Delivery of oral doses of vitamin A deficiency and nutritional blindness: A state–of–the–art review – Nutrition policy discussion paper No. 2

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Delivery of oral doses of vitamin A deficiency and nutritional blindness: A state–of–the–art review – Nutrition policy discussion paper No. 2

by

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and an introduction by J. B. Mason with S. J. Eastman and M. Lotfi

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ADMINISTRATIVE COMMITTEE ON COORDINATION – SUBCOMMITTEE ON NUTRITION

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UNITED NATIONS – ADMINISTRATIVE COMMITTEE ON COORDINATION – SUBCOMMITTEE ON NUTRITION (ACC/SCN)

The ACC/SCN is the focal point for harmonizing the policies and activities in nutrition of the United Nations system. The Administrative Committee on Coordination (ACC), which is comprised of the heads of the UN Agencies, recommended the establishment of the Sub–Committee on Nutrition in 1977, following the World Food Conference (with particular reference to Resolution V on food and nutrition). This was approved by the Economic and Social Council of the UN (ECOSOC). The role of the SCN is to serve as a coordinating mechanism, for exchange of information and technical guidance, and to act dynamically to help the UN respond to nutritional problems.

The UN members of the SCN are FAO, IAEA, IFAD, ILO, UN, UNDP, UNEP, UNESCO, UNFPA, UNHCR, UNICEF, UNRISD, UNU, WFC, WFP, WHO and the World Bank. From the outset, representatives of bilateral donor agencies have participated actively in SCN activities. The SCN is assisted by the Advisory Group on Nutrition (AGN), with six to eight experienced individuals drawn from relevant disciplines and with wide geographical representation. The Secretariat is hosted by WHO in Geneva.

The SCN undertakes a range of activities to meet its mandate. Annual meetings have representation from the concerned UN agencies, from 10 to 20 donor agencies, the AGN, as well as invitees on specific topics; these meetings begin with symposia on subjects of current importance for policy. The SCN brings certain such matters to the attention of the ACC. The SCN sponsors working groups on inter–sectoral and sector–specific topics.

The SCN compiles and disseminates information on nutrition, reflecting the shared views of the agencies concerned. Regular reports on the world nutrition situation are issued, and flows of external resources to address nutrition problems are assessed. State–of–the–Art papers are produced to summarize current knowledge on selected topics. SCN News is normally published twice per year. As decided by the Sub–Committee, initiatives are taken to promote coordinated activities – inter–agency programmes, meetings, publications – aimed at reducing malnutrition, primarily in developing countries.

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3. This document is based on a monograph entitled *Periodic, Large Oral Doses of Vitamin A for the Prevention of Vitamin A Deficiency and Xerophthalmia: A Summary of Experiences,* International Vitamin A Consultative Group (IVACG), The Nutrition Foundation, 888 Seventeenth Street, NW, Washington DC 20006, May 1984.

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FOREWORD

The ACC/SCN State–of–the–Art Series aims to provide authoritative information to help policy–making and implementation of programmes to improve nutrition in the world. This document concerns prevention of vitamin A deficiency, which is the objective of a Ten–Year UN Programme, launched in 1985. It is a coordinated effort between UN and national governments, currently with components from FAO, UNICEF and WHO. This paper contains very useful information for governmental and non–governmental organizations cooperating in the solution of this widespread problem.

The paper by Drs. West and Sommer concerns immediate alleviation and prevention of vitamin A deficiency by distribution of large doses. This intervention provides the first step in eliminating vitamin A deficiency – a major cause of blindness and ill–health. Fortification of a dietary vehicle with vitamin A, and increasing the consumption of vitamin A and carotene–rich foods, the other major interventions, are introduced in the discussion. The information in this document should facilitate the decisions for undertaking preventive measures, and provide guidance on design and implementation of programmes.

Papers in the State–of–the–Art Series centre around a contribution from acknowledged experts in the field, with discussion to round out the subject. An introduction provides the context and highlights the bases for policy formulation and programme implementation.

Concerted action by international and national agencies is needed. The role of the SCN and its structure – member UN and Bilateral Agencies, Advisory Group on Nutrition, and the Secretariat – is to facilitate these coordinated efforts. We hope that this publication will be useful for an effective attack on vitamin A deficiency, saving sight and lives.

A Horwitz
Chairman ACC/SCN

INTRODUCTION AND POLICY IMPLICATIONS

John B. Mason
with Susan J. Eastman and Mahshid Lotfi

John Mason is Secretary, ACC/SCN. Susan Eastman and Mahshid Lotfi were consultants to the ACC/SCN.

Deficiency of vitamin A has long been identified as a serious and preventible nutritional disease. A survey first published in 1964 (Oomen et al, 1964) formed the basis for WHO's (1976) estimates of an incidence of some several hundred thousand children going blind each year due to the deficiency. More recently, awareness has broadened of the extent of the population affected by the deficiency, and of the seriousness of the effects.

The populous countries of Southern and South–East Asia still account for the most cases of vitamin A deficiency, but attention is also focusing on the many countries in Africa, the Near East, and the Americas where vitamin A deficiency is a serious public health problem. This increased awareness stems from better availability of epidemiological information from many researchers and institutions, disseminated by WHO (1976), through the efforts of the International Vitamin A Consultative Group (IVACG, 1981), and many others. Now at least 34 countries are known to have serious vitamin A deficiency problems (WHO, 1985a; ACC/SCN, 1985).

Preventing blindness has been regarded as the major reason for controlling vitamin A deficiency. As IVACG (1981, p.7) put it: “Blindness is one of the most serious disabilities from which an individual can suffer and constitutes a great social and economic burden for the community. This is especially the case in xerophthalmia in which blindness almost always occurs in early childhood with resultant life–long handicaps for those who survive.”

Basic research has now demonstrated far–reaching biological effects of the deficiency, predisposing to a range of disabilities, including effects on the intestine, respiratory tract, immune system, as well as involvement of the eyes. These mechanisms cause vitamin A deficiency, probably even in mild form, to increase the susceptibility to infection and exacerbate the effects of many diseases. For example, the severity

of measles and eye damage from the disease – which is particularly serious in poor countries especially in Africa – may be worsened because of vitamin A deficiency (Oomen, 1971; Franken, 1974). The association of vitamin A deficiency with increased morbidity is well–established, and the mechanism is becoming better understood.

Damage to the eyes is the most obvious and dramatic result of vitamin A deficiency, but these signs may in fact be only the later and more readily observable effects. First, studies many years ago in man demonstrated histopathological changes, similar in nature to those observed in the eye, in epithelial tissues of the respiratory, urinary and gastrointestinal tracts (data from 1925–1938, quoted from Sommer et al, 1984); this has been widely confirmed in animal studies. Thus we would expect that internal damage, especially to the growing child, may be proceeding insidiously with inadequate vitamin A intake, before any eye signs become apparent. This is in line with clinical descriptions of vitamin A deficiency including growth retardation, defective bone formation, and other developmental abnormalities (McLaren, 1966). Xerophthalmia seems to be related to growth both in animals and in man; for example, protein supplementation of malnourished subjects with low vitamin A reserves has precipitated many cases of xerophthalmia in the past (IVACG, 1981 p.9). Second, immune function is impaired in vitamin A deficiency, and is enhanced with repletion (McLaren, 1978; Lotan, 1985); this mechanism helps explain observations of increased morbidity with mild deficiency (Sommer et al, 1984) which in turn may account for the increased mortality specifically associated with the deficiency (Sommer et al, 1986 – see below). Finally, a range of other extra–ocular effects are suspected in man, based mainly on animal results (Reddy, 1985). Of particular interest is the finding that vitamin A deficiency may cause anaemia in man, reversible by iron only when vitamin A is administered (Hodges et al, 1978; Reddy, 1985 and others).

This picture corresponds to a syndrome of vitamin A deficiency, including but wider than the eye damage on which attention has hitherto been largely concentrated. Indeed, McLaren (1966, p.441) proposed that the term 'xerophthalmia', although implying only eye involvement, should be used to describe the entire syndrome. Terminology is not the key issue, except insofar as it promotes understanding. At this point we should recognize that vitamin A deficiency may be as far–reaching in its pathological effects on the individual as protein–energy malnutrition; and that prevention of the deficiency syndrome, even in its mild form, may have very important effects on child health, development and survival.

Children going blind from severe vitamin A deficiency are seriously sick and many die in the subsequent weeks. An association of severe deficiency with infant and child mortality had been established for some time (WHO, 1976, p.9; IVACG, 1981, p.8), when the deficiency was seen as at least a contributory cause of death. Of more extensive potential consequence, the possibility that mild or moderate stages of deficiency increased mortality risk was suggested from a number of studies, notably in Indonesia (Sommer et al, 1983). This was attributed to the findings that the risk of respiratory disease and diarrhoea were associated with vitamin A status, more closely here than with general nutritional status (Sommer et al, 1984). An intervention study of the effectiveness of vitamin A capsule distribution in preventing eye damage, also in Indonesia, gave crucial evidence of a direct effect of vitamin A in reducing mortality (Sommer et al, 1986). How far this may be mediated through preventing mild as well as severe deficiency awaits further study. But the demonstrated direct effect of vitamin A in reducing mortality gives added urgency to programmes for preventing vitamin A deficiency.

The Advisory Group on Nutrition of the ACC/SCN was asked to review the evidence (from the work of Sommer et al, 1986, in Indonesia) for a direct effect of vitamin A deficiency on mortality, and concluded as follows (ACC/SCN, 1986a):

> (i) The approximately 30% difference in mortality in preschool children (one through five years of age) between treated and control villages was likely to be attributable to the vitamin A supplementation.
>
> (ii) There is justification to expect that effects of this magnitude would be seen in other settings with similar conditions including at least similar severity of vitamin A deficiency with associated xerophthalmia, similar high prevalences of childhood morbidity and mortality and similar effectiveness of the xerophthalmia control programme.
>
> (iii) It is appropriate to advise countries mounting high dose vitamin A programmes for the control of xerophthalmia that reduction of childhood mortality is a reasonable expectation and is further justification for such programmes.

Extent of the Problem

The rate of appearance (incidence) of new cases of severe vitamin A deficiency, measured as active corneal lesions (of which about 25% result in partial or total blindness) was estimated in Indonesia at around 2.7 cases per 1000 preschool children per year (Sommer, 1982). This led to an estimate of up to 500,000 new cases of active corneal lesions per year for Asia (WHO, 1985a). Applying this rate to all countries with known vitamin A deficiency gives worldwide estimates of some 700,000 new cases per year, among preschool children.

What happens to these children? It is estimated that some 60% die, and of the survivors 25% remain totally blind, and 50–60% partially blind (IVACG 1981, p.8). This amounts to some 250,000 children going blind or partially blind each year. The resulting prevalence of cases of blindness is hard to estimate, for lack of data and because of the high mortality associated with the deficiency. However, an estimate from available surveys (quoted in WHO, 1985a) of 0.2–0.4% prevalence of eye damage caused by vitamin A deficiency among pre–school children in affected countries is consistent with the incidence rate of 2.7 per 1000 per year. This would give nearly 3 million children blind from this cause, over a million of whom are in India. Vitamin A deficiency is the largest single cause of the total of 40 million people estimated worldwide to be blind (Kupfer, 1987).

Similar calculations (from basic data from the same sources) give an incidence estimate of 6–7 million new cases per year of children with mild deficiency, and some 20 to 40 million suffering from at least mild deficiency at any one time, of which nearly half are in India. This assumes around a 15% prevalence of mild/moderate deficiency, as indicated from surveys quoted by WHO (1985a) from India, Sudan and Yemen Arab Republic.

Estimates of numbers affected such as these give an idea of the extent of the problem to be prevented; but actual prevention requires reaching a much larger population. This is because, first, many more people are at risk of the deficiency than actually show signs of it, and second, because preventive measures cannot be precisely targeted only to those who would otherwise develop the disease. We need to consider the size and distribution of the population at risk, and different methods of prevention, to assess the magnitude of the task of tackling vitamin A deficiency.

A country–by–country survey conducted by WHO (1985a) was used as the basis for the ACC/SCN's formulation of a 10–year prevention plan (ACC/SCN, 1985). The geographic distribution of countries where xerophthalmia is a significant public health problem, and where sporadic cases occur, is shown in Figure 1 (DeMaeyer, 1986a).

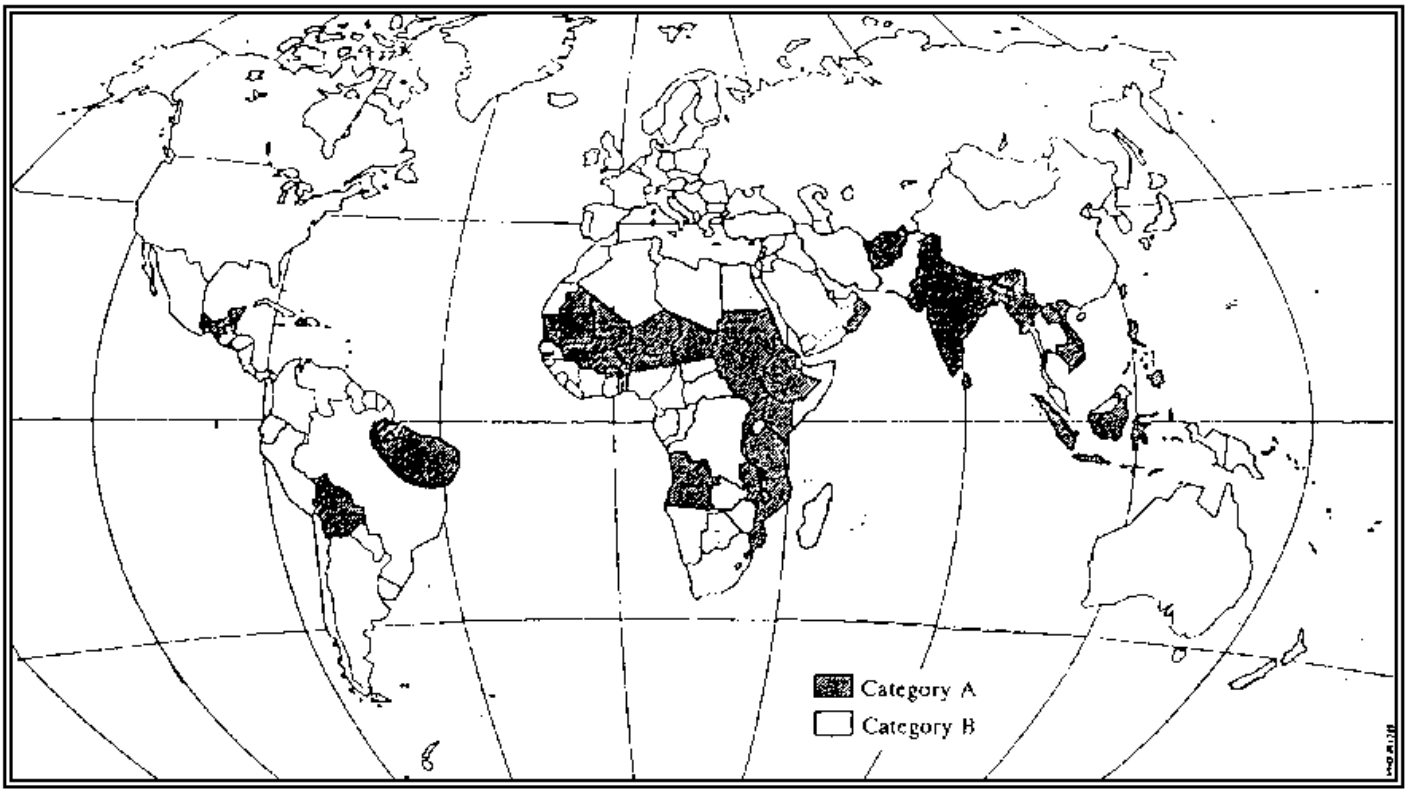

Figure 1 – THE GEOGRAPHICAL DISTRIBUTION OF XEROPHTHALMIA IN 1986

A: Xerophthalmia a significant public health problem
B: Sporadic cases of xerophthalmia do occur

Four categories of countries were defined by WHO:

A: those where assessment has been made, with national prevention and control programmes (8 countries);

B: those where assessment has been made, or partially made, but prevention and control programme is not yet under way (13 countries);

C: those where assessment has not been made, but with high probability of problem based on indirect evidence (13 countries);

D: those where vitamin A deficiency does not appear to be a significant public health problem, but where the prevalence picture should be closely monitored (23 countries).

In 1984, 34 countries were in categories A, B, and C, of which eight had national prevention and control programmes underway (category A). Of these 34 countries, 23 have received international assistance, particularly from UNICEF and USAID (21 UNICEF, 6 USAID in 1985–6: calculated from Eastman, 1986; UNICEF, 1987; USAID, 1987).

The distribution by region of child populations in countries having vitamin A deficiency is shown in Table 1. Only those countries with established national programmes have substantial coverage of their child populations – notably Bangladesh, Haiti, India and Indonesia. For the others, coverage of the total child population is generally around 10% or less (calculated from data on capsule distribution). This demonstrates the need for greatly increased coverage, as well as where feasible more targeting: methods are introduced below and discussed in detail in this paper by Vest & Sommer. The range of need can be estimated from these figures. The total child population in the 34 countries is about 280 million – in a sense many or most of these are at risk. With a prevalence of 15% for at least mild deficiency, some 40 million are already affected. Fortunately, the most populous countries (Bangladesh, India and Indonesia) have control programmes already established, so that the immediate needs are substantially lower: excluding these three countries, the child populations in the other 31 countries amount to about 150 million, and those affected to about 22 million. Thus, to give an idea of magnitude, some 20 million children need help if the programme were perfectly targeted, or perhaps up to 100 million with less targeted delivery.

These calculations are based on preschool children, because prevalences are better known for this, the most vulnerable group; but school–age children and adults, especially pregnant and nursing mothers, are also in need. Prevention programmes must reach these people also.

In practical terms, effective prevention depends on establishing national programmes, with resources – depending on the approach chosen – for service delivery and supplies of vitamin A doses; for fortification; and/or for dietary modification. Although efforts are increasing, as of 1987 most of the 34 countries known to be affected do not yet have such programmes – a list is given in a footnote to Table 1 – and in the majority of these the coverage of preventive programmes is still very low.

TABLE 1

ESTIMATED CAPSULE DISTRIBUTION AND PROGRAMME COVERAGE OF CHILDREN IN COUNTRIES WITH VITAMIN A DEFICIENCY (1984/85)

Region (WHO)	Number of Countries with deficiency (WHO categories)[1]	Total 1–4 yr Child population in these countries (millions)	Child Pop. covered by UNICEF + AID programmes[2] %	Number of Mild/Moderate Vitamin A Deficient Children[5] (millions)
Africa	16	53	8%	7.9
Americas	5	38	2%	5.6

S.E. Asia (excl. India)	5	51	65%[3]	7.7
India	1	111	27%[4]	16.7
E. Mediterranean	3	7	21%	1.0
Western Pacific	4	20	3%	3.0
	34	280	–	41.9

[1] Countries by WHO category:

A – El Salvador, Haiti; Bangladesh, India, Indonesia, Nepal, Sri Lanka; Philippines.

B – Benin, Burkina Faso, Ethiopia, Malawi, Mali, Mauritania, Tanzania, Zambia; Brazil (north–east) Mexico; Oman, Sudan; Viet Nam.

C – Angola, Chad (north), Ghana (north), Kenya, Mozambique, Niger, Nigeria (north), Uganda; Bolivia; Burma; Afghanistan; Dem. Kampuchea, Lao People's Dem. Republic.

[2] Calculated from capsule distribution data (1985) from Eastman (1986, Attachment 3) assuming two capsules per child per year; and from data in USAID (1987).

[3] Note that coverage in Burma, Nepal and Sri Lanka were approximately 5 to 25%.

[4] In India, 60 million vitamin A capsules produced domestically were distributed in 1985 (Eastman, 1986, Table 17).

[5] Estimated as 15% prevalence (see text).

Possible Solutions

Vitamin A deficiency is caused by inadequate dietary intake of the vitamin itself (pre–formed retinol from animal products) or its precursors (carotenes, from plant sources), often aggravated by low absorption from the intestine. The solution is therefore to increase the dietary intake, and sometimes the absorption. Unlike most other micronutrients, reserves of vitamin A are stored in the body, and thus periodic high intakes can give adequate nutrition.

Three approaches are feasible, and have been widely put forward (e.g, WHO, 1982, 1985b, 1986; IVACG, 1984; DeMaeyer, 1986b; FAO, 1985, 1986; ACC/SCN, 1985). These correspond to short–, medium– and long–term interventions, and form the basis of the inter–agency plan endorsed by the UN (ACC/SCN, 1985, pp. 18–19).

(a) The distribution of single large oral doses of vitamin A (as capsules or oil solution) approximately every six months to vulnerable groups, usually through the health system: this is the main topic of this State–of–the–Art review.

(b) The fortification with vitamin A of a widely distributed food commodity: this is familiar in developed countries (e.g. margarine), and has been attempted at national scale, using sugar, in a few developing countries.

(c) Increasing the intake of vitamin A from the normal diet: this is clearly the long–term solution, and is the reason vitamin A deficiency has disappeared from many countries.

These interventions, particularly the first two, have been developed systematically. In principle, after identifying causes and testing remedies in the laboratory or hospital, the next step involves field trials to assess the efficacy of an intervention under controlled conditions (e.g. Solon et al, 1979). When this is established, large–scale intervention programmes can be initiated, monitored and evaluated. This process

and the results for distribution of large oral doses of vitamin A is described in detail in this paper by West and Sommer. It is clearly established that such programmes are efficacious and effective, and indeed the cost–effectiveness has been assessed.

Fortification has been studied as a preventive measure, at field trial level and as national programmes, and shown to be effective in Costa Rica and Guatemala (Arroyave et al, 1979): Dr. Arroyave, in his discussion paper included here, gives some details. However, the sad fact is that the national fortification programmes in Central America have been discontinued for economic and political reasons, and other programmes have yet to progress from their successful field trial stages to national programmes. So, at the present time, there is inadequate support to establish and sustain national fortification programmes anywhere in the developing world, although a number of countries in Asia are moving in this direction.

In the long–term, increasing the regular dietary intake of vitamin A is clearly the best approach to preventing the deficiency – referred to as dietary modification (FAO, 1985). Increased intake usually occurs with economic development, vitamin A availability being closely associated with, for example, GNP (DeMaeyer, 1986a). Data from FAO Food Balance Sheets (1975–77) give an estimated average availability of vitamin A (from both retinol and carotenes) in 1975 of less than 600 mcg/caput/day (range 100 – 1700 mcg/caput/day) for many of the most seriously affected developing countries, compared with an average requirement of 250 – 575 mcg/day for children between one and twelve years of age, and 750 mcg/day for adolescents and adults. Information on trends in vitamin A supply is available for a few countries, indicating no general improvement (ACC/SCN, 1987). It seems clear that it will be many years before the deficit in vitamin A intake, particularly among the poorest population groups is made up in the absence of intervention. But several interventions are possible in principle to increase the regular intake of vitamin A from the diet itself, without waiting for economic development to solve the problem. Some examples of these are discussed by Dr. Devadas in her commentary on this paper. Options for intervention include: nutrition education; improving home production and consumption through gardens; and marketing of certain vitamin A rich commodities. These have been tested with some success in pilot programmes, but few if any are yet clearly established as effective on a large scale.

Nutrition education in this context aims to increase the intake of dark green leafy vegetables and other carotene and vitamin A rich foods. Where necessary, increasing fat consumption may also be promoted. Devadas describes in her commentary one study where dietary practices were modified, and signs of vitamin A deficiency reduced. In general, nutrition education has a mixed record (see Hornik, 1985), but, for example, the recently successful social marketing approach in Indonesia apparently improved vitamin A status among other benefits. Messages aimed at increasing vitamin A intake should be part of nutrition education programmes, even if such programmes may usually have broader objectives.

Promotion of local production of carotene–rich foods for home consumption, by home and school gardens, has obvious potential for preventing vitamin A deficiency. Households with even small gardens in Bangladesh, for example, had less vitamin A deficiency than those with no gardens (Cohen et al, 1985). The Asian Vegetable Research and Development Centre (AVRDC), supported by USAID, has long experience in this. Again, the position seems to be that small–scale trials are efficacious, but expansion for wide impact is yet to come.

Certain carotene–rich commodities, of which red palm oil is an important example, are culturally well–accepted in the diet, indeed potentially in high demand in certain countries where vitamin A deficiency occurs. The prospect of preventing vitamin A deficiency by more effective marketing of red palm oil has been put forward in Tanzania, for instance (Kavishe, 1985). In such cases, the economic and social constraints to wider consumption must first be understood. Here interventions on supply, pricing and market distribution could bring long–term improvement in vitamin A status.

Choice of Interventions

The decision on the part of agencies and governments to commit resources to controlling vitamin A deficiency depends on an appreciation of the priority of the problem – severity, extent, trends, and consequences; and knowledge of possible solutions – in terms of feasibility, costs (financial, organizational), effectiveness, sustainability, benefits, and the like. Present knowledge relating to the priority for controlling vitamin A deficiency was introduced above, and the West and Sommer paper gives many more details. Possible solutions are widely agreed as mass distribution, fortification, and/or dietary modifications. West and Sommer focus on mass distribution below. What guidance is available on the choice of control method, and specifically where does mass distribution fit?

Recommendations from international bodies, and decisions taken by governments and agencies, are consistent in the view that a combination of interventions is usually appropriate. Mass distribution is considered an essential first component of a control programme, certainly where severe deficiency exists, because of the immediate risks to sight, health and life and the possible rapid effectiveness of the distribution programme, moreover at moderate initial cost. The case for fortification, made by Dr. Arroyave in his commentary, requires initial research on suitable methods, and although widely applicable, it may not invariably reach those most at risk. Nonetheless, fortification programmes once established hold promise of sustained control over periods of years. Both mass distribution and fortification need to be underpinned by the increasing dietary intake of vitamin A, as discussed above; but this approach will take the longest time to establish. Thus in most cases, the first intervention to be established should be distribution of oral doses of vitamin A as capsules or oil solution.

A decision to tackle vitamin A deficiency will thus usually need to consider the details of mass distribution methods laid out in this paper. In principle there are three major systems for vitamin A capsule delivery, defined by West and Sommer (Section 3) as: medical, targeted and universal. “Medical” delivery means treating with vitamin A children with xerophthalmia or those at risk because of sickness; “targeted” delivery refers to a periodic preventive dosing directed to designated groups, generally within the health outreach programme; and “universal” delivery refers to a wider distribution aiming to cover all children (and other select groups) on a regular basis. These systems overlap. Vest and Sommer compare combined medical and targeted approaches with universal delivery. To maximize the impact of the vitamin A dose delivery, they also note the possibility of selecting target groups based on age (in Indonesia, 89% of corneal disease were found in children between one– and three–years–old), neighbourhood (in Indonesia, a “clustering” of xerophthalmic children was found in neighbouring houses) or region (in Bangladesh, a six–fold difference in mild xerophthalmia prevalence rates was reported between regions). Policy makers must determine the most efficient and effective approach for their country, based on the extent to which xerophthalmia is a problem, the degree to which an infrastructure exists for intervention, as well as resources available for programme implementation. One purpose of the Vest and Sommer paper is to provide information to guide this choice.

Resources Needed for Distribution of High Doses of Vitamin A

The major resources required are more the means to deliver doses than the cost of the capsules themselves. Cost estimates are available based on existing studies, as discussed below by Vest and Sommer. For example, although one standard dose vitamin A capsule costs less than $0.02, the cost to actually deliver the vitamin in the field is estimated at around $0.4 per recipient per year. The principle of marginality may be applied, so that costs normally occurring without vitamin A distribution should not be attributed to the vitamin A programme, and additional costs may be less than this figure. Thus integration is critical in determining cost–effectiveness. For example, essential drug programmes include delivery of standard medical packages to the field clinics. In designating vitamin A as an essential drug in the country's health system, an efficient mechanism of distribution may exist, and the marginal cost of distributing vitamin A may be reduced. A comparable estimate for fortification would be around $0.5 per child recipient per year (Arroyave et al, 1979).

The major supplier of the standard dose vitamin A capsule is UNICEF, except in India where doses are manufactured locally. UNICEF's vitamin A procurement increased between 1981 and 1985 from 3 to 80 million capsules annually, with a 1985 expenditure of $1.2 million. However, only around 20% of estimated global requirements are being met (Eastman, 1986).

Vest and Sommer discuss cost–benefit calculations for vitamin A distribution (See Section 7). In preventing nutritional blindness in children, not only are the well–being and livelihood of the child affected, but also the status of the surrounding support system. Additionally, with the data emerging from Indonesia on child survival, preventing vitamin A deficiency can clearly impact on child morbidity and mortality. With the lifetime disability arising from nutritional blindness, compounded by the morbidity and mortality influences which now seem evident from vitamin A deficiency, the authors are clear that economic benefits are far in excess of programme costs.

Both managerial and technical issues are discussed in this paper and the commentaries. The managerial issues of programme implementation are crucial. These are not unique to vitamin A. The vitamin A dose itself is considered generally safe, with due attention to preventing too–frequent dosing; distribution does not require a cold chain; and the programme is normally well accepted by a community. Operational difficulties range from logistics and supplies to supervision and worker incentives, from training and use of all levels of health workers to community participation and education. Many vitamin A programmes begin semiautonomously, as part of a health system yet retaining a separate budget and specific mandate, expecting that once institutionalized within a medical/health training curriculum, incorporated into existing job

descriptions, and part of routine supply packages, the programme will be sustained over time. Experience with sustainability is limited, and is a question of continuing concern.

Prevention and Control of Vitamin A Deficiency

Vitamin A deficiency can be prevented by well–proven interventions. The mass distribution of high doses periodically, as described by Vest and Sommer, would almost always form an early and crucial part of any control programme. Activities in this area are underway, but must be greatly accelerated otherwise preventible blindness and child deaths from vitamin A deficiency will continue far into the future. The United Nations system has put forward a ten–year plan (ACC/SCN, 1985), launched at WHO in Geneva in October (ACC/SCN, 1986b). The objective of this inter–agency programme is to reduce the worldwide prevalence and severity of vitamin A deficiency, xerophthalmia and nutritional blindness to the point where they are no longer significant public health problems. What needs to be done to start this process?

Countries with vitamin A deficiency in their populations need to establish or build up national prevention and control programmes. A number of government sectors may be involved, particularly agriculture, education, health and social services. Programme development requires assessment of the problem and of potential interventions; decisions on policy and resource commitments; and, in many cases, access to external assistance – financial, supplies, and/or technical. National capabilities may need to be strengthened in these areas.

There are three aspects of possible external assistance in this. In the first place, national prevention and control programmes require planning, as a prerequisite for funding and organizational commitments. Governments should be able to call on the UN agencies, and donor governments, to help where necessary: often through assistance to national institutions. Second, many countries will wish to request external assistance for implementing prevention programmes, which in turn requires drawing up suitable proposals for donor agencies and governments: here again, help either in developing the proposals themselves, or in building the capability to do this may be warranted. Third, national capacity for implementing prevention programmes – for organization, monitoring, and administration – may be inadequate and external assistance may be appropriate to develop this capacity. Assistance in these and other areas is proposed in the UN ten–year programme, to support a sustained effort.

The costs of a global ten–year programme to control vitamin A deficiency can only be approximated at this stage. Early steps in the programme would involve better assessment of the extent and distribution of the problem, and methods of delivery of vitamin A. Results of these assessments will determine expected costs. Here, we should distinguish costs of supplies – primarily for vitamin A capsules – and for programme development and delivery. Cost of supplies is a relatively small proportion of the overall need. Vitamin A is cheap, about two US cents per capsule, and only two per person per year are required for effective prevention. Delivery costs depend on targeting, degree of reliance on existing services, etc., and are hard to estimate (especially as additional or marginal costs). However, some preliminary estimates can be made, from UN agency contributions to the ACC/SCN ten–year proposal, and from estimates of populations at risk discussed above (see Table 1).

First, the estimated pre–school population in the 34 affected countries is about 280 million. Total coverage of pre–schoolers would thus require about 500 million capsules per year. UNICEF (1987) estimates that current (1985) capsule procurement is 21% of need; this procurement is estimated at 148 million (Eastman, 1986, Table 17), i.e. total requirement is about 700 million capsules, including older children and mothers. On the other hand, the numbers of cases of mild/moderate vitamin A deficiency may be around 40 million children, so with exact targeting 80 million capsules per year would be needed for this group. This data at least gives bounds to the estimate, say between 100 and 700 million capsules per year, i.e. $2 to $14 million per year, for supplies. Second, WHO's (1985a) proposal is costed at $25 million over 5 years, which includes planning, support to delivery systems, etc. FAO (1985) has estimated that $7.5 million over 5 years is required to develop programmes for dietary modification in 21 countries (those in WHO categories A and B). In addition, USAID's prevention programme in 6 countries is budgeted at approximately $3 million (excluding research, USAID, 1987).

Such estimates do not generally include the costs of the delivery system, for capsules; Vest and Sommer below quote estimates of around $0.2 per capsule dose taken, about ten times the cost of the capsule itself. These figures attempt to estimate the marginal or additional cost of delivering vitamin A doses, for example through the health system. However, the additional costs will vary greatly and can presumably be substantially reduced by effective use of – or integration with – the existing services. For example, distribution as part of essential drugs programmes, and with immunization campaigns, is being explored.

The inter–agency meeting for launching the ten year coordinated programme for prevention of vitamin A deficiency was attended by representatives of many agencies and governments. The proposed programme was firmly supported, coordination of roles and sharing of experience were agreed, and the intention of finally reducing the human toll from vitamin A deficiency whole–heartedly endorsed. The technology and the coordinating mechanisms at international level are in place. The reality has now to be brought about.

This State–of–the–Art paper, by two of the leading researchers in the vitamin A field, Drs. Keith West and Alfred Sommer, is intended as a contribution to the worldwide, inter–organizational efforts. It can provide authoritative guidance and practical details based on their own and others' work. The commentaries, from experienced contributors to the vitamin A field, expand on their views, give alternatives, and introduce the two other strategies of fortification and dietary modification.

Finally, we can echo the conclusion of the meeting (ACC/SCN, 1986b) that launched the ten–year programme – when the reality of scarce resources was addressed. “It would be a terrible irony, at a time when all of the major ingredients for success are at hand – scientific knowledge, inexpensive and effective technology, and accumulated practical experience – if the world development community were prevented from taking action for want of a modest increase in resources. It is indeed possible to envision a time when vitamin A deficiency will rank among the nutritional scourges of the past. Participants in the meeting were unanimous in the view that this historic opportunity must not be missed”.

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CONCLUSIONS AND SUMMARY

Administration of large doses of vitamin A to young children (and often to lactating, non−pregnant mothers as veil) is a commonly practiced intervention against nutritional blindness, and may emerge as a major strategy to reduce childhood mortality where vitamin A deficiency is endemic. Based on available evidence from nearly two decades of experience, large−dose vitamin A distribution can generally be regarded as a safe and potentially effective intervention to prevent xerophthalmia. While conceptually simple, the adequacy and efficiency of programmes pose major challenges and determine their success in preventing nutritional blindness.

A 200,000 IU dose of vitamin A with 40 IU vitamin E in an oil solution for oral administration given every six months is used in most prevention programs. This is preferred to water−miscible preparations for reasons of safety and practicality of delivery. A gelatine capsule, provided to governments by UNICEF, is the most widely used form of dose, except in India where a domestically produced oil concentrate is used.

The protection afforded by six−monthly dosing seems very adequate as measured by clinical signs of the deficiency. Controlled field and other clinical studies indicate effective protection by a single dose (prophylactic efficacy) of 90% or better, against developing mild xerophthalmia for at least 4 to 6 months. Data from a case−control study in India suggest this degree of efficacy extends to severe, potentially blinding xerophthalmia as well. However, the protective period is likely to vary with the frequency and severity of precipitating and contributory factors such as infection and protein−energy malnutrition. Efficacy establishes the upper limit of effectiveness when large−dose vitamin A delivery is implemented through a routine programme.

The presence of certain infections reduces absorption and retention of vitamin A, such that while 40−50% of a large dose is retained in healthy children, only 20−30% may be stored and utilized in those with respiratory or gastrointestinal infections. But treatment for xerophthalmia using standard oral doses of vitamin A appears effective even in the presence of such infections. Absorption and retention of vitamin A appear to be inversely related to the dosage; thus, a 200,000 IU dose is proportionally less well absorbed and retained than a physiologic amount (e.g., 3,000 IU) of vitamin A.

Theoretical estimates the sufficiency of hepatic stores conferred by a 200,000 IU dose range from 60 to 240 days; however, the observed protective period against low serum vitamin A levels in children who are “at−risk” of vitamin A deficiency may last little more than 56 days. This may in part be explained by degrees of inaccuracy of serum vitamin A levels in representing true vitamin A status. The short−term effect of a large vitamin A dose may be greatest when regular dietary intake is most restricted, but routine intake of as little as 15−30 grams of dark green leafy vegetables per day may extend to several months the protective period afforded by a single large dose of vitamin A.

Three basic systems are employed to distribute vitamin A to the “at−risk” community: medical, targeted, and universal. Medical distribution (essentially treating those presenting with deficiency signs or infection in endemic areas) is usually incorporated into the other two systems and has not been independently evaluated. Targeted distribution focusses on specific high risk groups, defined usually by age and/or location. One targeted system, in Haiti, has been evaluated, which showed a nine−fold reduction in corneal xerophthalmia three years after initiation of the programme. Other environmental improvements may have contributed to this reduction in disease as well. Targeted delivery can be expected to reach only 10−15% of the “at−risk” population, at existing levels of utilization of the health services. A routine dosing schedule is also difficult to

achieve. While effectiveness may be less than that expected from a high−coverage universal distribution, higher target group specificity and efficiency could make targeted delivery a more attractive option. The opportunity costs associated with conducting universal distribution, before making full use of the present health care system for targeted delivery, should be explored.

The effectiveness of universal distribution in preventing mild xerophthalmia is, in part, directly related to coverage. A 75 to 80% reduction in prevalence among one− to four−year−olds has been repeatedly associated with universal distribution that achieves at least 65% coverage. For example, in the Philippines, reduction in Xerophthalmia of nearly 70% was directly attributable to capsule distribution. Conversely, no measurable impact on xerophthalmia has been observed when coverage has been less than 25%. In the Philippines, an 80% associated reduction in xerophthalmia could be linked to a 70% reduction in disease directly attributable to capsule distribution. Above 85% coverage, the effectiveness of universal delivery in preventing the less prevalent but more severe corneal xerophthalmia may be as high as 90%.

Vitamin A distribution programme infrastructures tend to be similar, administered by the Ministry of Health and implemented through local health centers. Originally designed to be single−purpose, vitamin A delivery is being increasingly built into health services, with nutrition education components.

Programme efficiency needs to be sustained at practically every level. Problems arise in ensuring the uninterrupted supply of vitamin A doses, in supervision, training and retraining of personnel, and in administration (e.g. record−keeping). Maintaining acceptable coverage at each distribution cycle represents a formidable challenge to almost every vitamin A distribution programme. Declining target group coverage is likely to be the single most important cause of ineffective xerophthalmia prevention.

Information on programme costs and effects is still scarce. Development of a standard budget schedule has been recommended by WHO. Suitable indicators of cost−effectiveness include the cost per dose recipient and cost per target group recipient. Based on sparse data, the current cost per six−monthly universal delivery dose recipient may be about U.S. $0.44 per year, and between U.S. $0.22 and $0.33 per capsule distributed in a targeted system.

Biological cost−effectiveness indicators include the cost per percent change in the prevalence or incidence of xerophthalmia, and possibly in mortality rates. Such information requires concurrent data on programme costs and effects, which are rare as yet. Preliminary benefit−cost analysis shows that the benefits of preventing xerophthalmia calculated in monetary terms can far outweigh programme costs, thus supporting the continued use of periodic vitamin A distribution campaigns. Given the emerging evidence that vitamin A supplementation may reduce mortality among children with even mild vitamin A deficiency, the benefits from improving vitamin A nutrition in a population may be even greater than those so far assessed.

1. INTRODUCTION

Vitamin A is an essential nutrient for normal growth and survival. Chronic vitamin A deficiency plagues many developing regions of the world, with its most tragic consequences seen in young children. The term xerophthalmia (xeros−dry, ophthalmia−eye) refers to the eye diseases specifically caused by vitamin A deficiency.

Xerophthalmia is widely recognized as the leading cause of childhood blindness in developing countries.(1) Current estimates are that in Asia alone, some one−half million children under six years of age develop potentially blinding corneal xerophthalmia each year.(2) Worldwide, the number of incident cases annually may reach one million. As many as half of these children progress to bilateral blindness if left untreated.(3) Severe corneal xerophthalmia is often accompanied by other precipitating or contributory factors such as moderate to severe protein−energy malnutrition (PEM), low fat intake, debilitating diarrhoea, respiratory tract infections, and acute measles.(4) The devastating impact of severe vitamin A deficiency combined with these nutritional and infectious risk factors on child survival is evident in the excessive mortality rates of between 10 and 65% that have been observed among treated children with corneal xerophthalmia.(5−9)

Approximately 8−10 million children worldwide, are believed to develop “milder” noncorneal xerophthalmia, manifested by night blindness or conjunctival xerosis with Bitot's spots, each year. While not the medical emergency that corneal destruction represents, “mild” xerophthalmia has been shown to be associated with a two to three times higher risk of respiratory infection or diarrhoea(10) and, more tragically, a several−fold higher risk of mortality among preschool age children.(11) Varied in its magnitude, this increased risk of

morbidity and mortality with xerophthalmia is present among acceptably protein– and energy–nourished children as well as those with more acute stages of wasting PEM.(10, 11)

Vitamin A deficiency is a nutritional disease with a primary, nutritional solution: improve vitamin A nutriture to a physiologically acceptable level by removing the determinant of disease – chronic dietary insufficiency, and/or absorption of vitamin A. This solution incorporates both notions of treatment for xerophthalmia, as well as prophylaxis in populations where such malnutrition is manifested. Concurrent reduction in the magnitude and severity of precipitating or contributory risk factors such as measles, acute diarrhoeal and respiratory infection, and moderate to severe PEM through a variety of public health measures can serve to further reduce the morbid consequences of inadequate vitamin A nutrition in the community.

In this paper, we first review the clinical stages of xerophthalmia, its treatment, and the public health approaches for preventing xerophthalmia and vitamin A deficiency. This is followed by a critical analysis of the large–dose vitamin A delivery strategy.

XEROPHTHALMIA

The term “xerophthalmia” refers to the spectrum of ocular manifestations due to systemic vitamin A deficiency. Such signs include those involving the retina leading to night blindness and other fundus changes, xerosis of the conjunctiva including the formation of “Bitot's spots,” and xerosis, ulceration, and necrosis of the cornea. Xerophthalmia can occur in any age groups and especially in preschool children, adolescents and pregnant women. However, the highest incidence has been observed in preschool children.

THE RETINA

Vitamin A is required for synthesizing the pigment rhodopsin, also known as visual purple, in the retina of the eye. Rhodopsin is needed for proper excitation of rod photoreceptors which are responsible for vision under low levels of illumination.(12) Impaired dark adaptation, or night blindness, occurs when vitamin A has been sufficiently depleted from the rods to impair function, and currently represents the earliest ocular manifestation of vitamin A deficiency. Among children in developing countries, night blindness may be reliably ascertained by history from a parent or guardian.(13) Where vitamin A deficiency is endemic, a local phrase may exist which relates specifically to the inability of a child to see in the dark such as “twilight blindness” or “chicken eyes.” (This latter behaviorally–related term has an anatomical basis in that chickens lack rods in the back of their eye.) Normal night vision usually returns within one to three days following vitamin A therapy.

The occasional appearance of numerous small, yellowish dots on the fundus of the eye can be observed with vitamin A deficiency. These lesions represent loss of pigment from the retinal pigment epithelium and may be accompanied by blind spots or scotomas, congruent with their distribution on the retina.(14) Xerophthalmic fundus, as it is called, has usually been reported among older children and adults and is at present primarily of investigational interest.

THE CONJUNCTIVA

Conjunctival xerosis, or drying, represents the earliest, clinically detectable, structural change on the surface of the eye due to vitamin A deficiency.(15) Consisting of dry, non–wettable and rough patches of conjunctiva, it usually occurs in both eyes.(16) Often, fine bubbles or cheesy material, comprising keratinized epithelial cells, may accumulate above the conjunctival surface forming “Bitot's spots” (Figure 1) which are merely an extension of the xerotic process.

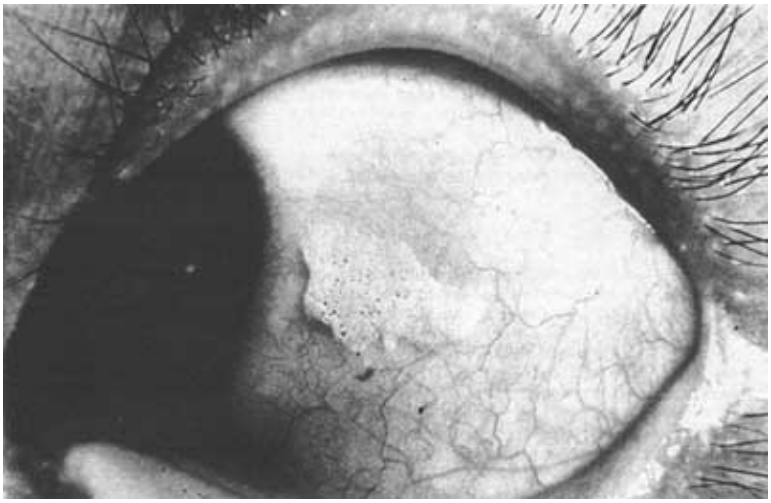

Figure 1 – Bitot's Spots – Fine bubbles of cheesy material accumulate on conjunctival surface

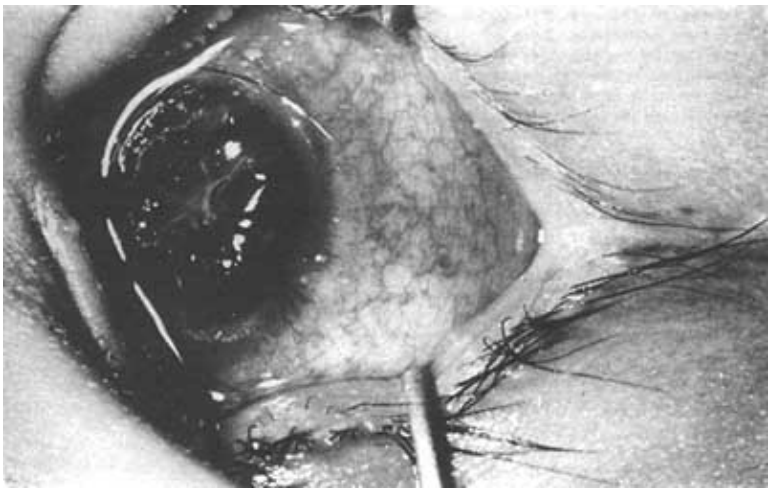

Figure 2 – Keratomalacia and Progressive Necrosis affecting the full thickness of the cornea

Although the presence of Bitot's spots, particularly in preschool age children, generally represents significant vitamin A deficiency, diagnostic sensitivity improves when night blindness and Bitot's spots occur together.(16, 17) With vitamin A treatment, Bitot's spots begin to regress within two to five days, and will disappear within two weeks in most cases. However, a significant proportion may persist in shrunken form for months.(16)

THE CORNEA

Superficial depressions in the cornea begin to occur even during the early stages of xerophthalmia, although these are not clinically apparent until vitamin A deficiency becomes severe. As corneal involvement increases, these lesions become more dense, stromal edema develops, and the cornea appears hazy, granular, and pebbly upon examination with a handlight. (16, 17) Treatment with vitamin A at this stage usually results in complete healing of the eye within one to two weeks with no scarring. Corneal ulcers are “punched–out defects” which represent permanent destruction of part or all of the corneal stroma. Ulceration may be shallow, but is commonly deep with resultant perforation of the cornea. With therapy, superficial ulcers may heal leaving little scarring, while deeper ulcers and perforations form dense scars, with their extent and location in relation to the pupillary zone being the principle determinants of useful vision.

Keratomalacia (kerato = cornea, malacia = softening) is a far more rare stage of xerophthalmia, representing rapidly progressive necrosis or death of tissue, affecting the full thickness of the cornea (Figure 2). Necrotic stroma may slough off leaving a large ulcer or descemetocele and extrusion of intraocular contents resulting in permanent distortion or loss of the globe.(16) Blindness is usually inevitable, although prompt vitamin A therapy may save the other eye and the child's life. Secondary infection of the eye is commonly associated with keratomalacia and should be treated with antibiotic eye ointment. Severe PEM, measles, diarrhoea, respiratory and other infection often precede or accompany corneal xerophthalmia, making the prevention and treatment of these diseases important adjunct therapies to those which address vitamin A deficiency alone.

Healed corneal ulceration and keratomalacia result in scars on the cornea of varying densities, permanent outpouching of the remaining cornea (“staphyloma”), or, where intraocular contents have been lost, a shrunken globe (“phthisis bulbi”). Although scars may have other causes than xerophthalmia, determining their prevalence and collecting a pertinent history associated with their occurrence during surveys can provide useful information on the likelihood of their being attributable to vitamin A deficiency.

XEROPHTHALMIA CLASSIFICATIONS AND WHO CRITERIA

Based on severity of vitamin A deficiency, xerophthalmia can be manifested in various clinical eye signs. Using clinical and biochemical parameters, a classification system with recommended minimum prevalence criteria has been developed by the World Health Organization (WHO) to assist in determining the extent to which vitamin A deficiency and xerophthalmia may be considered of public health importance among children in a community (Table 1). These range from .01% of the target population with corneal diseases to 1% with night blindness. The prevalence rates may appear deceptively low due to the rare occurrence of corneal disease with its attendant high risk of mortality. For epidemiologic purposes, a person with active xerophthalmia is classified by the most severe clinical stage present. Xerophthalmic scars (XS) are evaluated separately from indicators of active disease since persons with XS may or may not have concurrent active xerophthalmia.

TABLE 1

CRITERIA FOR ASSESSING THE PUBLIC HEALTH SIGNIFICANCE OF XEROPHTHALMIA AND VITAMIN A DEFICIENCY, BASED ON THE PREVALENCE AMONG CHILDREN LESS THAN SIX YEARS OF AGE IN THE COMMUNITY (1982 REVISION) (16, 17)

Indicator	Minimum Classification	Prevalence
Clinical		
Nightblindness	XN	1.0%
Bitot's spots	X1B	0.5%
Corneal xerosis	X2	
Corneal ulceration	X3A	0.01%
Keratomalacia	X3B	
Xerophthalmia–related corneal scars	XS	0.05%
Biochemical		
Serum retinol (vitamin A)		
less than 10 ug/dl 1 (0.35 umol/1)		5.0%

TREATMENT

The standard vitamin A treatment schedule recommended by the WHO(16) for all forms of active xerophthalmia is as follows:

Treatment Schedule for Xerophthalmia

Immediately on diagnosis	Oral Vitamin A (200,000 IU)
The following day	Oral Vitamin A

	(200,000 IU)
Prior to discharge, or if clinical deterioration occurs, or 2–4 weeks later	Oral Vitamin A (200,000 IU)

NOTE: Infants under 12 months of age, very small and very low weight children should be given half the dosage. Water–miscible retinol palmitate (100,000 IU) injections can be substituted for the oral dose in case of repeated vomiting or severe diarrhoea. Oil–based injections are considered ineffective in xerophthalmia control and should never be used, because retinol is absorbed very slowly, if at all, and less efficiently than water based preparation, from the injection site.

The above schedule should similarly be followed for all children with severe PEM, measles, or other severe infection who come from endemically vitamin A–deficient areas.

PROPHYLAXIS

The major goal of prophylaxis is to reduce and control the prevalence of xerophthalmia and vitamin A deficiency to minimum tolerable levels in a population known to be “at risk”(18) of vitamin A malnutrition. Embarking on a prevention programme requires that the extent and severity of vitamin A deficiency have been established (16, 19) and found to be at a level to justify intervention, that an operational target group in the population has been identified,(20) with some knowledge of prevalence of PEM among them, that political will to act and financial support have been committed by the government,(21) and that an active public constituency for the programme exists within the country. (22) Experience to date indicates that a national committee for the prevention of blindness can play a crucial role in facilitating and directing the planning, organization and development, implementation, evaluation and public liaison components of a prophylaxis programme. (22, 23) Such a committee typically is represented by members of governmental and private health service and research institutions, private industry, leading social welfare organizations, and prominent individuals from the public domain.

Prevention of vitamin A deficiency requires that the usual intake of vitamin A be increased to acceptable levels in the high–risk population, primarily among children under 6 years of age. Currently, three major intervention strategies exist, which form the basis for the ACC/SCN ten–year programme for the prevention and control of vitamin A deficiency, xerophthalmia and nutritional blindness:

1. Dietary modifications, directed toward achieving a continuous, adequate intake of vitamin A–rich foods.

2. Fortification of an appropriate dietary vehicle with vitamin A.

3. Delivery of a single, large dose of vitamin A on a periodic basis.

DIETARY MODIFICATIONS

Dietary modifications have long been recognized, and recently re–emphasized(24) as the preferred major long–term solutions to controlling vitamin A deficiency in a population. The major dietary sources of provitamin A (primarily beta–carotene) include the multitude of dark green leafy vegetables, and deep yellow fruits, vegetables, tubers, and roots. Red palm oil is the richest source of carotenoids, containing 0.5mg/ml of mixed and beta–carotenes. Thus about 7ml/day would meet the vitamin A needs of a preschool child. Preformed vitamin A exists either as retinol or, more typically, as one of its esters, and is found in egg yolk, fish liver and oils, animal liver, and dairy products. Among the above foods, the most ubiquitous and affordable sources of vitamin A throughout the developing regions of the world are the families of dark green leafy vegetables.(25) A strategy to improve dietary intake of these foods may draw upon any combination of agronomic, horticultural, educational, and socioeconomic inputs.(26) The common goal is always to improve availability of these food sources of vitamin A, and gradually increase and maintain an acceptable level of their intake among the

vulnerable segments of the population. Due to synergistic relationship between vitamin A and infectious/parasitic diseases, and interactions with other nutrients, it is better to take care of other nutritional deficiencies, especially PEM, health and sanitary issues as well, if possible.

The mix of required inputs can be determined following a critical analysis of local feeding patterns and their determinants, as well as environmental resources, including the availability of foods high in preformed or provitamin A. For example, in areas where vitamin A–rich foods are readily available among the target population, nutrition education directed toward modifying food consumption patterns could be emphasized. In areas where seasonality is a critical factor in limiting the availability of dark green leafy vegetables, promotion of home gardening and appropriate local food preservation technology(27–29) might be expected to yield higher intakes. Given the characteristically low fat content of many traditional diets,(30–32) and the essential role of dietary fat in facilitating beta–carotene absorption,(33–35) the dietary approach should include methods for increasing fat intake as veil. As little as 5 grains of fat added to children's meals can have a substantial impact on absorption of beta–carotene.(35) However, overall food intake itself, in terms of preventing PEM is also important. Under most circumstances, sustained breast–feeding remains the best guarantee of adequate vitamin A intake throughout the weaning years as it appears to exert a major preventive influence against both mild(32, 35, 37) and severe xerophthalmia.(38)

VITAMIN A FORTIFICATION

Fortification of a widely consumed food “vehicle” with vitamin A offers a second major intervention strategy which can be relatively inexpensive(39) and effective in increasing vitamin A intake throughout the year, reflected by sustained elevations in serum vitamin A(40–42) and reductions in xerophthalmia(42) among the vulnerable members of a population. Vitamin A fortification of foods such as margarine and dairy products, now practiced in some 30 nations around the world, has provided a strong technological basis for extending the feasibility of vitamin A fortification to numerous other potential food vehicles,(43) including monosodium glutamate (MSG), both in the Philippines(42) and most recently in Indonesia,(44) and sugar in Guatemala in order of 15 mcg retinol/g sugar.(40, 41) During a limited trial in Indonesia, fortification of salt at a level of 440 IU/gram had a favorable impact on child vitamin A status.(45)

However, a number of necessary preconditions must exist before fortification can be considered a viable intervention. These include identifying a food vehicle which is consumed in adequate amounts by the “at risk” population, is technically fortifiable, is manufactured or processed in only a few locations, and retains its potency and acceptability after being fortified. Further, the range of intake should be relatively narrow so as to minimize the risk of vitamin A toxicity. During at least the initial years of a programme, governments should be prepared to bear the incremental costs due to fortification. Depending upon local dietary trends and programme costs, fortification can offer both a medium– and long–term solution for improving vitamin A nutritional status in a chronically deficient population.

PERIODIC DOSE DELIVERY

Periodic oral delivery with a standard 200,000 IU (60,000 mcg) dose of vitamin A as retinyl palmitate, and nearly always with 40 IU of vitamin E (to improve absorption), comprises the third and most direct intervention strategy.(17) First suggested in 1964,(46) and soon followed by early pilot field trials,(47–49) large–dose vitamin A distribution has gained wide acceptance as a standard intervention throughout the world.(17) Currently, UNICEF distributes approximately 80 million 200,000 IU vitamin A capsules annually(50) (Figure 3), while in India, some 20 to 25 million children receive this same oral dose of vitamin A in oil by spoon each year (Figure 4). The physiologic objective of periodic dosing is to maximize liver reserves from a single, large, oral dose of vitamin A while minimizing the risk of acute toxicity.(43, 51) The operational objective of the periodic dosing strategy is to achieve the widest coverage of the target group throughout the high–risk years by a system that is culturally acceptable, administratively feasible, and economically practical.

As noted, the oral dose vitamin A is recommended for both treatment and prevention of vitamin A deficiency and xerophthalmia. Due to its widespread use as a major prophylactic strategy, this paper will examine in detail the experiences and effectiveness of oral dose delivery, as well as means for its evaluation.

2. EFFICACY OF ORAL VITAMIN A

Considerable research has been directed toward establishing the efficacy of orally administered vitamin A preparations in terms of efficiency of absorption and impact on common indicators of vitamin A status (e.g., serum retinol, clinical xerophthalmia). Efficacy,(52) within the context of preventing vitamin A deficiency and xerophthalmia, incorporates three distinct components: (1) the efficiency of intestinal absorption of oral vitamin A, (2) the retention of oral vitamin A, (3) and the duration for which acceptable vitamin A status can be maintained as a result of the vitamin A dose (i.e., the “protective period”).

EFFICIENCY OF ABSORPTION

Evaluating the absorptive efficiency of vitamin A at different dosage levels and under varying conditions of health and disease is a preliminary step in quantifying the expected improvement in vitamin A status attributable to an oral dose of vitamin A. Efficiency of absorption, in man, may be determined either by computing the difference between the total dose administered and fecal losses of vitamin A for several days after administration, or by quantifying the changes in serum vitamin A levels at specified intervals during the 24 hours following dose administration (“vitamin A absorption curve”), noting the timing and magnitude of the peak rise in serum retinol. In animals, changes in hepatic stores of retinol can also be used to determine the efficiency of absorption.

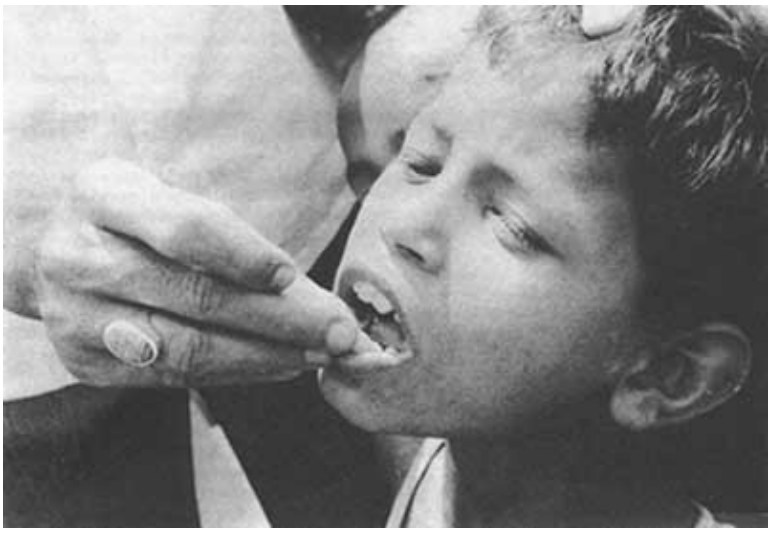

Figure 3 – Capsules containing doses of vitamin A are given six–monthly by mouth

Figure 4 – In India vitamin A doses are prepared in syrup and given by spoon

TYPES OF PREPARATIONS

Studies over the past fifty years provide evidence about the absorption of vitamin A when administered as an ester or alcohol, in an oil or water–miscible ("aqueous") solution, to healthy or diseased individuals. Human studies have shown vitamin A as an ester (acetate or palmitate) or alcohol to be equally veil absorbed from a healthy gut,(53–55) while in some malabsorptive disorders, the chemical form can influence absorption. For example, in celiac disease both the ester and alcohol are poorly absorbed in oil and well absorbed in aqueous form; in cystic fibrosis, and other malabsorptive diseases, the oil–based vitamin A alcohol may offer an absorptive advantage over the ester in oil.(53)

Vitamin A–replete individuals consistently reveal a markedly higher peak in the 3– to 6–hour serum retinol level following oral administration of aqueous or emulsified preparations versus oil–soluble solutions of vitamin A,(56–60) although comparable serum levels can be noted at 24 hours.(57, 58) Animal experiments have indicated more efficient absorption of megadoses of vitamin A in aqueous and emulsified preparations than in oil solutions,(56, 58) by demonstrating lower fecal loss (5–12% versus 20–23% of the dose), higher peaks in serum retinol, and greater hepatic storage (38–55% versus 23–28%). This can be attributed, in part, to a smaller fat particle size being presented to the intestinal mucosa,(56, 61) and to possible emulsifier–specific influences on vitamin A absorption.(62) Similar differences in fecal excretion levels of vitamin A from both forms have also been reported for healthy infants(58) and adults(63) receiving single doses ranging from 33,000 to 400,000 IU. While these studies suggest there is greater absorption of aqueous vitamin A, satisfactory absorption has been observed after administration of pharmacologic doses of oil–soluble vitamin A to healthy individuals(63–65) and ill patients with normal gut function.(66) Experiments in vitamin A–depleted animals have also demonstrated that aqueous and oil–soluble preparations produce comparable liver stores at 24–48 hours,(67, 68) similar serum values at 24 hours(68) and, most importantly, resolution of xerophthalmic signs accompanied by equivalent rates of growth.(67)

In the presence of severe malabsorptive disease, aqueous vitamin A has consistently been shown to be better absorbed than an oil solution.(63, 65) This is attributed, in part, to less dependence on enzymatic and micelle–forming activities. In the presence of common gastrointestinal infections from giardia,(69) ascaris,(69–71) salmonella,(72) and other entero–pathogenic organisms,(73) vitamin A absorption from both oil–soluble and aqueous preparations is significantly impaired. Following treatment, there is usually marked improvement in absorption.(69, 70, 72, 73)

Severe protein–energy malnutrition, specifically kwashiorkor, causes profound histopathologic changes in the intestinal mucosa(74) and markedly reduces the secretion of pancreatic enzymes into the gut.(75) These changes are likely to account for much of the fat malabsorption accompanying severe PEM.(76) Since children with severe PEM are at greatly increased risk of developing blinding corneal xerophthalmia,(3, 77) improvement in their vitamin A status needs to be accomplished as quickly as possible. Under these conditions, an aqueous vitamin A preparation may be expected to be more rapidly absorbed than an oil solution. Several investigators have observed flat or erratic vitamin A absorption curves following an initial oral dose of up to 75,000 mcg vitamin A in oil among children with frank kwashiorkor and severe xerophthalmia.(74, 78) These observations prompted the original WHO recommendation that such high–risk children, indeed all children with corneal xerophthalmia, be treated initially with intra–muscular aqueous vitamin A.(17, 79) Widely practiced,(7, 78) this treatment appears to be effective in halting and healing corneal destruction, and preventing a relapse for up to one year among surviving children.(7)

Recently however, severely xerophthalmic Indonesian children with moderate to severe PEM or diarrhoea exhibited comparable clinical responses to 200,000 IU oral vitamin A in oil and 100,000 IU vitamin A as an intra–muscular aqueous injection. Release from the liver into the blood of the vitamin A transport protein (retinol binding protein) 24 hours after treatment suggested adequate absorption of the oil–based vitamin A even when treating such "worst case" clinical profiles.(80) Following these observations the WHO recommendations were revised to include oral administration of 200,000 IU of vitamin A in oil for initial treatment.(17) It was also noted that regardless of the vitamin A preparation and method of administration, children with severe PEM were "at–risk" of early relapse.(3) It is therefore important that these children continue to receive repeated doses of vitamin A periodically while their PEM status improves.(77)

TOXICITY AND CHOICE OF VITAMIN A PREPARATION

Given the evidence, aqueous vitamin A appears to out–perform the oil solution in terms of rapidity of absorption and total vitamin A stored in the liver under conditions of similar gut integrity and general nutritional

status. A water−miscible dispersion would appear to be the preferred vehicle for a vitamin A deficiency prevention strategy based on these factors alone. However, for two major reasons aqueous dispersions have not been used for prophylaxis: (1) concern for safety, and (2) the technological problems of packaging a single−unit water−miscible preparation.(62)

Rapid absorption of aqueous vitamin A may result in acute hypervitaminosis A in a significant proportion of children following a large oral dose. The slower absorption rate of oil−based vitamin A is likely to result in an attenuated “spike” in serum retinol and a decreased risk of acute toxicity. Following a single, large oral dose (200,000−300,000 IU), toxicity, commonly evidenced by nausea, vomiting or headache, is self−limited.(42) The literature related to hypervitaminosis A toxicity in children attributable to oral dosing with large amounts of vitamin A has been extensively reviewed by the International Vitamin A Consultative Group (IVACG).(51) In one study,(81) nearly 25% of the children developed toxic manifestations following oral administration of a single dose containing 300,000 IU of a water−miscible preparation, while three other studies reported no toxic symptoms. Ten investigations using vitamin A in oil, ranging from 165,000 to 330,000 IU with or without added vitamin E, reported no toxic symptoms, while seven others reported transient signs of toxicity in up to 4% of recipient children.(51) In Indonesia, a somewhat higher incidence of vomiting and diarrhoea (16%) has been recently reported following administration of 300,000 IU in oil,(31) although a markedly lower toxicity rate of 6% was noted when 250 IU of vitamin E were added. During recent, carefully supervised studies of some 50,000 children in India receiving 200,000 IU vitamin A in oil every 6 months, vomiting or diarrhoea was noted in only 0.7% of the children.(82) Thus, reduced risk of toxicity appears to attend the use of an oil solution, although even a low incidence of mild symptoms could severely reduce future compliance in a population−based programme.

The second problem deals with the practicalities of designing an efficient production and delivery system at low cost which maintains vitamin A stability and potency over extended periods of time under a range of environmental conditions. An oil solution can be readily encapsulated in a gelatin shell or enclosed in a bottle, remains potent under ambient temperatures during storage periods of over three years,(43) and does not run the same risk of separation over time as does an aqueous dispersion.

These concerns for safety and practicality directed the development of vitamin A delivery systems using a standard 200,000 IU dose in oil, which has become the recommended preparation for nearly all direct−dosing supplementation programmes. The remainder of this paper deals primarily with the efficacy of oral, oil−based preparations, and the effectiveness and costs of country programmes utilizing oil solution.

RETENTION OF OIL−SOLUBLE VITAMIN A

A number of studies in India have been conducted on both absorption and retention of oil−soluble vitamin A in apparently normal and ill children in physiologic and large pharmacologic doses.(70, 83−86) Table 2 lists these studies by dosage of vitamin A and health status of the subjects. “Healthy” children lacked clinical evidence of infection, though in one study they were reported to be substandard in weight and height.(85) Several important and consistent findings are apparent regarding the absorption and retention of vitamin A in oil:

1. When administered in physiologic amounts (approximately 3,000 IU) to apparently normal children, oil−soluble vitamin A is nearly completely absorbed and is approximately 80% retained.(70, 83, 85)

2. In the presence of systemic and enteric infection, absorption is reduced to 75% and retention to some 60−65%; (70, 83) however, retention of the total amount actually absorbed remains at approximately 80%, suggesting reduced absorption is responsible for lover retention.

3. In healthy preschool children, of a large dose (e.g., 200,000 IU) of oil−soluble vitamin A, only 70% is absorbed,(84−86) and 40−50% of the total dose is retained(86) (or 65% of absorbed dose).

TABLE 2

RECENT STUDIES FROM INDIA REPORTING PERCENT ABSORPTION AND RETENTION OF ORALLY ADMINISTERED, OIL−SOLUBLE VITAMIN A PREPARATIONS AMONG CHILDREN

Authors	(Ref)	No.	Age (years)	Clinical status	DOSAGE		Ester form	% dose absorption	% dose retention
					IU	mcgRE			
I. Physiologic dose, healthy children									
Sivakumar and Reddy	(85)	5	2–4	normal*	3,000	900	palmitate	96±21	80±1
Sivakumar and Reddy	(83)	5	2–10	normal	2,900	873	acetate	99±1	82±2
Sivakumar and Reddy	(70)	5	2–6	normal	3,300	1,000	NR2	99±1	82±2
II. Physiologic dose, ill children									
Sivakumar and Reddy	(83)	5	2–10	resp. infection	2,900	873	acetate	74±7	58+6
	(83)	3	2–10	diarrhea	2,900	873	acetate	70+1	NR
Sivakumar and Reddy	(70)	6	2–6	ascariasis	3,300	1,000	NR	80+3	68+4
III. Pharmacologic dose, healthy children									
Sivakumar and Reddy	(85)	5	2–4	normal*	200,000	60,000	palmitate	67+4	47+4
Pereira and Begum	(84) (4)	6	4–5	normal	182,000	54,000	palmitate	75+4	38+13
Kusin et al	(3)	7	3–6	normal	200,000	60,000	NR	68+3	49+3
	(86)	7	3–6	normal	200,000	60,000	NR	73+3	50+3
	(5)	3	3–6	normal	200,000	60,000	NR	82+2	55+2

1 Mean percent absorbed +1 SD.
2 Not reported.
3 4 children received 40 mg vitamin E.
4 Plus 100 mg vitamin E.
5 Plus 500 mg vitamin E.

* Undernourished by weight and height.

It has been suggested that 30–50% of the 200,000 IU dose of vitamin A is retained;(79) the above studies imply that higher levels of retention may best relate to children who are free from overt infection or advanced malnutrition (Table 2). (Calculations of retention subtract the amount excreted in the first few days after the dose.) In the presence of enteric infection, markedly reduced absorption and therefore retention of a large dose of vitamin A is likely to occur.(53, 69, 71, 72) In addition, common respiratory infections, during which absorption of physiologic doses of vitamin A decreases from nearly 100% to about 75%,(83) may be expected to also reduce absorption of a large dose of vitamin A. During respiratory tract and other infections, metabolic losses of vitamin A are increased, sometimes dramatically (?3000 IU/day),(87–89) which may further reduce retention. Given the hyperendemicity of gastrointestinal and respiratory tract infections among undernourished populations where periodic vitamin A supplementation is needed, as little as 20–30% of the large oral dose may be retained.(70)

THE PROTECTIVE PERIOD

THEORETICAL ESTIMATES

The prophylactic efficacy of a large, oral dose of vitamin A in preventing vitamin A deficiency and xerophthalmia is ultimately determined by the period of protection conferred upon “at−risk” individuals known to have received the vitamin A supplement.

A variety of models have been employed to compute a theoretical time interval during which acceptable vitamin A status would be achieved and maintained following receipt of a 200,000 IU dose. Assuming 50% retention, WHO has estimated a protective period of about 100 days for a young, growing child.(79) This estimate applies most suitably to a clinically normal child, weighing approximately 15 kg, requiring 20 mcg retinol equivalents (RE) (91)/kg body weight per day,(92) and consuming a diet nearly devoid of vitamin A. Thirty percent retention would decrease this interval to 60 days. Under conditions in which half of a one− to three−year old child's recommended allowance, or about 200 mcg RE,(93) is provided by the diet,(30) these intervals would be extended to 200 and 120 days, respectively.

The above estimates assume a linear rate of retinol depletion from the liver over the stated time period. Models based on animal data indicate that release of vitamin A from the liver is an exponentially decaying function of the adequacy of hepatic stores. That is, in the presence of significant reserves, retinol leaves the liver at a relatively high rate, but in the depleted state the rate of hepatic release is lower.(90, 94) This liver−depletion−rate model has been adapted to estimate the protection period against xerophthalmia in a typical 10−kg child (Figure 5) Again, assuming 50% retention, a 200,000 IU dose of vitamin A would provide approximately 30 mg of stores, conferring protection for about 240 days. The protective period against severe, blinding corneal xerophthalmia should be even longer than that for milder disease.

Under this model, the longer protective period should be interpreted with caution since a decreasing rate of hepatic release of retinol over time would produce a concurrent, gradual decline in vitamin A nutriture throughout all dependent body tissues. Even if the protective period for corneal lesions is extended, prolonged systemic depletion of vitamin A during the pre−xerophthalmic state is likely to carry other risks. Studies among animals only marginally depleted in vitamin A have clearly demonstrated reduced rates of growth and significant atrophy of the thymus and other lymphoid organs.(95) In addition, epithelial tissue integrity,(96, 97) mucus production, and phagocytosis are adversely affected by vitamin A deficiency,(98) compromising resistance to infection.

Evidence is now emerging from human studies which corroborates animal data indicating increased susceptibility to infection in the presence of milder stages of xerophthalmia.(10) Results from the Indonesian Nutritional Blindness Prevention Project indicate that children with night blindness and Bitot's spots may be at three times the risk of developing diarrhoea, and twice the risk of developing respiratory infection as children without “mild” xerophthalmia.(10) Findings from a large randomized community trial to evaluate vitamin A supplementation in northern Sumatra showed a 34% reduction in mortality attributable to the programme, suggesting an increased risk of dying to be present even among non−xerophthalmic children who live in areas of endemic dietary vitamin A deficiency.(99) Thus it may be that the latter stage of a “protective” time interval is more of a “latent period,” during which ordinarily inapparent but significant systemic deficiency is developing.

PROTECTION AGAINST LOW SERUM RETINOL LEVELS (100)

One widely used indicator of vitamin A status is the level of vitamin A in the serum, usually expressed as micrograms of retinol per decilitre (mcg/dl). While serum retinol levels bear reasonable correspondence to vitamin A stores in the low ranges of status, it is recognized that indicator accuracy becomes more suspect at higher serum levels.

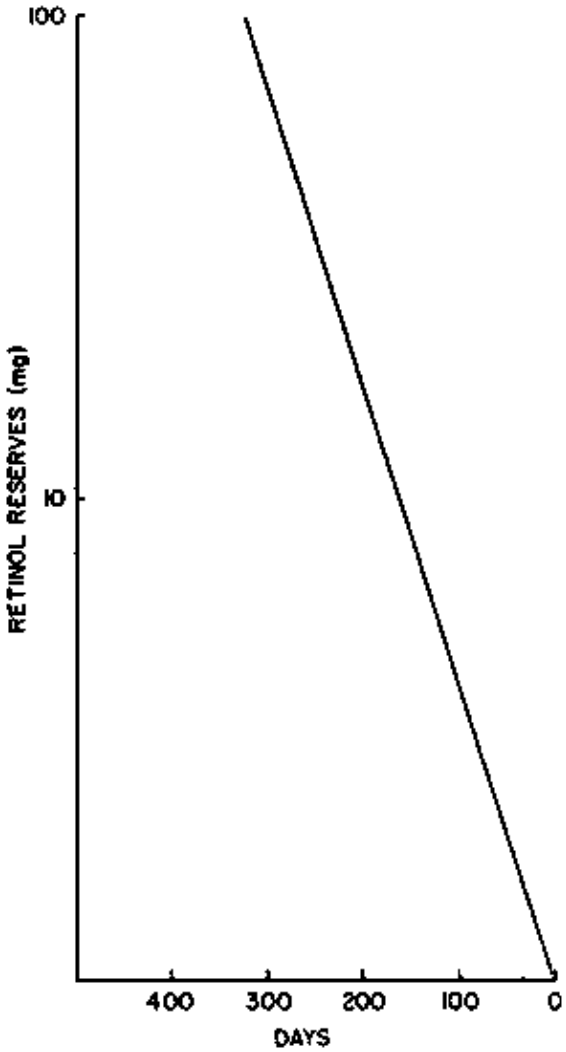

Figure 5 – Estimated Relationship Between Total Body Vitamin A and the Period of Protection Against Vitamin A Deficiency[90, 94]

Table 3 summarizes controlled studies that prospectively investigated the effects of a single large oral dose of vitamin A on serum retinol levels. Firstly, while each study has an acceptable comparison group, follow–up varies between studies, from essentially complete at six months(31) to approximately 50% at 22 weeks.(101) Secondly, the vitamin A dosage employed varies from study to study, ranging from 50,000 to 300,000 IU. Thirdly, subjects were followed for varying periods of time. And lastly, the populations differed markedly in their baseline vitamin A status, and presumably in their subsequent level of dietary vitamin A intake.

Results of a single large oral dose of vitamin A, in Table 3, do not leave a clear impression of long–term efficacy in maintaining elevated serum retinol levels. The study of healthy, breastfed newborns by Thanangkul et al.(102) suggests a prolonged elevation of serum retinol above control levels for up to 7.5 months ($p<0.01$), following a single supplementation with 50,000 IU of retinyl palmitate. Although the control infants also had normal vitamin A levels (>20 mcg/dl) during the first 36 weeks (values not shown in Table 3) without any vitamin A supplement, their serum retinol levels had fallen below 20 mcg/dl at 42 weeks, while supplemented group levels remained normal (18 vs 32 mcg/dl, respectively).

In Jordan, Patwardhan et al.(47) demonstrated similar elevations of serum retinol levels above baseline ($p<0.01$) in both 300,000 IU and placebo recipient infants after two months. After twelve months (not shown in Table 3) only 50% of the infants were successfully followed; serum retinol levels were still similar and acceptable in both groups, (29 versus 26 mcg/dl, respectively), i.e. no effect of a 300,000 IU vitamin A was observable in this study.

In India, Pereira and Begum(103) demonstrated that two weeks following a 182,000 IU oral dose of retinyl palmitate, vitamin A remained some 7 mcg/dl higher in experimental versus control group, among two– to five–year–old children with normal baseline serum retinol values. Both groups had an apparently acceptable baseline vitamin A status despite having received a low beta–carotene diet (300 IU or 30 mcg RE/day) for three months prior to the study. Though this difference was not statistically significant between two weeks and

ten weeks, the supplemented recipients appeared to retain more serum retinol for over 10 weeks, after which average serum retinol values steadily decreased to low levels in both groups. Subsequent re−dosing of the same amount to the same children, including the previous control group, elevated serum levels to approximately 30 mcg/dl one week later. The average concentrations remained at or above 20 mcg/dl for 11−15 weeks following this dosage (not shown in Table 3).

In a second study by these same authors among children with low baseline vitamin A status,(104) the ability of a single 50,000 IU dose of retinyl palmitate to elevate and maintain serum retinol levels was influenced by the quantity of beta−carotene in the diet. The supplement had no effect when recipient and control children regularly consumed some 15−30 grams of dark green leaves per day (approx. 150 mcg RE) throughout the 18 week follow−up period (not shown in Table 3). However, during a beta−carotene deficient diet (approx. 20 mcg RE/day), vitamin A supplemented children displayed significantly and acceptably elevated serum retinol levels for up to eight weeks compared to the low concentrations among unsupplemented controls, as shown in Table 3. After that time, levels among the supplemented children gradually decreased, becoming deficient by 18 weeks (12±3 mcg/dl). Pereira and Begum(105) had already shown that a diet of 30 grams of dark green leafy vegetables per day for three months could elevate serum vitamin A levels from a baseline of 22 mcg/dl to 32 mcg/dl. More importantly, when a group of these same children were later placed on a controlled, low beta−carotene diet (30 mcg RE/day), serum retinol continued to remain at acceptable levels (>20 for mcg/dl) for more than five months.

TABLE 3

CONTROLLED STUDIES ON THE EFFICACY OF A SINGLE LARGE ORAL DOSE OF VITAMIN A TO ELEVATE AND MAINTAIN SERUM RETINOL LEVELS FOR EXTENDED PERIODS OF TIME

Authors (Ref)	Country	Age	Dosage (in 000's)	Number		Follow up period	Serum retinol (mcg/dl)±SD	
				E(1)	C(2)		E(1)	C(2)
Patwardhan et al.(47)	Jordan	0−6 mos	300 IU	57	58	Initial	14+10	17+7
				57	58	8 wk	26+20	26+23
Pereira and Begum (103)	India	2−5 yrs (healthy)	182 IU	14	16	Initial	26+8	25+7
				14	16	2 wk	28+7(a)	21+6
				14	16	10 wk	25+9	22+5
				14	16	25 wk	14+6	12+3
Pereira and Begum (104)	India	2−6 yrs (healthy)	91 IU	12	12	Initial	13+4	13+3
				12	12	2 wk	29+6(c)	15+3(d)
				12	12	8 wk	20+6(a)	15+4(b)
				12	12	18 wk	12+3	11+2
Thanangkul et al. (102)	India	newborns (healthy)	50 IU	62	59	Initial	15+1	13+1
				62	59	18 wk	29+2(c)	20+1(d)
				62	59	30 wk	37+3(a)	26+2(b)
				62	59	42 wk	32+5(a)	18+3(d)
Dhanamitta et al. (101)	Thailand	preschool	100 IU	78	78	Initial	14	15
			(24 mos)	54	54	10 wk	22	18

			or	39	39	22 wk	19	17
			200 IU					
			(?24 mos)					
Kusin et al. (31)	Indonesia	1–5 yrs	300 IU	134	134	Initial	16+6	16+6
				99	85	12 wk	18+8	18+6
				134	134	24 wk	16+6	17+8

(1) Experimental group
(2) Comparison group (control or placebo)
a, b: difference significant at (0.01 < p <0.05) level
c, d: difference significant at (p < 0.001) level.

In Indonesia, Kusin and colleagues(31) found that a 300,000 IU supplement had no demonstrable effect on serum retinol measured after 3 and 6 months, among one– to five–year–old children with marginal baseline vitamin A status. Dhanamitta et al.(101) similarly demonstrated little or no discernible effect associated with a 100–200,000 IU supplement throughout 5 1/2 months of observation. In Brazil, Araujo et al.(106) have also reported no difference from baseline serum retinol levels 4 weeks after a 200,000 IU dose was administered to poor children consuming a low vitamin A diet (not shown in Table 3).

The critical importance of an appropriate concurrent comparison group in evaluating these results is obvious from the sometimes dramatic shifts in serum retinol levels, in either direction, observed over time from influences unrelated to the intervention itself.(47, 102, 103) In both the Jordanian and Thai infant studies(47, 102) in particular, lacking control groups, the data would have suggested a strong and persistent impact of the vitamin A supplement on serum retinol levels. However, inclusion of control groups showed the actual dose effect to be minimal or absent.

Based on these studies, the period during which elevated serum retinol levels can be maintained in children who initially exhibit low or marginal vitamin A status is highly variable, with optimistic estimates ranging from 8 to 42 weeks. Dietary intake of as little as 150 mcg RE/day from dark green leafy vegetables or other dietary sources of provitamin A may lengthen this period of protection.

PROTECTION AGAINST XEROPHTHALMIA(107)

The efficacy of large–dose vitamin A distribution in protecting against xerophthalmia was first suggested by results from a two–year field trial conducted in India,(49) during which 1785 one– to five–year–olds received an oral dose of 300,000 IU in oil once a year. The study design included no comparison group and the results suffer from a nearly 50% attrition rate at the two–year follow–up. Given these limitations, an 87% “prophylactic efficacy”(108) against Bitot's spots among three– to five–year–olds can be computed according to guidelines provided by Milton(109) for a pre–/post–intervention study design. While this effect cannot be entirely attributed to the annual dose of vitamin A, given the usual seasonal patterns of xerophthalmia and other influences on vitamin A status, the estimate is quite similar to those derived from better controlled studies noted below.

Table 4 presents results from three controlled clinical studies in which the follow–up period after each single vitamin A dose ranged from four to six months. In a study by Tarwotjo et al.(110), 2,680 one– to five–year–old, urban and rural, Indonesian children were examined and enrolled in a large–dose supplementation trial, with alternate assignment to either a vitamin A capsule or placebo capsule in a double masked fashion. The overall baseline prevalence of xerophthalmia was 4.7%. Children were carefully monitored for correct capsule receipt status, and 92% of the subjects were re–examined for xerophthalmia six months later, at which time a second vitamin A or placebo capsule was administered to children by the examination teams. At twelve months, 85% of the originally enrolled children were again examined for xerophthalmia. The findings show a striking and statistically significant difference in the six–month incidence of conjunctival xerosis and Bitot's spots: 0.5% among the capsule recipients versus 3.6% among placebo children, resulting in a prophylactic efficacy of 86%. Also, xerophthalmic lesions had completely regressed among 91% of the initial cases who were treated with a single 200,000 IU dose and successfully followed up at the six–month interval. Still, nearly 10% of the Bitot's spots persisted, representing either failure in efficacy

or sequelae from previous vitamin A deficiency that was no longer active, a sign often found among older children.(111) At twelve months (six months after the second capsule distribution), prophylactic efficacy remained at 90%, reflected by six–month incidence rates of 0.3% and 2.9% ($p < .001$) among vitamin A supplemented and placebo children, respectively.

During the Ichag Study in India,(112) Sinha and Bang reported equally striking differences in the incidences of night blindness (XN) and Bitot's spots (X1B) between preschool children receiving, in a double–masked design, either a 200,000 IU vitamin A or placebo capsule every 4 months. The seasonal dynamics of xerophthalmia incidence, in addition to numerous other disease and nutritional factors operating in the village, were first monitored for two years.(113) The vitamin A capsule and placebo intervention study then began during a third, subsequent year and children were followed each month for 10 months. Night blindness was essentially eliminated after the first vitamin A dosing and throughout the entire period of observation, while the prevalence of X1B was reduced by approximately 50% during the peak incidence season.(112) Receipt of the vitamin A capsule had no effect over the placebo in preventing recurrent Bitot's spots during the peak season among children who had exhibited X1B during the previous year.

TABLE 4

CONTROLLED STUDIES ON THE EFFECT OF A SINGLE LARGE ORAL DOSE OF VITAMIN A TO PREVENT XEROPHTHALMIA FOR AN EXTENDED PERIOD OF TIME

							Incidence or Prevalence of Xerophthalmia			
Authors (Ref)	**Country**	**Age**	**Dosage (000)**	**Number**		**Follow up period**	**XN**		**Clinical Signs(3)**	
				E(1)	**C(2)**		**E**	**C**	**E**	**C**
Tarwotjo et al. (110)	Indonesia	12–60 mos	200 IU every 6 months	1340(4)	1340(4)	Initial	NR(5)	NR	4.7%*	4.7%*
				1286	1183	6 mos	NR	NR	0.5%#(c)	3.6%(d)
				1197	1072	12 mos	NR	NR	0.3%#(c)	2.9%(d)
Sinha and Bang (112)	India	2–5 yrs	200 IU every 4 months	153	153	Initial	3.0%*	3.0%	7.0%*	7.0%
				153	153	4 mos	0.0%*	4.0%	10.0%*(a)	19.0%(b)
				153	153	8 mos	0.0%*	1.0%	5.0%*	7.0%
Kusin et al. (31)	Indonesia	1–5 yrs	300 IU	142	147	Base	NR	NR	2.7%#	2.1%
						6 mos	NR	NR	1.3%#	0.0%

(1) Experimental group
(2) Comparison group (control or placebo)
(3) X1A and/or X1B
(4) Approximate allocation
(5) Not reported
* Prevalence data
# Incidence data

a, b difference significant at (0.01 p 0.05) level
c, d difference significant at (p 0.001) level

Newly incident cases, however, were reduced from 8.8% among controls to 0.8% (not shown in Table 4), among supplemented children ($p < 0.004$), reflecting a degree of efficacy (91%) similar to that observed in Indonesia(110) and elsewhere in India.(49)

In a field trial conducted in North Sumatra, a six−month follow−up study showed no effect of a 300,000 IU dose of oral vitamin A on the occurrence of xerophthalmia.(31) Given the small number of cases observed in this study, these results neither support nor refute vitamin A large−dose efficacy in preventing clinical vitamin A deficiency.

Treatment of a sufficient number of outpatient children exhibiting mild xerophthalmia with a single, oral dose of vitamin A and observing their relapse rate over time may be most analogous to testing the prophylactic efficacy of a community−based strategy which successfully reaches those children most “at−risk” of developing corneal xerophthalmia. Sommer observed 48 Indonesian children with Bitot's spots who were eligible for examination at monthly intervals for up to 14 months following administration of a single 200,000 IU oral dose of vitamin A.(3) A modified life table analysis indicated no relapses at five to six months, with a 5 to 11% relapse rate at seven to fourteen months (Table 5).

TABLE 5

RELAPSE RATE OF BITOT'S SPOTS AMONG PRESCHOOL AGE INDONESIAN CHILDREN TREATED WITH A SINGLE 200,000 IU VITAMIN A CAPSULE

Follow−up(1)	Eligible for exam	Examined		Relapsed		
(months)	No.	No.	%	No.	%	Cum. %
1−2	48	33	68.8	0	–	–
3−4	47	20	42.6	0	–	–
5−6	44	19	43.2	0	–	–
7−10	35	19	54.3	1	(5.3)	5.3
11−14	24	18	75.0	1	(5.6)	10.9

(1) Maximum number of months for which treated children could be followed prior to termination of the study.

Data from Sommer. (3)

If a single, large dose of vitamin A is successful in treating corneal xerophthalmia, then it should also bolster vitamin A stores sufficiently to prevent corneal xerophthalmia (X2/X3) from developing in vitamin A−depleted children who have not yet developed corneal lesions. However, data on treating children with corneal xerophthalmia using a single dose of vitamin A is sparse. In Indonesia, 10 severely protein−energy malnourished children with corneal lesions were treated with a single 200,000 IU oral dose of vitamin A on an outpatient basis.(3) During the subsequent two weeks, 67% of the 15 diseased eyes (9 children) that were successfully followed were cured, while the remaining 33% had improved. One severely malnourished two−year−old child developed punctate keratopathy by the fifteenth day after treatment. Hospitalization was refused by the mother, and on the twenty−third day a house visit examination revealed bilateral, moderate corneal xerosis with ulcerations. Despite further treatment at that time the child expired two days later. Corneal deterioration also occurred in a second child within three months of receiving the single dose. The remaining 8 children showed no signs of relapse within six months after receiving the single dose, although one severely malnourished child developed corneal xerosis eight months after treatment. These few observations permit a cautious estimate of up to several months protection against corneal disease associated with a single 200,000 IU dose in children who are initially severely vitamin A−deficient and moderately to severely protein−energy malnourished. The early failures that occurred indicate that corneal xerophthalmia can respond to a single oral dose of vitamin A despite severe protein energy malnutrition, but absorption, storage and subsequent utilization may be too markedly impaired to achieve sustained protection.

Recently, Indian investigators have concluded a four−year, hospital−based, case−control study of the efficacy of 200,000 IU of vitamin A given every six months to prevent corneal xerophthalmia.(114) Children with

corneal xerophthalmia (n = 32) and their nutritional status–matched controls (n = 99) from 375 slums in Hyderabad and Secunderabad were questioned about their previous receipt of at least one large dose of vitamin A during the previous year in the community. Over 90% of all cases were severely protein–energy malnourished. Ninety–four percent of the cases versus 55% of the controls had not received a large dose of vitamin A from a programme which had achieved an overall coverage of 87%. An odds ratio of 12.5 (95% confidence limit: 3.2, 49.5) was computed to approximate the relative risk of developing corneal xerophthalmia among severely malnourished children who did not receive a vitamin A dose in the intervention programme. The efficacy of the 200,000 IU vitamin A dose in preventing corneal xerophthalmia was 92% [e = 100(12.5–1/12.5)]. Assuming that cases and controls broadly represent their respective populations “at large” of malnourished children in these slums, this study provides the first quantifiable estimate of risk protection against severe xerophthalmia conferred by a 200,000 IU dose of vitamin A. Moreover, incidence of corneal xerophthalmia, measured by monitoring hospitalized cases from study areas, decreased more than four–fold from 0.47 to 0.10 per 1,000 per year in distribution areas during the four–year study, while incidence in non–programme slums varied between 0.80 to 0.60 per 1,000 during this same time period.(114)

Evidence from controlled and other supportive clinical studies suggest a 90% or better protection against developing mild xerophthalmia for at least four to six months. A similar high degree of protection appears to be conferred against corneal disease as well. These conclusions support the use of supplementary vitamin A to prevent vitamin A deficiency and nutritional blindness.

3. VITAMIN A DELIVERY SYSTEMS

Three basic delivery systems have evolved for large–dose vitamin A supplementation in the community: medical or therapeutic, targeted, and universal.

MEDICAL DELIVERY

Medical delivery is essentially a low–cost, low–output, narrowly focused, “targeted” system which involves treating children with xerophthalmia as well as those at particularly high risk of developing eye signs, for example, children with severe PEM, diarrhoea, or measles. It typically represents the first intervention in an endemically vitamin A–deficient area, since it is treatment–oriented, requires little data on the distribution of disease in the community, uses small quantities of supplies, involves upgrading already–trained medical and paramedical workers, and is carried out through existing government and private health facilities. At present, this system represents the sole distribution mechanism in several African countries where xerophthalmia is known to exist, but where the magnitude and severity of the disease in high–risk regions have yet to be more firmly established.(116) Medical distribution is nearly always a component of “targeted” and “universal” delivery in countries where these latter interventions exist, at least within designated programme areas.(23)

TARGETED DELIVERY

Targeted delivery attempts to prevent xerophthalmia among high risk groups in the population (e.g., all children under 6–years–old, lactating and non–pregnant women in the child–bearing years) who present to the health care system. It is often carried out in regions where no universal distribution exists, and seeks to exploit the existing health care infrastructure by delivering vitamin A, every 4–6 months, at every point of interaction between the health care system and the community, including occasional mass immunization campaigns(117, 118) and refugee relief operations.(119) In addition to maintaining sufficient vitamin A stock levels and staffing primary care facilities with trained personnel, effective, targeted delivery of vitamin A depends directly on the routine access of health services by these “at–risk” members of the community. Low and sporadic clinic utilization rates often do not permit specific dosing intervals to be routinely achieved. Haiti provides the most thoroughly documented targeted delivery system to date which aims to provide supplemental vitamin A to all 6–month to 7–year–olds and lactating (non–pregnant) women who present to clinics.(117, 120)

UNIVERSAL DELIVERY

Universal delivery comprises the most widely practiced of the three intervention systems, aiming to dose all children of defined age (and other designated groups) within communities in specified regions with a large dose of vitamin A according to a pre−established time schedule. Programmes are usually single−purpose at the outset,(17) whereby the actual dosing and documentation of beneficiary receipt is the sole function of the distributor. Eventually most programmes incorporate vitamin A distribution into broader packages of health care services utilizing multi−purpose workers.(17, 23) Implementation may be carried out according to locally established schedules or on a national or regional “crash” basis (i.e., within a 1− to 4−week period every 6 months). Actual distribution can occur either at a central site in the community with some degree of home follow−up to reach missed children,(121) or house to house.(121−123) The output of universal delivery (i.e., capsules distributed) can be expected to exceed a targeted system by 3 to 8 times on a population basis.

4. MEASURES OF DELIVERY PROGRAMME EFFECTIVENESS

Few vitamin A distribution programmes have been evaluated according to observed changes in the serum retinol distribution in the target population. This is appropriate in light of the generally poor response of serum retinol to a single large dose of vitamin A under conditions of marginal to low vitamin A status, and the desire to measure programme impact in terms of the primary clinical goal. Thus, achievement of an acceptable reduction in the prevalence of mild to severe xerophthalmia constitutes the criterion by which programme effectiveness is usually evaluated.

To measure the reduction in prevalence of xerophthalmia in programme evaluation, several techniques may be applicable:

1. Pre−/Post−Intervention Difference, which measures the difference in prevalence between baseline and a second point in time following programme implementation.

2. Intervention and Comparison Population Difference, which measures changes in prevalence of vitamin A deficiency in a programme population compared with a concurrent comparison population.

3. Slope Test For Association Between Age and Prevalence, which permits programme effect to be estimated without baseline prevalence data.

4. Estimator of Population Prophylactic Efficacy, which permits the reduction of prevalence to be estimated at specified programme coverage rates, based on calculated changes in relative risk.

PRE−/POST−INTERVENTION DIFFERENCE (d)

A widely used(42, 124−127) measure of impact involves computing the difference (“d”) in xerophthalmia prevalences between a baseline (p1) and a second (p2) point in time following implementation of the programme such that d = p(1)−p(2). Often “d” is re−expressed as a percent change, q, from baseline prevalence such that q = (1−p2/p1)100. This difference reflects a degree of association between the operation of a vitamin A intervention programme (at a stated coverage) and a change in disease prevalence during the interval. However, the larger the reduction in prevalence of xerophthalmia and the shorter the time period over which reduction takes place (e.g., 3 to 6 months), the more likely a causal inference can be made, especially if “d” is found to decrease consistently across various population groups. Further credibility is earned by this measure if “d” is observed to vary with adequacy of coverage.

Confounding factors which obscure the interpretation of this measure of programme effectiveness in the absence of a comparison group include: (1) lack of control for the numerous seasonal, socioeconomic, cultural, and other environmental factors which can change dietary and disease patterns over time and, consequently, the incidence or duration of xerophthalmia in the community; and (2) the cohort effect which, because of the known positive age−xerophthalmia prevalence relationship,(128) can exert an independent effect on disease. Relevant dietary and disease patterns should be described during the period of intervention so as to consider these influences on “d”.

UNIVERSAL DELIVERY PROGRAMMES

Interim effectiveness evaluations that have employed a pro−/post−intervention design in several countries are summarized in Table 6. Each intervention utilizes the universal, biannual distribution of 200,000 IU of vitamin A, either in capsular(42, 126, 127) or bottled concentrate(124, 125) forms, with a health system−based vitamin A treatment component. Each evaluation controlled for seasonal but not annual variability in xerophthalmia prevalence. Marked differences exist among the evaluation methodologies in terms of sample design, xerophthalmia indicator used, rigor of observer standardization, and follow−up response rate. Moreover, each target population is likely to have had different nutritional and other risk factor profiles which would tend to influence the expected impact associated with the same 200,000 IU dose of vitamin A at a given coverage rate.

TABLE 6

SEVERAL PRE−/POST−INTERVENTION EVALUATIONS OF 200,000 IU VITAMIN A UNIVERSAL DISTRIBUTION PROGRAMMES

Location (Ref)	Year/Follow up period	Number studied	Percent coverage	Indicator(1)	Prevalence (%)	Indicator(1)	Prevalence (%)
Mysore, India (125)	1971	600	0	X	6.5	–	–
	1 yr	600	85	X	2.4	–	–
Kerala, India (124)	1971	4,913	0	X	6.0	–	–
	1 yr	4,752	65−70	X	1.3	–	–
Bangladesh (2, 3) (127)	1979	12,494	55	XN	3.3	X1B	0.50
	3 mos	12,494	100	XN	1.9	X1B	0.42
	6 mos	10,502	–	XN	1.0	X1B	0.24
	9 mos	10,128	100	XN	0.9	X1B	0.15
Cebu, Philippines (42)	1973	471	0	X	3.2	–	–
	2 yrs	471	78(4)	X	0.6	–	–
Nepal (126)	1980/81	1,326	NR(5)	XN	0.45	X1B	3.37
	6 mos	1,400(6)	NR	XN	0.14	X1B	2.24

(1) X = all signs of xerophthalmia (in the Philippino Study “X” is accompanied by serum levels of 20 mcg/dl). All other symbols denote the WHO classification (Table 1).

(2) Study conducted only among high prevalence villages throughout country.

(3) Initial assessment in 1979 represents prevalence under usual coverage conditions since the survey occurred several months after the 10th capsule distribution cycle (assumed to achieve 55% coverage) but prior to the 11th cycle during which 100% coverage was reported. The 3 and 6 month surveys would have been conducted after the 12th cycle.

(4) Percent coverage among 1−16 year olds after the second distribution at one year.

(5) Numbers as reported (cross sectional study).

(6) Not reported.

The Indian,(124, 125) Filipino,(42) and Nepalese(126) studies address the effectiveness of their respective programmes during either the pilot phase or first one year to three years of operation. The Bangladesh results(127) refer to an evaluation conducted after the programme had been in operation for several years.

The Indian studies comprise the earliest series of impact evaluations under actual programmatic conditions. While more than half of the 1285 1− to 3−year−old children enrolled into the Mysore study(125) were lost to follow−up, the baseline prevalence rate is reported only for the 600 children who were successfully re−examined one year later providing a basis for limited interpretation. The large Kerala study(124) achieved a remarkable 97% follow−up response rate. Results from both evaluations show reductions in the prevalences (q) of xerophthalmia of 78% and 63%, respectively, after two 6−month vitamin A distribution cycles which had achieved 65 to 85% coverage rates. A similar study in Karnataka State reported an associated 74% reduction in prevalence.(17, 129) The magnitude and consistency of the direction of changes in prevalence across these populations suggest a strong programme effect, which served to justify the expansion of India's periodic vitamin A prophylaxis programme to a national strategy in the mid−1970s.

Results from the Bangladeshi evaluation in 1979−80 form part of that country's extensive ongoing efforts to assess the impact of its national capsule distribution programme.(127) The investigation involved a special impact survey in areas of known high risk of xerophthalmia where 100% coverage was reported for two consecutive distribution cycles. Despite this complete coverage rate, the programme was still unable to reduce XN to substantially less than 1.0%, reflecting 73% efficacy associated with a 6−monthly dosing schedule in these high−risk areas. In contrast, in adjacent West Bengal, XN was entirely eliminated from Ichag Village when 200,000 IU were delivered to children every 4 months.(112) The pre−/post−intervention findings on X1B rates also suggest a prophylactic efficacy of 70%. This estimate may be conservative since initial prevalence rates were observed after the ongoing capsule distribution programme had already achieved an approximate 55% coverage on the previous distribution cycle.

In the Philippines,(42) a two−year field trial was conducted to test the relative effectiveness of three vitamin A intervention strategies: fortification of monosodium glutamate (MSG), 200,000 IU vitamin A (plus 40 IU vitamin E) capsule distribution, and a multifaceted public health intervention (PHI). Both fortification and capsule distribution resulted in reductions in the prevalences of xerophthalmia but only fortification elevated and maintained acceptable serum vitamin A levels. The PHI population experienced an insignificant decline in xerophthalmia prevalence, as veil as a reduction in mean serum retinol level. Prevalence of clinically active disease (i.e., clinical signs accompanied by serum retinol levels <20 mcg/dl) decreased 80% with the capsule programme (Table 6) at coverage rates of 90% and 78% during the first two cycles. The problems of attributing the entire 80% reduction in xerophthalmia to the capsule delivery programme are discussed later.

In Nepal,(126) a repeat survey conducted 6 months after initiation of a capsule distribution programme shoved a 67% reduction in the prevalence of XN accompanied by a decline in X1B of only half that magnitude. A similar refractory response of Bitot's spots to vitamin A therapy has been observed elsewhere among older children,(3, 112) particularly in India,(112) and may represent persistent, non−responsive conjunctival metaplasia.

Taken together, these findings suggest that a universal vitamin A distribution system that achieves reasonable coverage of its target group (e.g., 65% or better) can have a favorable impact on mild xerophthalmia. Percent reductions in xerophthalmia associated with one or more 6−month distribution cycles generally range from 60 to 80% of the baseline prevalence estimates.

TARGETED DELIVERY PROGRAMMES

A pre−/post−intervention design has also been utilized to evaluate the Haitian xerophthalmia prevention programme.(117) This intervention differs from those previously discussed in that capsule distribution is specifically targeted to sick, malnourished, and all clinically treated children 6 months to 7 years of age and to lactating non−pregnant mothers. In addition, single doses are distributed to all children during periodic vaccination campaigns. Usual distribution is implemented through existing hospitals, health clinics, and nutrition centers, which achieves an approximate 10% coverage rate. A 1975 baseline survey of 5,000 children estimated a prevalence of corneal scars due to xerophthalmia (XS) of 8.1/1,000 in the northern districts of the country.(130) The prevention programme was implemented within a year and a follow−up survey in 1979 showed a 9−fold reduction in XS to 0.9/1,000. While this dramatic decline in the corneal scar

rate suggests a highly effective impact on disease in relation to the minimal programme coverage, the investigators cautiously note a variety of other events which occurred in the population during the four–year interval between surveys, including widespread distribution of vitamin A–fortified dried skim milk in schools, a new highway in the region providing improved access to the capital Port–au–Prince, and an above–average rainfall during 1978. Still, given the cumulative nature of corneal scars, it is unlikely that recent environmental improvements alone would produce a reduction in prevalence of this magnitude.

INTERVENTION AND COMPARISON POPULATION DIFFERENCES

Concurrent observation of a randomly selected, non–intervention, comparison population permits direct estimation of the effect of a large–dose vitamin A intervention programme. Upon demonstration of a relatively similar initial risk of xerophthalmia in both the comparison and the intervention populations, the percent change in prevalence in the comparison group may be used to adjust the baseline prevalence of the intervention group. This adjusted prevalence is used to derive the percent change in xerophthalmia attributable to programme impact. (162)

Often randomization of communities to intervention programme status is socially and politically unacceptable and unethical in the presence of adequate programme resources and high risk of vitamin A deficiency. In a region of apparently uniform risk of disease and where limited programme resources necessitate a gradual implementation, it may be possible to prospectively follow both intervention and non–intervention communities for a limited period of time. While the use of a concurrent comparison group requires a sophisticated evaluation design, high technical input, and a large study population, and is itself expensive, it provides a rigorous method to assess the impact of an ultimately much more expensive vitamin A distribution campaign.

Two studies, in Bangladesh and the Philippines, have used concurrent comparison groups in assessing the effectiveness of the universal 200,000 IU vitamin A capsule distribution programme. One of the several capsule programme evaluations in Bangladesh(127) included prevalence surveys conducted in each of 1979 and 1980 (n = 3651 and 2409, respectively) in several areas throughout the country where 60% programme coverage had been achieved at approximate 6–month dosing intervals since 1975, and in a single “comparison” area where, despite no formal programme input, sporadic distribution may have previously occurred (n = 578 and 815 in 1979 and 1980, respectively). In the intervention areas, the prevalence of XN declined from 2.8 to 0.8%, X1B remained at approximately 0.8%, while X2/X3 appeared to increase from 0.14 to 0.33%. In the comparison area, increases were observed in XN from 3.0 to 5.6%, X1B from 1.5 to 4.0%, and X2/X3 from 0.17 to 0.36%. These results suggest that 60% coverage, at a distribution interval of about 6 months, may have a considerable impact on mild xerophthalmia (i.e., XN and X1B).

This differential impact on mild and severe xerophthalmia may be due to poor coverage of children most “at–risk” of corneal xerophthalmia (X2/X3) or to a dosing interval (e.g., > 6 months) which extends beyond the conferred period of protection against severe xerophthalmia, particularly in children who are moderately to severely protein–energy malnourished.(5, 82, 131–133) As previously noted, severely malnourished and xerophthalmic (X2/X3) Indonesian children treated with a single, large dose of vitamin A began to relapse from two weeks to several months after treatment.(133) However, a problem which clouds the above study is the question of comparability between the intervention and comparison populations, the former being selected by an unreported technique from several areas around the country, while the comparison region (Dinajpur) is among the poorest and most famine–stricken areas in Bangladesh.(134)

The Filipino study was an evaluation of the relative effectiveness of MSG fortification, capsule distribution, and PHI strategies,(42) the latter not being a direct vitamin A intervention. Because communities within each of four ecological study zones were randomized to an intervention, and the PHI population appeared to change very little in vitamin A status during the two–year study period, this latter group could be viewed as a concurrent comparison group.(135) Prevalence of active xerophthalmia in the capsule intervention group decreased 80% from 3.1 to 0.6%, but prevalence in the PHI “comparison” population also decreased from 4.9 to 3.4%, a 30% reduction. Under an assumption of no PHI effect, the prevalence in the capsule areas would have decreased from 3.1 to 2.5% (i.e., 30%) without a distribution programme. Thus, an approximate 70% reduction in xerophthalmia could be directly attributed to the capsule programme.(163)

SLOPE TEST FOR ASSOCIATION BETWEEN AGE AND PREVALENCE

In general, there is a positive association between the prevalence of mild xerophthalmia (especially X1B) and age among preschool children. Figure 6 depicts this relationship as reported from prevalence surveys in several different countries.(110, 113, 128, 136, 137) Based on this age trend, Indian investigators have introduced an evaluation method which permits an assessment of programme effect on mild xerophthalmia in the absence of a baseline prevalence estimate. They had already noted that this general trend for prevalence–on–age was essentially absent (slope = +0.65%) from Indian communities where a universal vitamin A distribution programme had been introduced and achieved at least 85% coverage.(128)

To evaluate programme effectiveness throughout the country, prevalence surveys were conducted among 1– to 10–year–olds in areas where large–dose (i.e., 200,000 IU) vitamin A distribution had been in operation for two years or more. A test for a linear trend in proportions(138) was applied to the regression of X1B prevalence on age among 1 to 5 year olds in each of these intervention areas,(128, 139) against a null hypothesis of the slope being significantly larger than either zero or 0.65% (Figure 7). Testing against the latter slope value recognizes some degree of dose inefficacy and imperfect coverage associated with even acceptably performing programmes.

While a positive slope which significantly departs from the null hypothesis is interpreted to reflect ineffectiveness, a slope that does not depart from it significantly may either indicate true impact or that a programme had been operating in an initially low–prevalence area. To account for this, high– and low–risk regions were identified by noting the prevalence of X1B among 6– to 10–year–olds, a non–targeted age group. A prevalence of 3% or more was assumed to reflect communities previously at high risk of xerophthalmia, for which slope values were then evaluated. Investigation of this relationship in India showed that among areas where programme data were analyzable, adequate coverage was strongly associated with a flat slope, and poor coverage with a significantly positive slope.(139)

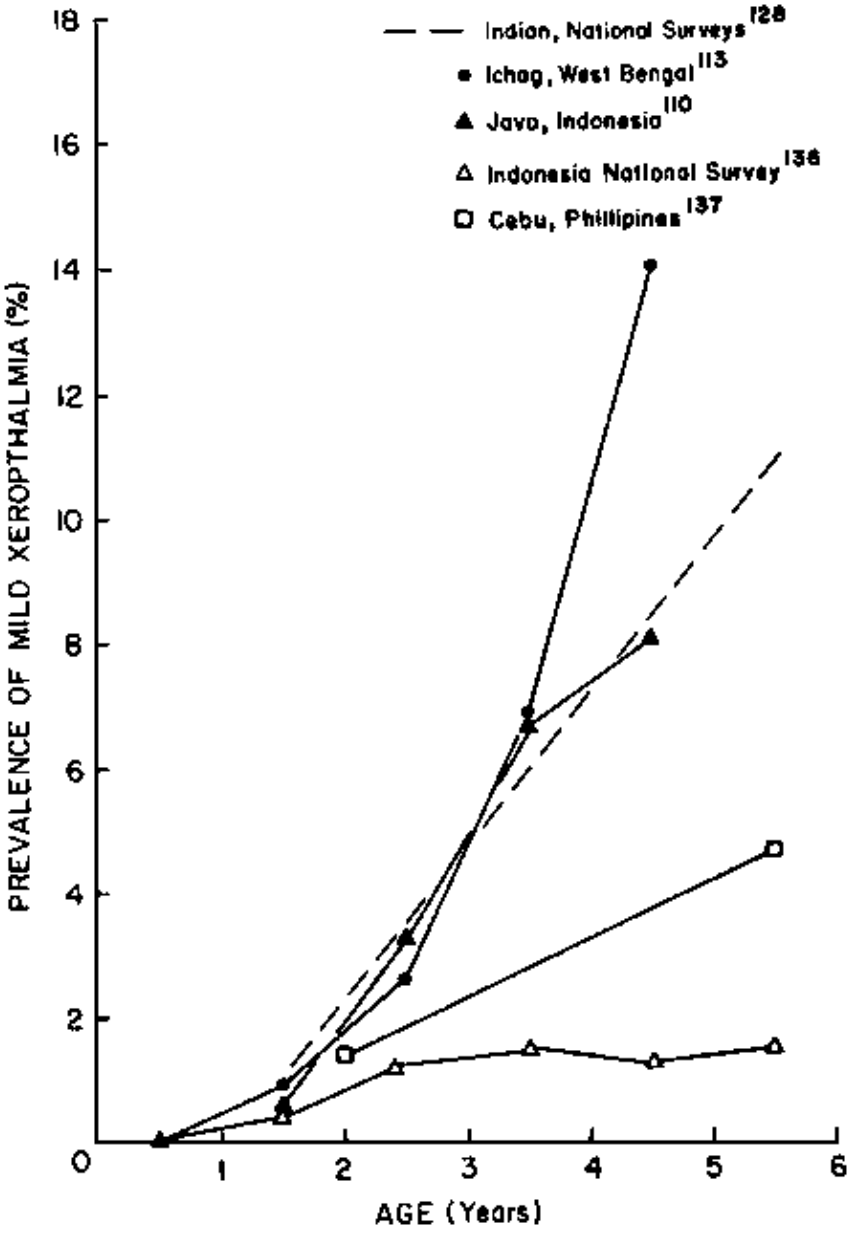

Figure 6 – Association Between Age and Prevalence of Mild Xerophthalmia Among Preschoolers in Several Asian Countries.

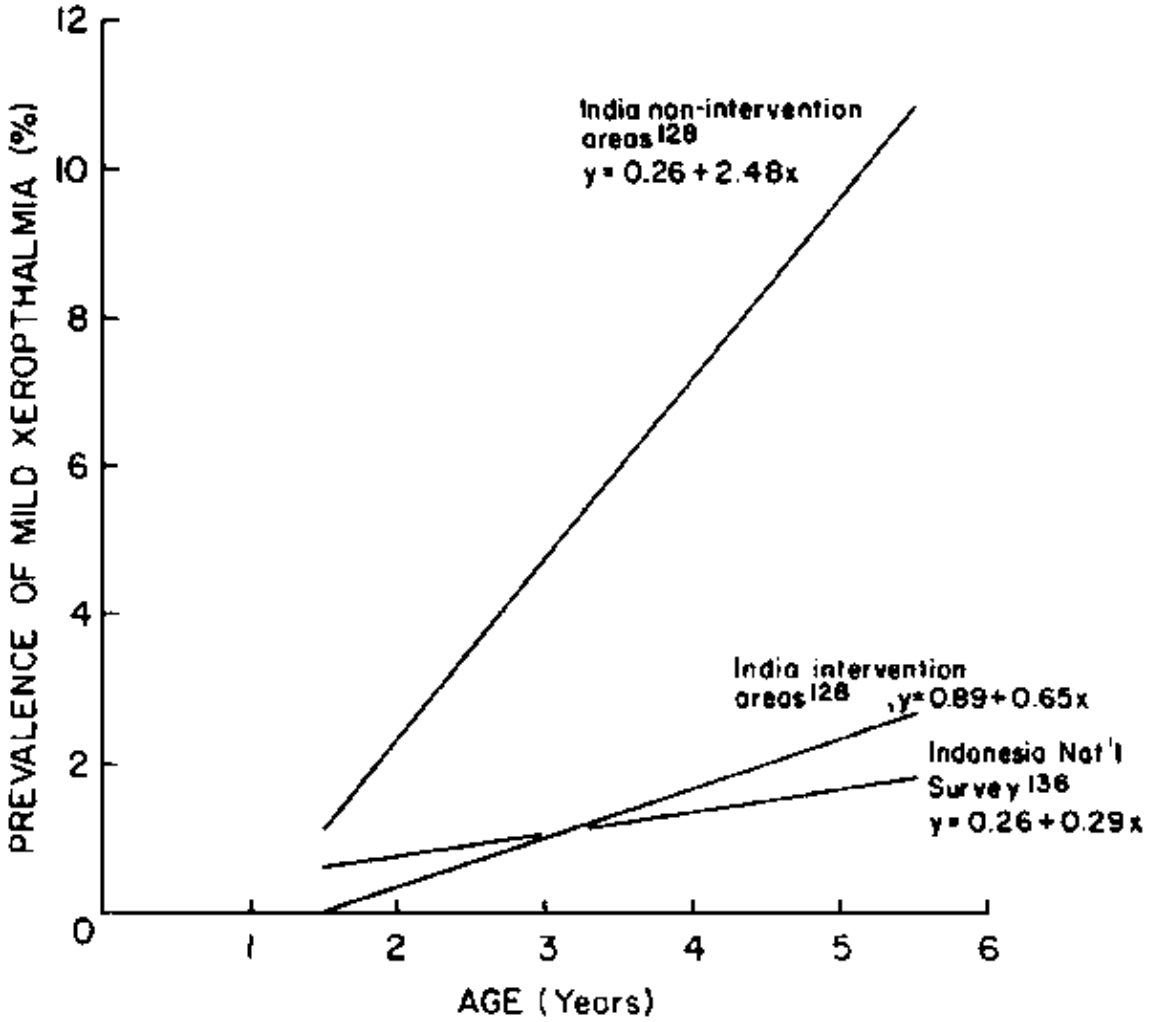

Figure 7 – Simple linear regression equations describing relationship between prevalence of mild xerophthalmia and age in intervention and non–intervention areas in India, and from prevalence survey in Indonesia.

This highly innovative technique permits evaluation of a distribution programme in previously high–risk areas in the absence of suitable baseline data. However, the results may be subject to the same confounding influences which complicate the interpretation of "d" in the absence of a comparison group and require an assumption of a positive relationship between prevalence and age which may not always have existed. During the national xerophthalmia survey in Indonesia from 1976 to 1978,(136) the estimated regression coefficient of X1B on age (Figure 7) was +0.29%, well below the null value of +0.65% used in India, reflecting a relatively weak association between age and prevalence of X1B. Prevalence among 6– to 10–year–olds was not ascertained, although based on this criterion an interpretation of low risk might reasonably be made since few mass distribution programmes were ongoing among the numerous surveyed areas. However, as seen below, practically all of the age–specific prevalence rates of active corneal xerophthalmia (X2/X3) and xerophthalmic scars (XS) in this same multi–regional population were well above the WHO minimum criteria for public health significance presented earlier in Table 1:

RATE PER 10,000

Xerophthalmia	Age in Years					All Ages	
Status	1	2	3	4	5	Unweighted	Weighted
X2/X3	5.0	14.7	9.8	3.6	1.6	7.1	6.0
XS	10.2	24.7	32.7	28.6	17.8	15.9	13.0

While there are likely to be substantial differences in the prevalence and severity of contributory factors in India and Indonesia, the latter population is an example where a relatively flat slope of X1B on age was associated with a high prevalence of severe xerophthalmia across most age groups.

ESTIMATOR OF POPULATION PROPHYLACTIC EFFICACY

Prophylactic efficacy (e), as noted earlier, is based upon the computed relative risk of disease generated from a cohort or case–control study under conditions of nutrition, disease, and environment which ate similar to those experienced by the actual target population. This measure specifies the percent reduction in xerophthalmia that can be expected from initiating a large–dose vitamin A intervention strategy which achieves 100% coverage of all "at–risk" individuals (i.e., the upper limit of programme effectiveness) at a specified dosing interval. However, since vitamin A distribution programmes never achieve complete coverage, impact on xerophthalmia prevention in the population in terms of percent prevalence or incidence reduction will vary with programme coverage (ep).(164)

As the proportion covered increases to near 1.0 (i.e., 100% coverage), the prophylactic efficacy of the large vitamin A dose previously estimated under the prevailing conditions of disease risk in the target population will approach 100% efficacy. The proportion of the remaining xerophthalmia in the population which could be eliminated if all "at–risk" children were to receive the supplement can also be determined (the population attributable risk – PAR).(140, 165).

The usefulness of the population prophylactic efficacy measure (ep) rests on the degree to which the estimated relative risk correctly applies to those children in the target population who typically are missed by the distribution programme. Use of a relative risk which relates to the entire target population carries an assumption that the probability of developing xerophthalmia in the absence of a large dose of vitamin A is similar between children who would and would not be dosed; an assumption which appears not to hold in some countries.(42, 126) Milton(109) provides ample caution for applying and interpreting these percent efficacy and, by its association, population prophylactic efficacy measures.

The population prophylactic efficacy measure (ep) can be used to further evaluate the vitamin A distribution programme being carried out by the National Institute of Nutrition in the urban slums of Hyderabad, India.(114) The case–control–derived prophylactic efficacy (e) against corneal disease (X2/X3) associated with receipt of at least one capsule during the previous year was 92.5%. At 87% coverage of the targeted one– to five–year–old population, (ep) is 80%, or 80% of all children "at–risk" of X2/X3 in these communities are protected through their receipt of vitamin A in the programme. Although pilot in nature, since the nationally affiliated, state–operated prophylaxis programmes often achieve coverage rates of 50% or less,(139) this large urban study does provide the first evidence of effectiveness against potentially blinding corneal xerophthalmia by a universal delivery programme when supervision is excellent and coverage is high.

5. POPULATION COVERAGE

Although coverage and effectiveness are not necessarily synonymous, maintaining a programme's effectiveness in preventing xerophthalmia relies heavily on achieving high coverage of those individuals most "at–risk" of becoming vitamin A deficient. Paramount to this coverage–effectiveness relationship are the accurate targeting of high–risk groups (i.e., "operational target group"), particularly in terms of demographic strata and geographic locale, and the type of delivery system to be employed.

DEMOGRAPHIC STRATA

In Indonesia, the vast majority of mild, active xerophthalmia (X1B) occurs between the ages of two and four years, with few cases observed in younger years. Night blindness cannot generally be detected below two years, and its prevalence decreases markedly by age five. Corneal disease peaks during the third year of life (age two years) with over 89% of cases observed between one and three years of age.(3) Thus, the one– to four–year age stratum may be considered a highly specific target group for periodic vitamin A distribution. The narrower the targeted age interval, the greater the loss in programme sensitivity (i.e., proportion of vitamin A–deficient children in the population reached by the programme) by not conferring protection to individuals outside this age group who are at high risk of disease. Incremental gains in sensitivity resulting from expansion of the target age interval are partially offset by losses in specificity (i.e., increased coverage of lower risk individuals). The balance between these two tendencies is eventually decided by the costs of being more effective.

During two sequential immunization campaigns in El Salvador, dosing children one– to six–years of age may have cut the programme's maximum effectiveness against corneal xerophthalmia by 50%, since half of the corneal cases were later estimated to occur at either less than one year or over six years of age.(118, 141) Actual coverage of the operational target group was about 80% suggesting programme effectiveness over an assumed 6–month period of protection to be only 36%, at a 90% dosage efficacy against corneal disease. During the early phases of the Indonesian universal capsule distribution programme, only children 12 to 48 months were dosed, potentially restricting maximum effectiveness by a factor of 0.82 (beyond dosage inefficacy) since 18% of corneal cases (X2/X3) identified in the 1978 national xerophthalmia survey were either less than 12 months or greater than 48 months of age. In practice, village level distribution often extends to children beyond the designated upper age limit due to the usual uncertainties about a child's age.(23)

GEOGRAPHIC LOCALE

Geographic targeting comprises the second stage in defining a programmatically feasible target population. Common associations between differences in wealth, food availability, dietary preferences, environmental hygiene, disease patterns, cultural practices and other risk factors encourage geographic clustering of xerophthalmia. In Indonesia, the national xerophthalmia survey found vitamin A deficiency clustered at the family, neighborhood, village and regional levels.(3) Although targeting individual families may be inefficient, focusing a programme by neighborhood in urban areas and clusters of villages within rural regions is likely to yield substantial gains in effectiveness while keeping the scope of intervention within practical and affordable limits. For example, in Bangladesh a more than six–fold difference in the prevalence of mild xerophthalmia has been reported by region.(38, 142) Based on these estimates, 100% target group coverage with vitamin A capsules in only the seven highest prevalence districts would theoretically reduce the national incidence of mild (and to some correlated degree, severe) xerophthalmia by two–thirds while reducing the number of capsules distributed to approximately one–third of current levels.(38)

TYPE OF DELIVERY SYSTEM

TARGETED DELIVERY

Given adequate utilization of health care services within endemically deficient regions, a combined medical and targeted distribution should be highly efficient in reaching and preventing nutritional blindness in the highest risk groups (i.e., ill and malnourished children). In Indonesia, 72% of 141 cases of X2/X3 presenting to the Cicendo Eye Hospital were classified as clinically ill, 58% with moderate to severe systemic illness.(3) In India, 83% of a series of 64 children presenting to the Government Erskine Hospital with X2/X3 were less than 60% of their expected weight for age, most of whom were marasmic with accompanying diarrhoea, worms, and upper respiratory tract infections.(143)

Evaluation of the Haitian targeted delivery system from 1976 through 1978 indicated that approximately 30% of its 6–month to 7–year–old population utilize the health care system (i.e., are “clinic attenders”).(117) Fifteen percent of the children in this age group live in Port–au–Prince, where approximately 30% of all capsules in 1978 were distributed, reaching nearly 60% of the clinic attending population. This reasonably high target group coverage rate is in stark contrast to other more rural districts in the country where little more than 25% of the estimated 270,000 clinic attenders had received a vitamin A capsule during the year. The enhanced urban utilization meant that approximately 18% of the entire Port–au–Prince 6–month to 7–year–old population were dosed at least once during the three–year start–up period through routine health service contact, versus only 8 to 10% in rural areas. These figures highlight the essential linkage between health services utilization and coverage in a targeted delivery system. The degree to which this limited rural coverage contributed to the previously observed nine–fold reduction in corneal xerophthalmic scarring rates(130) cannot be strictly ascertained, since other nutritional and environmental improvements in the area could have impacted on vitamin A status. However, even if only 50% of the reduction in XS prevalence can be attributed to the programme, targeted distribution merits further intensive investigation, given the low incremental input into an existing health infrastructure and modest increases in output (capsules, trained individuals, etc.) needed in relation to its potentially significant impact on xerophthalmia.

In Bangladesh, targeted delivery would appear to be a low−cost but potentially effective alternative in “lower” risk regions, to complement universal distribution in the higher prevalence areas. However, poor attendance at the primary health care center by high−risk, ill and malnourished children is likely to be a major constraint to the success of a targeted approach. A UNICEF study in Bangladesh has shown that only 13% of seriously ill and even fewer mildly ill patients receive treatment at local health centers.(38) Another study indicated that less than a third of seriously ill individuals receive care from any doctor or government health facility.(38)

UNIVERSAL DELIVERY

Generally, properly conducted house−to−house distribution offers a better chance of achieving higher coverage of children than does targeted delivery, especially of those who are ill and malnourished, though it may be more time−consuming for the field worker. Typical numbers of children reportedly dosed per worker day may range from 20 to 40,(110, 120) rarely exceeding 100−200.(139) Coverage at each distribution cycle is usually considered adequate if it reaches at least 80% of the designated target population. A successful programme must sustain this high−level performance over time. Each of the eight or so distribution cycles required by young children throughout their most vulnerable years presents a renewed challenge to the system. Unfortunately, highest target group coverage is usually achieved only at the outset of the programme, followed by a gradual decline to a markedly lower level as seen in Table 7. Few evaluations have been reported that investigate impact on disease associated with this gradual decline in coverage. In the first Indian evaluation listed, a more than four−fold reduction in the prevalence of X1B from 3.2 to 0.7% was noted after the first two distribution cycles.(79) However, prevalence figures were not reported after the next two cycles, during which coverage had fallen to an estimated 6% of those children who were eligible. Even at sustained, acceptable levels of coverage, there is continuing concern about whether children at greatest risk of xerophthalmia are reached on a regular basis,(110, 121, 123) and whether coverage of these children is at least proportional to overall coverage of the population. The national prophylaxis programme evaluations in India(139) and Bangladesh(127, 144) have shown there is no measurable effect on xerophthalmia when universal coverage is less than 20−25%. This stands in marked contrast to the potential impact of targeted delivery when overall coverage is only half this proportion but directed toward a higher risk operational target group.(117)

TABLE 7

REPORTED COVERAGE RATES ACHIEVED DURING UNIVERSAL LARGE DOSE VITAMIN A DISTRIBUTION PROGRAMMES

Target	Percent (%) of target population dosed					
Country (Ref)	Population		Cycle	Cycle	Cycle	Cycle
size	I	II	III	IV		
India (79)	NR(1)	85(2)	47	21	6	
India (122)	24x10(6)	20−80	20−90	NR	NR	
Bangladesh (127)	16x10(6)	78	67	58	63	
Philippines (42)	1,200	90	78	78	−	
Indonesia (110)	96,000	87	77	71	53	

(1) Not reported
(2) Assumed initial rate of coverage.

6. PROGRAMME CHARACTERISTICS

ORGANIZATIONAL NETWORKS

An overview of vitamin A distribution programme infrastructures for India,(17, 122) Bangladesh,(17, 123) Indonesia,(17) and Haiti(17, 117, 120) is presented in Table 8. Although some differences exist, particularly in terms of programme administration at the national level, the overall pattern of both universal and targeted systems is similar in that programme authority originates within the Ministry of Health, and ultimately distribution is implemented through the local primary health care center. In addition to formal activities within these networks, there is frequently close collaboration with other governmental, international, and private agencies, particularly to strengthen nutrition education programme components.

TABLE 8

VITAMIN A DELIVERY SYSTEM INFRASTRUCTURES FOR SEVERAL SELECTED COUNTRIES

Unit level	India(17, 122)	Bangladesh (17, 123)	Indonesia(17)	Haiti(17, 117, 120)
National				
Directive:	MOH and Pop, Dir Health Services	MOH, Dir Health Services	MOH, Dir Community Health	MOH and Pop, Dir Nutrition Bureau
Administrative:	State Health Dept (Family Welfare Office)	Divisional Dir Health Services	Provincial Health Services	Regional Health Office
District				
Administrative:	District Health and Family Planning Office	District Commissioner	District (kabupaten) Health Office	District Health Office
Local				
Administrative:	Primary health centre and sub−centre	Thana health centre	Primary health centre (puskesmas)	Health establishment (public, private)

Vitamin A is provided by UNICEF in the form of a 200,000 IU capsule with 40 IU vitamin E in each listed country except India, where the Government provides an arachis oil concentrate that is manufactured in−country and distributed in 100 ml bottles.(23) In other countries, procurement involves a formal request from the government to UNICEF for a specified quantity of capsules. UNICEF processes all requests and insures delivery to the country's port.(23, 117) Supplies are usually received by the national or central administrative unit, distributed to district or state depots, and dispersed from there to local health centers upon requisition. Capsules or concentrate are then issued to trained, single or multi−purpose workers for distribution.

A medical officer is usually responsible for overall programme management at the health center level. Several countries, including Bangladesh(123) and Indonesia,(145) assign programme administrative and supervisory responsibilities to trained health inspectors, nutritionists, and other non−physician personnel. Vitamin A distributor qualifications vary widely between country projects. Since most programmes were originally single−purpose, several countries attempted to recruit under−utilized or recently unemployed field workers from other mass, single−purpose campaigns such as malaria and yaws eradication, or BCG vaccination.(23, 110, 123) The single−purpose worker has steadily given way to increased usage of a multi−purpose health worker to improve overall health programme efficiency.

TRAINING COMPONENTS

An efficient prophylaxis programme requires personnel trained in vitamin A intervention rationale, administrative concepts, and procedural tasks appropriate to each level of activity. Usually a country's national nutrition institute undertakes the training of programme executive and administrative officers at the national and district levels. A basic curriculum would include the following topics:(23)

– Goals and objectives
– Rationale for vitamin A administration
– Organizational network
– Administrative and costing procedures
– Supervision
– Job tasks, including dosing techniques
– Beneficiary registration
– Record–keeping and reporting
– Appropriate nutrition education techniques
– Purpose and methods of evaluation

Distributors and their immediate supervisors at the primary health center level attend 1– to 4–day training seminars which, in addition to selected topics from above, usually cover the following issues in detail:(23, 117, 120, 121)

– Overall programme strategy

– Detection, treatment and prevention of xerophthalmia

– Specific job tasks including registration procedures, dosing technique, record–keeping, reporting, and nutrition education messages and techniques

– Purpose and techniques of supervision

– Importance of achieving maximum coverage

Continuing education and retraining, especially at the district and local level, are essential support activities which upgrade the skills of programme staff, facilitates information exchange and problem solving, and may have a measurable influence on programme performance. In Haiti, distribution centers from which staff attended two or more training seminars during the year were twice as likely to send in monthly reports than less participative centers.(117) In Bangladesh, district level re–orientation meetings to provide evaluation feedback to lower level programme supervisors has been associated with subsequent increases in reported coverage.(123)

Prior to implementation, villages tentatively selected for participation are visited by project officers to discuss the programme and gain local support. Information is provided and questions answered about vitamin A deficiency and blindness, the reason for periodic dosing, the dosing schedule and procedures, who receives the supplement, and other pertinent programme details.(23)

OPERATIONAL COMPONENTS

Despite meticulously planned periodic dosing programmes, operational difficulties arise at the national, regional, and local levels which may impair coverage and, ultimately, effectiveness. Most problems are related to the commitment, allocation, and mobilization of scarce personnel and other resources to provide continuous programme support. The basic difficulties are remarkably similar for targeted and universal delivery systems, although on different scales of operation.

LOGISTICS

Timely movement of adequate supplies of capsules or concentrate through channels to the peripheral sites is a prerequisite for an efficient delivery system. In Haiti, exhaustion of vitamin A central stores occurred four times over a five–year period. In only two of these years were peripheral stocks in the health establishments sufficient to buffer interruptions in capsule distribution. In each case, capsule depletion was attributed to delays in requisitioning stock from UNICEF by national programme managers and to “bureaucratic delays”.(117, 120) In Indonesia, an internal change in supply channels within the Ministry of Health caused a disruption in capsule distribution in two–thirds of its project areas for several months. Six hundred worker days were estimated lost and 20,000 children failed to receive their six–monthly dose.(110) Difficulty in transporting the concentrate on a regular basis has been cited as a frequent cause of short supply.(23)

COORDINATION

Although distribution programmes are usually operated through local health centers, other government agencies within the Ministry of Health may be responsible for programme implementation in different, but occasionally overlapping, rural areas of the country. Urban distribution is often implemented through a variety of hospital clinics, mobile teams, and private organizations. Different agencies working in demographically poorly defined areas pose the simultaneous risks of incomplete and duplicate coverage, as well as lack of standardization in distribution, reporting, and evaluation.(23) One potential solution may lie in coordinating all vitamin A distribution to occur during a single week (i.e., “Vitamin A Week”) every six months, as has been tested successfully in Indonesia.(146, 147)

SUPERVISION

At the national level, regularity of supervisory visits to regional or district staff may have a beneficial effect on motivating the timely submission of progress reports.(117) The corollary to this is that ineffective procedural review, feedback, and supervision of regional managers and staff do little to encourage supervision, routine submission of reports, and compliance with established field procedures at the local level. Central programme directors often have insufficient time to carry out effective monitoring and supervision due to multiple commitments to other health projects.(23) In India, where supervision of the vitamin A programme is one of numerous nutrition responsibilities assigned to the state nutrition officers, maintenance of records by district and local officers has been identified as the weakest administrative link in the national vitamin A prophylaxis programme.(122) Poor supervision and feedback are likely to contribute to what might be called “system fatigue”; that is, a gradual loss of motivation and interest among staff as the programme transits from the new to the routine.(23, 110) System fatigue may be reflected in incomplete child registration or coverage by the distributor, as well as by poor inventory monitoring,(23) record maintenance,(122) and compliance with monthly reporting procedures(117) at the health center level.

SUPPLY SHORTAGES

Depletion or shortage of capsules or concentrate at distribution points is consistently the most widely quoted reason for impaired programme performance at the local level.(23, 110, 117, 120, 122) Reasons cited include exhausted inventories in the state warehouses, interruption in transport, and breakdown in procurement procedures, any of which can cause distribution cycles to be missed. In India, local shortages (versus complete supply exhaustion) of vitamin A concentrate have resulted in poor coverage during scheduled distribution cycles.(23) Management of inventories with minimum stock levels to be used for reordering at each supply level of operation may help to reduce the risk of shortages.(120)

RECORD–KEEPING

While poor record–keeping may not directly affect coverage, it prohibits coverage from being properly evaluated.(23, 122) In the field, reliable registration and documentation of vitamin A receipt by the child also serves to protect against repeated dosing within too short a time.(121)

Each country programme establishes its own documentation system. In both India(122) and Indonesia,(110) the field worker completes two forms: a community registration form and a capsule distribution card. The registration form is a sequential listing of target–aged children in the community, including the house number, each child's name, age and sex, head of household name, and date of each dose receipt. It is first filled out prior to or concurrently with the first distribution cycle of vitamin A and is updated at each subsequent round. This registration form is filed in the local health center and serves as the source document for compiling distribution reports which are forwarded to district, regional or national headquarters.(23, 122, 148)

The capsule distribution card is a household–retained record which contains, as a minimum, village and house identification information, the child's name, and date of each dose receipt. In Indonesia, the excessive amount of time required to complete the card, as well as its high loss rate,(121) prompted its discontinuation.

Recently, a stick–to–the–wall version of the card has been reintroduced and is currently undergoing field testing.(145) The card continues to be in use in India; however, programme evaluations have shown record–keeping to be inconsistent and patchy.(122) Rates of home loss of the card by families have not been reported but are believed to be high.

Once a basic reporting system is established, sufficient time is required to allow procedures to become routine. Once established, any changes in the system are difficult to implement. Nine months after the introduction of a one–column addition to a capsule distribution register in Haiti requesting numbers of “first dosed” children to be recorded, 86% of the centers were using the column, but only 40% of all centers appeared to be completing it correctly.(117)

These problems emphasize the difficulties facing programme managers in striking a balance between minimum required recordkeeping, other responsibilities of the worker, and programme efficiency.

DOSING TECHNIQUES

Currently practiced techniques for administering vitamin A pose a variety of challenges. While the gelatinous capsule can be consumed intact, often the nipple is cut from the capsule and the contents squeezed into the child's mouth. In the absence of blunt scissors, workers pinch the tip of the capsule or use a knife to cut the nipple, frequently resulting in loss of a significant portion of the dose.(23) In India, part of the oil concentrate may be spilled when using a small spoon. Community concern has also been expressed about the potential for workers' hands or the use of a single spoon to act as vehicles for disease transmission during the administration of oral doses of vitamin A.(17, 23) In the Hyderabad project,(114) this problem has been partially resolved by transferring the 2 ml dosage to the mother's spoon whenever possible.(149) A possible solution to both the above spillage and hygienic problems is to use a properly calibrated 5 ml dropper or syringe to administer concentrate from a small bottle. Development and testing of new dosing techniques are currently underway in Indonesia as well as in refugee relief programmes in the Sudan and Ethiopia.(150)

WORKER INCENTIVES

Multi–purpose health workers are frequently not compensated for providing the added service of vitamin A distribution.(23, 117) Often, capsule or concentrate administration is carried out during a regularly scheduled visit to a village or distribution center; thus, no incremental personnel costs are explicitly incurred by vitamin delivery over any costs already borne by the health service programme. While programmatically attractive, this practice may give the worker little motivation to maintain acceptable coverage on a consistent basis. Increased funding for worker incentives and training seminars may help alleviate some of these difficulties,(117) although extra pay offers no guarantee of effective field performance in face of the multiple health programme responsibilities at the local level.

COMMUNITY COMPLIANCE

When the community is routinely updated on programme issues and participates in the local implementation and monitoring of operations, vitamin A distribution is usually well received.(23) To avoid undesirable publicity for a programme, it is not uncommon to withhold the dose from children with diarrhoea or other serious illnesses, thus avoiding having a child's sickness or possible death be associated with receipt of vitamin A.(17, 23, 110, 121) Unfortunately, this may result in missing just those in greatest need. In a recent Bangladesh survey, a negative six– to nine–month history of capsule receipt was associated with severe malnutrition among children one to four years of age.(144) Despite instructions to follow undosed children,(110) it is often not known whether children are followed and administered vitamin A upon showing either signs of xerophthalmia or recovery. The degree to which these children are not followed represents reduced coverage of this very high–risk group.

NUTRITION EDUCATION

Countries utilizing the large−dose vitamin A distribution scheme are attempting to introduce nutrition education components aimed at increasing home cultivation and consumption of food sources of vitamin A, especially dark green leafy vegetables. In Bangladesh a multi−media campaign was launched by placing posters in clinics and schools, developing a 16 mm film for showing in cinema houses and mobile film units, broadcasting messages on radio, and by equipping some 13,000 Family Welfare Workers with flip charts on vitamin A−rich foods for use during capsule distribution.(127) The UPGK programme(151) in Indonesia incorporates an array of nutrition education, diarrhoea management, and home hygiene messages with capsule distribution. In pilot areas, distributors are instructed to deliver simple nutrition messages during each capsule distribution cycle. Special mass media campaigns, including cartoon shows, are being coordinated with crash distribution programmes in Indonesia to achieve greater programme coverage and enhanced nutrition awareness.(152) In Haiti, where only 10% of the rural population owns a radio and where little group listening to educational programmes takes place in rural areas, district auxiliary nutritionists routinely conduct seances d'education about relevant nutrition and health topics at distribution centers. Initial assessment suggests that the seances may have a positive effect on maternal awareness of the role of vitamin A in eye health.(117)

Coordinated vitamin A distribution−nutrition education programmes directed toward increasing vitamin A intake are relatively new, still evolving, and may not yet have been adequately planned, carried out, nor evaluated. Nutrition education delivered during the house visit affords valuable opportunity for personal contact, although the actual distribution of a capsule or concentrate does little to reinforce any dietary vitamin A message. Still, the importance of incorporating vitamin A nutrition education at the community level of any intervention strategy continues to be a high−priority, long−term service goal toward which countries are striving.(153)

7. PROGRAMME ECONOMICS

COSTS

A straightforward but comprehensive accounting system which includes both cash and in−kind costs incurred at each operational level is essential for programme budgeting and analysis. The vitamin A programme budget and activity plan should correspond to the same time period (e.g., annual budget for a set of planned activities during the fiscal year), and should employ a standard classification of resources and expenditures(154) (e.g., personnel salaries, training, material, etc.). A distinction should be made between programme start−up costs (e.g., design testing, initial organizational work, equipment purchase) and ongoing, operating costs. In addition, costs of activities which support distribution at each organizational level should be itemized, such as supervision, in−service training, administrative functions,(155) and evaluation components. Capital resources such as vehicles (including bicycles), can be amortized on an annual basis to buffer against cost distortions during years of purchase. Budget items requiring the outlay of foreign exchange (e.g., vitamin A capsules, foreign technical assistance) should be distinguished from local costs, given the usual constraints limited foreign exchange places on health programmes.(155)

A sparsity of cost data has been reported from ongoing vitamin A delivery programmes.(110, 117, 135) Part of the problem may lie in the difficulty with which cost information can be extracted form complex central, state, or provincial health programme budgets.(23) The few programme cost estimates which are available have varied considerably, not because of marked differences in the delivery systems, but because of variation in the selection of programme resources and activities included in the cost estimates.(17) One programme budget may include only cash outlays while another may strive to identify and valuate in−kind resource expenditures. Development of a standard budget schedule has been recommended by WHO as a step toward more efficient programme management.(17) An example of a basic programme budget schedule is sketched in Figure 8.

Each input into the programme must be costed either at its current market price or, preferably, at its adjusted economic cost, which may involve shadow pricing.(20) There are major constraints which often impede the development of adequate costing systems. One involves the need to impute a cost on resources which require no cash disbursement when utilized in the programme, but from which opportunity costs nonetheless exist. In the Haitian programme,(117) examples of such in−kind expenditures included government−provided

office space, utilities, and the part–time services of district health commissioners and auxiliary nutritionists whose salaries were not paid directly by the programme. The inclusion of part–time government officers in the vitamin A programme raises the second common problem of allocating shared or joint costs. Here, the "marginality principle" states that costs which would normally occur without vitamin A distribution should not be borne by the programme – that only incremental costs directly attributable to vitamin A delivery should be included in the budget.(20) In Haiti, district health commissioner and auxiliary nutritionist costs for programme assistance were estimated at 5 and 10 percent of their time, respectively. No incremental costs for health worker salaries were allocated since vitamin A distribution was considered a normal job function.(117) Alternatively, distributor salaries form a prominent portion of a budget in a single–purpose universal delivery system.

FIGURE 8

BASIC PROGRAMME BUDGET SCHEDULE

	1st year		2nd year		3rd year	
Line item	**In cash**	**In kind**	**In cash**	**In kind**	**In cash**	**In kind**
Personnel						
Administrator						
Supervisors						
Field Workers						
Personnel Training						
Administrator						
Supervisors						
Field Workers						
Others						
Material						
Vitamin A(1)						
Shipping, Handling, Storage						
Programme Support						
Transport						
Miscellaneous Equipment						
Report Forms						
Nutritional Educational Material						
Travel and Per Diem						
Technical Assistance (External)						
Other						
Monitoring and Evaluation						
Personnel						
Travel and Transportation						
Data Analysis						
Preparation of Reports						

	Other						
Total							

(1) 200,000 IU in liquid or capsule form

COST–EFFECTIVENESS (CE)

In countries where xerophthalmia prevention programmes are either being planned or are already ongoing, there exists a basic welfare objective to control nutritional blindness among children. The level of xerophthalmia that can be tolerated is largely determined by the numbers and amounts of resources that can be committed to prevention given other societal objectives. The basic economic challenge then becomes the effective control of xerophthalmia in the most efficient manner – that is, at the least cost.

Cost–effectiveness analysis is useful to the programmer for comparing different types of vitamin A intervention since the costs are taken directly from the budget schedule and reduction in xerophthalmia is the common biological goal. Useful cost–effectiveness (CE) measures which can be employed to monitor programme efficiency include indicators of delivery system CE and biological CE.(20)

DELIVERY SYSTEM COST–EFFECTIVENESS

Delivery system cost–effectiveness indicators reflect the costs ($) of achieving target group (TG) coverage. Indicators include, but are not limited to, (a) $/dose recipient and, (b) $/TG recipient.

Limited financial information is available from the Indonesian(110) and Filipino(135) pilot projects to provide some estimates of $/dose recipient. To do this, it is assumed that “capsule recipients” and “capsules distributed” are equivalent terms, which may not be the case.(117) The cost of the UNICEF 200,000 IU vitamin A capsule with 40 IU vitamin E is under US $0.02 delivered to a country's port.(115, 116) Computed $/dose recipient estimates are based solely on the costs of the capsules and delivery system but do not include private costs (e.g., travel and waiting time by the family). In the 1973–75 Filipino three–strategy field study,(42) where assumptions regarding economies of scale were incorporated into the calculations,(135) a single, large dose of vitamin A delivered to a child cost approximately US $0.035.(156) This cost is far below the widely quoted estimate of the same time period from Indonesia of US $0.19 per delivered dose every six months.(17, 23, 110) This five–fold difference is due in part to the computational basis for each estimate. The Filipino study sought to approximate the cost of a mass vitamin A distribution programme from data generated by a relatively small project. The Indonesian cost estimate, on the other hand, was based on budgeted disbursement to provincial offices for a 200,000–child programme which ultimately covered only half of the expected number of children. While adjustments to the cost estimate were attempted, the investigators note that the amounts of allocated funds actually spent on the distribution are unknown since surplus provincial funds were probably redirected into other local programmes at the end of a fiscal year rather than returned to the central treasury. Caution was expressed about generalizing this cost estimate to any universal capsule distribution model.(110) Thus, a closer $/dose recipient approximation for the mid–1970s was likely to have been between these two project estimates.

Given little further information on vitamin A programme finances, some approximations of current $/dose recipient can be made from these data. Assuming a 1975 cost of U.S. $0.10 per dose delivered, and an annual rate of inflation of 8% in real terms since 1975, the approximate cost per dose recipient of a six–monthly universal distribution programme achieving 75–85% coverage in 1985 would be approximately U.S. $0.22 per six months, or U.S. $0.44 per year. Given the tendency for some “over–coverage” among older children,(122) the $/TG recipient would be slightly higher. The economic consequences of “system fatigue” during which overhead costs, at the very least, remain fixed while coverage deteriorates, have not been investigated.

Only a crude comparison can be made between a universal and targeted delivery system. In the Haitian targeted system,(117) the 1978 $/dose recipient ranged from U.S. $0.13 to $0.19. At 8% inflation this is equivalent to U.S. $0.22 to $0.33 in 1985, slightly more than the estimated cost of one distribution in a universal delivery programme. However, the lower “targeted” output is intended to achieve greater specificity with particular emphasis on reaching higher risk children. Comparing targeted with universal delivery using the

latter target group definition, the $/TG recipient may be considerably more attractive for a targeted delivery system. This relatively low $/TG recipient must then be viewed against the potential for poorer programme sensitivity and irregularity of dosing intervals.

BIOLOGICAL COST–EFFECTIVENESS

These measures are usually ratios between programme cost and the percent change (%) in vitamin A status (e.g., clinical or biochemical) directly attributable to a programme.(20) Estimates of effectiveness may be generated from serially collected cross–sectional (prevalence) or longitudinal (incidence) data. Indicators include $/% in any clinical stage of xerophthalmia and $/% in mortality. Alternatively, the cost of preventing nutritional blindness in one child can be computed if estimates of change in X2/X3 or XS are available. Because of the large sample size required to assess changes in corneal disease and blindness,(157) most evaluations have assessed programme impact on night blindness and/or Bitot's spots. However, cost–effectiveness evaluations of ongoing programmes have generally not been performed due to the relative neglect of cost analyses in large–dose vitamin A distribution programmes.

BENEFIT–COST (BC)

Benefit–cost analysis in the health sector is a macro–level technique for evaluating the net economic benefits expected to accrue in the future from alternative health programmes. In benefit–cost (BC) analysis, future “streams” of both benefits and programme costs must be enumerated, quantified, and explicitly valuated in terms of present value of a common unit, usually money.(158) An advantage to this approach is that programmes with varying initial costs and short– or long–term benefits can be compared on similar economic terms.

While appealing, BC analysis is fraught with difficulties. In terms of xerophthalmia control programmes, benefits include cost savings from treating fever would be xerophthalmic cases, caring for fever blind adults, and improved future productivity resulting from avoided mortality, blindness, and other associated morbidity.(159, 160) While quantifiable, the accuracy of these imputed estimates is questionable. Furthermore, benefits such as future time saved by the family not having to care for the blind, and personal fulfillment and enjoyment in life as a result of maintained sight are even more difficult to measure.(159) Recently, a benefit–cost study has been carried out on the three pilot vitamin A intervention strategies conducted in the Philippines. The findings concluded that both large–dose vitamin A distribution and fortification of monosodium glutamate with vitamin A displayed ranges of economic benefits far in excess of their costs: 2.4 to 3.4:1 and 5.8 to 21.0:1, respectively.(135, 160) A preliminary analysis of an Indonesian capsule distribution programme has also shown a 68:1 BC ratio in relation to preventing xerophthalmia.(161)

Despite the vast array of assumptions underpinning BC analysis at present, these early results support the notion that xerophthalmia prevention through capsule distribution or fortification may not only be socially correct but economically sound to pursue.

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$$q' = [1 - p(i)(2)/(p(i)(1) - q(c)\, p(i)(1)]100$$

where

- q' = percent change in Xerophthalmia attributable to programme impact.
- $p(i)(1)$ = baseline prevalence in the vitamin A intervention group.
- $p(i)(2)$ = follow–up prevalence in the vitamin A intervention group.
- $p(c)(1)$ = baseline prevalence in the comparison group.
- $p(c)(2)$ = follow–up prevalence in the comparison group.

q(c) = change in prevalence in the comparison group.

$$= (p(c)(1) - p(c)(2)/p(c)(1)$$

163. An approximate 70% reduction in Xerophthalmia could be directly attributed to the capsule programme [q' = (1 – 0.6/2.1)100].

164. The proportion of Xerophthalmia in the target population prevented during the specified dosing interval can be determined as follows.

$$e(p) = p[(r-1)/r]100$$

where

e(p) = “population prophylactic efficacy”; that proportion of Xerophthalmia in the target population which is prevented during the specified dosing interval as a result of vitamin A intervention.

p = proportion of targeted individuals dosed during the vitamin A distribution cycle.

r = relative risk of developing xerophthalmia during the specified dosing interval associated with not receiving vitamin A, ideally estimated from a controlled study in the same population in which vitamin A non–receipt (“exposed”) subjects present a similar risk profile as those in the target population who are usually also missed (“exposed”) by the delivery system (i.e., 1–p).

e = prophylactic efficacy generated from a cohort or case–control study, and equal to 100(r–1)/r. See also references 108, 109.

165. Population attributable risk (PAR) can be determined as follows:

$$PAR = (1-p)\ (r-1)/[(1-p)\ (r-1) +1]$$

where “p” and “r” are as above (See 164).

ALTERNATIVE STRATEGIES WITH EMPHASIS ON FOOD FORTIFICATION

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West and Sommer present an in–depth analysis of the periodic mass–dose approach. They highlight its potential effectiveness, but warn about the fact that the efficiency of its operation still poses a major challenge. Very good programme management is required and, unfortunately, most developing countries lack the necessary administrative sophistication. Another limitation of this approach is that it focuses only on one sector of the population, the so–called “high risk years” which corresponds to the preschool age children. In countries where the diet is poor in vitamin A, other subgroups of the population may also be vitamin A deficient. If pregnant and lactating women remain deficient, the newborns will have poor liver reserves, the breast milk will have a low vitamin A content and the breast–fed infant will have, therefore, a poor start regarding vitamin A nutrition.

The alternative strategy based on vitamin A fortification of a widely consumed food does not suffer from the latter limitation. Because West and Sommer in their paper cover this methodology only briefly, I will devote the major part of the present note to comment on its potential and limitations. I will also review the available evidence of the effectiveness of the national programmes of sugar fortification with vitamin A in Central America, as case examples of successful vitamin A deficiency preventive programmes.(1)

There is general agreement that the sound and logical solution of the vitamin A deficiency problem should be based on the modification of the pattern of food production, distribution and consumption through agricultural,

educational and, in general, socioeconomic strategies. However, the implementation and successful outcome of these measures takes a long time and the extent and magnitude of the vitamin A dietary shortage is such that the application of specific interventions expected to result in positive impact at short term is imperative. In this context, food fortification must be considered. This approach has been shown to be very effective for other micronutrients.

Food fortification strategies have the advantage that the active participation of the consumers is not required. The target population continues consuming the food in question, but once fortified, this becomes a good source of the needed nutrient.

The very first step in the establishment of a fortification programme must be the determination of the magnitude and extent of the vitamin A deficiency, as veil as its distribution among the different ecological regions, socioeconomic levels and age groups.

The next step is the selection of the local food or foods that would be suitable vehicles for fortification. This selection is based on the following criteria: 1) the “carrier” must be a food consumed by essentially all the population including, of course, the most vulnerable groups; 2) the per capita intake of such food must vary within a narrow range from day to day and from person to person; 3) the added vitamin A compound should not alter appreciably the organoleptic characteristics of the food in order to ensure continuous acceptability by the consumer; 4) the food should pass through central “stations” of processing (or storage) where the nutrient can be added under well controlled conditions at minimum expense.

The basic premise is that the food to be fortified should be part of the dietary pattern of the target population. Because the dietary patterns in developed nations include large numbers and variety of food items, the probability of identifying some appropriate carriers for vitamin A fortification is high. A few of the common ones are milk, margarine, prepared infant formulas, instant and ready–breakfasts. The situation in most developing countries is very different. Diets of the poor are notorious for their simplicity, with only around two and often even one, predominant staple. The “classic” carriers for the lipid soluble vitamin A, milk, margarine, butter, are rarities in the low socioeconomic groups. In Guatemala for instance, around 85 percent of the energy intake is supplied by white corn and beans devoid of vitamin A. The possibility of using corn was in theory attractive, but it soon became evident that it was not feasible. The vast majority of the population, suffering from lack of dietary vitamin A, process and cook their corn at home, leaving no chance for centralized fortification. For rice, the central staple of millions of people in the world, no vitamin A fortification technology has been developed.

Faced with these limiting circumstances the INCAP researchers in Central America, after a systematic process of elimination, selected sugar as the promising carrier. Using a similar rationale the Philippine researchers favored monosodium glutamate (MSG) for that country. At the time (some 15 years back) the advent of excellent industrial preparations of water–miscible forms of retinol palmitate facilitated the laboratory and pilot investigations which led to the development of appropriate technology using sugar as a “universal” carrier in Central America. A similar technology was soon developed for MSG. Research proved that this vitamin A compound was sufficiently stable and very well absorbed and that the final fortified sugar was well accepted. The application of this strategy was proposed to the governments of Central America and sugar fortification with vitamin A became compulsory at the national level in four countries: Costa Rica (1974), Guatemala (1974), Honduras (1976), and Panama (1976). Only the first three countries continued fortification for a sufficient number of years to permit evaluation.

The model evaluation of this type of intervention was carried out in Guatemala. I shall devote, at this point, a few paragraphs to the most important component of the intervention programme. The basic premise to be kept in mind is that the implementation of an intervention without adequate built–in evaluation is wasteful since the potential of the programme for application in similar situations elsewhere would be undetermined. Unfortunately, more often than not, programmes are implemented but never evaluated correctly.

As in any intervention the objectives of a fortification programme have to be clearly defined since the indicators of effectiveness have to be carefully chosen to measure the extent to which such objectives are met. In the case of the Central American programmes the stated objective was: “To increase the intake of vitamin A and, through this improved intake, to raise Vitamin A levels in the body fluids and serum of the population at large, increasing thereby the supply of retinol to the tissues.”

The primary specific indicators selected were intake of retinol equivalents, serum retinol levels of preschool children, breast milk retinol concentrations, and liver reserves in a selected urban sample.

As published extensively elsewhere (1), the sugar fortification programme proved to be very successful, resulting in a highly significant improvement in the vitamin A nutritional status of the population. In 1965–67 the percent prevalence of preschool children with low and deficient serum retinol (<20 ug/dl) were: Costa Rica 32.5%, Guatemala 26.2%, Honduras 32.5%, and El Salvador 50.0%. The first three countries implemented national sugar fortification programmes. El Salvador did not. In 1977–80, prevalence of such low and deficient serum values were 1.6%, 9.2%, and 2.8%, for the first listed three listed countries with fortification programmes and 33.3% for El Salvador.

Important collateral benefits from this programme were the significant decrease in the percent of preschool children with less than 80% of standard weight for height and the improvement in iron nutrition parameters attributable to vitamin A, observed during the first two years of fortification. Furthermore, although the sample was not designed to measure changes in eye lesions with high statistical validity, the clinical observations did suggest a positive effect.

The negative note about this “success story” is that, at the present time, the political and economic disturbances in Central America are impairing the operation of the programme. It is difficult to continue giving priority to vitamin A deficiency in the face of a generalized economic and political crisis threatening the integrity of society itself.

The only other study that has contributed some information on the validity of vitamin A fortification is the experimental MSG project in the Philippines.(2) The second of the four–phase complete plan (Field trials) has been finished shoving a positive effect on raising blood serum retinol and decreasing the prevalence of xerophthalmia. One interesting feature in this study was that it compared with MSG fortification with a public health–horticultural strategy and a periodic high dose capsule. The preliminary conclusion of the researchers was that the fortification of MSG was the most effective and least costly of the three interventions. Phase IV (implementation of a national control programme) of the project is still awaiting to be carried out. This last phase, which depends on several factors including political decision making, will be the only way to obtain the final answers as to the feasibility and effectiveness of the MSG intervention.

As pointed out by West and Sommer, dietary modification is the major long–term solution to controlling vitamin A deficiency. “Dietary modification”, however, defines a goal and not a strategy. The recognized specific strategies aiming at that goal are food–agricultural (horticultural) approaches, nutrition education and socioeconomic measures. All of these are theoretically sound, but they are costly and their implementation in developing countries has proved discouragingly difficult. The results are slow coming (not visible short–term) and this undermines both the “political appeal” of the programmes to the temporal political leaders as well as the sustained cooperation and receptivity of the target communities.

In my opinion, the most attractive specific strategy to increase the availability of vitamin A from local food sources is the horticultural approach (home and school gardens) wherever climate and soil conditions permit. The opportunities that this strategy offers for dietary modification, nutrition education and even economic benefits at the family level, are theoretically exciting. Recent research seems promising and projects in this area should receive special encouragement, guidance and financial support.

In the meantime, vitamin A fortification programmes would seem the least costly and most manageable. One of the major factors limiting their application in many developing countries is the identification of a food meeting the criteria of a good “universal” vehicle for vitamin A.

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COMMENTS ON VITAMIN A SUPPLEMENTATION

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Xerophthalmia has disappeared from industrialized countries during the 20th century in the absence of any special programme to control the disease. This is undoubtedly due to the improvement in the socioeconomic status of the population, accompanied by an increased dietary intake of vitamins, including vitamin A. Better sanitation, lover incidence of childhood diseases and gastrointestinal infections have certainly contributed to the disappearance by reducing the overall requirements for vitamin A and preventing a reduced intake during infectious episodes. The same trends are clearly occurring in a number of developing countries: this is the case, for instance, of such countries as Singapore and South Korea, where xerophthalmia has disappeared over the last thirty years. It is interesting to note that while xerophthalmia has disappeared, many of these countries are still fortifying some of their foods with vitamin A: margarine is typical of this practice. While carotenoids are added for aesthetic reasons, there is no doubt that the addition of retinol is motivated by nutritional objectives.

Xerophthalmia is still highly prevalent in a number of developing countries; most of them are located in Asia and in Africa, a few pockets remaining in Latin America and the Caribbean. In most of these countries, the socioeconomic situation will not improve at a sufficiently fast rate for the disease to disappear spontaneously within an acceptable length of time. Given the present tools available to correct the situation, action must be taken immediately. There is no doubt that the distribution of large oral doses of vitamin A constitutes at the present time the most effective answer to the problem. A programme of distribution can be organized relatively rapidly, using the health and social structures existing in the country. This type of programme has often been called an emergency or short–term programme. This appellation is somewhat misleading as it gives the impression that the programme will be terminated relatively quickly, say within a few years. However, even if this is true in some countries approaching a fair level of development, many others distribution of Vitamin A, especially targeted or medical distribution may be needed for many years to come if the population, and particularly children, are to be fully protected against vitamin A deficiency. A good example of this situation is the prevention of rickets in Europe which was achieved during this century by the administration of cod liver oil at weekly intervals or, more recently, using large doses of pure vitamin D once or twice a year. Although living habits have changed considerably over the last sixty years and children are commonly exposed to sunlight and provided, therefore, with sufficient vitamin D, the administration of a vitamin D supplement before and in the middle of winter is still widely recommended by the paediatricians and practised by mothers. It seems, therefore, that once a practice has been recognized as useful by doctors and parents alike, it may take a long time before it is discontinued, even if it is little or no more justified.

Several delivery systems for vitamin A supplementation have evolved. The selection of the most appropriate one is largely based on the strength of the health infrastructure and financial considerations. The “universal” distribution is, in principle, the most attractive and the most effective one. It is very difficult to cover 100% of the child population, and those who are left out are usually those at greatest risk. Compliance also decreases with time. The difficulty of reaching all children is illustrated by the distribution programme in Indonesia. The Nutrition Directorate of Community Health in the Indonesian Ministry of Health is the authority responsible for the vitamin A capsule distribution. The latter is carried out through four types of community outreach programmes, as follows:

1. The Special Vitamin A Distribution Programme is a vertical activity where single–purpose volunteers distribute capsules twice a year to children aged 1–6 years, under the supervision of district health centres (Puskesmas).

2. The Usaha Perbaikan Gizi Keluarga (UPGK), which stands for Family Nutrition Improvement Effort, is a programme that includes the weighing of children, distribution of oral rehydration salts and iron tablets, nutrition education, and help with home and village gardens. Vitamin A capsules are distributed twice a year.

3. The Nutrition Intervention Project (NIP), which has broadly–based nutrition activities, includes the distribution of first aid packages to selected primary health workers in several districts in four provinces. These packages include vitamin A capsules for distribution every six months.

4. The BKKBN, a family planning programme, includes a “nutrition package”, one of the components of which is the distribution of vitamin A capsules.

These four distribution systems operate in different parts of the country, and attempts are being made to test them for efficiency and results. In Lombok(1), for example, a survey conducted in 1977 revealed a high prevalence of ocular signs of vitamin A deficiency. The area was subsequently identified as a priority high−risk area and a massive dose vitamin A distribution programme was initiated. Vitamin A capsules were distributed using three systems: the Special Programme, UPGK, and NIP. A particular effort was made in 1982 to coordinate the activities of the various programmes in order to make them more effective. Capsule distribution was backed up by radio messages in order to increase public awareness of the significance of night blindness as an early sign of nutritional blindness and the importance of giving vitamin A capsules to children. Information concerning capsule distribution in Lombok is presented in Table 1.

TABLE 1

VITAMIN A CAPSULE DISTRIBUTION IN LOMBOK, INDONESIA, 1977−1982
(number of capsules in thousands)

	1978	1979	1980	1981	1982
Special Programme	0	0	88.9	270.7	456.0
UPGK	0	27	68.4	−−	−−
NIP	5.4	16.2	16.2	36	36
BKKBN	0	0	0	0	0
Total number of capsules	5.4	43.2	173.5	306.7	492.0
Average number of children covered (in 000's)	2.7	21.6	86.7	153.3	246.0
Total number of children covered (percentage)	0.8%	6.8%	27.1%	47.9%	76.9%

The results of the Lombok evaluation indicate that the prevalence of xerophthalmia decreased dramatically during the period 1977−1982. The prevalence of Bitot's spots decreased from 1.6% in 1977 to 0.24% in 1983 ($p < 0.01$) (See Figure 1). The prevalence of corneal xerophthalmia decreased from 0.21% in 1977 to 0.04% in 1983 ($p < 0.01$). While the prevalence of corneal scars remained about the same – 0.21% in 1977 compared with 0.2% in 1983 – it should be noted that the majority of scars detected in 1983 were more than two years old.

All data indicate that there is a marked decrease in the prevalence of xerophthalmia in Lombok since 1977. In the absence of a control group it is not possible to attribute the decline to the vitamin A distribution programme alone; other factors such as changes in the socioeconomic status of the population may also have contributed to the improved situation. One thing is certain, however: in those areas throughout Indonesia where distribution programmes have been pursued with diligence, the prevalence of xerophthalmia has decreased, and in those areas where there are no control programmes, prevalence has remained stable, or even increased.

The difficulty of reaching a significant percentage of children is veil illustrated in the case of Indonesia, where it was necessary to set up a special programme of distribution to achieve a significant coverage.

Dose of Vitamin A. So far, a dose of 200,000 IU of vitamin A has been used routinely. The vitamin A may be diluted in vegetable oil or presented in the form of capsules. In some instances, secondary effects such as nausea, vomiting and headaches, have been observed in a small percentage of children after administration of the vitamin. If the supplement is given for medical reasons such as measles, diarrhoea, pulmonary infections or protein energy malnutrition, there is always the possibility that the administration is repeated several times, causing eventually a state of hypervitaminosis A and the occurrence of signs of toxicity. It has, therefore, been suggested that a smaller dose, say 100,000 IU would be more appropriate when the supervision of the distribution system is weak. This obviously reduces the length of protection but insures a greater safety of the programme. These two factors must be carefully weighed; indeed, it is difficult to use simultaneously the two dosages for logistic reasons and also because of the danger of confusion among little trained personnel.

Nutrition education. There is no doubt that sensitization of the public and especially of the parents is essential for the success of a distribution programme. All types of media, including radio, TV, newspapers and posters, can and should be used to achieve this objective.

Another form of supplementation can be achieved through **fortification** of food with vitamin A. As mentioned above, this has been practiced for several decades in many industrialized countries. It can also be implemented in developing countries provided that the right food vehicle(s) is identified and that other necessary conditions are fulfilled. A well–designed food fortification programme has the great advantage of reaching almost automatically every individual; once the programme has been launched, the cost is very low in terms of expenses per caput per year. Preparing a fortification programme cannot be done on a crash basis. Identification of the food vehicle(s), development of the fortification technology, field testing, enactment of necessary legislation, setting up control laboratories, training supervisors and inspectors, are all steps that require some time, usually three to four years at minimum. Financially sound programmes can be continued over long periods of time without requiring great expenditures of time or effort. Over the medium term, fortification programmes whenever they are applicable constitute an effective alternative to the distribution of supplements.

A number of trials have been undertaken to test the feasibility and effectiveness of fortifying tea, cooking oil, monosodium glutamate and sugar with vitamin A. As a result of the studies, sugar has been fortified with vitamin A since 1976 in Costa Rica, Guatemala, Panama and Honduras. Fortification was still going on in 1985 in Guatemala and Honduras, whereas it had been discontinued in Costa Rica and Panama because vitamin A dietary intake had apparently improved sufficiently so as to make it unnecessary. The changes in the vitamin A status of the Guatemalan population have been assessed after one and two years of fortification; these were spectacular in terms of increased vitamin A concentrations in the blood, liver and breastmilk of almost all individuals and provide an excellent illustration of the effectiveness of a veil–designed fortification programme in correcting a nutrient deficiency.

Increasing the vitamin A dietary intake of the population and especially of young children is obviously the long–term solution. It is possible in certain cases to achieve this objective in the absence of major advances in socioeconomic development through nutrition education or through increased availability of vitamin A–rich foods. Development of horticulture, and of small husbandry schemes including fish culture can be done independently and can contribute significantly to the vitamin A intake of the population. Most of these schemes take a certain time to develop and require capital investment. There is no doubt that they should be undertaken but one must realize that their results will not become apparent before a certain time. The right combination of required measures will vary from country to country and, possibly, from region to region within countries.

In conclusion, periodic supplementation with large doses of vitamin A is an effective and possibly the only measure that can be taken on a crash basis to control xerophthalmia whenever it constitutes a public health problem. Primary health care can play a major role in facilitating the distribution of the vitamin A supplements. Once a supplementation programme has been established, medium– and long–term approaches should be developed which could lead to a permanent improvement of the vitamin A status of the population.

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CURRENTLY AVAILABLE TECHNOLOGIES IN INDIA TO COMBAT VITAMIN A MALNUTRITION

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Malnutrition among the vulnerable sectors of the population is one of the crucial public health problems in large areas of the world. Among the various nutritional disorders, vitamin A deficiency is receiving increasing interest in recent years, since it is the major cause of blindness in several parts of the world.

Around one million children suffer from vitamin A deficiency in India at any one point of time (UNICEF, 1981). Bhaskaram (1981) states that five percent of the preschoolers and ten percent of the school children belonging to the poor socioeconomic groups in India show signs of vitamin A deficiency, primarily due to a meagre intake of vitamin A, which is far below the recommended level. Leafy vegetables which appear to be

the only practical source of dietary carotenes are not generally consumed by the poor rural families (Devadas, 1983). Devadas and Saroja (1980) observed a high prevalence of xerophthalmia among six year old children in the rural areas of Tamil Nadu. Among them, 12.5 percent had developed conjunctival xerosis with Bitot's spots. Their serum retinol level ranged from 10 to 15 mcg/100 ml. This widespread problem of vitamin A deficiency, stresses the need for a scientific, social and political commitment to eradicate hypovitaminosis A.

Some of the factors contributing to vitamin A deficiency are: poverty, ignorance, superstitious beliefs that green leafy vegetables cause diarrhoea (even when they are free from contamination!), malabsorption, low dietary intake and of course poor availability of foods rich in vitamin A, protein malnutrition and infectious diseases. These conditions call for simple technologies to bring about a significant reduction in the problem of nutritional blindness. Some such technologies which have been applied successfully in the prevention of vitamin A deficiency in India are: nutrition education, nutritional feeding (intervention) programmes, promotion of nutrition gardens, prophylaxis through the administration of massive doses of vitamin A and general improvement of the nutrient intakes. Some results obtained from performing each of the above mentioned strategies are described here.

Nutrition Education

Nutrition education brings about an awareness in individuals and communities of the need for proper selection of foods and creation of sound eating patterns. Imported food mixtures, injections and capsules do not provide permanent solutions and realistic approaches to the problem of nutritional blindness. Families need to learn to use the foods around them or foods that can be easily introduced and accepted. The author's experiences over the last two decades, with nutrition education as an intervention to children in the schools and their parents, and the communities in the rural and urban areas, have indicated that it is a powerful means of bringing about changes in knowledge, attitudes, practices, and nutritional profiles of families and communities in the long run.

In a longitudinal study covering three years by Devadas and Premakumari (1983), 80 mothers of preschool children were given nutrition education for over 12 months. Table I presents a part of the improvement observed in the use of green leafy vegetables.

TABLE I

FREQUENCY OF USE OF GREEN LEAFY VEGETABLES BY THE 80 MOTHERS BEFORE, IN THE MIDDLE AND AT THE END OF A 12 MONTH NUTRITION EDUCATION PROGRAMME
(% of group with given frequency of use is given in cells)

Frequency	Intervention Group (%)			Control Group (%)		
	Initial	Middle	Final	Initial	Middle	Final
Every day	12	15	15	10	10	10
Four times a week	9	20	57	24	24	24
Twice a week	10	32	20	20	20	20
Once a week	15	33	8	10	15	10
Occasionally	54	0	0	34	31	36
Total	100	100	100	100	100	100

An enormous improvement was registered in the frequency of use of green leafy vegetables by the mothers. The dietary intake of the children had also improved after the nutrition education programme. The deficit in the carotene intake was reduced from 55 to 22 percent of the Recommended Dietary Allowances in the experimental group, whereas it increased from 35 to 40 percent in the control group. Clinically, xerosis of the cornea was reduced from nine to two percent, and angular conjunctivitis from 12 to 5 percent in the experimental group receiving the intervention, whereas a prevalence of 8–10 percent was observed in the control group throughout. The gradual improvement observed among the preschool children and the improved practices of the mothers were due to nutrition education.

In another study (Devadas et al, 1979), 100 mothers from the Parent Teacher Association of a primary school, were given intensive nutrition education with emphasis on vitamin A intake. After a six month period, the nutrition knowledge, practices and attitudes of the mothers were evaluated.

Table II gives the scores obtained by the mothers for nutrition knowledge.

TABLE II

SCORES OBTAINED BY 100 MOTHERS FOR NUTRITION KNOWLEDGE, BEFORE AND AFTER PARTICIPATION IN A 6 MONTH INTENSIVE NUTRITION EDUCATION (Maximum Scores = 100)

Details	Percent scores
Initial	39.00±5.99
Final	87.40±6.98
Difference	48.40±5.81
t value	26.59 (P < 0.01)

The scores obtained by the mothers increased significantly (P < 0.01) due to their participation in the education programme.

The frequency of use of milk and milk products, leafy vegetables, raw vegetables and fruits such as papaya and mango had also increased to an appreciable extent after the education programme. Previously only 10 percent of the mothers maintained kitchen gardens. This increased to 68 percent after conducting the nutrition education programme. Similar results were observed in all the nutrition education camps conducted in the rural areas around Coimbatore. This gives an assurance that nutrition education programmes can contribute towards the reduction in the incidence of Vitamin A deficiency.

In another educational programme, 40 Multi−Purpose Health Workers belonging to Nallur Block Tamil Nadu, were given training in health and nutrition education activities. The trained workers, in turn, educated the people in the entire Block comprising 67 villages. Within a period of three months the prevalence of xerophthalmia and dry rough skin was reduced from 12.4% and 33.4% to 10.1% and 10.2% respectively among the preschoolers.

Children and parents can be approached easily through the school teachers when they use a nutrition oriented curriculum. In a longitudinal study 6000 teachers belonging to three districts of Tamil Nadu were trained to use a nutrition integrated curriculum. This resulted in an increase in nutritional knowledge of children and their parents together with an improvement in clinical signs, caused by nutrient deficiencies, among these children.

Nutritional Feeding Programmes

In a developing country like India where the prevalence of vitamin A deficiency is rampant, provision of a nutritious meal or any similar type of supplementary feeding programme helps in the reduction of the incidence of vitamin A deficiency. The Honourable Chief Minister's Nutritious Meal Programme operating in Tamil Nadu, today, feeds 8.5 million children from 2 to 14 years of age. The ingredients of the meal are 80 to 120g rice, 10 to 20g pulses, 3g oil, 25g of leafy vegetables and 25g of other vegetables. The calories provided by this meal are in the range of 400 to 600 kcal/child/day, and the protein and carotene content are about 10 to 16g and 1870 mcg/child/day respectively.

An assessment of the initial and final clinical picture of 3857 children participating in the feeding programme over a period of one year is presented in Table III.

TABLE III

PERCENTAGE OF CHILDREN WITH OR WITHOUT SOME CLINICAL SIGNS OF NUTRITIONAL DEFICIENCIES, BEFORE AND AFTER PARTICIPATION IN THE FEEDING PROGRAMME (n = 3857)

	Percent of Children	
	Initial	**Final**
Healthy and free from disease	32	78
Angular stomatitis	39	12
Poor musculature	40	12
Mild anaemia	30	10
Bleeding gums	29	5
Dry skin	25	5
Bitot's spots	7	2

The results showed that Bitot's spots were reduced from 7 to 2 percent among the children who participated in the programme. The feeding programme reduced not only the incidence of vitamin a deficiency but also some other deficiencies, thus leading to general improvement in health.

Promotion of Nutrition Gardens

Increased production of vitamin A rich foods through home gardens, school gardens and community gardens can result in increased consumption of vitamin A rich foods and lead to a reduction in the incidence of vitamin A deficiency. This was observed in the nationwide Applied Nutrition Programme (ANP) carried out in Tamil Nadu. The ANP has a three pronged approach: (a) stepping up the production of protective foods, like green leafy vegetables, fruits and eggs; (b) consumption of protective foods by the vulnerable groups: expectant and nursing mothers and children under five years of age; and (c) nutrition education.

In Bhavanisagar Block in Tamil Nadu there were 8 poultry units under the ANP. The production and distribution of eggs in three villages of the block over a period of seven years increased from 6344 eggs in 1962 to 39473 in 1968. The production and distribution of vegetables including green leafy vegetables raised through the home gardens, school gardens and community gardens in the block increased from 2723 kilogram vegetables to 4672 kg during the same period of time. The substantial contributions made by the Applied Nutrition Programme towards the production of vitamin A rich foods were utilized for relevant nutrition education.

Devadas and Prema (1965) observed that 66 percent of the mothers were anaemic with initial signs of vitamin A deficiency. They were given eggs and vegetables, including leafy vegetables from the ANP gardens. At the end of six months the nutritional status of the mothers improved to a considerable extent with the disappearance of all the clinical signs of vitamin A deficiency. Similar observations were recorded with regard to the preschoolers and expectant women.

One long term solution to the problem of vitamin A deficiency is to increase food production through home gardening. Properly designed gardens can contribute considerably towards the supply of vitamin A to meet the family's requirements. Garden vegetables can provide variety to a poor family's monotonous diet. The gardens can be grown even within the constraints of time and money by the rural households. Wherever possible, gardens could also be made income–generating propositions. Hence home gardening, school gardening as well as community gardening should be encouraged widely. Community gardens are helpful to conducting the feeding programmes in the community. Through community gardens, mothers could also be motivated to start designing home gardens. In one of the efforts to encourage rural mothers to produce low cost sources of beta carotene foods, 455 papaya saplings were distributed to the parents of preschool children who were participating in a feeding programme along with nutrition education. Of the 455 saplings, 201 survived and gave fruits. This horticultural effort can be further strengthened to pave the way for eradication of xerophthalmia.

As one of the attempts to improve the food production and consumption pattern of families, the Chief Minister of the state introduced 'Life Oriented Education' in the High Schools in 1984. Sri Avinashilingam Higher Secondary School for Girls availed itself of the opportunity to offer the 'Nutrition gardening' as one of the life oriented courses to pupils of VIII standard in the year 1984–1985 (Devadas, 1985). The specific objectives of the course were to:

(1) promote the utilization of available space and waste water for the production of nutritious foods;

(2) give pupils skills in gardening;

(3) promote the health of the pupils through consumption of the garden products, and;

(4) help to supplement the pocket money of the pupils through sale of the products from their nutrition garden.

Under this programme, 424.6 sq. meters of land was allotted to a group of 48 students. They worked in groups in the garden as part of their course and raised different vegetables.

Table IV presents the quantity of vegetables obtained from the nutrition garden from July 1984 to March 1985 and their monetary value.

TABLE IV

QUANTITY AND MONETARY VALUE OF VEGETABLES PRODUCED IN NUTRITION GARDENS BY STUDENTS

Vegetables	Quantity (kg)	Income (Rs)
Tomatoes	331.50	977.80
Leafy green Vegetables (Amaranth)	455.00	825.90
Brinjal	195.75	360.60
Ladies Finger	100.50	217.75
Pumpkin	16 nos.	52.00
Beans and other vegetables	97.25	120.80

Around 31 percent of the total income was from the green leafy vegetables. The products were sold to the school hostel at a reasonable price and this experience encouraged the students to produce protective foods more in their homes and consume them.

Administration of Massive Oral Dose of Vitamin A

A quicker way to combat blindness is the administration of a massive dose of vitamin A orally to children below five years of age. In this programme each child receives 200,000 I.U. of vitamin A every six months.

Devadas and Saroja (1985) conducted a study on the impact of oral administration of 200,000 I.U. of vitamin A every six months, on the serum retinol levels in 50 children in a rural area. The initial mean serum retinol levels of these children was in the 'low' category (11.3±2.8 mcg/100 ml). Three months after the administration of the massive dose, the level rose to 26.9±2.3 mcg per 100 ml and after six months, the levels dropped considerably to a value close to their initial value. In another study of Devadas and Saroja (1985) three groups of preschool children were supplemented with 1200 mcg of beta Carotenes in a standard lunch in the form of either papaya, carrots or amaranth every day over a period of one year. Serum retinol level of the target children were determined, before and at 3rd, 6th, 9th and 12th months after supplementation. Initially all the children were having low serum retinol levels between 11.4 to 12.3 mcg/100 ml. The levels gradually improved as the experiment progressed and by the end of 12 months, the serum retinol level of the group fed papaya, amaranth and carrots were 46.8, 42.9 and 52.7 mcg/100 ml respectively. The findings of these studies indicated that the oral massive dose of vitamin A is not as effective as the daily supplementation of the diet with papaya, amaranth or carrots, in maintaining raised serum retinol levels.

Simple technologies can be applied effectively towards the reduction of nutritional blindness among children. Nutrition education with provision of vitamin A rich foods and horticultural approach are effective strategies in tackling the existing problems of vitamin A deficiency. These efforts should be undertaken simultaneously by national and international agencies throughout the world to bring down the incidence of vitamin A deficiency.

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PROGRAMMATIC ISSUES IN VITAMIN A DOSE DELIVERY

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The West/Sommer paper presents a wealth of data supporting the use of vitamin A dose delivery as a critical intervention for xerophthalmia control. With the findings emerging from Indonesia demonstrating a positive correlation between vitamin A supplementation and child survival, the effects of vitamin A programming have yet to be fully determined. To be thorough, the authors review numerous and divergent findings from a variety of field studies. Their paper allows the manager to have the technical background leading to the use of the WHO–recommended standard dose of vitamin A. On the other hand, the authors do not address certain technical issues relevant to current program development, e.g. identifying the xerophthalmia problem in a country. Some details on such issues are given here.

In presenting studies on the safety of vitamin A supplementation, much of the analysis concerns the effects of doses higher than the standard recommended by WHO. Data from those studies led to the decision to recommend the 200,000 IU (rather than, for example, the 300,000 IU) dose. Although these findings are important in emphasizing the need for program supervision, they are less relevant in the choice of the delivery itself.

Secondly, in looking at the issue of vitamin A absorption the emphasis is on the limitations of the body to absorb the oral vitamin A, in both the ill and healthy child. However, the information needed by the policy maker is that – given the limitations – there is enough absorbed to be effective in the control of xerophthalmia.

Finally, in presenting the dramatically different results of vitamin A oral dosing on serum retinol levels, the limitations of that indicator as an accurate assessment of body stores of vitamin A should be appreciated. Instead, the program manager is presented with conflicting results on which to base key decisions.

Xerophthalmia Problem

Although it was not the purpose of the paper to help the manager make a decision on whether or not to intervene in vitamin A, it is worth suggesting when, where and how that decision might be made. Some suggestions follow.

A problem must first be identified. Presumably limited information is available on xerophthalmia in the country. Methods of gathering additional data include:

- examining the records of blind schools on the etiology of blindness in their students
- an analysis of medical records from hospitals and clinics
- rapid assessment surveys in the field
- national prevalence surveys

Choice in methodology depends on technical and financial resources available. Once the extent and location of the problem are identified (or suggested), decisions can be made concerning the degree to which program intervention is required. Criteria for determining whether or not a significant public health problem exists are given in the paper by West and Sommer, based on WHO guidelines.

The discussion does not distinguish between countries where there is clearly a high prevalence of xerophthalmia (i.e. Asia), to countries where there are clearly high rates of severe protein–energy malnutrition and measles complications, although data on xerophthalmia are limited (i.e., Africa), and countries which have reported low levels of vitamin A deficiency and moderate protein–energy malnutrition without significant rates of xerophthalmia (i.e., Latin America). How does periodic dosing with vitamin A apply to these different situations? To what degree are programs and protocols similar in such varying contexts?

The decision–makers must then be directed to use the guidelines by the International Vitamin A Consultative Group (IVACG) as well as the WHO listings of priority countries.

Target Groups

Specific target groups and their respective treatment protocol need to be clearly outlined. The paper refers to preschoolers (i.e., under six–years–old) as well as non–pregnant or lactating women, and presents the most recent vitamin A dose delivery formally endorsed by WHO. Definition of the “preschool population” has varied: under–five (to 60 months), under–six (to 72 months), and through six years (to 84 months). Furthermore, when and how often do you dose non–pregnant women (i.e., lactating or not, for treatment or prophylaxis)? Finally, what is the preferred dose delivery interval in periodic dosing? The recommendations is every four to six months, although twice – yearly is often used. The data presented in the paper would support every four months; operational challenges generally limit delivery to every six months.

Both research studies in child survival and the data demonstrating Africa as a continent is in need of immediate vitamin A intervention indicate that alternative vitamin A dose protocols may need to be considered. At present, the manager should depend on the WHO guidelines presented in the paper, but should also be aware that these are under review, with the possibility of expanding the treatment protocol and definition target groups.

Delivery System

To assist management decisions, the authors present three strategies for dose distribution used in vitamin A intervention: medical, targeted, and universal. The suggestion is that a combined medical and targeted would maximize the cost efficiency in reaching those considered at most risk. The paper itself focuses on the preventive capability of vitamin A supplementation, perhaps paying too little attention to the need for medical treatment in clinic and hospital patients. In emphasizing primary health care and village–level interventions, the hospital pediatric ward can be neglected (in terms of appropriate vitamin A supplies and training of medical staff). Since the sick child is at most risk of the deficiency, the clinic situations must be covered for the sake of expediency, efficiency, and care.

It is an uncomfortable fact that the coverage of most health systems in the developing world do not reach the majority of their country's children. Thus, in focusing on a medical and even targeted intervention, we are accepting the limitation of current reality. This does not minimize the need of the innovative manager to look around to determine ways to reach special risk groups. An effective strategy is the multi–media approach used in Lombok Indonesia, which demonstrated that with community participation and communication, there was a reduction in disease and increase in program coverage. Although this could be considered problematic in terms of sustainability, in fact it allows the health staff to work with whole communities rather than

attempting to track individual children on a six−monthly basis, In recommending this model to all its field managers, Indonesia has demonstrated the possibility for integration yet innovation.

The paper examines at length measures to determine program impact in terms of change in prevalence of disease. Techniques to evaluate program operations themselves are also important. For example, the authors emphasize the need to look at program coverage in terms of at−risk groups, and offer varying strategies to reach them (i.e., targeted delivery). However, there needs to be in place a surveillance or monitoring system to routinely inform the individual managers the extent to which such critical groups are being reached.

Determining costs for vitamin A programming depends on assumptions made. The authors present the principle of marginality, which suggests that costs not attributable to the vitamin A program itself need not be considered part of the equation in determining program costs. This is a liberal perspective on costing, and can be used to support what then is an incredibly inexpensive intervention, i.e. averaging U.S. $0.015/capsule (fluctuating in terms of unit ordered and rate of foreign exchange). In using delivery costs to the field, the pricing has been assessed as high as $0.33 per dose. However, with the increased popularity of essential drugs programs − where a predetermined selection of drugs are routinely sent to the district health centers − the inclusion of vitamin A allows for a relatively reliable and sustained mechanism for getting the capsule to the field.

In presenting the periodic dosing as a recommended first−run intervention, less is said on the costs and benefits of food fortification with vitamin A and dietary modification. The paper reports that food fortification with vitamin A is relatively inexpensive, and that initial costs should be borne by the governments. Both of these are personal viewpoints not further substantiated. If the target population for food fortification can be considered an entire population, the costs per unit might be comparable but the program costs are relatively large and constant. Hence, in Central America, where fortification has been an effective intervention to increase serum retinol levels, a major factor leading to its demise has been the need for foreign exchange to procure the vitamin. So the cost becomes a critical issue. Secondly, whether or not the government, the industry, or the consumer should absorb the cost to improve both the nutrition and market value of the foodstuff is an open question for local policy makers to determine.

Dietary modification is considered a “long−term” yet essential component in xerophthalmia control. It generally refers to the need to assure vitamin A intake levels. However, in addition, fat and protein consumption must be assured to maximize the absorption and utilization of the vitamin. Three factors influence the body's vitamin A status: intake, absorption, and utilization. All three need to be of concern to those creating vitamin A programs. Nutrition education and horticulture are then critical components in any comprehensive approach to xerophthalmia control.

Finally, infection and vitamin A deficiency impact on each other in a relentless cycle. This synergistic relationship is not explored in the paper. The authors do insist on the intricacy of the problem in noting that severe protein−energy malnutrition, measles, diarrhoea, respiratory and other infections often precede or accompany corneal xerophthalmia. Hence, the prevention and treatment of them are important adjunct therapies.

In sum, the paper has given us the background to support the development of vitamin A programs and methods of assessing their impact, with specific operational issues less well defined. The paper rightly concludes that in vitamin A supplementation, we have both the technological promise and the operational challenge.

DELIVERY OF LARGE DOSES OF VITAMIN A

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Vitamin A deficiency has now been accepted as one of the major nutrition problems among preschool children, and perhaps the most important cause of childhood blindness in developing countries of the world. The subject of vitamin A deficiency and its control, which West and Sommer have discussed so impressively, is of paramount importance. Their estimate that half a million children in Asia develop blinding corneal xerophthalmia each year is not an exaggeration. In India alone, even at the conservative estimate of incidence

at one per thousand, every year about 80,000 preschool children belonging to low socioeconomic groups develop corneal lesions due to vitamin A deficiency. Follow–up studies at the National Institute of Nutrition have indicated that about a third of the children with corneal xerophthalmia become completely blind and another third die within the first six months.(1)

There are three major approaches to the control of this problem: 1) improvement in the diet to ensure adequate intake of vitamin A; 2) fortification of foods with vitamin A; and 3) periodic administration of large doses of the vitamin. A great deal of research has been carried out in different countries on developing these intervention programmes and evaluating their impact on the problem. The WHO statement (2) that “although the goal of controlling the florid forms of severe malnutrition like keratomalacia, marasmus and kwashiorkor by the turn of the century may be difficult to attain, it is not unrealistic as far as keratomalacia is concerned, provided that the knowledge now in hand is applied” appears very relevant. West and Sommer's essay substantiates it convincingly: by the turn of the century we may be able to considerably reduce nutritional blindness. The main focus of their paper is on the use of large doses of vitamin A, which is the most direct intervention strategy. Of the various measures available, the massive dose vitamin A programme can be regarded as a safe and potentially effective intervention to prevent xerophthalmia. The effectiveness of periodic large dosing of the vitamin was demonstrated in India as early as 1970(3). In fact, India was the first country to launch a national programme of vitamin A prophylaxis against nutritional blindness. The recent studies carried out by the National Institute of Nutrition laid to rest the skepticism about the efficacy of this method, and demonstrated for the first time that proper distribution of massive dose vitamin A can bring about a significant reduction in the incidence of corneal xerophthalmia(4). And yet, despite the fact that this programme has been in operation in the country for about fifteen years, nutritional blindness continues to be a serious problem. West and Sommer's concluding caution – that while periodic large dosing of vitamin A is conceptually simple, adequacy and efficiency of operation pose major challenges and determine the likelihood of success in preventing nutritional blindness appears very appropriate. In other words, however effective the technical solutions may be, operational aspects of a programme should receive much attention as otherwise any programme will be marred.

There are three basic systems for the delivery of vitamin A to the community: medical approach which offers treatment for children with xerophthalmia, targeted approach which covers high risk groups, and the universal system in which all preschool children are given the dose. In India, universal distribution is adopted, covering all children in selected poor rural communities. Although the first two components can be incorporated into the universal system, they are often neglected. As a result, the children who need the vitamin most, and who are missed by the universal system, do not get it. Proper training of health workers is essential, with adequate emphasis on identification of children at risk of blindness, particularly those with signs of vitamin A deficiency or protein energy malnutrition, and those with diarrhoea or respiratory infection. In the universal distribution system, the general tendency is to withhold the dose when the child is ill, particularly if there is diarrhoea. It is true that the absorption of vitamin A is incomplete in such cases, but this does not mean that they do not benefit from therapeutic doses of vitamin A. It has been observed that even in malnourished children with diarrhoea, corneal xerophthalmia responds well to oral doses of vitamin A.(5) A recent study carried out in Indian children has shown that when a large dose of water–miscible vitamin A was given during acute diarrhoea, 60–70% of it was absorbed and retained.(6) Though the absorption may be lower with oil soluble preparation, a child would still benefit from the amount absorbed.

A community health worker is more likely to come in contact with a child when he is ill, offering a better opportunity to give vitamin A than in the routine programme. Based on health care system utilisation rates, West and Sommer say that targeted delivery can reach only 10–15% of the “at risk” population. A routine dosing schedule is also difficult to achieve. But a combined approach may be more successful.

For the prophylaxis programme to be effective, it should be aimed at the widest coverage of population which is at risk, and this should be done at minimum cost and with maximum community participation. However, due to resource constraints in developing countries, complete coverage of the target group may not be possible. Of an estimated 80 million preschool children in India, only 25 million (i.e., less than a third) presently receive the massive dose of vitamin A. Obviously such a coverage cannot be expected to make a significant dent in the problem. It is here, perhaps, that the international agencies like WHO and UNICEF can contribute significantly by meeting the supply requirements.

Operationally speaking, the distribution system should be designed and implemented on the basis of existing infrastructure. The main drawback in such a system will be in areas where the priorities are different, and some of the programmes take a back seat. In India, the peripheral multi–purpose health workers (MPW) distribute the massive dose to the children, at the homes of the beneficiaries in their respective areas. Administration of vitamin A is but one of the multifarious activities carried out by the MPWs. Unfortunately,

distribution of vitamin A has not been given the place it really deserves, and is overshadowed along with other nutrition programmes, by the family planning programme. This problem can be overcome only if the administrators are convinced that nutrition programmes, such as massive dose vitamin A, contribute at least indirectly to the success of family planning programmes by reducing the morbidity and mortality in preschool children. This could be a motivating factor for mothers to accept small family norms.

Optimal use of manpower available can help to improve the coverage in countries like India. The coverage can be increased by utilising the services of Village Health Guides (village level workers). In India, there are about 300,000 VHGs providing primary health care to the community. At present, these workers assist the MPWs and do not directly distribute vitamin A. Being village−based workers, the six−monthly distribution could be allocated to the VHGs and consequently, the follow−up could also be expected to be better. Similarly, administration of vitamin A to all the children participating in supplementary feeding programmes, where children are collected at a centre daily, can significantly improve the coverage. Vitamin A delivery, which was originally started as an isolated programme, is now being incorporated into integrated health care programmes like the ICDS (Integrated Child Development Scheme). Distribution of vitamin A through the ICDS, which is in operation in about 1000 community development blocks, would also help increase the coverage. What the above measures call for is coordination between various departments.

Proper supervision and monitoring are absolutely necessary to achieve optimal coverage of 80−90% in each six−monthly round. In the programme undertaken by the NIN in slum areas of Hyderabad, effective coverage was achieved through a close monitoring system. Evaluation of the national vitamin A programme revealed that monitoring and supervision are the weakest links(7). Hardly any records were maintained and consequently the actual coverage figures were not available either at the State or National level. The medical officers in charge of the programme either did not have the time or the motivation to keep track of the programme. Unless the officers of the rural centres are oriented and motivated, it will be difficult to achieve optimal coverage.

It is well realized that any public health programme can be successful only if the community is made aware of the benefits of the programme. Education of the community thus becomes an important component of any nutrition programme. However, in our experience, this appears to be one of the weakest links. Consequently, the community is not aware that a programme of distribution of massive dose is in operation in the area and even if they do, they don't know its purpose. This is mainly because the peripheral workers do not make any effort to contact the mothers and educate them about the programme and about other measures to improve vitamin A status.

Vitamin A deficiency is a nutritional disease with a primary nutritional solution. The most rational method to control this problem would be to improve the diets of poor communities and ensure a continuous and adequate intake of vitamin A−rich foods. Animal products are good sources of vitamin A, but due to their high costs or limited availability, a majority of the population in developing countries must depend upon green leafy vegetables and certain fruits for pro−vitamin A. But these foods may not be readily available, or if they are, they may not be consumed in adequate quantities by the young children. Nutrition education acquires great importance in this context. Women play a crucial role in maintaining vitamin A nutrition of their children: through breastfeeding, through the acquisition and preparation of vitamin A−rich foods, and through their work in home gardens and in the fields growing pro−vitamin A−rich foods. Unfortunately, nutrition education has been one of the neglected components of most intervention programmes in developing countries. No concerted education campaigns seem to have been taken up to control vitamin A deficiency. Innovative approaches like the ones experimented in Hyderabad, where a multi−media package utilized all available village level personnel as agents for nutrition education, are required.

Choice of intervention programmes will naturally depend upon the local conditions and resources available. In areas where vitamin A deficiency is widespread, periodic distribution of large doses of vitamin A is the most commonly practiced intervention. This is no doubt a simple and potentially effective measure for preventing nutritional blindness. However, it is important not to lose sight of the fact that this programme was conceived only as a temporary measure to reduce the quantum of blindness. It should be coupled with more long−term measures to improve the diet and increase the intake of vitamin A among the populations at risk, which is the ultimate solution to the problem. A combined approach is more likely to succeed in achieving the goal.

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