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MASS DISTRIBUTION OF VITAMIN A

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1.0. INTRODUCTION

1.1. PREVENTION AND TREATMENT

A basic premise for vitamin A intervention is that there is a defined segment of the population at risk of developing clinical or biochemical vitamin A deficiency of sufficient severity so as to warrant the implementation of a strategy designed to improve the vitamin A status of that 'targeted' population group. Secondly, prophylaxis should be cost effective yet as non-invasive as possible, carrying with it a minimum risk. The biologic goal of prophylaxis is to prevent further deterioration and, if possible, improvement of vitamin A nutriture in the population already at risk of vitamin A deficiency. Changes in vitamin A nutriture are reflected by changes in various indicators of vitamin A status.

A distinction is made, as in all public health issues, between treatment and prevention. Treatment (comprising successive administration of a pharmocologic dosage of vitamin A) is rendered to an individual presenting with vitamin A deficiency, commonly reflected by one or more indicators of vitamin A status; i.e., the presence of clinical eye disease, or by a serum vitamin A (or holo-retinol binding protein) level below a specific cut-off point. If the individual presents only with a low serum value in the absence of disease, the treatment objective is to elevate total body stores of vitamin A for an extended period of time usually reflected by that individual's serum level response. If the patient presents with clinical eye disease, the treatment objective has three components: to halt the disease process, restore vision if impaired, and replete body stores of vitamin A to

within a normal range. This process of diagnosis, treatment, or prevention at the individual level is carried out in a clinic setting or during a screening program. Prevention (achieved through a variety of intervention strategies, see section 1.2), on the other hand, is directed towards one or a group of persons who, either through individual ascertainment or through assessment of a community as a whole, present a profile of disease or associated risk factors which indicate a need for improvement of vitamin A nutriture. Whether a person has the disease and therefore is treated, or is 'at risk' of disease, meriting a prophylactic dose of vitamin A, is a function of the indicator(s) used to define vitamin A status (i.e., biochemical and/or clinical) and its associated cut-off or threshold criteria upon which a diagnosis of vitamin A deficiency disease is made.

A mass dose vitamin A intervention strategy by its very nature is intended to reduce or control (1) the incidence of vitamin A deficiency, however defined, to an acceptably low rate within the designated 'at risk' population. In biochemical terms, it is intended to shift to the right, at a minimum, the lower tail of the distribution of serum vitamin A or holo-RBP levels in the target population such that few values are in a deficient range (a maximum of 5% of values less than 10μg/dl according to the recent WHO guidelines for determining the public health significance of xerophthalmia and vitamin A deficiency) (2). In most countries where vitamin A deficiency exists, the raison d'etre for intervention is to prevent severe xerophthalmia which may lead to blindness and death (3), although evidence is now emerging to suggest possible increased risk of childhood mortality associated with even the milder stages of xerophthalmia (A. Sommer, personal communication).

Because serum data are not readily obtainable in a population and because incidence of xerophthalmia is very difficult to determine prospectively (3), prevalence of xerophthalmia (i.e., clinical disease) estimated from a probability sample is often used to identify the magnitude, severity, and the population group at risk of developing vitamin A deficiency. Minimum prevalence rates that determine whether xerophthalmia is a problem of public health significance have recently been revised and published by the World Health Organization (2). When rates reach or exceed these criteria, a vitamin A intervention strategy is considered desirable.

A change in the prevalence of xerophthalmia over time, that can be attributed to an intervention, is used to assess effectiveness. Thus, prevention is intended to improve the vitamin A status of individuals, who, at the time they receive the vitamin A may even be free of clinical disease, but who are, nonetheless, at high risk of developing xerophthalmia in the future because of the prevalence of marginal to deficient vitamin A status. Individuals with xerophthalmia who subsequently are cured of the clinical disease as a result of receiving vitamin A through the intervention strategy have received treatment, not prophylaxis, at the time of receipt of vitamin A except where (1) prophylaxis serves to reduce the risk of relapse in that individual, or (2) prevention is assessed in terms of blinding sequelae whereby individuals with mild xerophthalmia are protected from developing severe corneal involvement.

1.2. ALTERNATE PREVENTION STRATEGIES

Currently vitamin A prophylaxis is approached through one of three

major intervention strategies:

(1) enhancement of the diet over time directed toward achieving a continuous, adequate intake of vitamin A-rich foods,

(2) fortification of an appropriate food vehicle commonly eaten in the community at risk,

(3) or a single pharmocologic dose of vitamin A administered on a periodic basis.

1.2.1. Enhancement of dietary vitamin A intake

Dietary modification has long been recognized and recently re-emphasized (4) as the major long-term solution to controlling vitamin A deficiency in a population. Through a combination of agromonic, horticultural, educational, and socio-economic inputs (2), the habitual intake of food sources of vitamin A is gradually increased and maintained at a level which minimizes the risk of developing vitamin A deficiency among the vulnerable segments of a population. The mix of required inputs is determined following a critical analysis of the local feeding patterns and environmental resources, including the local 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 intra-family food consumption patterns would appear to merit emphasis (3), while in areas where seasonality is a critical factor in limiting the availability of normally consumed dark green leafy vegetables, promotion of appropriate local food preservation technology (5, 6) might be expected to yield higher intakes during the dry season within a relatively short period of

time. Universally, sustained breastfeeding remains the best guarantee of adequate vitamin A intake among infants and young children (3) and appears to exert a major preventive influence on the prevalence of xerophthalmia (3).

1.2.2. Vitamin A fortification

Fortification of a widely consumed food ('vehicle') with vitamin A offers a second major, technically feasible intervention which can be relatively inexpensive (7) and effective in increasing vitamin A intake throughout the year, reflected by sustained elevations in serum vitamin A (8, 9, 10), and reductions in xerophthalmia (3, 8, 9, 10) among the vulnerable members of a population. A number of necessary pre-conditions must exist before fortification can be considered a viable alternative including the identification of a 'core' food in the diet of particularly the 'at risk' population which is technically fortifiable, is manufactured or processed in only a few centers, retains potency and acceptability, and is consumed daily with a truncated intake distribution at the upper levels. It has recently been noted that in the presence of a choice between fortified and unfortified brands of a product, and absence of mandated fortification of all brands, the consumer is not willing to pay the added cost associated with fortification (4). The requirement for governments to pay for vitamin A in foreign exchange also requires consideration (2). Depending upon local factors and program costs, fortification can offer both short and long term impact capability in a chronically vitamin A deficient population.

1.2.3. Mass dose vitamin A distribution

The periodic dosing of target groups with a capsule or spoonful of 200,000 IU vitamin A in an oil solution comprises a third major intervention strategy (2). It is viewed as a short term, or at least 'interim', approach to protecting a vulnerable population from overt vitamin A deficiency by 'immunizing' (3) children usually every six months until one or more long term solutions to controlling vitamin A deficiency can be implemented. Such a 'transition' has yet to take place in countries where a periodic capsule or syrup distribution exists, due to the difficulty in developing the more appropriate long term approaches. It now appears that such a strategy may have a place as a limited component in a long term vitamin A deficiency prevention program.

This paper provides a comprehensive review of the origin, rationale, efficacy, effectiveness, and costs of this third intervention strategy.

2.0. EFFICACY OF ORAL VITAMIN A ADMINISTRATION

Given the characteristically high incidence of recurrent respiratory, gastrointestinal and other infectious diseases among young children in regions of the world where vitamin A deficiency exists (11, 12), and the apparent adverse affects of infections on vitamin A absorption (13-19), and retention (14), considerable research has been directed toward establishing the efficacy of orally administered vitamin A preparations in animals and in humans in terms of efficiency of absorption and impact on various indicators of vitamin A status (e.g.,

serum retinol, clinical xerophthalmia).

Efficacy, within the context of preventing vitamin A deficiency and xerophthalmia in a population incorporates three distinct components:

1) Efficiency of absorption of a dose of vitamin A (under conditions of varying dosages, schedules, and disease states which are prevalent in a target population),

2) Retention of the vitamin A dose, and

3) The duration for which adequate vitamin A status, reflected by the absence of xerophthalmia and/or an acceptable serum vitamin A or holo-retinol binding protein level, can be maintained as a result of the vitamin A dose (the 'protective period').

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1 For the purposes of this paper, 'efficacy' refers to the ability of a mega dose of vitamin A to prevent either clinical or biochemical vitamin A deficiency considered in isolation of programmatic considerations; 'effectiveness' refers to the impact of massive vitamin A dosing on reducing the incidence or prevalence of vitamin A deficiency when implemented through a delivery infrastructure to a target population (20).

2.1. EFFICIENCY OF ABSORPTION

Definition of 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 that can be attributed to a massive dose of vitamin A. Efficiency of absorption has been determined by computing the difference between the total dose administered and fecal losses of vitamin A for several days after administration, often using labelled retinyl acetate. Alternatively, the shape of the serum vitamin A absorption curve has been estimated before and at intervals during the 24 hours following dose administration, noting the timing and magnitude of the peak rise in serum retinol.

During the middle of this century, the absorption of varying quantities of vitamin A, either as an ester (acetate or palmitate) or alcohol (retinol), (17, 21, 22), in an oil base or a water-miscible ('aqueous') solution (22-33) was a particularly active focus of human (21, 22) and animal (23, 24) nutrition research. Work was motivated largely by interest in comparing differences in absorption associated with various disorders (including prematurity (26, 33), celiac disease (17, 27, 28), pancreatic cystic fibrosis (17, 29), nephrotic syndromes (22), and other diseases which are often accompanied by malabsorption (17, 23), to absorption under conditions characterized by normal gut function (21, 22, 24, 31, 32), with the aim of identifying defects in vitamin A metabolism and defining appropriate physico-chemical forms and delivery modalities for vitamin A supplementation. Many of these early studies were conducted during a period when synthetic vitamin A

synthetic vitamin A preparations were just becoming commercially available and thus, provide the initial evidence about the absorption of orally administered vitamin A in physiologic and pharmacologic doses.

2.1.1. Ester versus alcohol absorption

Findings from early studies demonstrated similar rates of absorption for both of the vitamin A esters (acetate and palmitate) and retinol (vitamin A alcohol) when orally administered either in an oil solution to healthy infants, older children, and adults (17, 32), or as a water-miscible dispersion to older children (21). Similar results were reported from animal experiments (23), although, in some malabsorptive disorders, the chemical form was shown to influence absorption. For example, in celiac disease both the ester and alcohol are poorly absorbed in oil (17) but well absorbed in water-miscible form, while in cystic fibrosis, and other malabsorptive diseases the vitamin A alcohol may offer an absorptive advantage over the ester in oil (17).

2.1.2. Water-miscible vs. oil-soluble: the normal gut

Studies among normal, apparently vitamin A replete individuals (24, 26, 33) have consistently revealed a markedly higher peak in the 3 to 6 hour serum retinol level following oral administration of water-miscible or emulsified preparations versus oil-soluble solutions of vitamin A, although comparable serum levels are usually noted at 24 hours. Early rat experiments demonstrated lower fecal excretion (5-12% versus 20-23% of the dose, respectively), higher peaks in serum retinol, and greater hepatic storage (38-55% versus 23-28%, respectively) from megadoses of

vitamin A in water-miscible and emulsified preparations (23, 24) suggesting more efficient absorption then from oil solutions, attributed, in part, to a smaller fat particle size being presented to the intestinal mucosa (23, 33), and to possible emulsifier-specific influences on vitamin A absorption (J. C. Bauernfeind, personal communication). Differences of similar magnitude in fecal excretion of vitamin A for both water-miscible and oil forms were also reported for healthy infants (24) and adults (27) receiving single doses of up to 33,000 and 400,000 IU, respectively.

The weight of evidence generated from these studies suggests a greater absorption of vitamin A in a water-miscible dispersion. Nonetheless, satisfactory vitamin A absorption curves, (several-fold peak in the 3 to 6 hour serum retinol response) have been observed among apparently healthy individuals (27, 28, 29) and ill patients with normal gut function after administration of pharmocologic doses of oil-soluble vitamin A (31). Animal experiments using vitamin A depleted rats have also demonstrated comparable (25), and even superior (34) restoration of 24 hour liver stores, similar 24 hour serum values (28) and, most importantly, resolution of xerophthalmic signs accompanied by equivalent rates of growth (25) using either preparation.

2.1.3. Water-miscible vs. oil-soluble: the malabsorbing gut.

2.1.3.1. Primary Malabsorption

In the presence of primary malabsorption (27, 29) water-miscible vitamin A has consistently been shown to be better absorbed when compared to an oil solution, attributable, in part, to a reduced dependence on enzymatic and micelle-forming activities for absorption.

2.1.3.2. Enteric Infection

A number of recent human studies investigating the effects on absorption of various gastro-intestinal infections such as giardiasis (15) ascariasis (15, 18, 19), chronic salmonella septicemia (16) and other enteric pathogens (13) which are endemic throughout developing regions of the world, have provided evidence for significant impairment of vitamin A absorption from both the oil-soluble (13, 16, 18, 19) and water-miscible (15) preparations, reflected by marked improvement in the vitamin A absorption test (13, 15, 16, 19) or in the amount of labelled retinyl acetate (18) absorbed following treatment for the infections.

2.1.3.3. Severe Protein-Energy Malnutrition (PEM)

Severe protein-energy malnutrition, specifically, kwashiorkor is known to cause profound histo-pathologic changes in the intestinal mucosa (35) and marked reductions in secretion of pancreatic enzymes (36). These changes also are likely to account for much of the fat malabsorption accompanying severe PEM (37). Since children with PEM are at enormously increased risk of developing blinding corneal xerophthalmia (RR= 49:1, see (3) p. 109) improvement of their vitamin A

status needs to be accomplished as quickly as possible. Under these conditions, a water-miscible vitamin A preparation may be expected to be more rapidly absorbed than an oil solution. Several investigators have observed flat and/or erratic vitamin A absorption curves following an initial oral administration of up to 75,000μg vitamin A in oil to children with frank kwashiorkor and severe xerophthalmia (35, 38). These observations prompted the original WHO recommendation that such high risk children, and children with corneal xerophthalmia be treated initially with intra-muscular water-miscible vitamin A (2, 38). It was expected that this would avoid absorption inefficiencies and facilitate movement of vitamin A to extra-hepatic target tissues. Widely practiced (38, 39), this treatment appears to be effective in halting and healing corneal destruction, and preventing a relapse for up to one year among surviving children (39). More recently, severely xerophthalmic Indonesian children with moderate to severe PEM and/or diarrhea, while exhibiting lower 24 hour serum retinol levels after 200,000 IU oral vitamin A in oil versus intra-muscular injection, exhibited comparable clinical responses. In addition, 24 hour serum holo-RBP responses to the two regimens suggested adequate absorption of the oil-based preparation even when treating such 'worst-case' clinical profiles (40). Following these observations the WHO recommendations were revised to include oral administration of 200,000 IU of vitamin A in oil for treatment in the absence of repeated vomitting or severe diarrhea (2). 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. It is therefore recommended, in addition, that they continue to receive repeated (physiologic) doses of vitamin A periodically until

protein status improves (41).

Simultaneous comparisons of absorption differences between water-miscible and oil-soluble vitamin A preparations among children with marginal PEM and common enteric infections, a characteristic profile for many children in developing countries, have not been reported in the literature.

2.1.4. Water-miscible or oil-soluble vitamin A?

Upon viewing the evidence at hand, a water-miscible preparation of vitamin A appears to outperform 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) a concern for the safety of megadose water-miscible preparations, and,

(2) the technological problems of packaging a single unit water-miscible preparation (J. C. Bauernfeind, personal communication).

In the first case, the rapid absorption of water-miscible vitamin A results in acute hypervitaminosis A in a significant proportion of children following massive dosing. The slower absorption rate of vitamin A from an oil solution results in an attenuated 'spike' in serum retinol and a decreased risk of toxicity. Following a single

megadose (200,000 - 300,000 IU) such toxicity is self-limited and, commonly includes nausea, vomiting and/or headache (10). The literature related to hypervitaminosis A toxicity in children attributable to massive oral dosing with vitamin A has been extensively reviewed by the IVACG (42). In one early Indian study (43) nearly 25% of the children developed toxic manifestation following oral administration of a single dose containing 300,000 IU of a water-miscible preparation. Three other studies of water-miscible preparations reported no toxic symptoms. Ten investigations using an oil solution 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. A somewhat higher incidence of vomiting and diarrhea (16%) has been recently reported following administration of 300,000 IU in oil (44). A markedly reduced toxicity rate of 6% was noted when 233 IU of vitamin E were added. Even a 3% to 6% incidence of such symptoms among recipient children could severely reduce future compliance with a population - based program (10) causing a high attrition rate over time.

The second problem deals with the practicalities of designing an efficient production and delivery system at low cost which optimizes vitamin A stability, shelf life, 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, is stable in terms of potency under warm ambient temperatures, and does not run the same risk of 'separation' over time as does a water-miscible dispersion.

These concerns for safety, cost, and practicality directed the development of mass dose vitamin A delivery systems during the 1960s toward use of oil based solutions, which have, therefore, become the predominant preparations in use by nearly all mass dose supplementation programs.

The remainder of this paper deals with the efficacy of oral, oil preparations, and the effectiveness of country programs utilizing the oil-soluble vehicle.

2.2. RETENTION OF THE (OIL-SOLUBLE) VITAMIN A DOSE

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 pharmocologic doses using radio-labelled retinyl acetate (14, 18, 45, 46, 47). These studies improve upon the ability of previous absorption studies to estimate the enhancement of vitamin A nutriture, since they measure urinary as well as fecal losses of administered labelled vitamin A (48, 49, 50, 51) during a characteristic four to five day post-administration period.

Table 1 presents these Indian 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 (46). In general however, data on nutritional status were not reported. One must therefore be cautious in extrapolating these results to chronically undernourished Indian or other childhood populations. Still, several key and consistent findings are apparent on the absorption and retention of vitamin A from retinyl

esters 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 (14, 18, 46).

(2) In the presence of systemic and enteric infection absorption at the same dosage is reduced to 75%, and ultimate retention to some 60-65% (14, 18); however, percent retention of the total amount actually absorbed remains at approximately 80%.

(3) A megadose (approximately 200,000 IU) of oil-soluble vitamin A is less efficiently absorbed than a physiological-sized-dose, approximately 70%, (45, 46, 47) and is only 40-33% retained (comprising only 65% of the absorbed dose) when given to healthy, preschool children in the absence of a large vitamin E supplement (47). An expected 30-50% retention and hepatic storage for dietary vitamin A has long been suggested by the WHO (52).

Similar radio-tracer studies on the absorption and retention performance of pharmacologic doses of vitamin A administered to clinically ill children have not been reported, but would be expected to show even even less retention. Using a 45% retention value for normal children and an estimated daily requirement of 25μg retinol/kg, a 200,000 IU dose of vitamin A in palmitate (60,000μgRE) given to a 15 kg child would theoretically provide 70 days of protection in the complete absence of dietary sources and stores of vitamin A. While more sophisticated computations regarding estimated protective periods have been performed (10), the most reliable estimates are derived from data

collected on human populations.

2.3. THE PROTECTIVE PERIOD

The efficacy of a mass dose vitamin A intervention to prevent clinically significant vitamin A deficiency and xerophthalmia is ultimately determined by the protective time period afforded to 'at risk' individuals, known to have received the vitamin A supplement. Evaluation of the preventive efficacy of a strategy designed to combat either clinical or biochemical vitamin A deficiency, known to fluctuate seasonally and probably annually with variations in diet and contributory diseases (53), requires multiple prospective studies with appropriate comparison groups.

Tables 2 and 3 briefly summarize studies which have prospectively investigated the effects of a mass oral dose of vitamin A on serum retinol levels and xerophthalmia, respectively, relative to indicator changes observed in a control or placebo group. A few preliminary comments deserve mention. While each study listed has an acceptable comparison group, loss to follow-up haunts several of the studies to varying degrees, ranging from essentially complete six month follow-up in an Indonesian study by Kusin et al. (44) to only 56% follow-up at 22 weeks for an unpublished study by Dhanamitta et al. (54). Secondly, the vitamin A dosage employed varies from study to study, ranging from 100,000 to 300,000 IU, after which the protective period was observed for varying intervals of time in populations that differ markedly in their baseline vitamin A status, reflected by the serum retinol differences (see Table 2).

2.3.1. Preventive Efficacy Against Low Serum Retinol Levels

Results in Table 2 do not leave a clear impression of the long term efficacy of a massive dose of vitamin A in maintaining elevated serum retinol levels. While the study of healthy, breastfed newborns by Thanangkul et al. (58) suggest a prolonged elevation of serum retinol above control levels for up to 7 1/2 months ($p<0.01$) and possibly for 10 1/2 months (N.S.) following supplementation with 50,000 IU of retinyl palmitate, the control infants exhibited an apparently normal vitamin A status (>20μg/dl) for the first 9 months (not shown) without added vitamin A. It may be argued that a more truly prophylactic effect may have been seen beyond 10 1/2 months since control serum retinol values were apparently decreasing more rapidly than supplemented group levels. In Jordan, Patwardhan and Kamel (55) demonstrated significant elevations of serum retinol levels ($p<0.01$) in both 300,000 IU and placebo supplemented infants at two months. At twelve months 50% of the infants had been lost to follow-up but serum retinol levels were still similar and acceptable in both groups, 29 versus 26μg/dl, respectively.

Pereira and Begum (57) demonstrated an incremental benefit of over 7μg/dl at two weeks attributable to a 100,000μg retinyl palmitate (182,000 IU) supplement to older preschoolers with an apparently normal, initial vitamin A status, despite a low β-carotene diet (300 IU/day) for three months prior to the study. The supplement advantage, while statistically significant for only the first two weeks, appeared to remain for over 10 weeks, after which average serum levels steadily decreased to low levels in both groups. Subsequent redosing of the same children, this time in both groups, produced serum elevations to

approximately 30μg/dl within one week, average levels remaining at or above 20μg/dl for 11-15 weeks. In a second study by the same authors among two to six year olds with marginal vitamin A status (56), preventive efficacy of a single 50,000μg dose of retinyl palmitate was influenced by dietary β-carotene intake. No effect was observed between supplemented and control children consuming a moderate amount of β-carotene (900μg/day, roughly equivalent to 15g dark green leaves) throughout an 18 week follow-up period. However, supplemented children with deficient β-carotene intake (120μg/day), displayed significantly and acceptably elevated mean serum retinol levels above consistently low, unsupplemented control concentrations for up to eight weeks, after which supplemented child values gradually decreased to near deficient ranges by 18 weeks (12±3μg/dl). Previously, Pereira and Begum (60) had shown that a diet of 30g of dark green leafy vegetables per day for three months could elevate serum vitamin A levels from approximately 22 to 32μg/dl during this time. More importantly, when a group of these same children were subsequently placed on a controlled, vitamin A deficient diet (300 IU as β-carotene), serum retinol remained at acceptable levels (above 20μg/dl) for an additional five months.

Kusin and colleagues (44), in a well-designed study with an extraordinary follow-up rate of 99.6% at 6 months, showed virtually no serum effect of a 300,000 IU supplement among 1-5 year old Indonesian children exhibiting initially marginal serum vitamin A level. Dhanamitta et al (54) similarly demonstrated little or no discernable effect associated with a 100-200,000 IU supplement throughout 5 1/2 months of observation. In Brazil, Araujo et al. (61) have also reported no difference from baseline serum retinol levels 30 days after a 200,000

IU dose given to poor socio-economic class children consuming a low vitamin A diet.

The critical importance of an appropriate concurrent comparison group is obvious from the sometimes dramatic shifts (55, 57, 58) in the serum vitamin A levels, in either direction, observed over time from non-intervention influences. In both the Jordanian and Thai infant studies (55, 58) in particular, lack of a control group raises questions about the apparent strong and enduring impact supplementation had on serum vitamin A levels. In two widely quoted studies, long protective periods were reported, ranging from 6 months (34) up to 2 years (62), where either no control (34) or an unevaluable control (62) group were used.

Based on these studies, the protective period (retinol levels elevated to an acceptable range of $\geq$ 20μg/dl in children who are initially 'at risk' of vitamin A deficiency) is likely to be disappointingly short, with optimistic estimates ranging from 8 weeks to 7 1/2 months. Dietary intake of as little as 150mg RE (33% of RDA) as dark green leafy vegetables or other β-carotene - rich foods per day may serve to considerably extend this protective period.

2.3.2. Preventive Efficacy Against Xerophthalmia

The efficacy of massive vitamin A dosing in protecting against xerophthalmia was first suggested by results from a two year field trial conducted by Swaminithan et al. (63), 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. Considering these severe limitations, an 87% preventive efficacy[1] against X1A and X1B among three to five year olds can be computed according to guidelines provided by Milton (64) for a pre-/post-intervention study design. However, this entire effect can be attributed to the annual dose of vitamin A only under an unrealistic assumption of the absence of seasonal and other influences on clinical disease status.

Table 3 presents clinical results from three controlled studies in which the follow-up period after each single vitamin A dose ranged from four to six months.

Unfortunately, results of the most rigidly controlled trial yet attempted on the prevention of xerophthalmia in a community have never been published in a refereed journal (59). In this study, 2,680 one to six year old Indonesian children were examined and enrolled into a 200,000 IU capsule supplementation trial, approximately half being alternately assigned either the vitamin A capsule or a placebo in a double-blind fashion. The overall baseline prevalence of xerophthalmia was 4.7%. Children were carefully monitored for correct capsule receipt

1 Equivalent to attributable risk computed for a cohort study using the following formula: $e=100\ (r-1)/r$ where, e=preventive efficacy, or the proportion of observed xerophthalmia cases which can be attributed to non-receipt of the vitamin A capsule among those known not to have received the capsule. r=relative risk, the ratio of the incidence of xerophthalmia among the placebo ('exposed') group over the incidence in the intervention ('non-exposed') group.

status and 92% of the subjects were re-examined for xerophthalmia six months later, at which time a second capsule was administered to the supplement and placebo groups. At twelve months, 85% of the originally enrolled children were once again examined for clinical eye disease. The results show a striking and statistically significant difference in the six-month incidence of conjunctival xerosis and Bitot's Spots, 0.47% among the capsule recipients versus 3.6% among placebo children. The computed preventive efficacy (64) associated with vitamin A capsule receipt was 87%. Additionally, 91% of all initial cases who were treated with a single 200,000 IU dose and successfully followed up at the six month interval (90%) were found to be free of disease at six months. Still, 9% of the Bitot's Spots persisted, presumably representing stigmata from previous vitamin A deficiency that was no longer active and usually found among children four years of age and older (65). Ages of children with refractive X1B were not reported in this study. At twelve months (six months after the second capsule distribution round), preventive efficacy remained at over 90%, reflected by six month incidence rates of .25% and 2.89% among vitamin A supplemented and placebo children, respectively.

During the Ichag Study (53), Sinha and Bang reported equally striking differences in the incidences of night blindness (XN) and Bitot's Spots (X1B) between preschool children receiving 200,000 IUs of vitamin A every 4 months in a double-blind manner, and control children in the same village receiving a placebo capsule. 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 (66). The vitamin A capsule and placebo intervention study

was then implemented during the third subsequent year and children were followed in a masked fashion 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. Receipt of the vitamin A capsule had no effect over the placebo in reducing the prevalence of persisting X1B or on preventing recurrence of peak-season X1B incidence among children who exhibited X1B during the previous year. Newly incident cases, however, were reduced from 8.8% among controls to 0.8% among supplemented children ($p<0.004$), reflecting a degree of efficacy (91%) similar to that observed in Indonesia (59).

In the North Sumatran study conducted by Kusin et al. (44), cure rates and incidence among the total of six X1B cases reported in either the dosed or placebo groups during the first six months of follow-up showed no effect attributable to a 300,000 IU dose of oral vitamin A. The small number of observed cases in this study neither support nor refute vitamin A mass dose efficacy.

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 preventive efficacy of a community-based strategy which successfully reaches those children most at risk of developing corneal blindness. Sommer observed 48 Indonesian children with Bitot's Spots (X1B) 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 4). The routine clinic visits which included health education during the follow-up period may have had a positive, independent influence on dietary vitamin A intake and, thus, serve to extend the estimated protective period. However, intensive nutrition education efforts elsewhere, to date, have not shown significant effects on the reduction of xerophthalmia (10).

While the extended effect of a massive oral dose of vitamin A on serum retinol levels appears to be non-existent to highly variable in different populations, evidence from controlled and other supportive clinical studies suggests a 90% or better preventive efficacy against developing mild xerophthalmia for at least four to six months among children who are known to have received the supplement. Notably lacking are any studies which report the efficacy of a massive dose of vitamin A in preventing severe, potentially blinding xerophthalmia. The reasons for this critical lack of community-based data revolve around the rare occurrence, and short clinical duration (e.g., less than 2 months) of corneal xerophthalmia, and its attending 3% (39) to 90% (64) mortality rate.

3.0. EFFECTIVENESS OF THE ORAL VITAMIN A MASS INTERVENTION STRATEGY

3.1. INDICATORS OF EFFECTIVENESS

Few mass distribution programs have been evaluated according to observed changes in the serum retinol distribution in the target population. This is appropriate in light of the equivocal efficacy of a single, high level dose of vitamin A in sustaining elevated serum

retinol under conditions of marginal to low vitamin A status (10). Thus, the (clinical) assessment of xerophthalmia status constitutes the most widely used indicator of risk of vitamin A deficiency in the population. Achievement of an acceptable reduction in the incidence or prevalence of mild to severe xerophthalmia comprises the basic criterion against which program effectiveness is usually evaluated.

3.2. MEASURES OF EFFECTIVENESS

3.2.1. Pre/Post Intervention Difference

3.2.1.1. Intervention Population Only

A both widely used (10, 67, 68, 69, 70, 71) and criticized measure for assessing intervention impact involves computing the difference (d) in xerophthalmia prevalences between a baseline (p_1) and a second (p_2) point in time following implementation of the program such that $d = (p_1 - p_2)$. At the minimum and often, at best, this difference, d, reflects a measure of association between the operation of a vitamin A intervention program (at a stated coverage) and a change in disease prevalence during the interval. The larger the difference over a relatively short period of time (e.g. 3 to 6 months), the greater the strength of the association, and the more likely a causal inference can be made, especially if d is found to consistently decrease in the presence of an intervention across various population groups. Further credibility is earned by this measure if d is observed to vary with adequacy of coverage.

Confounding variables which plague the interpretation of this measure of program effectiveness in the absence of a comparison group

include:

(1) the lack of control for the numerous cultural, socio-economic and environmental factors which can change dietary and disease patterns, over time and, consequently, the incidence and/or duration of xerophthalmia in the community; and

(2) the cohort effect which, because of the known positive age xerophthalmia prevalence relationship (72), can exert an independent effect on disease.

As a minimum, dietary and disease patterns should be described during the period of intervention so as to consider these influences on d.

Evaluations which employ this measure of effectiveness and demonstrate consistency in the association, can lead to a confident statement regarding the direction of impact. However, it is more critical to estimate the magnitude of the reduction in risk directly attributable to the specific vitamin A intervention program in the target population.

3.2.1.2. Intervention and Comparison Populations

Concurrent observation of a randomized, non-intervention, comparison population permits direct estimation of the effect of a vitamin A megadose strategy. Usually randomization of community assignment is socially and politically unacceptable, and unethical in the presence of adequate program resources and high risk of vitamin A deficiency. In a region of apparently uniform risk of disease and where

limited program 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, a large study population, and is expensive, it provides the only mechanism available for rigidly assessing the impact of a much more expensive mass vitamin A distribution campaign on preventing severe xerophthalmia and nutritional blindness (73).

3.2.2. Slope Test for Age-Prevalence Association

A parameter of the prevalence of mild xerophthalmia (especially X1B) is its positive association with age among preschool children. Figure 1 depicts this relationship as reported from prevalence surveys in several different countries (59, 66, 69, 72, 74).

Based on this age trend, Indian investigators have introduced an evaluation methodology (72) which permits an assessment of program effect on mild xerophthalmia in the absence of a baseline prevalence estimate. The method is based on a previously observed near absence of this prevalence-on-age trend (slope = 0.0065) in communities where a mass dose intervention program had been introduced and had achieved at least 85% coverage (72). This relatively flat slope is interpreted to reflect significant program impact on the prevalence of xerophthalmia.

To evaluate program effectiveness throughout the country, prevalence surveys were conducted among 1 to 10 year olds in areas where megadose vitamin A distribution had been in operation for two years or

more. A test for a linear trend in proportions (75) was applied to the regression of X1B prevalence on age among 1 to 5 year olds in each of these intervention areas (76), against a null hypothesis of the slope being significantly larger than either zero, or 0.0065 (see Figure 2). Testing against the latter slope value recognizes some degree of dose inefficacy, and imperfect coverage associated with even acceptably performing programs.

While a 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 impact or that a program had been operating in a relatively low prevalence area. Thus, 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 previously high risk of xerophthalmia in the communities, for which slope values were then evaluated. While the etiology of Bitot's Spots which persist into later childhood is not entirely understood (3, 53, 65, 77), this assumption would appear to conservatively (and appropriately) bias results toward an indication of 'no effect'. Further gains in quantifying this relationship could be expected by regressing computed slope values on percent coverage in different regions. Investigation of this relationship in India showed that among areas where program data were analyzable, adequate coverage was strongly associated with a flat slope, and poor coverage with a significantly positive slope (76).

This innovative and inexpensive salvage technique permits detection of an association between xerophthalmia reduction and the introduction

of a distribution program in previously high risk areas where no baseline data had been collected. This method, however, does not obviate the need for appropriate baseline and, when possible, comparison group data prior to program implementation. Strategy effectiveness cannot be inferred directly from positive findings due to the same confounding influences which complicate the interpretation of 'd' in the absence of a comparison group (see section 3.2.1.).

Even more importantly, caution is warranted in drawing inference regarding a program's impact on severe, potentially-blinding xerophthalmia based on the absence of a significant regression of X1B on age. During the national xerophthalmia survey in Indonesia from 1976 to 1978 (74), the estimated regression coefficient of X1B on age (see Figure 2) was +0.0029, well below the null value of $+0.006^5$ used in India (72). Prevalence among 6 to 10 year olds was not ascertained, thus, permitting an interpretation of low risk (few mass distribution programs were ongoing among the numerous surveyed areas). However, the age-specific, unweighted prevalences of X2/X3 and XS per 10,000 in this same, multi-regional population were as follows (3, 74):

Xerophthalmia	Age in years					
status	1	2	3	4	5	Average (all ages)
X2/X3	5.0	14.7	9.8	3.6	1.6	7.09
XS	10.2	24.7	32.7	28.6	17.8	15.86

While there is likely to be substantial differences in risk factor prevalence and severity between these two populations, the Indonesian population is one example where a relatively flat slope of X1B on age was associated with high prevalences of severe xerophthalmia across all age groups.

3.2.3. Population Preventive Efficacy Estimator

Preventive efficacy (e), as noted earlier (see section 2.3.2.) 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 are similar to those experienced by the target population. This measure specifies the percent reduction in xerophthalmia that can be expected from initiating a massive dose vitamin A intervention strategy which achieves 100% coverage of all 'at risk' individuals (i.e., the upper limit of program effectiveness). However, since vitamin A distribution strategies never achieve complete coverage, a measure of expected impact on xerophthalmia prevention in the population, in terms of percent prevalence or incidence reduction, at a specified rate of coverage may be given by the following formula:

$$e_p = p[(r-1)/r]$$

$$p = p(e)$$

where, e_p = the population preventive efficacy, that proportion of xerophthalmia in the target population which is preventable during the dosing interval as a result of vitamin A intervention.

p = the proportion of targeted individuals reached by the mass distribution cycle.

r = the relative risk of developing xerophthalmia during the specified interval associated with not receiving the supplement, 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 distribution system (i.e., 1-p).

e = preventive efficacy generated from a cohort or case-control study, and equal to (r-1)/r.

As the percent coverage (p) increases to near 100% (or to the value 1.0) e_p approaches e, the preventive efficacy of the vitamin A megadose previously estimated under the prevailing conditions of disease risk in the target population. The value $(1 - e_p/e)$ is that proportion of the remaining xerophthalmia in the population which could be eliminated if all 'at risk' children were to receive the supplement, and is identical to the formula for population attributable risk: $(1-p)(r-1)/[(1-p)(r-1) +1]$ (78).

One hundred percent population preventive efficacy does not indicate complete efficacy in preventing xerophthalmia since a single megadose of vitamin A, given under known study conditions, fails to prevent some 10% (53, 59) of mild eye signs from developing during the specified period of protection. However, it may represent complete efficacy in preventing its blinding complications.

The usefulness of this weighted preventive efficacy (or attributable risk) formula rests on the degree to which the estimated

relative risk applies to those children who typically are missed by the distribution program. Use of a relative risk value which relates to the entire target population carries an assumption that the probability of developing xerophthalmia in the absence of a megadose of vitamin A is similar between dosed and non-dosed children; an assumption which appears not to hold in some countries (69, 71). Milton (64) provides ample caution for applying and interpreting these percent efficacy and, by its association, population preventive efficacy measures.

3.3. ESTIMATES OF EFFECTIVENESS

Apparent effectiveness can reflect actual program impact on the incidence of xerophthalmia. Alternatively, it can be an exaggeration of actual strategy impact, due to a poor evaluation design lacking an appropriate comparison group, or not otherwise accounting for possible seasonally-related and other environmental influences (52) which could reduce the prevalence of xerophthalmia independently of the program. Apparent ineffectiveness can be attributable to a true program failure to reduce xerophthalmia, often because of inadequacies in the delivery system, or again to weaknesses in the evaluation.

3.3.1. Estimates using the pre-/post-intervention measures

Interim effectiveness evaluations which have employed a pre-/post-intervention design are summarized for several countries in Table 5. Each intervention comprised the distribution of 200,000 IU of vitamin A either in capsular (10, 70, 79) or bottled concentrate (2, 74) form, implemented primarily as either a universal, bi-annual (2, 10, 70, 74, 79) or a targeted, clinic-based (70) distribution strategy, noting that

all programs incorporate a vitamin A treatment component. Each evaluation controlled for seasonal but not annual variability in xerophthalmia prevalence. The Indian (67, 68), Philippino (10), and Haitian (70) evaluations report the effectiveness of their respective programs during the first one to three years of operation. The Bangladesh results (79) refer to evaluations conducted after at least nine distribution cycles during the previous six to seven years.

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 be likely to influence the expected impact associated with the same 200,000 IU dose of vitamin A at a given coverage rate.

These evaluation findings consistently suggest that a mass distribution strategy, which achieves reasonable coverage of its target group, can have a favorable impact on reducing mild xerophthalmia. Percent reductions in disease associated with two or more distribution cycles range from 60 to 80% of the baseline prevalence estimates.

The apparent discrepancies in the concurrent Bangladesh evaluations may be partially due to the differences in sample selection and quality of data collection. The data reporting no change were culled from the 14,000 family welfare worker reports generated during each capsule distribution cycle. The second set of results were obtained from independent surveys in identified high risk villages throughout the country, conducted by 200 trained, program supervisors. A most unusual

feature of this latter evaluation was the assurance of '100%' coverage among these high risk villages. In the absence of annual variation these results could provide an estimate of expected population preventive efficacy attributable to the receipt of two 6 monthly capsules (73% for XN, 67% for X1B). However, observed changes in prevalences of X1B and X2 within non-intervention areas in Bangladesh during 1979 and 1980 (from 1.5 to 4.0%, and .17 to .36%, respectively) indicate strong annual variation in the prevalence of xerophthalmia, further emphasizing the critical importance of using appropriate, concurrent comparison groups for program evaluation.

Table 1. RECENT STUDIES REPORTING ON THE ABSORPTION AND RETENTION OF ORALLY ADMINISTERED, OIL-SOLUBLE VITAMIN A PREPARATIONS AMONG CHILDREN.

Author	Number	Age (years)	Clinical status	--DOSAGE-- I.U.	µgRE	Ester form	% dose absorption	% dose retention	Remarks	Reference
I. Physiologic dose, healthy children										
Sivakumar and Reddy	5	2-4	healthy	3,000	900	palmitate	96±2[1]	80±1	undernourished by weight and height	46
Sivakumar and Reddy	5	2-10	healthy	2900	873	acetate	99±1	82±2	-	14
Sivakumar and Reddy	5	2-6	normal	-	1,000	N.R.[2]	99±1	82±2	-	18
II. Physiologic dose, ill children										
Sivakumar and Reddy	8	2-10	resp. infection	2900	873	acetate	74±7	58±6	-	14
	3	2-10	diarrhea	2900	873	acetate	1±10	N.R.	-	14
Sivakumar and Reddy	6	2-6	ascariasis	-	1,000	N.R.	80±3	68±4	-	18
III. Pharmacologic dose, healthy children										
Sivakumar and Reddy	5	2-4	healthy	200,000	60,060	palmitate	67±4	10±4	undernourished by weight and height	46
Pereira and Begum	6	4-5	normal	182,000	54,600	palmitate	75±4	38±13	-	45
Kusin et al	7	3-6	normal	200,000	-	N.R.	68±3	33±3	4 children recv'd 40mg vitamin E	47
	7	3-6	normal	200,000	-	N.R.	73±3	33±3	plus 100mg vit. E	47
	3	3-6	normal	200,000	-	N.R.	82±2	55±2	plus 500mg vit. E	47

(1) percent of dose absorbed ± 1 SD (2) Not Reported

Table 2. CONTROLLED STUDIES ON THE EFFICACY OF A SINGLE ORAL MASSIVE DOSE OF VITAMIN A TO ELEVATE AND/OR MAINTAIN SERUM RETINOL LEVELS FOR EXTENDED PERIODS OF TIME

Authors (Ref)	Country	Age	Dosage (000)	Number E[1]	Number C/P[2]	Follow up period	Serum retinol (µg/dl) E[1]	Serum retinol (µg/dl) C/P[2]
Patwardhan and Kamel (55)	Jordan	0-6 mos	170 IU	57	58	Initial	14±10	17±7
						8 wk	26±20	26±15
Pereira and Begum (57)	India	2-5 yrs (healthy)	100 IU	14	16	Initial	26±8	25±7
						2 wk	16±7	21±6
						10 wk	25±9	22±5
						25 wk	14±6	12±3
Pereira and Begum (56)	India	2-6 yrs (healthy)	33 µg	15	23	Initial	12±3	13±3
						18 wk	20±6	15±4
						18 wk	24±7	20±6
Thanangkul et al. (58)	Thailand	newborns (healthy)	33 µg	62	59	Initial	15±1	13±1
						18 wk	29±2	20±1
						17 wk	37±3	26±2
						42 wk	32±5	18±3
Dhanamitta et al. (54)	Thailand	preschool	100 IU (<24 mos)	78	78	Initial	14	15
						10 wk	22	18
			200 IU (≥24 mos)			22 wk	19	17
Kusin et al. (44)	Indonesia	1-5.9 yrs	170 IU	134	134	Initial	16±6	16±6
						12 wk	18±8	18±6
						24 wk	16±6	17±8

1 Experimental group
2 Control or placebo group

Table 3. CONTROLLED STUDIES ON THE EFFECT OF A SINGLE ORAL MASSIVE DOSE OF VITAMIN A TO PREVENT XEROPHTHALMIA FOR AN EXTENDED PERIOD OF TIME

Authors	Country	Age	Number E[1]	Number C/P[2]	Dosage (000)	Follow up period	Incidence of Prevalence of Xerophthalmia XN E	XN C/P	Clinical Signs[3] E	Clinical Signs[3] C/P
Sinha and Bang (53)	India	2-5 mos	153	153	200 IU every 4 months	Base	3.0%*	3.0%	7.0%*	7.0
						4 mos	0.0%*	4.0%	10.0%*	19.0
						8 mos	0.0%*	1.0%	5.0%*	7.0
Tarwotjo et al (59)	Indonesia	12-60 mos	2680		200 IU every 6 months	Base	N.R.[4]	N.R.	4.7%*	
			1166	1183		6 mos	-	-	0.4%#	3.6
			1197	1072		12 mos	-	-	0.3%#	2.9
Kusin et al (44)	Indonesia	1-5.9 yrs	110	144	300 IU	Base	N.R.	N.R.	2.7%#	2.1
						6 mos	-	-	1.3%#	0.0

1 Experimental group
2 Comparison or placebo group
3 X1A and/or X1B
4 Not Reported
* Prevalence data
# Incidence data

Table 4. RELAPSE RATE OF CLINICAL XEROPHTHALMIA (X1B) AMONG PRESCHOOL AGE INDONESIAN CHILDREN TREATED WITH A SINGLE 2000,000 IU VITAMIN A CAPSULE (3).

Follow-up[1] (months)	Eligible For exam	Examined		Relapsed		
	n	n	%	n	(%)	Cum. %
1-2	48	33	68.8	0	(-)	-
3-4	10	20	42.6	0	(-)	-
5-6	44	19	43.2	0	(-)	-
7-10	26	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.

Table 5. SEVERAL PRE-/POST-INTERVENTION EVALUATIONS OF 200,000 IU VITAMIN A MASS DISTRIBUTION PROGRAMS.

Location (Ref)	Year/Follow-up period	Number studied	Percent coverage	Indicator[1]	Prevalence (%)	Indicator	Prevalence (%)
Kerala, India	1971	4913	0	X	6.0	-	-
(67)	1 yr	4752	65-70	"	1.3	-	-
Mysore, India	1970	1285	0	X	6.2	-	-
(68)	1 yr	600	85	"	1.9	-	-
Bangladesh[2]	1979	$11x10^6$	66	XN	1.2	-	-
(79)	6 mo	$10x10^6$	57	X	1.2	-	-
	12 mo	$11x10^6$	62	"	1.8	-	-
	18 mo	$11x10^6$	62	"	1.5	-	-
Bangladesh[3]	1979	12,494	55[4]	XN	3.3	X1B	0.33
(79)	3 mo	12,494	100	"	1.9	"	0.42
	6 mo	10,332	-	"	1.0	"	0.24
	1 yr	10,116	64	"	0.9	"	0.15
Cebu, Philippines	1973	400	0	X	3.5	-	-
(10)	2 yrs	343	78[5]	"	1.4	-	-
Nepal	1980/81	1326	N.R.[6]	XN	0.45	X1B	3.37
(71)	6 mo	1400	-	"	0.14	"	2.24
Haiti[7]	1975	5,000	0	XS	0.81[8]	-	-
(70)	4 yrs[9]	5,680	10	"	0.09	-	-

1 X = all signs of xerophthalmia (in the Philippine Study X is accompanied by serum levels < 20 μg/dl). All other symbols denote the WHO classification (2).

2 Data from 200 routinely collected program supervisor survey reports.

3 Study conducted among high prevalence villages throughout country.

4 Initial assessment occurred prior to the country's 11th capsule distribution round; 55% coverage reflects the program output during the 10th round which occurred several months before the baseline survey; the 12th capsule distribution round occurred between the baseline and 3 month survey, and the 13th round between the 6 month and the 9 month surveys.

5 Percent coverage among 1-10 year olds after the second distribu-

tion at 1 year.

6 Not reported.

7 Targeted, health care facility - based capsule distribution program.

8 Prevalence of northern region where program was subsequently started, and surveyed in 1979.

9 Three years after program start-up.

Figure 1. Association Between Age and Prevalence of Mild X[illegible]thalmia Among Preschoolers in Several Asian Countries

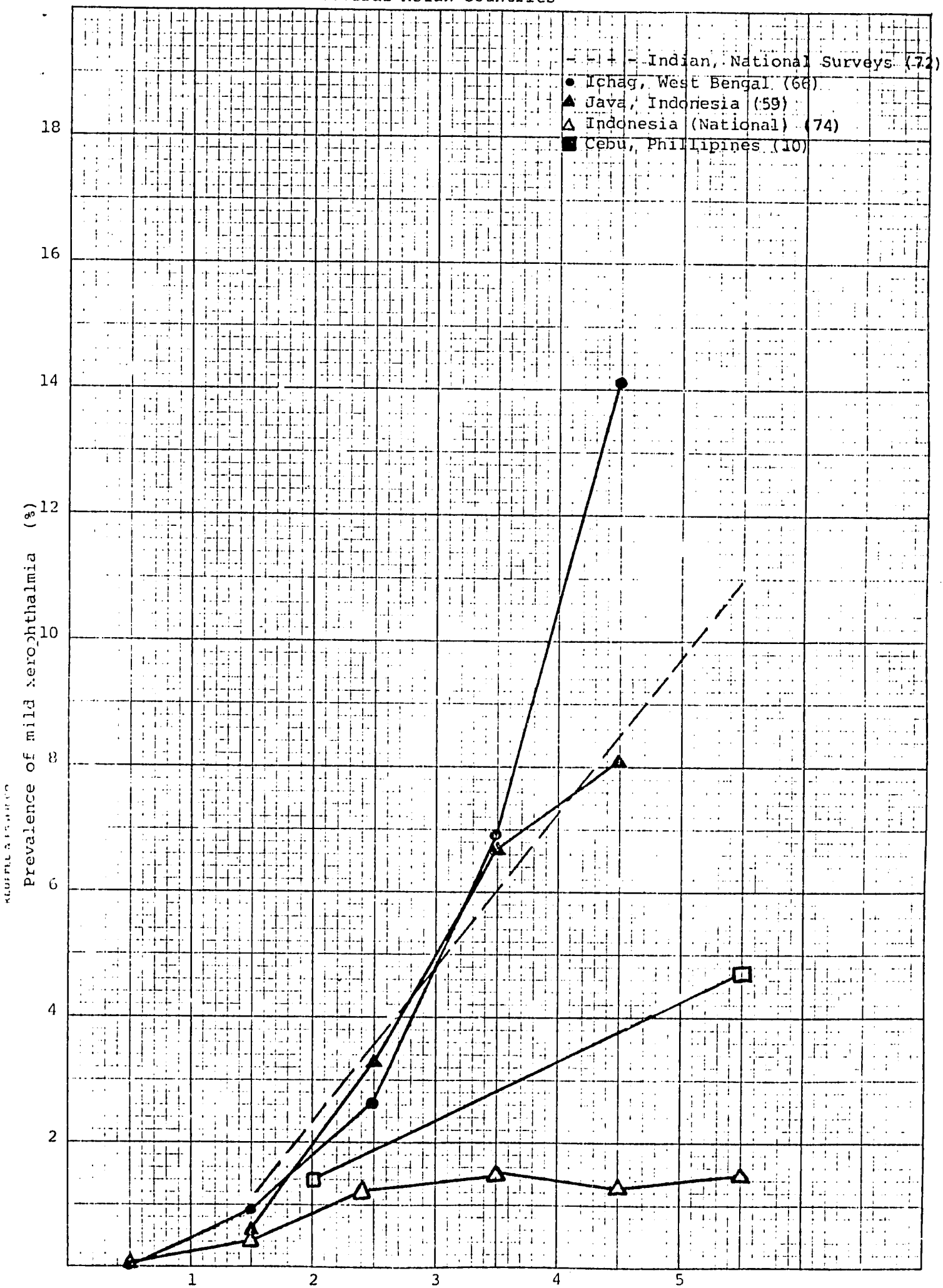
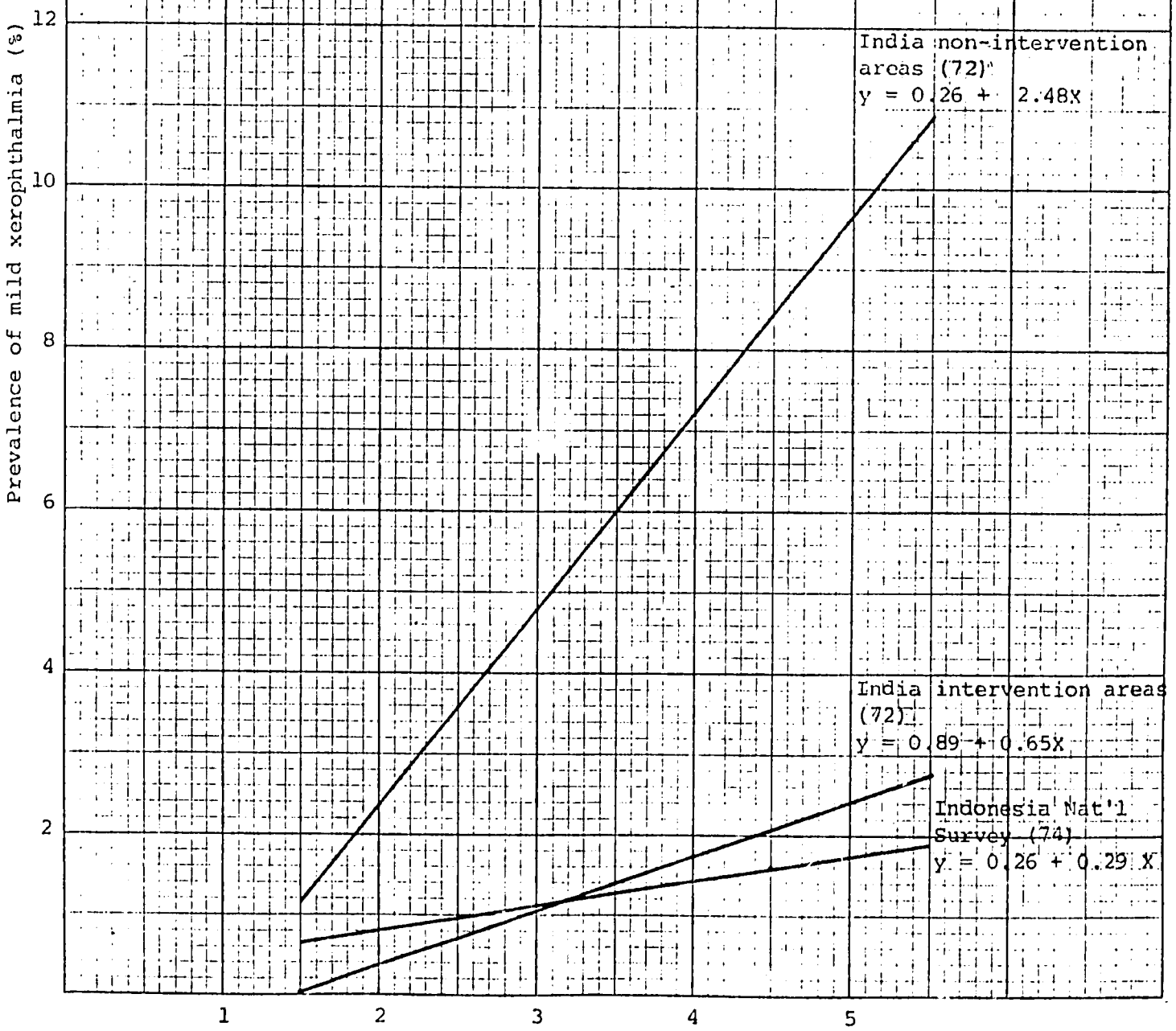


Figure 2. Simple linear regression equations describing relationship between prevalence of mild xerophthalmia and age in intervention and non-intervention areas (average line) in India, and from prevalence survey in Indonesia.



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