are largely hidden from view, they do not provide a ready basis for specific clinical diagnosis Among vitamin-A-deficient populations, therefore, children with measles, respiratory disease, diarrhoea, or significant protein–energy malnutrition should be suspected of being deficient and treated accordingly

Uncomplicated, gradual depletion of vitamin A stores results in xerophthalmia of increasing severity, manifest as night blindness, conjunctival xerosis and Bitot's spot, corneal xerosis, and corneal ulceration/keratomalacia (Plates 1 and 2) (1) All these conditions usually respond rapidly to vitamin A therapy, and the milder manifestations generally clear up without significant sequelae The loss of deep corneal tissue from ulceration/keratomalacia, however, results in scarring and residual opacification Sudden decompensation of marginal vitamin A status, as occurs in measles, can result in corneal ulceration that precedes the appearance of milder signs of xerophthalmia (1, 41)

The major signs and symptoms of xerophthalmia are classified in Table 1 and illustrated in Plates 1 and 2

Table 1. Classification of xerophthalmia[a]

XN	Night blindness
X1A	Conjunctival xerosis
X1B	Bitot s spot
X2	Corneal xerosis
X3A	Corneal ulceration/keratomalacia $< 1/3$ corneal surface
X3B	Corneal ulceration/keratomalacia $\geqslant 1/3$ corneal surface
XS	Corneal scar
XF	Xerophthalmic fundus

[a] Source reference 2

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XN. Night blindness

Retinol is essential for the elaboration of rhodopsin (visual purple) by the rods, the sensory receptors of the retina responsible for vision under low levels of illumination Vitamin A deficiency can therefore interfere with rhodopsin production, impair rod function, and result in night blindness

Night blindness is generally the earliest manifestation of vitamin A deficiency When mild, it may become apparent only after photic stress resulting from being in bright light, such as flying a kite on a sunny day. Affected children no longer move about the house or neighbourhood after dusk, but prefer to sit in a secure corner, often unable to find their food or toys

Night blindness of recent onset in a preschool child is typical of vitamin A deficiency Other causes of the condition are relatively rare and almost never present in this age group Some societies or cultures, particularly those in which vitamin A deficiency is endemic, use specific terms to describe the condition, such as "chicken eyes" (chickens lack rods and are thus night-blind)

The presence of night blindness is not always recognized, especially among children who have not yet begun to crawl or toddle When mothers or other care-givers do complain that they have observed the condition, however, they are almost always correct (*1, 42–44*), which makes objective assessment unnecessary in most routine clinical situations

Night blindness responds rapidly, usually within 24–48 hours, to vitamin A therapy

X1A, X1B. Conjunctival xerosis and Bitot's spot

The epithelium of the conjunctiva in vitamin A deficiency is transformed from the normal columnar to the stratified squamous type, with a resultant loss of goblet cells, formation of a granular cell layer (Plate 3), and keratinization of the surface (Plate 4) This is the histopathological picture of conjunctival xerosis

Clinically, these changes are expressed as marked dryness or unwettability, the affected area appears roughened, with fine droplets or bubbles on the surface, rather than smooth and glistening The changes are best detected in oblique illumination, they are often subtle and may be obscured by heavy tearing As the

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tears drain off, however, the affected areas emerge like "sandbanks at receding tide" [1]

The abnormalities are often overlooked or, in apparent overcompensation, over-diagnosed Thus they are not, by themselves, an accurate basis for establishing the prevalence of clinical xerophthalmia, and conjunctival xerosis cannot be regarded as an acceptable criterion for determining whether vitamin A deficiency is a significant public health problem

Conjunctival xerosis first appears in the temporal quadrant, as an isolated oval or triangular patch adjacent to the limbus in the interpalpebral fissure (Plates 5 and 6) It is almost always present in both eyes In some individuals, keratin and saprophytic bacilli accumulate on the xerotic surface, giving it a foamy or cheesy appearance Such lesions are known as Bitot's spots The overlying material is easily wiped off, and the amount present often varies from day to day With more severe deficiency, similar, though less prominent, lesions form in the nasal quadrant Bitot's spots are readily recognized and serve as a useful clinical criterion for assessing the vitamin A status of the population (Plates 7–13)

Bitot's spots should not be confused with pinguecula or pterygium, which are more often nasal than temporal and limited largely to adults Pinguecula is an elevated, fatty, yellowish lesion, pterygium is fleshy and actually invades the cornea

Generalized conjunctival xerosis, involving the inferior and/or superior quadrants, suggests advanced vitamin A deficiency The entire conjunctiva appears dry, roughened, and corrugated, sometimes skin-like (Plates 14–16) There may be prominent conjunctival thickening and folds This is an advanced lesion, almost always accompanied by gross corneal involvement

Isolated, usually temporal, patches of conjunctival xerosis or Bitot's spot are sometimes encountered in the absence of active vitamin A deficiency The affected individuals are usually of school age or older and may have a history of previous bouts of night blindness or xerophthalmia In most instances, these patches represent persistent areas of squamous metaplasia induced during an earlier episode of vitamin A deficiency The only certain means of distinguishing active from inactive lesions is to observe their response to vitamin A therapy Active conjunctival xerosis and Bitot's spots begin to resolve within 2–5 days Most will disappear within 2 weeks, although a significant proportion of temporal lesions may persist, in shrunken form, for months

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[1] McLaren DS, Ooman HA Escapini H Ocular manifestations of vitamin A deficiency in man *Bulletin of the World Health Organization*, 1966, **34** 357–361

X2. Corneal xerosis

Corneal changes begin early in vitamin A deficiency, long before they can be seen with the naked eye Many children with night blindness (without clinically evident conjunctival xerosis) have characteristic superficial punctate lesions of the inferior–nasal aspects of the cornea, which stain brightly with fluorescein (Plate 17) Early in the disease the lesions are visible only through a slit-lamp biomicroscope

With more severe disease the punctate lesions become more numerous, spreading upwards over the central cornea, and the corneal stroma becomes oedematous Clinically, the cornea develops classical xerosis, with a hazy, lustreless, dry appearance, first observable near the inferior limbus (Plates 14–16, 18–20) Thick, keratinized plaques resembling Bitot's spots may form on the corneal surface (Plates 19, 21), and are often densest in the interpalpebral zone With treatment, these corneal plaques peel off, sometimes leaving a superficial erosion that quickly heals

Corneal xerosis responds within 2–5 days to vitamin A therapy, with the cornea regaining its normal appearance in 1–2 weeks

X3A, X3B. Corneal ulceration/keratomalacia

Ulceration/keratomalacia indicates permanent destruction of a part or all of the corneal stroma, resulting in permanent structural alteration

Ulcers are classically round or oval "punched-out" defects, as if a trephine or cork-borer had been applied to the eye (Plates 22, 23) The surrounding cornea is generally xerotic but otherwise clear, and typically lacks the grey, infiltrated appearance of ulcers of bacterial origin (Plate 24) There may be more than one ulcer Small ulcers are almost invariably confined to the periphery of the cornea, especially its inferior and nasal aspects The ulceration may be shallow, but is commonly deep Perforations become plugged with iris, thereby preserving the anterior chamber With therapy, superficial ulcers often heal with surprisingly little scarring, deeper ulcers, especially perforations, form dense peripheral adherent leukomas (Plate 26)

Localized keratomalacia is a rapidly progressive condition affecting the full thickness of the cornea It first appears as an opaque, grey to yellow mound or outpouching of the corneal surface (Plate 25) In more advanced disease the necrotic stroma sloughs, leaving a large ulcer or descemetocele As with smaller ulcers, this is usually peripheral and heals as a dense, white, adherent leukoma (Plate 26)

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Ulceration/keratomalacia involving less than one-third of the corneal surface (X3A) generally spares the central pupillary zone, and prompt therapy ordinarily preserves useful vision More widespread involvement (X3B), especially generalized liquefactive necrosis (Plates 27–29), usually results in perforation, extrusion of intraocular contents, and loss of the globe Prompt therapy may still save the other eye and the child's life

It is not always possible to distinguish cases of ulceration/necrosis due to vitamin A deficiency from those due to bacterial or fungal infections, principally because vitamin-A-related lesions can become secondarily infected In addition, once ulceration/keratomalacia occurs, the conjunctiva usually becomes inflamed (Plates 23, 28), and — for reasons that are not well understood — the conjunctival xerosis disappears Conjunctival xerosis in the other, unulcerated eye, may reveal the true nature of the problem, although not invariably When vitamin A status deteriorates precipitously — as happens in measles, severe gastroenteritis, or kwashiorkor in children previously in borderline vitamin A balance — corneal necrosis can precede the appearance of night blindness or conjunctival xerosis In such instances it is safest to assume that both vitamin A deficiency and infection are present and to treat the children accordingly

XS. Scars

Healed sequelae of prior corneal disease related to vitamin A deficiency include opacities or scars of varying density (nebula, macula, leukoma as in Plate 26), weakening and outpouching of the remaining corneal layers (staphyloma as in Plate 31, and descemetocele as in Plate 30) and, where loss of intraocular contents has occurred, phthisis bulbi, a scarred shrunken globe Such end-stage lesions are not specific for xerophthalmia and may arise from numerous other conditions, notably trauma and infection

XF. Xerophthalmic fundus

The small white retinal lesions described in some cases of vitamin A deficiency are of investigational interest only (Plate 32) They may be accompanied by constriction of the visual fields and will largely disappear within 2–4 months in response to vitamin A therapy

Any child suspected, or at risk, of having xerophthalmia must have *both* eyes examined in full outdoor light, with his or her back to the sun, or with the aid of a flashlight and loupe, if available Unfortunately, because of the pain and reflex blepharospasm

accompanying corneal involvement, the child tends to keep the eyes tightly shut When necessary, the child's head can be stabilized by a parent or attendant, while a physician or other appropriately trained individual carefully separates the lids with a sterile Desmarres retractor, lid speculum, or bent paper-clip (as seen in many of the colour plates) The leading edge of the clip should be held parallel to the lid Once it has passed behind the lid margin it should be gently angled forward to avoid abrading the cornea or placing undue pressure on the globe

List of colour plates

Plate 1. Diagram indicating sites affected by xerophthalmia
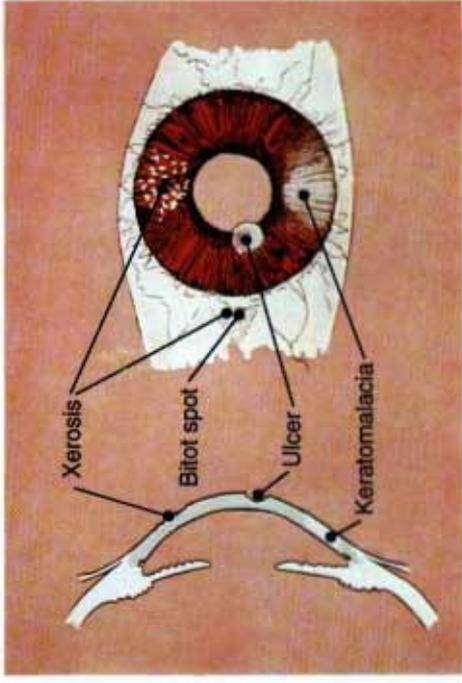
Plate 2. Diagrammatic representation of xerophthalmia lesions
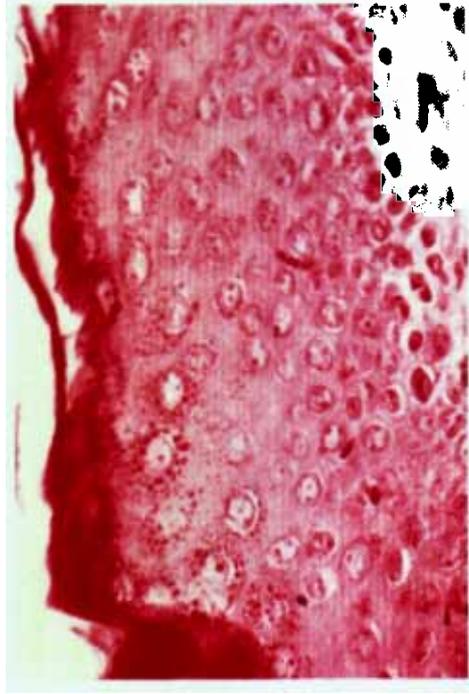
Plate 3. Conjunctival xerosis with a prominent granular cell layer and keratinized surface (haematoxylin and eosin) x 250
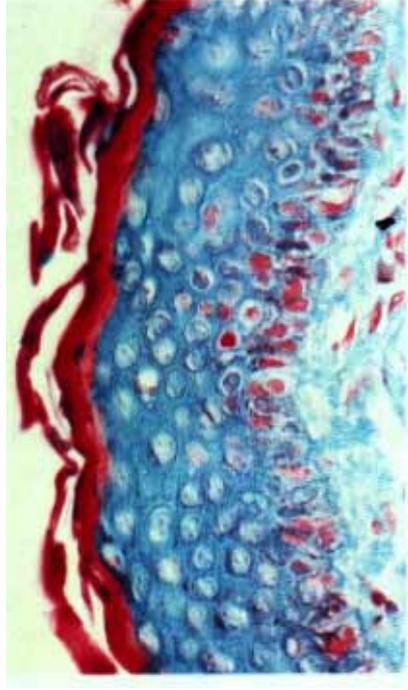
Plate 4. Conjunctival xerosis specially stained to demonstrate the heavily keratinized surface (haematoxylin and eosin) x 185

Plate 6. X1A

Plate 8. X1B ("foamy")

Plate 5. X1A

Plate 7. X1B ("foamy")

Plate 10. X1B ("foamy")
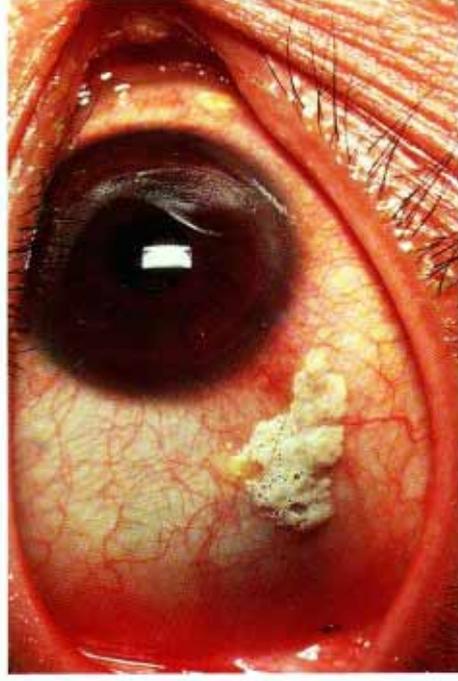
Plate 12. X1B ("cheesy")

Plate 9. X1B ("foamy")

Plate 11. X1B ("foamy")
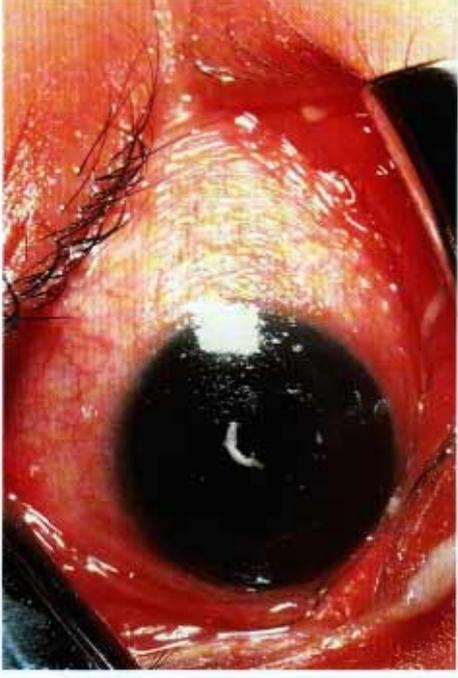
Plate 14. X1A (generalized), X2
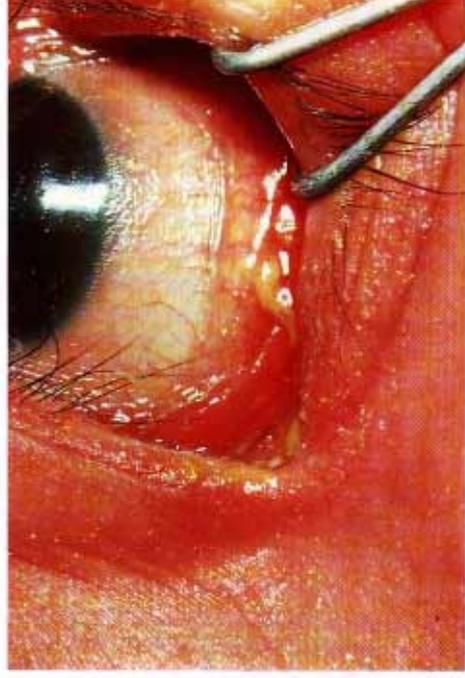
Plate 16. X1A (generalized), X2
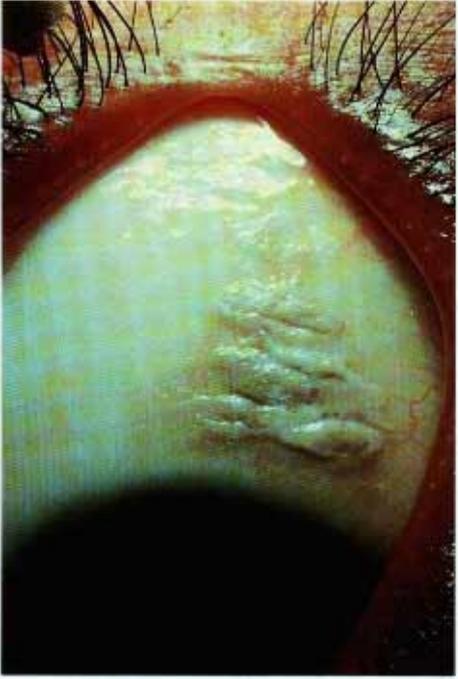
Plate 13. X1B ("cheesy")
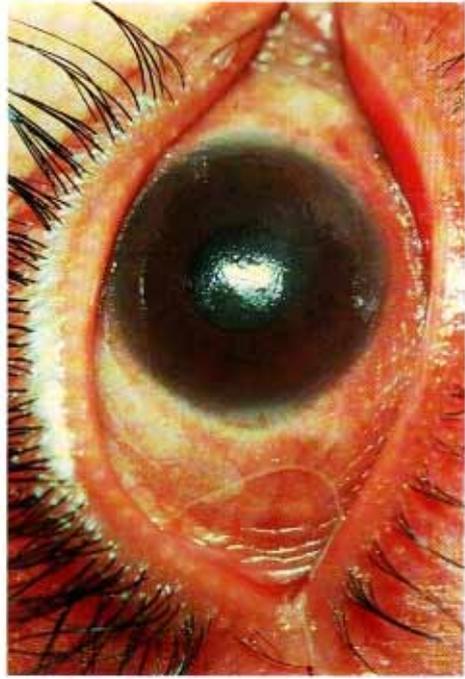
Plate 15. X1A (generalized), X2

Plate 18. X2 (haze; inflammation)
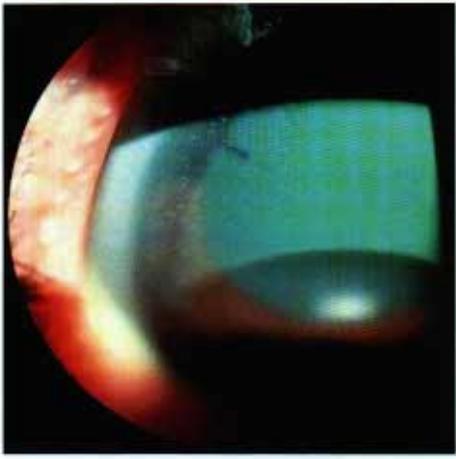
Plate 20. X2

Plate 17. Superficial punctate keratopathy

Plate 19. X2

Plate 21. X1A, X2 (with tenacious "foam")
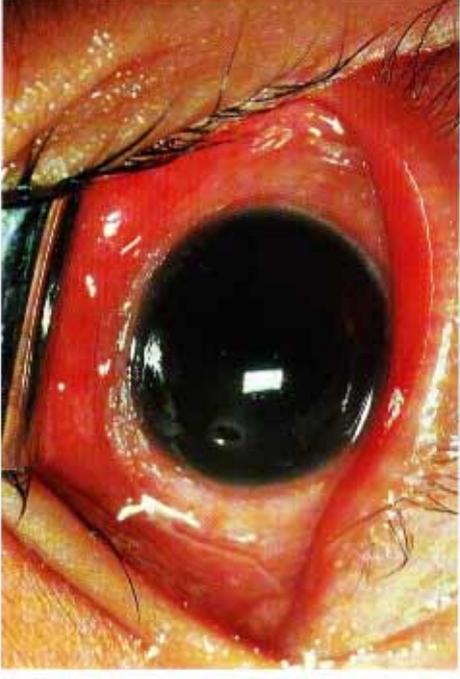
Plate 22. X3A (ulcer)
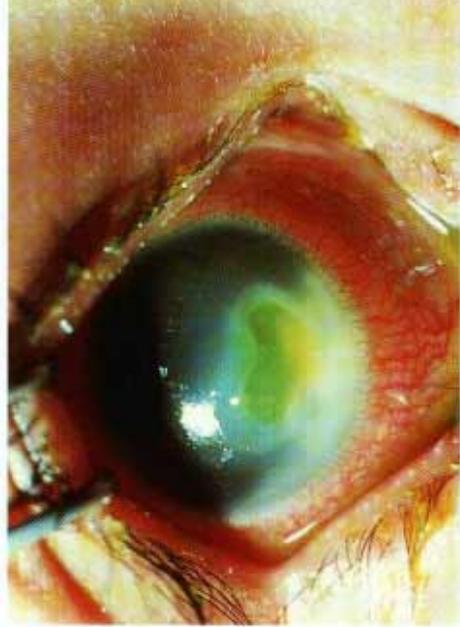
Plate 23. X3A (ulcer)

Plate 24. X3A (ulcer) with secondary infection

Plate 26. XS (healed eye in Plate 25)

Plate 28. X1B, X3B (generalized necrosis; inflammation)

Plate 25. X3A (localized necrosis)

Plate 27. X3B (generalized necrosis)

Plate 29. X1B, X3B (inflammation)

Plate 30. XS (descemetocele)

Plate 31. XS (staphyloma)
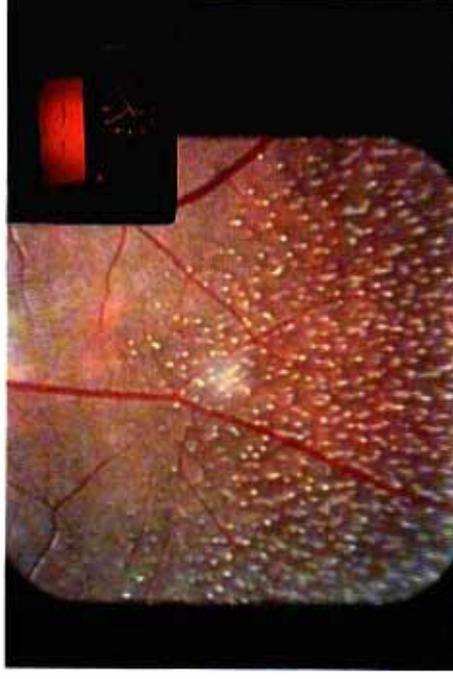
Plate 32. XF

EPIDEMIOLOGY

The cause of vitamin A deficiency can be quite complex, and depends on the type and amount of vitamin and provitamin (primarily β-carotene) ingested, and on the absorptive, transport, and storage capacities and metabolic needs of the individual. Seemingly unrelated disease states can dramatically alter each of these factors and, in turn, the individual's vitamin A balance. For example, gastroenteritis will affect both the types and amounts of food offered and a child's appetite, while the shortened transit time will decrease absorption of any vitamin A that is ingested. If the child is already protein-deficient, transport and storage may be decreased and the fever will increase metabolic needs.

The cause of, and contribution made by, each of these factors may vary from one community to another, resulting in different epidemiological patterns in terms of age, sex, season, number of people affected, and relative proportion of cases with and without xerophthalmia and corneal involvement. In general, however, clinically significant vitamin A deficiency resulting in increased mortality or blindness is predominantly a disease of young children, most often those from depressed rural communities and urban slums. Older, school-age children may suffer milder deficiency and the lesser consequences.

Age

Children are born with limited vitamin A reserves, and when a mother is deficient in vitamin A the newborn child's reserves are even smaller. Colostrum and early breast milk are concentrated sources of vitamin A. For the first 6–12 months of life many infants depend almost entirely on vitamin A provided in breast milk, which is readily absorbable. When a mother is deficient in vitamin A, however, the amount provided in her milk is reduced. Bottle-fed children are often at even greater disadvantage, particularly if they receive unfortified skimmed milk already low in vitamin A, or whole milk overdiluted with water (and frequently contaminated). After 4–6 months of life a child requires supplementary feedings with foods rich in vitamin or provitamin A. For a variety of reasons, principally ignorance, preference, cost, or unavailability, these foods may not be consumed in adequate amounts.

Children are also at increased risk of vitamin A deficiency as a result of intestinal infestations and infections, which impair vitamin A absorption; respiratory infections, tuberculosis, and measles (and

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other childhood exanthems), which increase metabolic demands; and protein–energy malnutrition, which interferes with the storage, transport, and utilization of the vitamin. As children grow older, they often receive food from a number of relatives and other households, so that they generally consume a more varied, nutritionally balanced diet and suffer fewer infections. As a result, general nutritional status and vitamin A status improve, and the risk of blinding xerophthalmia and other consequences of deficiency declines. While mortality rates for older preschool and early school-age children are low in comparison with rates for the first year or two of life, vitamin A status may have a greater impact on mortality rates of older than of younger children (*24, 28*).

Occasionally, the same or related factors are responsible for vitamin A deficiency among older individuals. This is particularly true of refugees, prisoners, and students who suffer similar privation (e.g. unsanitary conditions, nutritional deprivation), and patients with chronic malabsorption; all are at risk of blinding xerophthalmia and other serious consequences of deficiency.

Sex

Boys are frequently at greater risk of xerophthalmia (night blindness and Bitot's spot) than are girls. In most societies or cultures, however, the risk of severe blinding xerophthalmia (corneal ulceration and keratomalacia) is equal in both sexes; moreover, improvement in vitamin A status generally reduces mortality equally in both sexes.

Season

Xerophthalmia may be more prevalent at certain times of the year, the pattern being determined by the severity and concurrence of the various factors that impair vitamin A status. In many areas of the world, for instance, sources of vitamin A (and of food in general) are in short supply during the hot, dry season, and measles and diarrhoea are common. Measles is a particularly important seasonal factor, precipitating as much as 25–50% of cases of blinding xerophthalmia in Asia, and perhaps even more in Africa. In many parts of Africa, measles is said to be the commonest cause of childhood blindness, a large proportion of which is secondary to measles-induced decompensation of vitamin A status (*41, 45*). Measles is also a major cause of all childhood deaths; mortality can be reduced significantly by vitamin A prophylaxis and therapy (*5, 26, 28–30*).

Clustering

Since the dietary and health practices responsible for vitamin A deficiency are shared by most members of the same community, vitamin A deficiency and xerophthalmia tend to cluster within specific families and neighbourhoods. Children living in the immediate vicinity of an active case of xerophthalmia are more likely to be deficient in vitamin A, and at higher risk of xerophthalmia, than children of the same age, sex, and socioeconomic status living in a different neighbourhood of the same village or town.

General pattern of xerophthalmia

The prevalence of milder manifestations of xerophthalmia (night blindness and vitamin-A-responsive Bitot's spot and conjunctival xerosis) usually increases from the age of about 2 years up to 8 years. Malnutrition, if present, is usually mild. These signs may persist for months, tend to be seasonal, and usually disappear spontaneously, probably with increased availability and consumption of foods containing vitamin A (and provitamin A carotenoids). They probably represent relatively mild, isolated vitamin A deficiency and do little lasting damage, but they identify children and communities at increased risk of developing destructive corneal lesions or suffering systemic consequences of vitamin A deficiency, like anaemia, growth retardation, and increased mortality.

Children suffering from forms of the disease destructive to the cornea are usually younger (often 1–4 years of age), more severely

Table 2. Epidemiological distinction between mild and corneal xerophthalmia

	Mild (XN, X1)	Corneal (X2, X3)
Age (peak incidence)[a]	3–6 years	1–4 years
Protein–energy malnutrition	Usually mild	Usually severe
Precipitating illnesses: gastroenteritis exanthematous disease (particularly measles) respiratory tract Infection	Uncommon	Common

[a] Either form of the disease can occur at any age. Most cases, however, fall within the indicated range of peak incidence.

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malnourished, and more deficient in vitamin A. History of a recent precipitating event, for example pneumonia, measles, gastroenteritis, or tuberculosis, is common, and the mortality among untreated cases is often quite high (50–90%). These patterns are summarized in Table 2.

Magnitude and distribution of the problem

Significant levels of vitamin A deficiency are far more prevalent than is xerophthalmia, which is a relatively late and severe manifestation of deficiency. Unfortunately, there is no single sign, symptom, or laboratory test that distinguishes between adequate status and mild ("subclinical"or "marginal") deficiency. Available data suggest that vitamin A status is generally normal when serum retinol levels are above 1.0 to 1.4 µmol/litre (46). Levels below 0.7 µmol/litre are traditionally considered as low and those below 0.35 µmol/litre as deficient. In fact, clinical manifestations and other, subtler, tests of physiological function and adequacy of liver stores indicate that deficiency and its consequences are present in some individuals with serum retinol levels above 0.7 µmol/litre. Conversely, not all individuals with serum levels below 0.7 µmol/litre are necessarily physiologically deficient. However, it is probably safe to assume that, when xerophthalmia prevalence rates signify a public health problem, the prevalence of physiologically significant vitamin A deficiency is roughly 10 times that of clinical xerophthalmia (39). It is estimated that between a quarter and half a million children are permanently blinded every year as a result of xerophthalmia, only a small proportion of whom survive. Another million children die from infections that they would have survived had they not been vitamin-A-deficient (34).

WHO has identified 39 countries in which vitamin A deficiency is probably a significant public health problem. In addition to those Asian countries in which clinical xerophthalmia is commonly recognized (Bangladesh, India, Indonesia, Nepal), WHO also includes other African and Asian countries in which surveys have demonstrated a xerophthalmia problem, or where diet and general nutritional status strongly suggest its presence. With growing recognition of the importance of adequate vitamin A nutriture for normal health and survival, and the potential consequences of milder, subclinical or marginal deficiency, the list of countries in which vitamin A deficiency constitutes a significant health problem in at least some areas has expanded considerably.

CHARACTERIZATION AND ASSESSMENT
OF THE PROBLEM

Formulation of an effective intervention programme for vitamin A deficiency begins with characterization of the problem Although costly and time-consuming, assessment is far less expensive than intervention itself, may indicate that the problem is much more limited than was originally thought, and should identify the reasons for the existence of the problem Intervention strategies can then be specifically tailored to achieve maximum efficiency and effectiveness

Clinicians, nutritionists, or public health officials may suspect that vitamin A deficiency is a problem because of its existence in neighbouring countries, because of the dietary pattern of the population, or on the basis of other health indices likely to be accompanied by vitamin A deficiency (e g high infant mortality, high measles mortality, or prevalent protein–energy malnutrition), or case reports of clinical xerophthalmia

Preliminary assessment

The first concern is whether vitamin A deficiency exists and is likely to constitute a public health problem An exhaustive assessment is not always necessary preliminary observations can help to determine whether more intensive investigation is warranted If a nearby country or population, with similar dietary, general nutrition, and health parameters, has been thoroughly assessed, it is likely that the prevalence and cause(s) of the problem are similar This may be an adequate base for planning and initiating intervention activities, but local data are nevertheless useful in ensuring the appropriateness of intervention programmes and in monitoring their effectiveness Similarly, an inadequate diet among the population of interest or the identification of clinical cases of xerophthalmia, particularly among preschool children, is cause for concern

Searching for active or healed cases of xerophthalmia is, in many ways, the most traditional, specific, and efficient means of preliminary assessment The search should be directed by someone experienced in the clinical recognition of the disease and knowledgeable about its pathophysiology and nutritional determinants Local eye specialists may mistakenly believe that xerophthalmia does not exist, they may not encounter the disease, because it occurs in areas or socioeconomic groups with which they

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have no contact, or they may misdiagnose it Outside experts often provide a fresh perspective

Cases should be sought in those areas where they are most likely to occur in urban slums and impoverished rural villages, in paediatric services dealing with ophthalmic disorders, malnutrition, and infectious diseases, and in rehabilitation and feeding centres, refugee camps, orphanages, and the like Careful, written records are more likely to be accurate than informal or intuitive estimates of case numbers, and direct observation of active cases is the surest means of documenting the occurrence of the disease and the validity of past diagnosis and historical data

Where cases are positively identified by examination, chart review, or interviews, data should be collected on age, sex, seasonal trends, geographical distribution, and presence of antecedent or concomitant illnesses Information of this type is valuable in designing a definitive prevalence survey

Orderly, comprehensive, preliminary case-finding should include the following

- *Interviews,* preferably by structured questionnaire, with individuals who are likely to be aware of the problem central and provincial public health officials, clinicians, nutritionists, and community health workers, directors and staffs of hospitals, feeding and rehabilitation centres, and schools for the blind
- *Chart reviews* at institutions where the disease is recognized or where children are known or suspected to suffer from corneal destruction clinics and rehabilitation centres, schools for the blind, and hospitals Records for all children listed as having diseases likely to be accompanied by, or mistaken for, xerophthalmia (conjunctivitis, keratitis, blindness, malnutrition, measles, gastroenteritis) should be reviewed The conduct and interpretation of such reviews are often hampered by vagaries and inconsistencies in record-keeping and retrieval
- *Search for clinically active cases* among children at high risk those attending clinics and feeding centres, those admitted to ophthalmic, nutrition, infectious-disease, and general paediatric wards, and those living in urban slums or impoverished rural communities
- *Search for old, healed disease* among individuals with histories compatible with prior xerophthalmia (X2, X3) in schools for the blind and in rural and low-income urban areas
- *Collection of data on dietary intake and serum vitamin A levels* for the population and presumed active cases Where available, such data provide strong corroborative support both for the diagnosis of active xerophthalmia and for the *potential* presence of the problem in the population as a whole, even when xerophthalmia cases are not identified

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Where there is sufficient suspicion of vitamin A deficiency, definitive assessment will quantify the magnitude and distribution of the problem, seek to identify its cause(s), and characterize the individuals at greatest risk

Definitive assessment

Accurate assessment of the extent and characteristics of vitamin A deficiency requires a population-based survey The size of the sample and the communities covered will depend on the parameters of interest Xerophthalmia is relatively uncommon It remains the only condition for which there are generally accepted prevalence criteria defining a vitamin A deficiency problem of public health significance (Table 3) Recently, other criteria have been developed, and cut-off levels established, to indicate unacceptable subclinical deficiency (47) The prevalence of these subclinical indicators below their respective cut-off levels awaits verification through their widespread application in defining varying degrees of importance of a public health problem Milder manifestations of deficiency, such as abnormal impression cytology, abnormal RDR, or low serum vitamin A levels, are many times more prevalent than xerophthalmia, precise estimates can therefore be generated on much smaller samples (although results apply only to the population actually sampled)

Where a prevalence criterion depends on biochemical determinations (serum retinol or RDR), careful field techniques for preparation and storage of specimens and a carefully standardized laboratory for their assay are essential Malaria and other infections can cause transient lowering of serum retinol unrelated to body stores Special care must be taken in handling specimens in areas where human immunodeficiency virus (HIV) or viral hepatitis B infections are prevalent (see Annex 3) Impression cytology simplifies the storage, handling, and analysis of specimens, but can be undertaken only by trained technicians Moreover, results may be affected by the presence of trachoma and chronic conjunctivitis (48)

Data on dietary intake are critical for understanding the genesis of deficiency (non-availability of appropriate foods, cultural practices, cost, etc) and for overcoming potential obstacles to long-term, sustained intervention "Simplified" survey questionnaires for collecting dietary data may prove useful in mapping the extent and basis of the problem Asking about the use of locally available vitamin-A-rich foods educates community workers in the population about appropriate food choices and diets (38)

Whatever test or parameter is applied, the purpose of the survey is to estimate the severity and extent of vitamin A deficiency in the

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population as a whole, rather than among individuals Determinations of serum vitamin A and RDR (and its growing number of variants, like modified RDR, for indirectly assessing liver vitamin A stores), results of impression cytology, and diagnosis of clinical xerophthalmia all tend to identify *populations* with significant vitamin A deficiency However, results do not necessarily correlate with one another on an *individual* basis, presumably because they measure different aspects of vitamin A status

Prevalence surveys

Prevalence surveys determine the proportion of individuals in a sample with a particular attribute or abnormality at the time of examination When a sample is carefully chosen to be representative of the population under consideration, prevalence within the sample is representative of that within the population as a whole

Prevalence surveys are complex, expensive, and time-consuming In general, they need be undertaken only where preliminary investigations indicate the presence of a potentially significant problem Surveys with clinical, biochemical, and dietary components are the most efficient, definitive, and unbiased means of

- establishing the nature, magnitude, severity, and geographical distribution of xerophthalmia,
- determining whether it constitutes a significant public health problem,
- selecting suitable strategies for intervention,
- providing a baseline for evaluating the effectiveness of future intervention programmes

Clinical parameters

Only some of the clinical signs of xerophthalmia are sufficiently objective and easily recognizable to be useful in the definitive prevalence survey Conjunctival xerosis is excluded because it is frequently diagnosed where it is not actually present

- *Night blindness*

  A history of night blindness — often the most prevalent of the signs and symptoms of vitamin A deficiency — is easily collected Care must be taken, however, in accepting a positive history it should come from a responsible adult who recognizes that a child's behaviour after dusk or in a darkened room is distinctly different from that of other, normal children The history is most

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reliable when described with a local term specific for the condition It is thus imperative that members of the survey team make every effort to identify such terms before conducting their interviews

Being a mild sign of xerophthalmia, night blindness has the same significance and limitations as those described below for Bitot's spot New, objective techniques for assessing dark adaptation, even in children who have not yet learned to speak, are under development

● *Bitot's spot (X1B)*

Bitot's spot is an easily recognized and relatively specific marker of active vitamin A deficiency, at least among preschool children, and is more prevalent than corneal disease However, it does not provide information on the magnitude or extent of ocular destruction and blindness Areas in which the prevalence of Bitot's spot is similar may have widely varying levels of corneal destruction and vice versa In older, school-age children, the presence of Bitot's spots may reflect previous deficiency that has since been corrected

● *Active corneal lesions (X2, X3A, X3B)*

Corneal xerosis (with or without ulcers) and keratomalacia are the severest forms of xerophthalmia Easily diagnosed and highly specific, these conditions are rapidly progressive and associated with a very high mortality rate Their prevalence in the population is therefore usually extremely low

● *Inactive corneal lesions (XS)*

Although the prevalence of active corneal disease is difficult to establish, it is possible to assess the prevalence of its sequelae corneal scars and ocular destruction It is important to distinguish between those cases likely to be the result of vitamin A deficiency and those due to other causes This requires a careful examination, a detailed history from a responsible adult, and interpretation by an ophthalmologist

The following diagnostic criteria are cautious and would undoubtedly exclude some lesions actually due to vitamin A deficiency, however, their application makes it possible to establish with greater certainty the *minimum* prevalence of the condition

— a clinical picture compatible with that of the disease,
— the absence of other forms of disease capable of producing a similar picture (intraocular foreign bodies, advanced trachoma, etc),

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— age of at least 4 months when the child developed the lesion (this eliminates most congenital abnormalities and cases of neonatal ophthalmia),
— no association between the lesion's appearance and trauma or gross purulence

A history of malnutrition, respiratory infection, or gastroenteritis concomitant with the onset of the lesion supports the diagnosis

If the history is either vague or unavailable, this should be stated, and the case reported under a different category "possible" or "unlikely" to be the result of xerophthalmia, depending on the clinical picture Corneal destruction of other origin should also be tabulated, e g congenital, traumatic, arising from infection (see Annex 4)

Cases associated with measles should be tabulated separately since xerophthalmia, though possibly the major cause, may be only one of several mechanisms accounting for corneal destruction in this disease

Although the diagnosis of xerophthalmia-related corneal destruction is retrospective, few if any other conditions produce significant numbers of cases with a similar clinical and historical pattern Since only survivors are examined, the observed *prevalence* (number of cases in a population at any one time) of sequelae is an inadequate guide to the *incidence* (number of new cases occurring in a population over a given period) of active disease

Suggestions for examining children in the field are provided in Annex 2

● *Impression cytology*

Impression cytology (CIC) is a sensitive histological technique for identifying keratinizing metaplasia of the conjunctiva, a microscopic and much more prevalent form of the metaplasia that is responsible, at the macroscopic level, for Bitot's spot (X1B) Precise criteria for establishing the disorder as a public health problem are currently under review Impression cytology can also provide independent corroboration of the clinical diagnosis of xerophthalmia and, since abnormal CIC is also more common, a smaller sample size may be used to establish the prevalence and distribution of vitamin A deficiency Specimens are generally collected with a special applicator that applies a filter paper and removes it by suction in one quick step Techniques for the collection, staining, and interpretation of specimens are described elsewhere (*48*), they should be performed

only by individuals who have undergone specific "hands on" training, and they require a standardized approach to quality control

Biochemical parameters

Biochemical data can be used in at least two ways — as prevalence criteria in their own right, and to corroborate the accuracy of the clinical diagnosis of *active* xerophthalmia Traditionally, however, serum retinol levels have been considered to provide only corroborative evidence (Table 3) "Public health" criteria are under review for the prevalence of abnormal serum retinol and RDR or modified RDR (MRDR), and a training manual for assessing vitamin A status by use of RDR and MRDR assays has been recently prepared (*49*) Once sufficient experience has been gained in their interpretation under varying cultural conditions, these sensitive indices of vitamin A status will become increasingly important in efforts to identify and control the consequences of milder (marginal) vitamin A deficiency, including increased mortality

As part of a clinical prevalence survey, serum retinol or RDR or MRDR levels can corroborate clinical findings If determined in "abnormals" (children with active xerophthalmia XN–X3B), controls (non-xerophthalmic children from the same neighbourhood), and a random (or systematic) subsample of the study population (e g. one child in every 20), they can provide additional insights into the distribution of the disease Low serum retinol levels or a high prevalence of abnormal RDR or MRDR among abnormals compared with controls provide independent corroboration of the clinical diagnosis

Serum retinol and RDR or MRDR determinations on the random subsample establish the prevalence of subclinical or marginal vitamin A deficiency in the community Where depressed vitamin A levels are frequent, approaching those among children with xerophthalmia, vitamin A deficiency is widespread and the community as a whole is at risk of clinical consequences Where depressed levels are infrequent, however, the community as a whole is relatively normal, severe vitamin A deficiency uncommon, and the potential for clinical disease low How low may be determined from the serum levels among controls If these approach the relatively normal levels of the random subsample, the potential for disease is limited to those few individuals who already have active xerophthalmia On the other hand, if the levels are more like those among the xerophthalmic children, the potential for disease is higher and extends beyond individual children to entire neighbourhoods or localities, especially those in which the xerophthalmic children reside

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Where the opportunity exists, checking the distribution of vitamin A levels in breast milk will provide further indication of the neighbourhoods that are at risk

Prevalence surveys should include biochemical parameters only where adequate facilities exist for the collection, storage, and transport of samples, and where the necessary equipment and expertise are available within the country or arrangements can be made with a reference laboratory outside the country to carry out the chemical determinations

Suggestions for collecting and handling blood samples in the field are provided in Annex 3

Dietary parameters

Dietary histories alone cannot indicate the prevalence or severity of vitamin A deficiency in the community However, an understanding of food consumption patterns among children with vitamin A deficiency (particularly those with active xerophthalmia) and their families is indispensable for determining why these children became deficient and for designing appropriate programmes to increase dietary consumption of foods rich in vitamin A If there is reason to believe that fortification of a commonly consumed dietary item may be an effective intervention strategy, the dietary survey should also include potential vehicles for vitamin A fortification (50)

A variety of approaches to dietary assessment are available A generic, simplified approach suitable for prevalence surveys may be appropriately modified for local conditions (51) A family-based, qualitative history will indicate the frequency with which different foods are eaten by the family as a whole, and where these foods were procured, a similar form for individual children, with additional questions on breast-feeding and weaning practices (52), will help identify populations among whom intake of vitamin A is probably inadequate A quantitative or semiquantitative history can be used to determine the quantity of vitamin A actually consumed by a child during a given 24-hour period and will provide additional information for designing appropriate nutrition education and other dietary intervention strategies Comparison forms completed on all "abnormal" children (with active xerophthalmia) and their matched controls, or a random (or systematic) subsample of all children (e g one child in 20) examined and their families will validate the qualitative difference between the two Where children do not eat foods that are rich in vitamin A or provitamin A, it is important to enquire about the reasons (e g they are expensive, locally unavailable, not considered healthy for children, not enjoyed by children)

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For purposes of designing an intervention programme, the list of foods consumed in the community should include all locally available major sources of vitamin A and provitamin A, potentially fortifiable foodstuffs, staple foods, and major sources of protein

Qualitative and semiquantitative data can usually be collected by a suitably trained field worker, but quantitative data collection requires a trained nutritionist, samples of the foods under consideration, and scales to weigh the amounts consumed by each child (as indicated by a responsible adult)

Consumption of potentially fortifiable condiments, which are usually consumed only in small amounts, may be best assessed on the basis of expenditure for those items, rather than by attempting to gauge directly the quantity consumed (53)

Sample forms for data collection are provided in Annex 4

Preparatory data

Rough estimates of the magnitude of the problem and of seasonal variations will be useful in choosing the sample size and timing the survey to coincide with the period of maximum prevalence Such data should already be available from the preliminary assessment

The factors involved in selecting a suitable sample are discussed below The actual selection procedure employed, however, will vary from survey to survey, depending on local conditions and interests, and should be determined by an epidemiologist or statistician experienced in sampling design

Sample size

Ideally, the entire population should be included in the survey, but this is rarely practical, and an appropriate sample is used instead The sample size will depend on the expected prevalence of the least common indicator and the precision desired, the greater the precision and the lower the expected prevalence, the larger the sample required For example, assessment of a condition that occurs in one out of every 10 children requires, for equal levels of precision, a far smaller sample than assessment of a condition that occurs in one out of every 10 000

A simple prevalence figure for a particular condition in a sample population is almost meaningless there is no assurance that it accurately reflects the true prevalence in the community as a whole However, by bracketing this figure with confidence limits, it is possible to express the probability that the "true" prevalence falls

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between those limits It is common to use the detected prevalence plus or minus 2 standard errors, there is then a 95% probability of the "true" prevalence lying somewhere within the bracketed range

"Expected" prevalence can be estimated from existing data, or by employing the suggested minimum criteria for xerophthalmia levels representing a public health problem (see Table 3) or any other level of disease or parameter that the competent authority considers sufficient to justify an intervention programme

A clinical prevalence survey might seek, for example, to estimate the extent of corneal destruction related to vitamin A deficiency Data on healed sequelae (XS), usually the only evidence of corneal destruction that is sufficiently common to make such estimates practical, require a sample size of at least 10 000 children (using the suggested minimum criterion of a level of 0 05%) Since the corroborative biochemical criterion for vitamin A deficiency and xerophthalmia as a public health problem is severely depressed serum retinol levels ($<$ 100 µg/litre or 0 35 µmol/litre) in 5% of the population, which are far more prevalent than corneal scars, only one out of every 20 children undergoing clinical examination need be sampled

Comparisons between different regions require a complete survey of adequate sample size in each

Selection of sample

Sample selection begins by defining the population at risk, i e the segment of the community in which vitamin A deficiency is thought to occur and from which the sample will be drawn Individuals over the age of 6 years and families from the middle and upper socioeconomic classes rarely develop serious deficiency or active xerophthalmia, and are thus usually excluded Survey results will then apply only to preschool-age children from low-income families The urban sample can be limited to slum dwellers as long as they account for the bulk of urban xerophthalmia and are thus the group of interest

For every individual in the population at risk there must be a fixed, known probability of being chosen for the sample, otherwise it will not be possible to carry out the statistical manipulations necessary for estimating means, prevalence, and standard deviations in the population Limiting the sample to "captive", accessible children in hospitals, clinics, schools, and day-care centres is inappropriate the probability of inclusion in the sample is very different for these children than for others, and they are therefore not representative of the population

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Stratified, multistage, cluster sampling is the most practical and popular means of sampling the population at risk Instead of examining children scattered at random throughout the population, which would present almost insurmountable practical problems, small geographical or administrative units (clusters) are chosen in which all children, or a large proportion of them, are examined The larger the number of clusters, the more representative is the sample The size of the clusters is usually limited to the number of children a team can examine in a day roughly 50 to 100 per rural cluster, and two to four times as many in densely populated urban slums

Sampling accuracy is improved and useful comparisons are often made possible by *stratifying* the population into "like groups" (e g urban/rural, mountain/seaside, dry belt/wet belt, and even high/low or unknown risk of disease) and choosing the clusters separately from within each stratum Population-wide calculations are simplified if the number of clusters chosen from each stratum is proportional to the size of the stratum For example, if 40% of the group at risk live in urban areas, 40% of the sample is drawn from such areas Alternatively, equal samples can be drawn from each stratum and then weighted accordingly In the example above, the prevalence in the urban stratum would be multiplied by 0 4, and that in the rural stratum by 0 6, the two products would then be added

Sample clusters can be chosen from a list (or sampling frame) composed of all cluster-size units within the stratum

Multistage sampling is usually simpler In the first stage, the stratum is divided into relatively large administrative units (e g districts), and the number of clusters (if any) to be contributed by each is determined Every subunit (e g village) in the selected district is then listed, and the number of clusters (if any) to be contributed by each is determined The process is repeated until the final, cluster-size units (perhaps neighbourhoods) are selected In the early stages at least, the probability of selecting the units should be proportional to their size This ensures a more representative sample and eliminates the need for weighting factors in calculating stratum-wide results

In practice, it is rarely necessary to go through this entire process Other groups involved in survey work within the country (census bureaux, demographic and family planning units, disease control programmes, social research institutions, etc) will often have developed samples for their own purposes, complete with cluster maps, family registers, etc , that can be adopted with little if any modification If not, they can probably provide a list of administrative units and the rough population estimates necessary for constructing the sampling frames

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Survey teams must adhere rigorously to the selected sample, and any deviations must be analysed for bias Occasionally a selected site cannot be found or reached within a reasonable time and must be dropped, however, if remote sites are consistently ignored, the sample ceases to represent the entire population at risk, and reflects instead only the more accessible portion

Forms

The clinical examination and questionnaire should be as limited as possible The more observations to be made and questions asked, the greater the likelihood that each will be dealt with superficially and carelessly Depending on local interests and capabilities, however, ancillary data and special studies on *subsamples* of the study population can provide unique epidemiological information that greatly enhances the value of the survey for the subsequent design of appropriate intervention programmes Such information may include serum retinol levels, dietary histories, socioeconomic data, and anthropometric measurements (preferably on a random subsample of children, and on "abnormals" and age/sex/locality-matched non-xerophthalmic controls)

All clinical conditions should be easily recognizable and criteria for their diagnosis should be clear-cut and reproducible Questions must be clear, objective, and amenable to simple, codable responses It is always useful to review all questions, especially those of a socioeconomic nature, with rural sociologists or others who have had previous experience in the area Only questions that the population is likely to answer reliably should be retained, direct, specific questions on subjects such as land-holding and income are rarely answered fully or truthfully

Questions should be phrased in the basic working language of the survey team, as well as in any local languages or dialects likely to be encountered Field forms designed and pre-coded for direct transfer of data to computers will speed and simplify the analysis All forms should be reviewed at least twice for legibility, accuracy, and completeness before being forwarded for data entry, computer entries should be checked by special edit programs

Both forms and survey teams require one to two weeks' pre-testing in the field before the forms are finalized or any sample sites are visited Ambiguous questions can be changed or eliminated, interview techniques standardized, and unsatisfactory, unenthusiastic workers replaced

Sample forms for data collection are provided in Annex 4

Personnel and field activities

Depending on the size and complexity of the survey, a number of different specialists will be required

- An *epidemiologist* to design the survey, monitor its progress, deal with unexpected obstacles to following the initial design, and analyse the results If the epidemiologist is not fully competent in statistical matters, a *statistician* will be needed as well
- A *clinician*, competent in the diagnosis of xerophthalmia, to conduct all ocular examinations Ophthalmologists, through experience and training, are best equipped to recognize the milder conjunctival lesions, differentiate between various causes of corneal scarring, and recognize concomitant and possibly contributory ocular abnormalities Where more than one clinician is involved, the performances of each must be rigorously and repeatedly compared to ensure uniformity, and correlated with that of an outside expert Whenever possible, all ocular abnormalities should be photographed [1] This is a useful means of validating the reproducibility and standardization of the observations
- A *nutritionist* to collect dietary histories and supervise anthropometric measurements
- A *biochemist* to oversee the collection and handling of blood samples
- An *outside expert*, if possible, who has participated in similar surveys in other countries, to advise the team and standardize its methods

Each field team is commonly composed of an ophthalmologist, a nutritionist (where dietary histories are included), two nurses, four trained field workers (enumerators), and, whenever possible, an additional individual to deal with administrative, logistic, and financial matters

As mentioned previously, teams should spend at least two weeks familiarizing themselves with the forms and procedures, at first in a hospital or clinic and later in the field, before visiting the first sample site Nurses and enumerators should be taught interview techniques and the various means of determining a child's age (relating birth to major events in the community, siblings, etc) Field practice begins slowly, with one enumerator interviewing a family while the others watch In this way, team members overcome any initial reticence and learn from one another's mistakes As their confidence and skill increase, they can interview families on their

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[1] Certain dental photographic kits, which include a simple, inexpensive macro-lens camera, are suitable for this purpose

own, with the survey expert (or epidemiologist) and nutritionist periodically checking their performance

Once the team is working smoothly at full capacity, it is ready to visit the sample sites and begin the survey Whenever possible, site visits should be timed to find the largest number of preschool children at home Villages should not be visited on market day, for example, or while mothers are out in the fields

Enumerators visit every house in the cluster and keep a careful record of those that are empty, do not contain eligible children, or contain eligible children who were away at the time or whose parents refused to cooperate Such data are important in evaluating the results for bias If large numbers of families with eligible children are away in the fields or will not cooperate, it is reasonable to suppose that their characteristics and risk of xerophthalmia might well be different from those of families that were examined

The enumerators complete forms on all cooperating families with eligible children, filling in basic socioeconomic data and listing and identifying all eligible children, later assembling the forms at a central point for examination House-to-house visits are the only means of avoiding the bias of "volunteer" samples and of assessing the magnitude of the potential bias created by absent children

The supervisory nurse has three principal tasks checking the accuracy of the enumerators by re-interviewing 10% of the families, conducting anthropometric measurements and collecting blood samples when these are required by the survey, and assisting the ophthalmologist, when necessary, in examining children

Whenever more than one team is involved in the survey, they should all work in the same general area, rather than in widely separated regions This avoids any possibility that regional differences will be introduced by differences in the teams

All children with serious illness or evidence of xerophthalmia should receive appropriate therapy (see Table 4)

Data analysis

Background data should include maps and tables indicating the location and number of selected sites and those that were actually visited, as well as the number of children anticipated, the number present, and the number and proportion actually examined in each stratum by age (years completed) and sex This orients later study of the results and facilitates the search for bias

Clinical findings should be reported in accordance with the
xerophthalmia classification given in Table 1, each child with *active
disease* should be included only once, under his or her most severe
manifestation (X3B, X3A, X2, X1B, XN) Additionally, the
proportion of children with old, healed corneal disease (XS) should
be noted Tabulations organized by age and sex within each
stratum, indicating the number of "abnormal" children and the
prevalence rate (per 1000) of each sign, facilitate the construction of
age-, sex-, and stratum-specific rates, overall survey rates, and
corresponding confidence limits, as well as the search for clinically
and epidemiologically important differences The statistical
significance of these differences should be determined

The proportion of cases of corneal xerophthalmia with bilateral
involvement and monocular and binocular blindness, and the age,
sex, and geographical distribution of patients with corneal damage
due to other causes are also of interest

Serum retinol levels should be reported separately for "abnormals",
controls, and the random or systematic subsample "Abnormals" or
controls originally chosen as part of the subsample, before their
clinical classification, remain so and should be included in the
calculation of levels for the subsample as a whole as well as for
their clinical condition ("abnormal" or control)

The frequency distribution (within steps of 0 35 μmol/litre), mean,
standard deviation, and confidence limits of serum retinol levels,
number of eligible children, and number of specimens collected and
analysed should be tabulated for each category Wherever possible,
the data should be age-, sex-, and stratum-specific Values for the
random subsample reflect the vitamin A status of the population
from which the original sample was drawn

Qualitative *dietary patterns* of children with active xerophthalmia
or other evidence of vitamin A deficiency (e g biochemical evidence
or results of impression cytology) are reported separately from
those of their families The source and frequency of consumption of
each major class of foods and individual items of particular
importance (those rich in vitamin A or provitamin A, or potentially
fortifiable) should be tabulated

Interpretation

The prevalence survey documents the extent of the vitamin A
deficiency problem and its geographical distribution in the area
under investigation Health leadership must then determine
whether, and where, the problem is sufficiently serious to warrant
intervention Criteria for the community diagnosis of xerophthalmia
and assessing the public health significance of vitamin A deficiency

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Table 3 Criteria for assessing the public health significance of xerophthalmia and vitamin A deficiency, based on the prevalence among children less than 6 years old in the community[a]

Criterion	Minimum prevalence (%)
Clinical	
Night blindness (XN)	1 0
Bitot s spot (X1B)	0 5
Corneal xerosis and/or ulceration/keratomalacia (X2 + X3A + X3B)	0 01
Xerophthalmia-related corneal scars (XS)	0 05
Biochemical	
Serum retinol (vitamin A) less than 0 35 μmol/litre (100 μg/litre)	5 0

[a]Source reference *2*

have been proposed to assist government administrators in this task (see Table 3) [1] These apply only to children below the age of 6 years in the area actually surveyed The presence of one or more of the four *clinical* criteria should be considered as evidence of a significant xerophthalmia problem within the area (large or small) to which they apply Fulfilment of the biochemical criterion is strong corroborative evidence of the fulfilment of any clinical criteria Only the criteria for *corneal disease* (X2, X3, XS) directly document blinding, or imminently blinding, ocular disease

Given the importance of marginal (i e subclinical) vitamin A deficiency in the context of general health and survival, the competent national health authorities may wish to pay attention to more sensitive indices of vitamin A status (including low serum vitamin A levels, and abnormal RDR, MRDR, or impression cytology) Reports to date suggest that serum levels below 0 7 μmol/litre in more than 10% of children surveyed, or abnormal impression cytology, RDR, or MRDR in 20% or more of children surveyed may signify vitamin A deficiency sufficiently severe and prevalent to warrant community-wide intervention However, criteria have not as yet been precisely defined under varying field conditions

A rough estimate of the number of children who develop new corneal destruction related to vitamin A deficiency each year can be

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[1] The 1982 revision of these criteria (see reference *2*) takes account of data indicating that the critical rate of active corneal disease (X2 + X3) frequently correlates with significantly lower rates of X1B and XS than originally anticipated by the criteria formulated in WHO Technical Report No 590 (*Vitamin A Deficiency and Xerophthalmia Report of a Joint WHO/USAID Meeting*, Geneva, World Health Organization, 1976) and that a positive history of night blindness is a useful index of active vitamin A deficiency in selected cultures

calculated by multiplying the prevalence of corneal scars related to vitamin A deficiency (XS) among 5-year-olds (the cumulative prevalence) by the total number of 2-year-olds (the median "at-risk" age group) in the region (or country) under study Because the number of cases of XS observed in the survey is likely to be small, the chance variation in prevalence between adjacent age groups may be substantial A more accurate, if conservative, estimate is obtained by using the overall prevalence among 4- or 5-year-olds in the sample instead, as shown below

Cases of XS among 4- and 5-year-olds in sample
    Number of 4- and 5-year-olds in sample

× Total population of 2-year-olds

= Number of new surviving cases of XS each year

In most instances, one-quarter of these children will be bilaterally blind Since the survey enumerates surviving cases, and mortality is likely to exceed 50%, the true incidence is probably at least twice this rate In some areas mortality surpasses 90%, and the true incidence is therefore correspondingly higher

These criteria should not be interpreted rigidly They are only guidelines, to be interpreted in the light of existing health resources and competing priorities They should be compared with the overall mortality rates and with the rates in specific, high-prevalence areas, intervention programmes should be targeted accordingly

Available data suggest overall mortality in children aged 6 months to 6 years will be reduced by 20–50% by improving the vitamin A status of populations that meet existing prevalence criteria for a public health problem (7) Few data are available to indicate the level of mortality reduction likely to be achieved in populations that do not fulfil these criteria Treatment of severe measles with high-dose vitamin A can reduce case-fatality by 50% in populations in which xerophthalmia is not apparently common This highlights the likelihood of increased mortality as a consequence of vitamin A deficiency, and the potential reduction in childhood mortality that may be achieved by improving the vitamin A status of deficient populations that do not reach established clinical criteria for a "significant public health problem"

TREATMENT

Immediate, substantial improvement in vitamin A status is required in all instances in which deficiency poses an imminent threat to vision, health, and survival The most clinically apparent, urgent conditions are xerophthalmia, severe infectious episodes (particularly measles and dysentery or persistent diarrhoea), and severe protein–energy malnutrition The frequency of vitamin A dosing is dependent on the condition being treated

Xerophthalmia

Xerophthalmia is a medical emergency carrying a high risk of corneal destruction and blindness, and/or sepsis and death Effective therapy requires prompt recognition of children with active disease, immediate administration of massive doses of vitamin A, with concomitant treatment of underlying systemic illnesses and protein–energy malnutrition, and prevention of any recurrence

Vitamin A

Prompt administration of massive amounts of vitamin A is essential (Table 4) Oral administration is preferred, because it is safe, cheap, and highly effective 110 mg retinyl palmitate or 66 mg retinyl acetate (200 000 IU vitamin A) is administered by mouth immediately upon diagnosis and the dose is repeated the following day (54) An additional dose is commonly given 1–4 weeks later, in the hope of further boosting liver reserves Because children with severe protein–energy deficiency handle a massive dose poorly, it is

Table 4. Treatment schedule for xerophthalmia

Timing	Dosage[a]
Immediately upon diagnosis[b]	110 mg retinyl palmitate or 66 mg retinyl acetate (200 000 IU) by mouth
Next day	110 mg retinyl palmitate or 66 mg retinyl acetate (200 000 IU) by mouth
Within 1–4 weeks, whenever clinical deterioration occurs, every 2–4 weeks in the presence of persistent kwashiorkor	110 mg retinyl palmitate or 66 mg retinyl acetate (200 000 IU) by mouth

[a] Children 6 11 months of age should receive only half the dose shown in this table and children less than 6 months one-quarter of the dose

[b] Intramuscular injection of 55 mg *water miscible* retinyl palmitate (100 000 IU) is substituted in rare in stances when children with severe stomatitis cannot swallow in cases of persistent vomiting or if severe malabsorption (as in cystic fibrosis) prevents an adequate response

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essential that they are carefully monitored and given additional doses as needed, commonly every 4 weeks, until their protein status improves (55)

In the *rare* instances in which children are unable to swallow (as occurs sometimes in stomatitis accompanying severe measles), in cases of persistent vomiting, or in malabsorption syndromes (e g cystic fibrosis), which prevent adequate absorption of vitamin A, an intramuscular injection of 55 mg (100 000 IU) *water-miscible* retinyl palmitate should be substituted for the first oral dose Needles and syringes must be sterile Oil-miscible preparations should never be given by injection because they are poorly absorbed from the injection site

For children aged 6–11 months, intramuscular and oral doses should be reduced by half, infants under 6 months of age should receive one-quarter of the normal dose

Very large doses of vitamin A may be teratogenic, particularly early in pregnancy, and treatment of xerophthalmia in women of reproductive age therefore requires modification of the standard regimen For night blindness or Bitot's spots, 5 5 mg retinyl palmitate (10 000 IU vitamin A) should be administered daily for at least 2 weeks This dose can be safely administered throughout pregnancy Where corneal lesions are present, the risk of blindness outweighs the risk of congenital defects, and administration of the full therapeutic schedule is probably warranted

Where vitamin A preparations are not available, treatment should be instituted with foods rich in vitamin A (fish and animal livers, fish-liver oil, egg yolk, dairy products, etc) or β-carotene (lightly cooked green leafy vegetables, including leaves of the "drumstick" or "horseradish" tree (*Moringa oleifera*), the various amaranths, cassava leaves, etc, red palm oil, and red-, yellow-, and orange-coloured fruits, such as papaya and mango) Adding a small amount of edible oil will enhance the absorption of the β-carotene Even where high-dose supplements are used, a vitamin-A-rich diet should be initiated as well

Medical status and diet

Children with xerophthalmia, particularly its blinding forms, are often severely ill, malnourished, and dehydrated Proper treatment will help save their vision as well as their lives, and includes general supportive care, rehydration, and frequent feeding (by nasogastric tube if necessary) with easily digestible energy- and protein-rich foods Concurrent illnesses, such as respiratory and gastrointestinal infections, tuberculosis, worm infestations, and amoebiasis, should be treated with appropriate agents (antibiotics, anthelminthics, etc)

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Eye care

In the presence of corneal involvement, broad-spectrum antibiotic
eye ointment should be applied every 8 hours to reduce the risk of
secondary bacterial infection Established infections require
immediate, vigorous local and systemic therapy Until the causative
agent is identified, antibiotics that cover a wide range of organisms,
especially *Staphylococcus* and *Pseudomonas*, should be chosen (e g
topical bacitracin and gentamicin, plus sub-conjunctival and
systemic gentamicin and meticillin)

Every effort should be made to preserve the structural integrity of
the eye Where the cornea is weakened (by active keratomalacia,
ulceration, or thinning), the eye must be protected from undue
pressure examinations, applications of drugs, and dressing changes
should be performed with the utmost care, and the eye should be
covered, at all other times, by a firm plastic or metal shield (a
simple plastic shield can easily be fashioned from discarded X-ray
film) When necessary, a child's hands can be restrained

Preventing recurrence

Vulnerable children have already demonstrated that their home
environment is deficient in vitamin A Mothers and other care-
givers need to be convinced of the need to provide diets rich in
vitamin A and shown how to prepare them from inexpensive,
readily available sources (primarily mango, papaya, carrots, yellow
pumpkin and squash or sweet potato, and dark-green leafy
vegetables, see Table 5) As a rough guide, a handful of fresh green
or red varieties of amaranth (40 g) or drumstick leaves (35 g), or a

Table 5. Foods that provide daily vitamin A requirements[a]

Age group	Carrots	or	Sweet potatoes	or	Dark-green vegetables[b]	or	Mango
Food sources							
Children							
0–5 months			Exclusive breast-feeding				
6–11 months	$1\frac{1}{2}$ tbsp		1 tbsp		$\frac{1}{3}$ cup		$\frac{1}{2}$ med
1–2 years	$1\frac{1}{2}$ tbsp		1 tbsp		$\frac{1}{2}$ cup		$\frac{1}{2}$ med
2–6 years	2 tsbp or $\frac{1}{4}$ med		$1\frac{1}{2}$ tbsp		$\frac{1}{2}$ cup		$\frac{2}{3}$ med
Female							
Non-pregnant	$\frac{1}{4}$ cup or $\frac{1}{4}$ med		$2\frac{1}{2}$ tbsp		1 cup		1 med
Pregnant	$\frac{1}{4}$ cup or $\frac{1}{2}$ med		$2\frac{1}{2}$ tbsp		1 cup		1 med
Lactating	$\frac{1}{3}$ cup or $\frac{1}{3}$ med		$\frac{1}{4}$ cup		$1\frac{1}{2}$ cup		$\frac{2}{3}$ med

[a] Source *Vitamin A and breastfeeding a comparison of data from developed and developing countries*
Washington DC United States Agency for International Development 1993
[b] Vitamin A content averaged from cooked beet greens kale mustard greens and spinach

medium-sized mango (100 g) will provide the daily requirements for toddlers and preschool children

Large, simple wall posters in clinic and hospital waiting-rooms will alert mothers to the problem of vitamin A deficiency and means of preventing it Nutritionists, dietitians, and other specially trained personnel can provide more detailed instruction for those whose children are already affected Periodic follow-ups are important to check whether xerophthalmia has recurred and, if it has, to provide prompt treatment Administration of a large dose of vitamin A (appropriate for age) at intervals of 4–6 months will ensure that a child maintains adequate vitamin A stores

Measles and other high-risk infections

Severe infectious episodes, particularly measles but also malaria and chickenpox, can cause acute decompensation in vitamin A status If vitamin A status is marginal to begin with, the resultant deficiency greatly increases the risk of blindness, systemic complications (e g laryngotracheobronchitis), and death All cases of measles in populations in which vitamin A deficiency is known to occur, or where measles case-fatality rates exceed 1%, should receive the same initial treatment as if they had xerophthalmia a large dose of vitamin A (appropriate to age) on two successive days (56) [1] These children are *presumed* to be deficient in vitamin A, regardless of their appearance Children with severe, complicated, life-threatening measles and all children with measles who are under 2 years of age should be considered for vitamin A therapy even if they do not come from a "high-risk" population

Other high-risk groups

Children suffering severe protein–energy malnutrition or illness (chronic or recurrent diarrhoea, lower respiratory disease, acute otitis) and coming from communities in which vitamin A deficiency occurs are also at increased risk of clinically significant deficiency and its consequences They should receive vitamin A therapy appropriate to their condition and age (see Tables 4 and 6) The underlying illness requires prompt and specific attention If it persists, additional vitamin A supplements may be administered at appropriate intervals (every 1–3 months)

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[1] The official WHO/UNICEF recommendation for treating measles is a single dose rather than two successive doses However, all positive trials have utilized a double-dose regimen and a working group has suggested the more intensive schedule for measles in populations where complications are common and mortality is high

Table 6. Treatment and prophylactic schedule for other high-risk conditions[a]

Group	Dosage[b]
Children and adults with severe protein–energy malnutrition	Full treatment schedule and continue in prevention programme[c]
Children with measles	Single/double dose or full treatment schedule
Children with diarrhoea, lower respiratory tract disease or other acute infections	200 000 IU vitamin A orally once and continue in prevention programme[c]

[a] Source *Guidelines for the use of vitamin A in emergency and relief operations* Washington DC IVACG, 1988

[b] Children 6–11 months of age should receive only half the dose and children less than 6 months one-quarter of the dose

[c] See Table 7 for periodic supplementation guidelines

Logistics

Prompt and effective therapy requires that suitable vitamin A preparations are available at all hospitals, clinics, health units, and rehabilitation centres and to all primary health care workers who are likely to encounter the disease Standardized capsules of retinyl palmitate (55 and 110 mg, 100 000 and 200 000 IU, respectively, vitamin A) and concentrated solutions of vitamin A are cheap, increasingly available, and perfectly safe when given in the recommended amounts Larger doses or over-frequent administration may be toxic, however, resulting in bulging fontanelle, headaches, vomiting, seizures, changes in mental activity, and other evidence of increased intracranial pressure

It is also essential for doctors, nurses, and paramedical personnel to be trained in the recognition and treatment of children with xerophthalmia and other children at high risk of significant vitamin A deficiency These issues should be included in the basic curricula of all schools of medicine, nursing, and paramedical training, and short courses should be held for personnel already in practice Recognition and treatment guides should be available at each centre for future reference

Vitamin A therapy should be initiated by the first member of the medical network who encounters the disease Only then should cases of corneal involvement or of severe systemic infections or malnutrition be referred for more comprehensive treatment

PREVENTION

Anything that improves the vitamin A status of high-risk
individuals can have an impact on the problem of vitamin A
deficiency and its consequences Environmental sanitation and
better housing, for example, reduce the prevalence and severity of
respiratory tract infections, tuberculosis, diarrhoea, and worm
infestations, and thus increase absorption of, and reduce the
metabolic need for, vitamin A Effective measles immunization
eliminates one of the commonest precipitating factors of blinding
xerophthalmia and vitamin A-related childhood mortality

Only by ensuring that children receive adequate supplies of vitamin
A, however, will the underlying cause of the problem be removed
In general, such supplies for disadvantaged children must be greater
than the recommended daily allowances established for healthy
children They must be adequate to overcome reduced absorption
and increased requirements prevalent among disadvantaged
populations They must also provide sufficient excess to build
vitamin A stores that will protect high-risk children through
seasonal fluctuations in the availability of vitamin-A-rich foods.

The ultimate goal of any prevention programme must be the
regular, adequate dietary intake of vitamin A and provitamin A by
vulnerable children, and the elimination of all forms of vitamin A
deficiency This is generally a long-term goal, but efforts to achieve
it should be started immediately and should receive adequate
support Concurrently, short-term, necessarily expensive, emergency
measures may be needed to prevent vitamin A deficiency becoming
sufficiently severe to result in ocular destruction and increased
mortality How and to what extent this is accomplished will depend
on the severity and nature of the deficiency, the resources available,
and the degree of dedication and desire of health personnel to
attack the problem To be effective, all such programmes must
reach the children at greatest risk

An understanding of the dietary and socioeconomic determinants of
vitamin A deficiency is necessary in order to design appropriate
intervention programmes for each community Where the necessary
data have not already been collected in the course of the original
prevalence survey, limited secondary investigations should be
conducted in the areas of high prevalence Programmes to control
vitamin A deficiency should be developed, when appropriate, in the
context of controlling deficiencies of other micronutrients,
particularly iron and iodine, and other health problems

Three main intervention strategies are currently in use increasing
the dietary intake of foods rich in vitamin A and provitamin A,

periodic administration of large doses of vitamin A, and addition of vitamin A to one or more commonly consumed dietary items (fortification) Although fortification is an artificial means of compensating for inappropriate dietary practices, it has formed the basis for successful programmes to combat nutritional deficiencies in many industrialized countries For the majority of communities, however, the most logical and least expensive long-range solution is to change dietary practices These practices will become apparent from the socioeconomic and dietary data collected during the prevalence survey

Increased intake of dietary sources of vitamin A

Inadequate dietary intake of vitamin A commonly begins with early discontinuation of breast-feeding and late and inadequate introduction of carotene- or vitamin-A-rich foods Prolongation of breast-feeding and early dietary enhancement (preferably by 6 months of age) with tasty, easily digested provitamin-A-rich fruits (e g mango and papaya), appropriately prepared dark-green leafy vegetables, and animal sources of preformed vitamin A (egg yolk, chicken and other animal liver, dairy products, etc) are likely to have a significant impact

Dark-green leafy vegetables are often the least expensive and most widely and consistently available source of vitamin A The same amount of vitamin A is obtained from a handful of (fresh) spinach (68 g) as from a small portion of calf liver (63 g), 4 medium-sized hens' eggs (227 g), 1 7 litres of whole cow's milk, or 6 kg of beef or mutton However, parents may not know

- that dark-green leafy vegetables are appropriate for young children,
- that they should be boiled until tender to increase digestibility (and to remove toxic substances found in some varieties)
- that they should be shredded (mashed or sieved for infants) and mixed with the staple food to encourage consumption, if necessary, and
- that they should be combined with a small amount of edible oil to improve vitamin absorption

Before an educational campaign is initiated, small but intensive anthropological/dietary studies should be undertaken to determine exactly why deficient children are not consuming adequate amounts of foods rich in vitamin or provitamin A It makes little sense to encourage the consumption of green leafy vegetables if they are not locally available, or to encourage growing them at home if such vegetables are locally plentiful and inexpensive

Knowing which vitamin-A- and provitamin-A-rich foods are available and the reasons that they are not being consumed

provides a solid basis for designing effective intervention strategies For example, if it is found that parents of children with active xerophthalmia consume large quantities of foods rich in vitamin or provitamin A, but do not feed them to their children, the appropriate message will be quite different from the one that should be used if the families never consume such foods A finely focused approach, taking into account local cultural proclivities, will provide the greatest chance of success

In areas where green leafy vegetables and other sources of vitamin and provitamin A are scarce or expensive, it may be essential to promote home gardening or other horticultural activities such as the creation of local cooperatives to produce and sell vitamin-A-rich foods to the rest of the community at affordable prices Families may need motivating to plant home gardens and instructing in their upkeep, mothers may need to be informed about the importance of prolonging breast-feeding and introducing appropriate complementary foods at 4–6 months of age These and similar tasks have been carried out by primary health workers, village-level "extension" workers, and specially trained personnel, addressing "captive" populations in hospitals, clinics, and rehabilitation centres (where, for instance, mothers can be directly involved in growing and preparing foodstuffs) Mass media education (via radio, video, newspapers, etc), common in technologically advanced countries, is proving surprisingly effective in rural, agrarian societies

Ultimately, sustained change depends on developing community understanding and "ownership" of the problem, and an active involvement in formulating and implementing solutions Intensive work with and by community leaders is essential if local attitudes are to be modified and understanding enhanced However, once the community adapts and develops a locally appropriate response, changes and their impact can be maintained at relatively little cost

As in all development work, there is a significant time lapse between problem identification and problem control It is therefore essential that a food-based strategy be developed and implemented from the outset Depending on the severity of the problem, emergency measures such as periodic dosing with vitamin A may be needed until dietary changes achieve their desired effect

Periodic supplementation

Periodic supplementation takes advantage of the fact that large quantities of vitamin A can be stored in the liver for future use Oral administration of 110 mg retinyl palmitate or 66 mg retinyl acetate (200 000 IU vitamin A), and half this dose for children aged

6-11 months, every 4-6 months will protect the vast majority of recipients from severe deficiency and its consequences (Table 7) The vitamin can be given as a capsule or in concentrated liquid form Except for children suffering from active xerophthalmia, protein-energy deficiency (kwashiorkor), or some other severe precipitating illness, it is essential to ensure that the dose is not repeated more frequently than would be safe Current experience indicates that the appropriate dosage interval is 4-6 months, although it has been suggested that this could be safely reduced to 3 months

Large vitamin A doses are inexpensive, but distribution can be costly Where distribution can be accomplished through existing health programmes (e g malaria, family planning) or by village-level primary health workers, midwives, immunization personnel, etc, costs can be kept relatively low However, where workers have to be employed specifically to distribute vitamin A, they rise dramatically The efficiency and efficacy of distribution can be increased by targeting the children at greatest risk, i e those with persistent diarrhoea, generalized malnutrition, severe systemic illnesses, measles, etc It should be recognized, however, that this approach leaves large numbers of children unprotected these medically underserved children are characteristically from the lowest socioeconomic strata, often live in remote and inaccessible areas, rarely if ever make use of existing health facilities, and are at the highest risk of disease

Advantage can be taken of the fact that vitamin A deficiency and xerophthalmia cluster in families and neighbourhoods Thus, distribution of vitamin A (as well as nutrition education) can be targeted to regions, villages, neighbourhoods, and even families where the prevalence of xerophthalmia or other evidence of deficiency is particularly high Since children living in the same

Table 7   Vitamin A prophylaxis schedule[a]

Individual	Oral dose	Timing
Children 6-11 months old	55 mg retinyl palmitate (100 000 IU)	Once every 4-6 months
Children ≥ 12 months old	110 mg retinyl palmitate (200 000 IU)	Once every 4-6 months
Infants 0-6 months old[b]	13 75 mg retinyl palmitate (25 000 IU)	1-3 times over the first 6 months of life
Women of childbearing age (mass dose)	110 mg retinyl palmitate (200 000 IU)	Within 1 month (or 2 months at most) of giving birth[c]
Pregnant and lactating women (repeated dose)	2 75-5 5 mg retinyl palmitate (5 000-10 000 IU)	Daily

[a] Modified from reference 56
[b] See precautions page 45
[c] See page 45

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neighbourhood as others with active xerophthalmia are at higher risk of disease than those living elsewhere, it may prove more efficient for the village health worker (or field staff of the local dispensary) to treat the entire neighbourhood instead of just the children with clinically apparent disease

A variety of mechanisms are available for identifying active cases of xerophthalmia (and thereby the high-risk communities in which they live) In one innovative approach, schoolchildren are trained to screen their younger siblings for night blindness and report the results to their teachers

Massive vitamin A dosing can be usefully targeted to another "captive" group — babies and their mothers Where births are commonly attended by health personnel (often traditional birth attendants or community health workers), they can be instructed to administer vitamin A (200 000 IU, 110 mg retinyl palmitate) to the mother at any time during the first postpartum month (Table 7) (56)

Because of the potential risk of teratogenicity, a woman of childbearing age should receive a massive dose of vitamin A only when it is reasonably certain she is not pregnant (i e within 1 or at most 2 months of giving birth) or when she herself requires treatment for potentially blinding xerophthalmia (56) It is, however, safe and even advisable for lactating and pregnant women in high-risk communities to receive frequent, low-dose vitamin A supplementation where feasible — for instance, 2 75 mg retinyl palmitate (5 000 IU) daily Tablets, capsules, and syrups containing these dosage levels are widely available

Giving vitamin A directly to an infant ensures increased liver reserves, even if he or she is never breast-fed or breast-feeding is discontinued; giving vitamin A to a breast-feeding mother as well as her infant ensures that these reserves will continue to be augmented during at least the first 6 months of breast-feeding Specially calibrated spoons, droppers, or containers are required for administering the appropriate dosage, which must not exceed 13 8 mg (25 000 IU) for infants under 6 months of age (although preliminary data suggest that a single dose of 50 000 IU at birth may be effective in reducing subsequent mortality) Infants who are not adequately breast-fed may benefit from a dose of 25 000 IU vitamin A, given at 2- to 3-month intervals, for a maximum total of 3 doses, before 6 months of age, when they would receive one standard dose of 100 000 IU for children aged 6–11 months

Recommended doses rarely cause side-effects, and these tend to be transient A very small proportion of the youngest children may develop bulging fontanelle and/or vomiting (57, 58)

Fortification of dietary items

Fortification — the addition of selected nutrients to common dietary constituents — is a long-accepted and successful means of protecting nutritional status in countries with suitable food distribution systems It provides a method of delivering vitamin A to children without having to seek them out individually As fortification provides supplementary vitamin A more frequently and at lower dosage than does periodic mass dosing, it is more likely to result in sustained increases in liver stores It is also an effective means of increasing the vitamin A intake of pregnant and lactating women (and hence of their newborn and breast-fed infants) without the risk of teratogenic effects

In theory, a wide variety of food items can be fortified with vitamin A To be effective, however, the item fortified must be one that is consumed by a significant proportion of the target population and in a quantity that equals or exceeds that consumed in wealthier segments of society Otherwise, it will be difficult to deliver adequate supplementation to those who need it without overdosing those who do not For practical reasons the item must also be processed at a limited number of central sites where the fortification process can be carefully monitored and controlled Thus, the choice of suitable vehicles for fortification is extremely restricted in practice, especially since impoverished rural families, among whom most xerophthalmia cases and other instances of significant vitamin A deficiency arise, generally consume few centrally processed items Carefully conducted dietary studies are required to identify food items that meet these essential criteria

The qualitative dietary component of the clinical prevalence survey (or subsequent intensive investigations in high-risk areas) will have identified which food items, if any, are consumed by a majority of children (or, less ideally, families of children) with significant vitamin A deficiency, and which are therefore capable of reaching the target population Additional dietary studies, on a limited number of children hospitalized with active corneal disease or with other signs of severe deficiency, will ensure that the fortified food reaches those at highest risk The level of fortification required can be calculated from quantitative data

The additive should be inexpensive, stable, and virtually undetectable in the food vehicle selected Significant changes in the cost, colour, texture, odour, or taste of the final product are likely to discourage consumption Innovative work in the pharmaceutical industry has already developed preliminary technology for fortifying milk, tea, sugar, cereal grains, monosodium glutamate (MSG), and a variety of other foods and seasonings, although most of these products are still in the pilot stage (50) A premix, containing high

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concentrations of the nutrient in a form closely resembling the final product, is mixed with the food item itself Careful monitoring and controls are important to guard against under- and overdosage, settling of the premix, loss of potency, and changes in consumption patterns The successful fortification of sugar with vitamin A in Central and South America demonstrates the technical feasibility of this approach and its capacity to improve the overall vitamin A nutriture of the population (59) Similar results have been obtained in pilot trials of vitamin A-fortified MSG (25, 60)

Where possible, the cost of fortification should be passed to the consumer, thereby insulating the programme from the vagaries of subsequent health priorities and claims on the government's health budget Applying the principles of social marketing is an important means of creating a demand for the fortified product and ensuring that any price differential, where a choice between fortified and unfortified products exists, does not act as a disincentive to its use

Evaluation

Vitamin A deficiency prevention programmes are at varying stages of development and implementation, and no method, however successful in one country, is assured of success in another To avoid the needless expenditure on theoretically useful but ineffective prevention programmes, every new programme should undergo evaluation to establish whether or not it is having its desired effect A programme intended to prevent ulceration and keratomalacia (X3A, X3B) should be *shown* to be effective in reducing corneal destruction demonstrating changes in biochemical status or the prevalence of night blindness and Bitot's spot (XN, X1B) in the community is not sufficient If, on the other hand, keratomalacia is not a significant problem and the intervention is intended to improve the general vitamin A status of the population at large, such changes *are* legitimate criteria for evaluation

New intervention programmes should begin as pilot projects in limited, high-risk areas Their effectiveness can be assessed, problems identified, and modifications made before large amounts of time, money, and effort are expended on a potentially useless and inefficient approach

The effectiveness of a programme can best be determined from prevalence data, for which the assessment phase will already have provided a baseline, and from clinical records The latter approach is simpler, but potentially biased, and requires a clinical unit that encounters and accurately recognizes and records large numbers of xerophthalmia cases, measles fatalities, etc While these criteria are rarely fulfilled, simple standardized xerophthalmia-reporting forms can easily be developed for hospitals and clinics that deal with large numbers of cases (see Annex 1) Repeated prevalence surveys

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provide data more representative of the community as a whole, but less detailed information on active corneal disease Wherever possible, both techniques should be employed

Definitive evaluations compare populations covered and not covered by the programme Ideally, one group should be *selected* for participation in the pilot programme and another group should be concurrently *selected* as non-participant controls This system of *concurrent* controls ensures the most accurate comparisons The two groups should be as similar as possible, at least as regards socioeconomic conditions, dietary practices, ecological setting, age, sex, and prevalence of clinical disease (*Note* People who choose not to, or otherwise fail to, participate in health programmes are generally very different, though often in subtle ways, from those who do participate It is inappropriate to compare self-selected participants with self-selected non-participants The only valid comparison is between children (or communities) *assigned* to participate and those *assigned* not to participate) Since most programmes require time to involve additional communities, it is possible to choose randomly which communities are enrolled first and compare the results with those for communities enrolled later

Increasingly, countrywide programmes are launched without preliminary pilot evaluations, and concurrent controls are then unavailable In such cases, comparisons should be made between conditions prevailing before and after the institution of the programme (*historical* controls) Such comparisons are far less conclusive the incidence and prevalence of vitamin A deficiency and xerophthalmia can be influenced by variations in harvests, epidemic diseases (gastroenteritis, measles, etc), and similar factors independently of the intervention programme itself Nevertheless, where this is the only available basis for evaluation, it should be utilized Long-term follow-up will compensate for cyclical variation, and provide a valid basis for evaluation and for determining continued programme effectiveness

Adequate baseline data should be accumulated before the intervention programme is initiated, especially when historical controls are used As a rough guide, the control group should contain 40 cases if there is to be a reasonable chance of demonstrating effectiveness in a programme that reduces the rate of disease by at least 50% In less successful programmes or those with more modest goals, proof of effectiveness requires correspondingly larger numbers of control cases Sufficient numbers of control cases should be chosen to demonstrate effectiveness at the lowest level considered to justify continuing the programme

In addition to absolute levels of effectiveness, evaluation of the efficiency, strengths, and weaknesses of a programme may indicate how it could be improved

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CLINIC-BASED CASE-REPORTING FORM

A simple line listing, as shown here, is sufficiently detailed to monitor the number, types, and origin of xerophthalmia cases presenting at treatment facilities It has been kept short and simple to facilitate its use by busy clinic personnel

Xerophthalmia case-reporting form

Clinical facility ——————————————————————————————

Case number	Date	Patient s name	Village or locality	Age	Sex	XN	Record all abnormalities present					
							X1B		X2		X3	
							OD	OS	OD	OS	OD	OS
1												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												

OD (oculus dexter) = right eye
OS (oculus sinister) = left eye
RE and LE may be substituted where English is commonly used

EXAMINING EYES IN THE FIELD

Examining large numbers of children under field survey conditions can present a particular challenge to the clinician who is more used to hospital or clinical practice The following points should be kept in mind

- The children are likely to be quite frightened and expect "the worst" (a "needle" or vaccination) The ophthalmologist should be reassuring and adopt a non-threatening attitude
- Especially frightened or troublesome children should be examined last Their cries and struggles will only upset the others
- A child is often reassured if held or accompanied by a parent The ophthalmologist should avoid using his or her hands at first (e g by keeping them in pockets or behind the back), and get as good a view as possible before disturbing the child The hands may then be advanced slowly, preferably from behind the child's head If the child begins to squirm, the parent can be instructed to separate the lids gently These procedures are usually effective and preclude the need for a physical struggle
- Above all, the ophthalmologist's primary responsibility is to get an adequate view of the entire globe If the child is resistant to gentler techniques, he or she may be laid on a parent's or assistant's lap, with arms and legs held firmly and head stabilized between the legs of the examiner It is then usually possible to pry the lids apart with the thumb and forefinger of one hand, leaving the other hand free to direct the hand light In the rare instances in which the lids cannot be separated with the fingers, a Desmarres' retractor or bent paperclip may be employed by the ophthalmologist
- The best and least threatening means of illuminating the globe is with natural lighting The examiner should be seated in open shade (beside a building, under a tree, etc) or full outdoor light The child should face the examiner, with his or her back to the light, rather than looking into it After examination of the globe, a hand light may be slowly advanced to the side of the eye to reveal the fine irregularities of corneal and conjunctival xerosis with greater clarity
- The ophthalmologist's hands must be kept clean, and lid retractors must be disinfected (which is easily accomplished by soaking them in alcohol and then rinsing them in sterile water)

The following manuals provide guidance on obtaining and processing specimens, collecting data, and conducting other field tests

1   Wittpenn JR et al *ICEPO training manual assessment of vitamin A status by impression cytology* Baltimore, MD, Dana Center, Johns Hopkins University, 1988

2   Underwood B, Olson J, eds *Brief guide to current methods of assessing vitamin A status* Washington, DC, International Vitamin A Consultative Group, 1993

3   Furr HC et al *Training manual for assessing vitamin A status by use of the modified relative dose response and the relative dose response assays* Washington, DC, United States Agency for International Development, 1992

COLLECTING AND HANDLING BLOOD SAMPLES IN THE FIELD

Microbiological safety

All blood specimens from patients should be regarded as potentially infected with human immunodeficiency virus (HIV), hepatitis B virus, and other blood-borne pathogens They must always be handled carefully to minimize exposure of skin and mucous membranes to patients' blood and other body fluids

Universal precautions include thorough hand-washing and, in particular, washing hands and other skin surfaces *immediately* if they are contaminated with blood or other body fluids In case of accidental skin puncture, the affected part should be washed gently in running tap-water, without scrubbing

Disposable plastic or thin rubber gloves should always be worn when phlebotomy is performed on an agitated or uncooperative patient, when capillary blood is collected, and in all cases if there are cuts, scratches, or other abrasions or skin breaks on a health worker's hand(s) A fresh pair of gloves must be used for each patient

Used lancets (and other sharp items such as needles and glass slides) must be placed in a puncture-resistant container for later disposal by appropriate means, for example incineration

Capillary blood collections

Blood samples should be collected away from the general examining area, so as not to alarm other children The child should be held still by a parent or assistant Blood is taken from the lateral part of the plantar surface of the heel in infants or, in older children, from the distal phalanx of the third or fourth finger or its palmar surface, about 3–5 mm lateral from the nail bed A free flow of blood is essential, and the site from which it is obtained must be warm It may be necessary, for example, to bathe the heel in hot water The central plantar area of the heel and the posterior curvature should not be used because of the risk of damage to the tarsal bones

The chosen site is wiped clean with an alcohol swab and pierced with a sterile lancet A separate lancet is used for each patient The

first few drops of blood are wiped away to eliminate inaccuracies caused by dilution with tissue fluid The blood is allowed to enter the tube by capillary action, leaving at least 15 mm unfilled, in this way a total of 0 3–0 4 ml is collected, which may necessitate filling several tubes, depending on their capacity Each tube may be sealed by heating the dry end rapidly in the flame of a Bunsen burner or, more conveniently, by a plastic seal If these facilities are not available, the dry end may be sealed by heating it in the flame of a candle for 2–3 seconds, then pushing the heated end into the molten wax at the base of the flame

All capillary tubes from a single individual are placed, sealed end down, in a test-tube which is then capped and labelled using indelible ink The test-tube should be placed in a plastic container immersed in a vacuum flask containing ice Samples can be kept dark and cool in this way until the end of the day They are then spun in a centrifuge until the serum is clear, scored, and snapped above the level of the packed cells, tubes containing the remaining serum are then resealed using the same method as before The serum should remain in a cold vacuum flask or refrigerator protected from light, air, and dehydration until it is processed (preferably within 1–2 weeks) Frozen samples can be stored somewhat longer, but should be thawed only once, just before processing Extensively haemolysed samples should be discarded

When retinol determinations are performed locally, occasional split samples should be forwarded to a reference laboratory to ensure the local laboratory's standardization Whenever possible, analysis should be performed by high-performance liquid chromatography

Suggested further reading

Evatt BL et al Fundamental diagnostic hematology anemia, 2nd ed Atlanta, GA, Centers for Disease Control, 1992

Annex 4

XEROPHTHALMIA FIELD SURVEY FORMS

General comments

The field survey forms included in this annex are modifications of those found useful in the Indonesian Nutritional Blindness Prevention Project They are examples of the *types* of information and format that can be employed, but should be modified according to local conditions, interests, and abilities They have been kept simple and include only those factors felt to be most relevant to an understanding of the xerophthalmia problem

Clinical examination form

The clinical examination form is primarily intended for children under the age of 6 years If older individuals are to be examined or other major causes of blindness (e g trachoma, onchocerciasis) exist or are of interest, the form should be modified and expanded A full-scale paediatric or nutritional survey would include many additional measurements

Examination of the eye must be carried out by someone familiar with the clinical manifestations of xerophthalmia, preferably an ophthalmologist The location and size of all corneal abnormalities should be carefully indicated in the circles provided on the form

Simply check off each abnormality present Modern computers can be programmed in various ways to facilitate data entry and check the accuracy with which the form was completed and entered

WHO's Programme for the Prevention of Blindness has developed two forms, which may also be of interest The Eye Examination Record (Version III) is meant for general prevalence surveys on blindness and major causes of visual loss A more detailed examination form, for example the WHO Eye Examination Record for Children with Blindness and Low Vision, may be required for specific surveys on a particular disorder Such forms are available, for example, for onchocerciasis and xerophthalmia [1]

Dietary history form

The form shown in this section is an example of a "qualitative" individual dietary history form A family-based form would be quite

---

[1] Forms may be requested from the Programme for Prevention of Blindness, World Health Organization 1211 Geneva 27 Switzerland

Clinical Examination Form

Date ——————— Enumerator ———————————

Team ——————— Ophthalmologist ——————————

    Sample site ——————————————————

    Head of family Name ———— Family number ———————

    Individual   Name ———— Number ——————————

    *Sex male   female   ————

    *Age date of birth   day   month   year

    **Age in months completed   ————

        Age in years completed (often estimated)   ————

    Examination completed   0 = yes   1 = no   ————

---

* Include only if not already part of a census/socioeconomic form
** Collect only for those 6 years and under

Estimate of potential visual acuity	OD	OS
Clarity of cornea less than 6/60	—	—
Clarity of lens less than 6/60	—	—
Lids		
Entropion	—	—
Trichiasis	—	—
Inflamed	—	—
Conjunctiva	—	—
Injection	—	—
Phlyctenule	—	—
Non-purulent discharge	—	—
Purulent discharge	—	—
Xerosis temporal	—	—
nasal	—	—
other	—	—
"Foam" or "cheese" temporal	—	—
nasal	—	—
other	—	—
Cornea		
Xerosis	—	—
Erosion	—	—
Ulcer	—	—

Indicate location of abnormalities

$\bigodot$ = xerosis

$\bigodot$ = erosion

$\bigodot$ = ulcer

<table>
<tr><td></td><td></td><td>OD</td><td>OS</td></tr>
<tr><td>Keratomalacia</td><td>clear</td><td>—</td><td>—</td></tr>
<tr><td></td><td>opaque</td><td>—</td><td>—</td></tr>
<tr><td></td><td>perforation</td><td>—</td><td>—</td></tr>
</table>

Indicate location of keratomalacia

$\bigodot$ = keratomalacia

$\bigodot$ = keratomalacia
with perforation

<table>
<tr><td></td><td></td><td>OD</td><td>OS</td></tr>
<tr><td>Corneal scar</td><td>macula/nebula</td><td>—</td><td>—</td></tr>
<tr><td></td><td>leukoma</td><td>—</td><td>—</td></tr>
<tr><td></td><td>adherent leukoma</td><td>—</td><td>—</td></tr>
</table>

Indicate location of scar

$\bigotimes$ = macula/nebula

$\bigodot$ = leukoma

$\bigodot$ = adherent leukoma

<table>
<tr><td></td><td></td><td>OD</td><td>OS</td></tr>
<tr><td>Corneal destruction</td><td>descemetocele</td><td>—</td><td>—</td></tr>
<tr><td></td><td>staphyloma</td><td>—</td><td>—</td></tr>
<tr><td></td><td>phthisis bulbi</td><td>—</td><td>—</td></tr>
</table>

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Historical data on corneal scars and destruction

Historian reliable   ——

         possibly reliable   ——

         unreliable or unavailable   ——

Age at which lesion occurred

0 = less than 1 month	5 = 3 years completed
1 = 1–6 months	6 = 4 years completed
2 = 7–12 months	7 = 5–6 years completed
3 = 1 year completed	8 = over 6 years completed
4 = 2 years completed	9 = unknown

                                                 OD   OS

Other events 4 weeks or less before lesion
occurred

	OD	OS
Eye trauma	—	—
Measles	—	—
Purulent infection	—	—
Marked diarrhoea	—	—
Marked malnutrition	—	—
Marked cough	—	—

Medicine was applied to the eye before corneal lesion appeared

0 = no   1 = yes   —   —

Diagnosis based on clinical examination and history

1 = trauma
2 = measles
3 = purulent eye infection
4 = congenital
5 = keratomalacia
6 = other
7 = uncertain   —   —

Additional data

Classification
    1 = random subsample
    2 = abnormal
    3 = age/sex/local matched control   ——

Height (to nearest 0 5 cm)   ——

Weight (to nearest 0 1 kg)   ——

Blood obtained   0 = yes   1 = no   ——

Serum vitamin A level   ——

similar the investigator should enquire about foods prepared for the family (as opposed to merely those consumed by the child) and omit the questions about breast-feeding A wide range of alternatives could be used, depending on the purpose for which the dietary information is being collected This simple form identifies differences in food patterns between children with and without xerophthalmia, and potentially fortifiable dietary items A subsequent, detailed survey of a smaller sample of children and their families would concentrate on issues relevant to the specific foods and patterns of consumption discovered to be of interest

Major categories of food, but only a few specific items, are indicated The final choice of food items to be listed depends on local circumstances For example, wheat is a potentially important vehicle for vitamin A fortification in Indonesia none is grown locally and all imported wheat is processed in a very few factories An extensive list of wheat-based foodstuffs would therefore be included in an Indonesian study This would not be appropriate, however, where wheat is widely grown and processed at innumerable village mills

A quantitative (24-hour recall) dietary history follows the same format as the qualitative forms, but concerns the total amount of each food item consumed by the child during the past 24 hours (coded in appropriately graduated amounts), rather than the frequency

As in the case of the clinical examination form, a full-scale nutritional survey would require more detailed information covering a more extensive list of items A more detailed vitamin A dietary survey methodology has been developed and applied in a number of countries, as a means not only of collecting appropriate data, but also of educating those involved with the programme about locally appropriate dietary sources of vitamin A

Qualitative Dietary History Form

Sample site ————————————————————————

Head of family Name —————— Family number ——————————

Individual Name ————— Number ————————————

Classification abnormal ———
             control ———
             random subsample ———

Items consumed by the child during the past two months

Left-hand column Frequency with which items were consumed
1 = several times a day, nearly every day
2 = once a day, nearly every day
3 = less than every day, but at least once a week
4 = less than once a week, but at least once a month
5 = less than once a month
0 = never

Right-hand column Source of items consumed
1 = harvested by the family
2 = bought
3 = harvested and bought
0 = inapplicable (item not consumed)

Staples	*Frequency*	*Source*
Rice	—	—
Cassava etc	—	—
Sources of retinol	—	—
Liver	—	—
Meat	—	—
Eggs	—	—
Fish	—	—
Fish liver oil etc	—	—
Sources of β-carotenes		
Amaranth	—	—
Cassava leaves	—	—
Drumstick leaves	—	—
Mango	—	—
Papaya etc	—	—
Potentially fortifiable items		
Salt	—	—
Refined sugar	—	—
Monosodium glutamate	—	—
Cooking oils	—	—
Soy sauce	—	—
Powdered milk etc	—	—

If not consumed, reasons why
1 = unavailable
2 = too expensive
3 = child doesn't like it
4 = child too young
5 = bad for the child
6 = other

Sources of retinol ————
If considered "bad for the child", reason why

_____

If "other", explanation

_____

Sources of β-carotene
If considered "bad for the child", reason why

_____

If "other", explanation

_____

Frequency breast-fed per day

1 = once	4 = 4 times
2 = twice	5 = 5 or more times
3 = 3 times	0 = never or no longer breast-fed

Age of child when breast-feeding ceased

0 = never breast-fed
1 = less than 1 month   5 = 1–2 years
2 = 1–3 months   6 = more than 2 years
3 = 3–6 months   9 = not applicable (still breast-fed)
4 = 6–12 months

Suggested further reading

Underwood BA et al *Guidelines for the development of a simplified dietary assessment to identify groups at risk for inadequate intake of vitamin A* Washington, DC, IVACG, The Nutrition Foundation, 1989

ADDITIONAL READING

The publications listed in this section provide further insight into the general problem of xerophthalmia and related conditions and cover in greater detail certain aspects that are only touched on in this manual

Comprehensive coverage of vitamin A deficiency and xerophthalmia, plus extensive bibliographies

Sommer A *Nutritional blindness xerophthalmia and keratomalacia* New York, Oxford University Press, 1982

Sommer A, West KP Jr *Vitamin A deficiency health, survival and vision* New York, Oxford University Press (in press)

McLaren DS *Nutritional ophthalmology*, 2nd ed London, Academic Press, 1980

Control of vitamin A deficiency and xerophthalmia Report of a Joint WHO/USAID/Helen Keller International/IVACG Meeting Geneva, World Health Organization, 1982 (WHO Technical Report Series, No 672)

Vitamin A deficiency and xerophthalmia Report of a Joint WHO/USAID Meeting Geneva, World Health Organization, 1976 (WHO Technical Report Series, No 590)

Recommendations on intervention

Bellagio Brief vitamin A deficiency and childhood mortality New York, Helen Keller International, 1992

Ending hidden hunger Proceedings of a policy conference on micronutrient malnutrition, Montreal, October 1991 Atlanta, GA, Task Force for Child Survival and Development, 1991

Beaton GH et al *Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries* New York, United Nations Administrative Committee on Coordination/Subcommittee on Nutrition, 1993 (ACC/SCN State-of-the-art Series, Nutrition Policy Discussion Paper No 13)

Vitamin A supplements a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia Geneva, World Health Organization, 1988

Eastman SJ Vitamin A deficiency and xerophthalmia recent findings and some programme implications In Mandl P-E, ed *Assignment children* New York, UNICEF, 1987

West KP Jr, Sommer A *Delivery of oral doses of vitamin A to prevent vitamin A deficiency and nutritional blindness a state-of-the-art review* New York, United Nations Administrative Committee on Coordination/Subcommittee on Nutrition, 1987 (ACC/SCN State-of-the-art Series, Nutrition Policy Discussion Paper No 2)

Infections and vitamin A

Scrimshaw NS, Taylor CE, Gordon JE *Interactions of nutrition and infection* Geneva, World Health Organization, 1968 (WHO Monograph Series, No 57)

Tomkins A, Watson F *Malnutrition and infection a review* London, London School of Hygiene and Tropical Medicine, 1989 (ACC/SCN State-of-the-art Series, Nutrition Policy Discussion Paper No 5)

Assessment, intervention programmes, and evaluation

A series of International Vitamin A Consultative Group (IVACG) publications covering many practical aspects of vitamin A deficiency and its control are available from the IVACG Secretariat They include the following

Guidelines for the eradication of vitamin A deficiency and xerophthalmia A report of the International Vitamin A Consultative Group Washington, DC, IVACG, The Nutrition Foundation, 1977

Bauerfeind JC *The safe use of vitamin A A report of the International Vitamin A Consultative Group* Washington, DC, IVACG, The Nutrition Foundation, 1980

Arroyave G et al *Biochemical methodology for the assessment of vitamin A status* Washington, DC, IVACG, The Nutrition Foundation, 1982

Underwood B *The safe use of vitamin A by women during the reproductive years* Washington, DC, IVACG, The Nutrition Foundation, 1986

Guidelines for the use of vitamin A in emergency and relief operations Washington, DC, IVACG, The Nutrition Foundation, 1988

Methodologies for monitoring and evaluating vitamin A deficiency and intervention programmes Washington, DC, IVACG, The Nutrition Foundation, 1989

Underwood BA et al *Guidelines for the development of a simplified dietary assessment to identify groups at risk for inadequate intake of vitamin A* Washington, DC, IVACG, The Nutrition Foundation, 1989

Nutrition communications in vitamin A programs a resource book Washington, DC, IVACG, The Nutrition Foundation, 1992

Underwood B, Olson J, eds *A brief guide to current methods for assessing vitamin A status* Washington, DC, IVACG, The Nutrition Foundation, 1993

Nutritional requirements, surveys, food fortification

Jelliffe D *The assessment of the nutritional status of the community (with special reference to field surveys in the developing regions of the world)* Geneva, World Health Organization, 1966 (WHO Monograph Series, No 53)

Requirements of vitamin A, iron, folate, and vitamin B12 A report of a Joint FAO/WHO Expert Consultation Rome, Food and Agriculture Organization of the United Nations, 1988

Passmore R, Nicol BM, Narayana Rao M *Handbook on human nutritional requirements* Geneva, World Health Organization, 1974 (WHO Monograph Series, No 61)

Bauernfeind JC, Cort WM Nutrification of foods with added vitamin A *CRC critical reviews in food*, 1974, **4** 337–375

Hetzel BS *The story of iodine deficiency an international challenge in nutrition* Oxford, Oxford University Press, 1989

Gibson RS *Principles of nutritional assessment* New York, Oxford University Press, 1990

Related fields of blindness prevention

Methods of assessment of avoidable blindness Geneva, World Health Organization, 1980 (WHO Offset Publication, No 54)

Strategies for the prevention of blindness in national programmes a primary health care approach Geneva, World Health Organization, 1984

Guidelines for programmes for the prevention of blindness Geneva, World Health Organization, 1979

WHO Expert Committee on Onchocerciasis Third Report Geneva, World Health Organization, 1987 (WHO Technical Report Series, No 752)

Onchocerciasis control Report of a WHO Expert Committee
Geneva, World Health Organization (WHO Technical Report
Series) (*in press*)

Sommer A *Epidemiology and statistics for the ophthalmologist* New
York, Oxford University Press, 1980

Prevention of childhood blindness Geneva, World Health
Organization, 1992

Selected WHO publications of related Interest

	Price (Sw. fr.)*
Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia. 1988 (24 pages)	8.–
Prevention of childhood blindness. 1992 (58 pages)	15.–
Methods of assessment of avoidable blindness. WHO Offset Publication, No. 54, 1980 (42 pages)	4.–
Strategies for the prevention of blindness in national programmes. A primary health care approach. 1984 (88 pages)	11.–
Infant feeding: the physiological basis. *Bulletin of the World Health Organization*, Suppl. to Vol. 67. 1989 (130 pages)	25.–
A guide to nutritional assessment. Beghin I, Cap M, Dujardin B. 1988 (80 pages)	14.–
Diet, nutrition, and the prevention of chronic diseases. Report of a WHO Study Group. WHO Technical Report Series, No. 797, 1990 (203 pages)	26.–
The quantity and quality of breast milk. Report on the WHO collaborative study on breast-feeding. 1985 (148 pages)	17.–
The growth chart. A tool for use in infant and child health care. 1986 (33 pages)	12.–
The management and prevention of diarrhoea: practical guidelines. 3rd ed. 1993 (v + 50 pages)	12.–

Further information on these and other WHO publications can be obtained from Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland.

* Prices in developing countries are 70% of those shown here.

Ocular manifestations of vitamin A deficiency, particularly night blindness, have been recognized since antiquity. Animal research and clinical observations early in the twentieth century indicated that vitamin A was important for numerous bodily functions: animals and humans deficient in vitamin A grew poorly, suffered more persistent or severe infections, and subsequently developed characteristic ocular problems termed "xerophthalmia" or "dry eye". By the early 1940s these readily apparent eye signs had been eliminated from wealthier countries through dietary interventions. In developing countries today, however, at least 5–10 million children develop xerophthalmia every year, of whom between a quarter and a half a million go blind.

Recent data indicate that mortality rates are also increased among children with even mild vitamin A deficiency and that, in many areas, enhanced vitamin A intake can reduce the risk of mortality from childhood infections by up to 54%. It is estimated that the deaths of at least one million children would be prevented each year if vitamin A status were improved.

The first edition of this manual was published in 1978 to meet the need for a practical guide for use by clinicians, nurses, and public health officials concerned with preventing xerophthalmia. The second edition, which appeared in 1982, reflected advances in understanding of the overall problem. Since then, the extension and further refinement of knowledge about the importance of vitamin A in the broader realm of child health and survival have made it necessary to revise and expand the manual. This greater understanding, combined with growing commitment by governments, enhances the feasibility of achieving the declared goal of eliminating vitamin A deficiency as a significant public health problem by the start of the next millennium.