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Report *of* a Joint WHO/USAID/NEI Consultation *of* Principal Investigators

Vitamin A — Mortality and — Morbidity — Studies

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Report of a Joint WHO USAID NEI Consultation of Principal Investigators of Vitamin A Mortality and Morbidity Studies

Consensus Statement

Vitamin A is an essential nutrient and its role in preventing nutritional blindness is well established. In recent years, several intervention trials to test the effect of improving vitamin A status, including supplementation and fortification, have been implemented. Evidence has accumulated that, in areas where vitamin A deficiency is a problem of public health importance, vitamin A also reduces mortality in infants in the second six months of life and in young children, although there are variations between communities and regions in the extent of impact. Some of the reasons that may explain the differences between studies in impact of vitamin A supplementation on mortality include differences in baseline vitamin A status between communities, including diet, anthropometric (nutritional status) indices; exposure to illness and causes of death; access to health facilities, including immunization coverage; socioeconomic status, particularly literacy, affecting mothers and their children; and study design and implementation. There are several possible strategies to ensure and sustain an adequate vitamin A status in all population groups, especially in young children. The choice of intervention is the prerogative of governments and should depend on specific country factors, including the severity of the vitamin A problem, the resources available, and national priorities for their utilization.

Déclaration de Consensus

La vitamine A est un nutriment essentiel et son rôle dans la prévention de la cécité nutritionnelle est bien établi. Durant ces dernières années, plusieurs essais ont été mis en oeuvre afin de tester les effets d'une amélioration de la situation en vitamine A en ayant notamment recours aux compléments et à l'enrichissement. Les résultats montrent que dans les régions où les carences vitaminiques A posent un véritable probleme de santé publique, cette amélioration réduit la mortalité chez les enfants de 6 à 12 mois ainsi que chez les jeunes enfants, bien que l'intensité de l'effet varie d'une région et d'une communauté à l'autre. Plusieurs raisons expliquent les différences d'impact des compléments de vitamine A enregistrées dans diverses études. On citera notamment: différences dans les conditions vitaminiques de base des diverses communautés, par exemple dans leur ration alimentaire, indices anthropométriques (état nutritionnel), susceptibilité à la maladie et aux causes de mortalité, accès à l'infrastructure sanitaire (y compris vaccination), situation socio-économique (en particulier degré d'alphabétisation affectant les mères et leurs enfants) et conception et mise en oeuvre des études. Plusieurs stratégies peuvent être envisagées pour assurer et maintenir un état satisfaisant sur le plan de la vitamine A dans tous les groupes de population, et en particulier chez les jeunes enfants. C'est aux pouvoirs publics qu'il incombe de choisir les interventions appropriées. Ce choix doit dépendre des caractéristiques de chaque pays, dont la gravité de la carence vitaminique, des ressources disponibles et des priorités nationales régissant leur affectation.

Declaración de Consenso

La vitamina A es un nutriente esencial y el papel que desempeña en la prevención de la ceguera nutricional ha sido establecido claramente. Durante estos últimos años se llevaron a cabo varias pruebas para evaluar los efectos de una mejora del estado de vitamina A, recurriendo en particular a los complementos y al enriquecimiento de alimentos. Los resultados demuestran que en las regiones donde las carencias de vitamina A plantean un problema de salud pública, dicha mejora reduce la mortalidad en los niños de 6 a 12 meses y en los jóvenes de mayor edad, si bien es cierto que existen variaciones de una communidad y de una región a otra. Son varias la razones que explican las diferencias de impacto de los complementos de vitamina A observadas en diversos estudios. Mencionemos las siguientes en particular: diferencias de estado inicial de las comunidades desde el punto de vista de la vitamina A, incluso en su alimentación, índices antropométricos (estado nutricional), exposición a las enfermedades y a las causas de mortalidad, acceso a la infraestructura sanitaria (incluso a la vacunación), estado socio-económico (en particular grado de alfabetización que afecta a las madres y a sus hijos) y diseño y realización de los estudios. Pueden contemplarse varias estrategias para lograr y mantener un estado satisfactorio de vitamina A en todos los sectores de la población, y en particular entre los niños. Les incumbe a los poderes públicos elegir las intervenciones más apropriadas. Esta decisión ha de depender de las características de cada país, y de la gravedad de las carencias de vitamina A, de los recursos disponibles y de las prioridades nacionales para su asignación.

ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
ARI	Acute Respiratory Illnesses
CI	Confidence Intervals
CIC	Conjunctival Impression Cytology
ICEPO	International Center for Epidemiologic and Preventive Ophthalmology
IMR	Infant Mortality Rate
GOI	Government of Indonesia
MSG	Mono Sodium Glutamate
MSG-A	Vitamin A-fortified Mono Sodium Glutamate
MUAC	Mid-Upper Arm Circumference
NCHS	National Center for Health Statistics
NEI	National Institutes of Health's National Eye Institute
NNIPS	Nepal Nutrition Intervention Project, Sarlahi
NVACSP	Nepal Vitamin A and Child Survival Project
OR	Odds Ratio
ORT	Oral Rehydration Therapy
P	Probability
PEM	Protein-Energy Malnutrition
P.I.	Principal Investigator
RDA	Recommended Dietary Allowance
RR	Relative Risk
U5MR	Under 5 Mortality Rate
WHO	World Health Organization
WHO/CDD	World Health Organization's Program for the Control of Diarrheal Diseases
XIB	Bitot's spots
XN	Night blindness
"Z" scores	Parameter for assessing nutritional status

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I. SUMMARY

This Joint WHO/USAID/NEI consultation was held on May 28-29, 1991 to examine the available information on baseline population characteristics, study designs, implementation, and follow-up procedures on mortality and morbidity outcomes from supplementation with vitamin A. The intent was to identify factors that are likely to account for the variation in magnitude of the impacts that have been found and to identify information gaps needed to provide sound advice for both research and intervention programs.

Significantly more evidence now exists to support the hypothesis that subclinical as well as clinical vitamin A deficiency is a major health risk and that children suffering from it are at increased risk of mortality. However, it has proved difficult to understand from current data just what the quantitative relationship is between vitamin A status, mortality, and morbidity.

Of the seven completed studies (five using periodically administered high-dose supplements and two using continuous delivery at physiological levels), two studies in Indonesia, two studies in Nepal and one in India have all shown a significant impact ranging from about 30 percent to 50 percent of vitamin A supplementation in significantly reducing young-child mortality. On the other hand, two studies (both using periodic high-dose supplementation) -- one in India and one in Sudan -- have shown no significant impact on mortality. Nonetheless, evidence from the recently completed controlled, randomized community-based clinical trials, together with the existing base of information, indicates that beneficial health effects and a significant reduction in childhood mortality can be anticipated from improved vitamin A nutriture among many populations where an inadequate status exists.

Although improved vitamin A intakes in malnourished populations can be expected in most circumstances to reduce the risk of infant and young-child mortality, the magnitude of the effect will vary depending on the situation. This consultation examined information available from 10 completed or still ongoing, large community-based studies and identified factors that are likely to account for some of the variation. These factors include, but are not limited to, the following:

- the prevalence and severity of vitamin A deficiency -- both subclinical and of sufficient severity to meet the WHO criteria for a public health problem;
- the prevalence of acute and chronic malnutrition;
- the rates of infectious diseases, in particular diarrhea, respiratory infections, and measles;
- access to health facilities and immunization services; and
- socioeconomic status.

Results from five soon-to-be completed, randomized clinical community trials using the periodic high-dose supplement will be available within the next nine months. In particular, the two Ghana VAST studies (one each on mortality and morbidity), the Indonesia MORVITA (morbidity) study, and the morbidity studies in Delhi, India, and Bahia,

Brazil, are expected to provide additional evidence regarding the factors that determine the impact of vitamin A supplementation on morbidity and mortality outcomes.[1]

It is to be expected that the impact of vitamin A on mortality and morbidity will vary in these different settings. When the trials are all completed, a careful comparative evaluation of the critical influential factors will be needed to determine to the extent possible, how to select and target prophylaxis programs. In the interim, the consultation developed the consensus statement that precedes this summary.

The group concluded that there is no question that an adequate vitamin A status prevents nutritional blindness and enhances child health and survival. Therefore, governments are urged to determine the vitamin A status (both clinical and marginal) of high-risk child populations and to move aggressively to improve the dietary intakes by appropriate use of available foods and/or supplements among those whose intakes are currently inadequate.

1 ED. NOTE: Preliminary results of the Ghana morbidity study published in Lancet (339:361-2) have shown a pronounced positive effect on the severity of illness episodes, i.e., the rate of clinic admissions was 12 percent lower in the vitamin A group and the rate of hospital admissions 38 percent lower. However, mean daily prevalence of symptoms and conditions did not differ between the vitamin A and placebo groups.

II. BACKGROUND

The importance of vitamin A deficiency as a risk factor associated with morbidity and mortality has been demonstrated in both animals and humans since the second decade of this century. Animal studies clearly demonstrate a linkage between vitamin A deficiency and increased infection rates, severity of infection, and death. For example, vitamin A-deficient animals maintained under controlled conditions in a nonsterile environment become infected more frequently and die at higher rates than nondeficient animals; and deficient animals maintained under controlled sterile conditions live to near normal life expectancy (1). Vitamin A deficiency also is clearly implicated in compromised integrity of epithelial barriers, in the decreased production of protective mucoid secretions, and in suppressed immune function of animals, all of which contribute to mechanistic explanations for the susceptibility to, and lethality of, infections (2).

In human studies, however, the clear relationships found under controlled conditions in animals are less obvious or firmly established. The reasons for this include the many confounding factors that characterize human populations in whom childhood protein-energy malnutrition (PEM) is prevalent, the coexistence of other micronutrient deficiencies with vitamin A deficiency, and the prevalence of unsanitary environments.

It has been recognized for some 70 years that severe vitamin A deficiency causes xerophthalmia and this, in turn, is associated with higher-than-expected death rates in young children. There has also been a growing body of reports suggesting that children suffering from subclinical vitamin A deficiency, with no eye signs, also suffer from an increased risk of infection and death. Vitamin A intervention studies undertaken from 1960 to the present show that vitamin A intervention programs can successfully reduce the risk of xerophthalmia. Much uncertainty remains, however, as to the magnitude of other health benefits that could result from such programs or how different baseline population characteristics might influence these outcomes.

Prior to the early 1980s, research efforts to establish firm linkages between vitamin A deficiency, infection rates, and fatality among human populations in field settings suffered from insufficient sample size and from study design inadequacies. These limitations were substantially overcome in a large prospective field observational study in Indonesia published in 1983 (3). This study reported an increased risk of mortality associated with even mild vitamin A deficiency, which was evident even after stratifying and adjusting for potential confounders. The report served as an incentive for a prospective, randomized clinical trial in Indonesia to examine the effectiveness of the vitamin A prophylaxis program on the prevalence of xerophthalmia and to explore further the association with mortality risk.

Early in 1982, the clinical trial was started in the province of Aceh on the northern tip of the island of Sumatra, Indonesia. It consisted of a controlled field trial in which high-dose vitamin A capsules were distributed every six months to all preschool-aged children in 229 randomly selected villages out of 450 in the province. The effectiveness of the program on corneal eye signs was tested. Because the sample size was sufficiently large (12,771 and 12,209 in program and control villages) and the design and field procedures also sufficiently robust to allow the relationship of vitamin A supplementation and mortality risk to be examined, this additional outcome was added early in the study. A 34 percent risk-reduction was reported among treated villages using an intent-to-treat analysis (4) (i.e., among children in villages in treatment areas) and up to a 70 percent risk reduction using a compliance analysis (5) (i.e., among children receiving capsules). A protective effect against diarrheal and respiratory morbidities had been hypothesized based on epidemiological observations of a positive association between xerophthalmia and morbidity in

Indonesia (6) and, more recently, in Thailand (7) and for respiratory but not diarrheal morbidities in India (8). In the Aceh study, supplementation did not reduce the prevalence of diarrhea or respiratory disease as measured by their occurrence within the previous week as recorded by interviews conducted at the time of the baseline survey and again nine to 13 months later at the end of the study (9).

The remarkable mortality impact suggested by the work from Indonesia clearly required confirmation. Concern was expressed in several quarters about the replicability of the findings due to the absence of a placebo; to some consistent though insignificant differences in baseline characteristics between treated and control villages; to an unusual age structure in the baseline population; to the lack of information reported on the cause of death; and to sex-specific associations (10). Some of the concerns were addressed by the authors (11). Nonetheless, the applicability of these findings to other country and ecologic settings remained unclear (12).

The controversy about the Indonesia findings became the stimulus for initiating a series of clinical trials specifically designed to examine the vitamin A supplementation-mortality and/or -morbidity risk associations. These clinical trials have been, or are being, conducted (most by investigators not associated with the Indonesia studies) in different ecologies, where variable diets are found and where populations experience different degrees of severity of social and economic deprivation and nutritional deficits, including severity of vitamin A deficiency. Clearly, these randomized, controlled clinical trials will provide the most reliable information for evaluating the efficacy of vitamin A for child health, survival, and development.

Data from opportunistic studies and those less rigorous in design can, when critically and cautiously evaluated, also contribute to the body of available information when results from clinical trials are variable. However, positive findings from *reported* opportunistic studies must be weighed cautiously because often such studies that show no effects are *not reported*.

Recent large, population-based studies that fall into the categories of clinical trials or *reported* opportunistic studies include two initiated in India, three in Nepal, two in Indonesia, and two in Africa.

These 10 studies, seven completed and analyzed and three ongoing, were reviewed by principal

Objectives of the Joint WHO/USAID/NEI Consultation May 28-29, 1991, Geneva

- To provide a forum for the primary investigators to exchange information on population profiles and baseline characteristics in each of the studies, using common analytical approaches.
- To discuss study outcomes, where available, in terms of mortality and/or morbidity in relation to baseline characteristics.
- To identify gaps in the database and discuss how these might be addressed.
- To establish a framework to guide future data analysis and facilitate cross-study comparisons.
- In light of the above information, to develop a consensus addressing the impact of vitamin A nutriture and supplementation on morbidity and mortality as well as influencing factors.
- To explore what advice can now be developed regarding programs and policies for ensuring adequate vitamin A status in infants and children.

investigators at a Joint WHO/USAID/NEI consultation held at WHO in Geneva on May 28-29, 1991.[2]

At this consultation, an informal atmosphere to facilitate candid discussion and interaction among investigators was sought in order to attain the objectives. To achieve this, attendance was limited to no more than two investigators representing each of the studies reviewed and, when possible, with at least one being a representative from the country where the study was carried out. Logistical problems prevented country representatives from Sudan, the MORVITA study in Indonesia, and from Madurai, India, from attending.

2 Two additional randomized, masked, placebo-controlled trials on morbidity risk associations are in progress but were not reviewed at the consultation. One of these trials is being conducted in an urban slum area near Delhi, India, and is assessing the impact of a single large dose of vitamin A on the incidence and duration of diarrheal episodes during a four-month follow-up period among children aged 12 to 60 months. The second trial is in a semi-arid region in the state of Bahia, Northeast Brazil, and is evaluating the impact of the distribution every four months of a large dose of vitamin A to children six to 36 months of age (about 600 each in the treated and control groups) on the incidence, duration, and severity of diarrhea and acute respiratory infections over a 12-month follow-up period. These two studies are supported by the WHO Programme for Control of Diarrheal Diseases (CDD) and are expected to be completed in 1992. Their status at the time of the consultation was not known to the organizers.

III. IMPACT ON CHILDHOOD MORTALITY AND MORBIDITY

There is no question as to the importance for public policy and programs of clearly establishing the role of vitamin A status in child health and survival and to ascertain its relative position with respect to the allocation of scarce resources—human and financial—to achieve health for all by the turn of the century. If improved vitamin A status alone can substantially contribute to this global goal, then the application of existing knowledge and intervention technologies for improving vitamin A nutriture should become a predominant health strategy.

In recent years, prospective population-based research efforts to evaluate the impact of vitamin A have used selected interventions ranging from high-dose periodic supplementation to low-dose continuous supplementation, including food fortification. These studies have been implemented in a number of settings in various countries where vitamin A deficiency is known, or likely, to be a public health problem.

Figure 1 provides the 1987 WHO map of the geographic distribution of xerophthalmia onto which has been located the site of each of the studies reviewed and the two additional morbidity studies not reviewed. Table 1 summarizes the major current studies that are completed and most of those still in progress. Among the seven completed intervention trials, there has been a range of outcomes. Some studies report a considerable and statistically significant risk-reduction impact on mortality, whereas others have found no statistically significant impact.

With regard to incidence of morbidity, mainly diarrhea, respiratory infections, and measles, to date none of the completed field-based studies reviewed in this consultation has shown a statistically significant impact, although a protective tendency is consistently reported. (Hospital-based studies in Africa of severe measles have reported a significant protective effect of vitamin A supplementation on both mortality risk [13-15] and severity and duration of measles-related morbidity [16]. Field-based studies in Asia have indicated a beneficial effect of similar magnitude but, because of small numbers of measles-specific deaths, this has not always been statistically significant [17,18]).

Some morbidity studies yet to be completed that report more frequent and detailed morbidity assessment are awaited with considerable interest (MORVITA, VAST, and two studies supported by the WHO/CDD Programme in Brazil and Delhi India). It should be noted that, although efficacy of vitamin A prophylaxis in reducing the prevalence of xerophthalmia was not the primary concern of this consultation, all of the trials where baseline xerophthalmia was initially prevalent reported a reduction among the treated population compared to controls.

IV. BASELINE CHARACTERISTICS

Variations in some of the baseline characteristics of populations and ecologies may in part explain the wide range in observed differences in outcomes among the completed studies. These studies are listed in Table 1. Differences in baseline characteristics among these studies are summarized in Table 2. The most likely influential factors include differences in baseline mortality rates; vitamin A status between communities, including dietary patterns; severity and characteristics of nutritional deficiency status (measured by anthropometric indices); frequency and severity of illness episodes and the principal causes of death; access to health facilities, including immunization coverage; differences in study design and implementation; and, socioeconomic status, particularly literacy, affecting mothers and their children.

Comparable data were not available for all of the studies at the time of the meeting. An overview of the available baseline characteristics among studies indicates that, although all studies were conducted among underprivileged, mostly rural populations, there were considerable variations in the extent and character of the deprivations. Populations studied in the Madurai (India) and Jumla (Nepal) areas appeared to be most severely deprived, affected by terrain (extended period of drought preceding the study in Madurai and a remote, mountainous area in Jumla), extensive poor nutritional status (more than 70 percent chronically or acutely malnourished in Madurai and 26 percent with MUAC [mid-upper arm circumference] less than 12.. cm in Jumla), high prevalence of xerophthalmia (11 percent and 13 percent, respectively), and limited access to social and health services (high illiteracy rates and low immunization coverage). A comparison of dietary patterns among studies was not possible due to the lack of information or incomplete analysis at the time of the consultation.

Baseline infant and young-child mortality rates were best documented in Jumla and were exceptionally high. Among the other studies where baseline mortality rates were obtained by historical interview, in general, the historically obtained rates were higher than those obtained prospectively during the intervention period irrespective of treatment. The NNIPS study in Nepal was an exception, i.e., prospectively obtained mortality rates were consistent with those obtained by history at baseline. Anthropometric measurements of nutritional status suggested higher malnutrition rates (chronic and acute) among the children in both the Madurai and Jumla studies than were apparent among the Indonesian and African populations and perhaps the Hyderabad, India, population. However, comparable anthropometric data using the NCHS reference for Hyderabad and the Jumla and Sarlahi studies in Nepal were unavailable at the time of the consultation. Xerophthalmia rates were highest in Jumla and Madurai, similar in other study areas, with the lowest prevalence in the Ghana VAST study.

V. STUDY DESIGNS

Selected aspects of study design and implementation were reviewed during the meeting. These included unit of randomization, use of placebo and masking procedures, sample size, surveillance methods, completeness of follow-up, and data analysis. These variables are summarized in Tables 3 and 4.

The randomized double-masked, placebo-controlled trial was recognized by the participants as the methodological standard for the assessment of treatment effects. The trials reviewed with this design are listed in Table 3 under (A). However, only four of six studies with such design characteristics were completed and available for review at the meeting. All but one of these studies (Sudan, which randomized by household) used clusters as the units for randomization, reporting adjustments for clustering effects in the analysis. Randomization was reported as having been repeated prior to implementation in one study (NNIPS) after recognition of imbalance between groups in a preliminary comparison of their baseline characteristics. (This is a recognized and generally accepted alternative to using statistical procedures to adjust for substantial baseline imbalances.) Low doses of vitamin A (Sarlahi) or vitamin E (Madurai, Sudan, Ghana) or arachis oil (Hyderabad) were used as placebos in the studies. Masking procedures varied in their likely effectiveness of preventing an early identification of treatment status, ranging from two codes or colors (Sudan, Madurai, Hyderabad), four codes of numbers (Sarlahi), and cluster (Ghana) or individual (Indonesia, MORVITA) coding.

Sample sizes for most of the studies of mortality were adequate. The required total sample sizes for studying typical control mortality rates and treatment effects are given in Table 5.

There was high variability in the length of the interval between visits for surveillance of morbidity and mortality and in the length of the period of recall of events, varying from two to three times weekly with two-to three days of recall to 12 months with a one week to one month recall (see Table 3).

Table 4 summarizes information on completeness of coverage and follow-up in each of the completed randomized clinical trials.

VI. STUDY SUMMARIES

This section presents brief summaries and comments on each of the 10 studies reviewed in the consultation, considering first those six clinical trials that used a randomized masked, placebo-controlled design and one randomized but not placebo-controlled trial, then a placebo-controlled nonrandomized trial, and finally two opportunistic studies not originally designed to assess mortality outcomes as a primary objective.

SUDAN

Ministry of Health, Sudan/Harvard School of Public Health, U.S.A.

Impact

A randomized, double-masked, placebo-controlled trial was conducted in Khartoum and Gezira Provinces to measure the impact of high-dose vitamin A capsule supplementation delivered every six months on childhood mortality. At baseline, all children received an ocular exam and those with signs of xerophthalmia, including night blindness, were treated and dropped from the study. After 18 months (three experimental capsule distributions), *no significant impact on mortality risk was found.* Risk of mortality, however, differed significantly when children were stratified by baseline anthropometric status.[3] Mortality in stunted and wasted children was greater than the mortality observed in wasted children and this was greater than the mortality observed in stunted children. Mortality in normal children was the lowest. There was no significant difference in mortality by treatment group within each specific nutritional status category. Most deaths occurred among the under-three year age group. Although morbidity incidence (diarrhea, fever, cough) appeared to decrease over the intervention period from round one to round four, there was no significant difference between the treatment and control groups. Flooding delayed the initiation of the program for six weeks in two of the rural councils. It did not interfere with the follow-up schedule. A separate analysis of these data also revealed no treatment differences.

Comments

- Of the 29,615 children screened, about three percent had xerophthalmia. They were treated and not followed further—28,754 children, therefore, remained in the sample.
- Over the 18-month study period, 14 percent of the sampled population was lost to follow-up because they did not receive all the doses, died, or developed eye signs and were treated and dropped from further study: seven percent during the first round, four percent during the second round, and three percent during the third round. In total, 3,894 subjects permanently moved away from the area (13.5 percent) and 863 (3 percent) refused to continue in the study. The survival status of all but 165 of the subjects lost to follow-up was ascertained by questioning neighbors and relatives. There

3 Anthropometric indices (height for age, weight for age and weight for height) are frequently used as surrogates for "nutritional status." This is strictly incorrect because it does not consider other micronutrient deficits that could exist without influencing anthropometric measurements. For the purpose of this report, however, nutritional status refers to anthropometric status.

were no significant differences by treatment group in the number of children lost to follow-up. As a group, however, those lost to follow-up were less privileged than those who remained in the study.

- A one-day recall dietary intake survey was conducted on the entire sample at baseline and at every follow-up visit. Intake of foods containing carotene or preformed vitamin A was recorded and will permit the monitoring of changes in estimated intakes by treatment during the period of follow-up. Total energy intake and information on nutrients other than vitamin A will not be available. These data have not yet been analyzed.
- Anthropometric data were obtained at *each* follow-up visit.
- Flooding occurred prior to implementing the study in two of five rural councils in the study area. Relief efforts, including vitamin A supplementation, were not reported in the study area. An additional question regarding vitamin A distribution was added to questionnaires administered subsequent to the flood and confirmed this fact. A separate analysis of the data for the affected and non-affected areas revealed no treatment differences in either case.
- Two-color coding made it more difficult to maintain masking throughout the intervention period.
- Randomization by household, though preferable, complicated the logistics in trying to ensure consistent delivery of the assigned capsule.

Strengths and Weaknesses as Noted by P.I.s

- The strengths of this study include the following: randomization by household, thus reducing possible distortions introduced by high or low mortality in atypical villages or wards; repeated collection of anthropometric measures and dietary vitamin A, which will permit multivariate analyses to explore interaction of treatment with nutritional status and vitamin A intake; and monitoring of socioeconomic and sanitation parameters.
- It would have been desirable to obtain longitudinal information on morbidity, on etiology and severity of disease episodes, and on dietary intake in a subsample as well as to attempt a more precise diagnosis of the cause of death. Such an intensive follow-up substudy would permit investigation of pathogen-specific vitamin A effects.

INDIA, Hyderabad

National Institute of Nutrition

Impact

A randomized, double-masked, placebo-controlled trial conducted in a district of Andhra Pradesh provided a high-dose vitamin A supplement as a syrup at six-month intervals. Visits were made every three months for one year to obtain a one-month retrospective morbidity history and check on mortality. Signs of vitamin A deficiency were checked at baseline and at each six-month interval; those children with corneal signs were treated and dropped from the study. After 12 months of surveillance, the *impact* of vitamin A supplementation *on the incidence of mortality and morbidity was not significant.* Xerophthalmia rates were reduced from about six percent at baseline to 1.3 percent and 2.9 percent in the treatment and control areas, respectively. No notable implementation problems were reported, including no interruptions in the availability of the supplement or in the distribution schedule.

Comments

- Only children with corneal xerophthalmia were treated and excluded from the study; those with XN and X1B—about six percent of the sample—were neither treated nor excluded from the analysis.
- Information on those lost to follow-up, the reasons for their loss, and how they were distributed between the treatment and control groups is not available. (The investigators reported that losses were similar in the two groups.)
- Although about 92 percent received at least one dose during the 12-month intervention—about 58 percent received two doses and 34 percent a single dose—a detailed accounting of the low coverage is not reported.
- Only weights were measured directly; height was estimated from wall chart classification; comparison with NCHS "Z" scores is not possible, and it will not be possible to evaluate impact on linear growth.
- No baseline information on mortality or immunization coverage was available.
- Two-color coding made it more difficult to maintain masking throughout the intervention interval.

Strengths and Weaknesses as Noted by P.I.s

- It is difficult to explain the different results obtained between the Hyderabad and the Madurai studies, which were conducted in similar populations. The difference may be due to a higher prevalence of xerophthalmia and malnutrition in Madurai; the supplementation every six months in Hyderabad compared to a weekly supplementation in Madurai; use of community-based vs. outside field workers; and the "contact effect" of weekly visits to households in Madurai vs. a total of nine visits to most households in Hyderabad.[4]
- Hyderabad faced no specific problems of implementation of vitamin A distribution and there was no shortage of capsules reported.
- In the future, the investigators would definitely take a larger sample because overall mortality was much lower than expected. In addition, future studies should obtain more detailed information on serum retinol levels, dietary intake, and immunization status.

4 ED. NOTE: Many of these differences from the Madurai study also apply to the other clinical trials.

17x

NEPAL (NNIPS)

Nepal Netra Jyoti Sangh/Johns Hopkins University, ICEPO, U.S.A.

Impact

A randomized, double-masked, placebo-controlled trial delivered a high-dose vitamin A capsule supplement every four months to infants and children aged 0 to 72 months residing in the rural plains (Terai) district of Sarlahi (southeastern Nepal). A 15 percent random sample of wards was examined for signs of xerophthalmia, and all those identified with xerophthalmia, as well as children who were severely ill, were treated with vitamin A and included in the analysis. The study was planned as a two-year trial but was discontinued for age groups over six months after a 12-month formal review revealed a statistically significant reduction in mortality. The *impact* of vitamin A supplementation among the six to 72-month age group *on mortality was significant (P<0.001, RR=0.7, CI=0.56, 0.83)*. The study is yet to be completed among the under-six-month age group. Results pertaining to the effect of supplementation on the incidence of morbidity and xerophthalmia, and on growth, have not yet been analyzed. No disruptions in implementation of the program were reported and direct coverage was at least about 88 percent at each dosage visit.

Comments

- Vitamin A capsules were left behind with parents when the study child was unavailable after repeated household visits (about 10 percent of children). Return visits to a subsample of households at each round suggested that about 65 percent of those children missed were dosed according to instructions, providing an estimated coverage of about 93 percent at each visit.
- Random sampling procedures were carried out twice before implementing the study to ensure a high degree of comparability between treated and control groups at the ward, household, and child levels.
- An ocular status survey was carried out only on a random 15 percent of the sampled wards at baseline and at the fifth dosing round. The remaining 85 percent of the sample were not surveyed. Local health officials received repeated training in detection, treatment, and prevention of xerophthalmia and were regularly supplied with vitamin A capsules. Children with xerophthalmia were treated and referred. It is likely, however, that cases of untreated, active xerophthalmia were present during the study among both the control and treated populations. At baseline, however, there was no statistically significant difference in xerophthalmia rates by treatment group (2.6 percent treated vs. 3.5 percent controls) among the 15 percent randomly subsampled.
- Weight, height, arm circumference, and skinfolds were measured throughout the study on a random 15 percent subsample (about 5,000 of the approximately 28,600 total sample). Arm circumference measurements were made in about 89 percent of all study children at *each round*. Only arm circumference data were presented at the meeting and were similar at baseline in each treatment group. The "Z" scores for height and weight using the NCHS reference were not available at the consultation for baseline comparisons with other studies.
- Four number codes increased the chance of retaining masking throughout the trial period.

Strengths and Weaknesses as Noted by P.I.s

- The strengths of the study included intensive preparation and training; full and thorough documentation of all field, data management, and administrative procedures; attention to procedural standardization and validation throughout the study; strict supervision; excellent coverage; routine capsule analyses; committed staff; political and community support; written informed consent from local leaders of all participating communities;

two separate vital events surveillance systems; and treatment group comparability.

- No major problems were reported. Among the minor problems, many of which are inherent to most large field studies, all were handled adequately.
- It was noted that use of the Brass technique for assessing the baseline childhood mortality was found not to be practical in this culture because mothers anticipated the question and answered in advance. Minor logistical problems were encountered in reaching and closely supervising some of the hill regions. Many mothers (as usually encountered where vital records are incompletely, if at all, available) had problems in recalling the exact date of birth and death of their children. Deaths were ascertained within four months of death or earlier.

GHANA (VAST)

University of Science & Technology, School of Medical Sciences, Ghana/London School of Hygiene & Tropical Medicine, U.K.

Impact

Two studies are in progress in the Kassena-Nankana District (upper east region): 1) a randomized double-masked, placebo-controlled trial to assess the effect of large-dose liquid vitamin A supplementation, delivered from a dispenser every four months, on the survival of young children in an area where vitamin A deficiency appears to be marginal; and a study in the same area to assess the effect of supplementation every four months on morbidity (not reviewed at this consultation). The studies are still continuing and the results will not be available until early 1992.

Comments

- Minimum dietary information will be available with respect to vitamin A food intake specifically and macronutrient and energy intake in general.
- Information will be available for serum retinol and hemoglobin levels as well as for anthropometric indices and conjunctival impression cytology (CIC).

Strengths and Weaknesses as Noted by P.I.s

No information has been reported so far.[5]

5 ED. NOTE: Preliminary results from the morbidity study were published in Lancet 1992(339:361-2). The study population of 1455 children was followed by a combination of weekly and monthly visits by trained field workers. Mean daily prevalence of 19 of 21 symptoms and conditions did not differ between the vitamin A and placebo groups. The supplement seemed to have pronounced positive effects on the severity of illness episodes, i.e., the rate of clinic admissions was 12 percent lower in the vitamin A group and the rate of hospital admissions 38 percent lower.

194

INDONESIA (MORVITA)

University of Gadjah Madah, Indonesia/Johns Hopkins University, International Health Department, U.S.A.

Impact

A randomized, double-masked, placebo-controlled trial was undertaken in the District of Purworejo, Central Java, to assess the effect of large-dose vitamin A capsule supplementation every four months on the incidence, duration, and severity of diarrhea and acute respiratory illnesses (ARI) and on growth. Household surveillance occurs two or three times per week and microbiological examinations are performed on diarrheal stools. Weights are obtained every month and heights measured every four months. Blood samples will be obtained for retinol analysis twice during the study, and dietary intake of vitamin A-containing foods assessed. Field work is continuing and results will not be available until early 1992.

Comments

- Although information pertaining to food frequency is obtained every four months, this study highlights the overall limitation of such information that does not consider the quantity of foods consumed. In general, dietary assessment may be a useful descriptor of vitamin A deficiency at an aggregate level, but not at an individual level.
- Because a general resistance occurred against providing CIC specimens, the decision was made against using this technique for assessing vitamin A status. Baseline serum samples were obtained by venipuncture and caused some community concern; subsequent samples will be obtained by finger prick.
- A contact effect is likely, but it should be comparable between groups.

Strengths and Weaknesses as Noted by P.I.s

- Although this study is still in the field, the investigators would like to highlight the immense difficulties in handling the volume of data gathered.[6]
- A possible contact effect is likely due to the frequent visitation (every two days); therefore, it was decided to add new villages to the sample after 12 months to take this into account. "Ideally, we would have liked to pick yet another area for comparison where morbidity surveillance was carried out less frequently, every other week and not every other day."

6 ED. NOTE: Several investigators note the importance of having data entry capability as close to the field collection site as feasible to facilitate the timely entry and checking of the vast amount of information generated from trials that have such frequent surveillance.

INDIA, Madurai

Aravind Children's & Eye Hospitals/National Eye Institute, NIH-NEI, U.S.A.

Impact

A randomized, double-masked, placebo-controlled trial conducted in the drought-prone Trichy district of Tamil Nadu in southern India assessed the effect of a weekly, low-dose (8,333 IU) liquid vitamin A supplement — equivalent to the recommended dietary allowance for vitamin A — distributed from a dispenser on mortality, morbidity, and growth of children between four and 59 months of age. *A significant impact of vitamin A supplementation on mortality was observed, mainly in children under three years of age (RR=0.46, P<.01, CI=0.30, 0.71)* and in those classified by anthropometry as *stunted (RR=0.11, P<.01, CI=0.03, 0.36)*. There was no significant impact observed on the incidence, average duration of episodes, or severity (defined as total number of days ill) of diarrhea or respiratory disease. There was no impact on growth except for a barely significant effect (0.23 cm in the one-year period) on linear growth of stunted children only. Xerophthalmia was reduced from 11 percent at baseline to 3.4 percent among the treated group vs. 8.4 percent among the controls (20, 21). There was no significant difference in xerophthalmia rates between control and treated groups at baseline.

Comments

- The design of this study is not comparable to the other double-masked, randomized trials: the children were monitored for morbidity/mortality weekly and were supplemented every week at a level potentially obtainable from an adequate diet and, hence, at a level closer to continuous physiological needs. Under such circumstances, a temporary loss to follow-up will not have as limiting an effect as one may observe in the biannual or triannual large-dose supplementation study designs.
- The impact was obtained using preformed vitamin A at the level of the RDA. It is assumed, but not demonstrated, that a similar impact would occur if an equal intake of retinol equivalents were provided from carotenoid-containing foods, which are the usual sources of vitamin A in areas where deficiency is prevalent.
- A contact effect on mortality and health-related behaviors is likely but the contact was equal between the treated and control groups.
- Two-color coding made it more difficult to maintain complete masking for the duration of the study.

Strengths and Weaknesses as Noted by P.I.s

- The main strengths were: consistent delivery with high coverage rates (minimum of 88 percent weekly) of vitamin A at a dosage similar to the RDA for vitamin A; weekly surveillance of morbidity and ascertainment of mortality; close supervision and delivery using local community health workers; stable population and a high "contact rate;" and rapid feedback to workers with respect to the quality of their work and early correction of errors, where needed.
- The major weaknesses include a variable time lag from baseline assessment to the start of the study, which necessitated adjustments in age and anthropometric analyses; dietary intake and serum retinol levels — baseline and final — are taken from a small subsample; the large amount of data generated by the study and the resultant need to condense some aspects of the morbidity surveillance to retain on disk, e.g., only positive morbid events were recorded (see footnote 4 on page 11). There is a need to refine the cause-of-death data.

Anthropometric follow-up was unavailable on about 10 percent of the sample.

INDONESIA, Aceh

Ministry of Health, GOI/Johns Hopkins University, ICEPO, U.S.A.

Impact

A randomized, controlled (non-masked, non-placebo controlled) trial carried out in the northern tip of Sumatra provided a high-dose vitamin A supplement given every six months to children 12 to 71 months of age in 229 villages (treated) and a supplement *only* to those diagnosed with xerophthalmia in 221 villages (control). The *impact* of vitamin A supplementation *on mortality was found to be significant in children 12 to 71 months of age—34 percent effectiveness of supplementation (RR=0.66; CI=0.44, 0.97)*—and on the prevalence of xerophthalmia (decline from 1.9 percent to 0.3 percent in treated villages vs. 2.3 percent to 1.2 percent in control villages). A statistically significant mortality-risk protective effect occurred among males but not females. There was no significant impact on morbidity incidence as determined by a seven-day history obtained at baseline and nine to 13 months later (22). Ponderal growth increased significantly only among males three year f age and older (23).

Comments

- Except for xerophthalmia status, there was limited baseline information on vitamin A status reported. Baseline mortality rates, although obtained, were not reported[7] because the trial was not set up originally to assess impact on mortality.
- This was not a placebo-controlled or masked study. Insufficient information is available to evaluate fully possible differential effects during the study period (treated and untreated villages) resulting from contacts between study workers and local government volunteers (who provided the vitamin A) and the communities, and for possible bias in the ascertainment of deaths. Because mortality is an unambiguous end point and contacts were minimal, this is an unlikely confounding factor.
- No active surveillance for mortality occurred during the intervention interval. Ascertainment of deaths was based on enumeration of children at the 12-month follow-up survey. Causes of death were ascertained by interview at the final survey.
- Ascertainment of the delivery of capsules to individual children was obtained from parents at the end of study. Of the preschool-aged children, 78 percent of preschool age children were reported to have received two capsules, 18 percent one capsule, and seven percent received none. Independent capsule distribution monitors visited program villages to ensure a high level of coverage, and when not attained they encouraged adequate coverage by the distributors at each round.
- Losses to follow-up were about 11 percent and equal in both groups.
- At baseline, control villages had a small but significantly higher period prevalence of diarrhea than the intervention villages (eight percent vs. seven percent). Also, a small statistically insignificant higher prevalence of xerophthalmia and of stunting and wasting occurred in control villages. These baseline differences were included in a multivariate logistic regression analysis and *did not* influence the calculated impact.
- At the time of the study, area health centers were thought to see approximately 25 percent of illness cases. Growth monitoring and other nutrition programs were absent from the study villages.

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7 ED. NOTE: The investigators report that baseline mortality was collected by a modified Brass technique similar to that used in the longitudinal studies and countrywide surveys in Indonesia; no differences between groups were found.

Strengths and Weaknesses as Noted by P.I.s

- Although preexisting data were available on mortality risk, they were not reported in the original publication (see footnote 6 on page 22). Data on immunization coverage or serum retinol levels was not obtained. Dietary information was obtained during the study.
- Vitamin A deficiency was not as severe as originally expected. The investigators' randomization of treatment groups at the village level was a factor judged to enhance quality control and allowed for higher coverage rates. Finally, dietary considerations were taken into account and Muslim festivals such as "Eid" were avoided.
- Logistical problems existed in moving records long distances from North Sumatra to Java and the data entry center at Jakarta. These were anticipated and dealt with as best as possible.
- In future studies, it would be better to provide more intensive surveillance of mortality.
- At the time of the study, the government did not permit use of placebos and required that the regular vitamin A distribution program be utilized. Therefore, the investigators were not able to change the existing government program for research purposes and thus had less control over the situation than desired. On the other hand, this factor permitted the study of estimated effectiveness of an actual program in reducing mortality.

INDONESIA (MSG-A)

Ministry of Health

Impact

A placebo-controlled trial assessed the impact of vitamin A-fortified MSG (MSG-A) distributed through commonly available marketing channels on mortality in children over 12 months of age. *Impact on mortality was found to be significant (OR=1.45; P<.05; CI=1.19, 1.76).* Although the trial could not be randomized because fortified MSG was marketed through channels that were available to all in that area, the investigators were able to compare their results with an area with similar characteristics where MSG was not fortified. A significant treatment effect on linear growth was observed. Breastmilk and serum retinol levels increased as did hemoglobin levels. The prevalence of xerophthalmia declined from 1.2 percent to 0.29 percent (25).

Comments

- The design of this study could not be random because MSG was marketed via existing channels. However, the investigators selected non-fortified areas that were similar on baseline variables. Furthermore, all areas that may possibly have been contaminated by the MSG areas were excluded from the analysis.
- The study has considerable practical program planning significance. It shows the potential health impact of a national program which generally has low implementation costs in terms of personnel for delivery and other resources, as compared with a carefully controlled intervention trial.

Strengths and Weaknesses as Noted by P.I.s

- There was no baseline information on mortality reported.
- The main strength was that the presumed improvement in vitamin A status from fortification was supported biochemically by an increase in mean serum retinol and

breastmilk vitamin A levels and by a reduction in xerophthalmia rates.

- The one-year time frame eliminated problems of seasonality.

NEPAL, Jumla

Ministry of Health, Nepal/INTERCEPT, REACH Project, John Snow, Inc., U.S.A.

Impact

This study used the valuable opportunities of an ongoing child survival program, with emphasis on acute respiratory infections, to undertake a study in which a single, large-dose vitamin A supplement was introduced to 3,786 children under 59 months of age in some villages and, five months later to 3,441 children in the remaining villages. The study area was a remote, mountainous area poorly served by health programs. In this area xerophthalmia rates are high (13 percent) and infant and child mortality rates are very high (three-year monitoring of IMR and U5MR prior to supplementation revealed rates of 189/1,000 and 52/1,000, respectively). *The impact of vitamin A supplementation on mortality was significant in children between the ages of one and 59 months (about 26% risk reduction) and most notable among children above six months, particularly in the six to 11 month age interval (49 percent risk reduction).* Among infants under six months, it was difficult to discern a clear effect, but confidence intervals were wide. Some indication of effect was observed among children aged three to six months who received the supplementation.

It should be noted that the Jumla population is an extreme population with respect to high mortality and morbidity, poor nutritional status, and a high prevalence of xerophthalmia. In such circumstances, the chances may be enhanced for finding an impact on mortality for any positive health or nutrition-related interventions, including that of vitamin A supplementation.

Comments

- This was a valuable opportunity to take advantage of an ongoing child survival program to introduce vitamin A supplementation in a phased manner. An observation period of only five months was possible. This study does not have the strengths of the randomized, masked, placebo-controlled trials but has the strength of a long-term

close baseline surveillance on mortality, and ARI morbidity, which is lacking from the clinical trials.

- Some information on the impact of a single high dose on ARI morbidity over a five month interval will be available at a future time. The long-term pre-vitamin A ARI morbidity surveillance will provide a strong baseline from which to evaluate impact.

Strengths and Weaknesses as Noted by P.I.s

- The main weakness was that this was an ongoing study rather than a randomized intervention trial specifically designed to assess the impact of vitamin A supplementation on mortality and morbidity. Possible design effects were taken into account during the analysis even though the sample was comparatively small.

- Although data on neonates are available, the analysis specifically excluded them because newborns were not dosed during the five-month follow-up period.

- The main strengths were that it was an extremely simple design based on a highly popular pneumonia program that had been going on for about three years and therefore achieved a high vitamin A coverage; had very accurate three-year baseline figures for mortality, which allowed for a small sample and reasonable matching to assess the subsequent effect of supplementation on mortality; and the investigation was carried out in a population and during the season of increased morbidity and mortality, particularly due to pneumonia.

NEPAL (NVACSP)

Nepal Netra Jyoti Sangh/University of Michigan, School of Public Health, U.S.A.

Impact

An operations research study assessed the cost-effectiveness of alternative vitamin A deficiency control strategies in reducing xerophthalmia and vitamin A deficiency in rural areas of high risk. The strategies being implemented include large-dose vitamin A supplements distributed every four months or every six months; supplements distributed every six months and components of primary health care; and nutrition education and primary health care without direct vitamin A supplementation. The project is examining the appropriateness of the interventions for a national-level program. Mortality, morbidity, and growth are being monitored concurrently. Field work continues and results are expected toward the end of 1991.

Comments

- Overall, this study has a very complex design. It is not a controlled clinical trial whose primary outcome is to assess the mortality/morbidity impact of the various interventions. The design was a two-stage randomized selection with panchayats selected followed by a random selection of a cluster of 1,500 people from within selected panchayats.

- Implementation of some interventions relies heavily on the indigenous system for delivery of some of the services, e.g., many of the public health measures such as use of ORT, ARI medications, and immunization. This is appropriate for an operations research study seeking a basis for planning national intervention programs, but it complicates evaluation of the impact of vitamin A supplementation with or without added public health and/or educational interventions on mortality, morbidity, and growth. The operational research focus of the study, however, is not jeopardized by these limita-

tions since a cost-effective analysis of interventions using xerophthalmia rates as the primary end points is achievable.

- This study will provide important programmatic information on participation rates according to the intervention mix.
- Comparative cost data by intervention mix also will be available, which will be useful for program planning purposes.

Strengths and Weaknesses as Noted by P.I.s

- The main strength of the study is the commitment of staff, both local and expatriate technical assistants, which allowed the study to remain on schedule in spite of difficult internal disruptions that were occurring in the country.
- A noted weakness was that the study is randomized at the ward level and therefore mortality differences will have to be done by population adjustment of ward level rates for comparisons among interventions.
- The quality of the anthropometric measurements was found to improve over time, suggesting that changes in mean "Z" scores will be more important for comparisons than the percentages of children falling into the various nutritional deficiency categories.
- In the future, there needs to be a better evaluation of the cause of death than just a verbal autopsy.

VII. GAPS IN INFORMATION

Difficulties encountered in conducting large-scale, population-based, controlled field trials, such as the ones reviewed at this consultation, often highlight gaps in the design or knowledge base that limit full interpretation of study results. Investigators themselves are generally the best source of this information because they can reflect most clearly on what would improve their study and its interpretation were it to be repeated.

Below are listed some of the factors for consideration in future studies that would facilitate interpretation of variations of observed mortality from other studies, should these additional studies be deemed ethical and desirable.

1. Methodologies need to be improved for obtaining valid information on morbidity; standardized approaches are needed with respect to definitions of episodes, their severity, length of the recall period, etc.

2. Careful baseline information is essential on the availability and utilization of health services, morbidity incidence, mortality rates, and nutritional status (stunting and wasting), which may account for observed differences in the impact of vitamin A supplementation on mortality.

3. Better information is needed on the role of vitamin A on immunocompetence, the impact on children with mild vitamin A deficiency, and possible mechanisms of action.

4. Appropriate adjustment of existing results during the analysis stage must be made to account for the unit of randomization and inclusion criteria and for baseline imbalances.

5. Studies conducted to date have not been specifically designed to examine age-specific rates (sample sizes within certain age groups have been limiting).

6. Greatest impact in some studies appears to be in the six- to 12-month age group where the possible modifying effect of nutritional status and of breastfeeding and weaning practices requires additional study. Some other studies show a trend with the protective effect of vitamin A becoming stronger with age. See "5" above.

7. The effect of infectious disease load, diversity, and seasonality (malaria, ARI, diarrhea) or the impact of vitamin A supplementation on mortality risk is not clear.

8. Better dietary information is needed on the quantity and quality of foods consumed and the distribution of foods within the household to better assess variation in outcomes.

9. Complete information should be obtained and reported on coverage, quality control, and reliability of study procedures and implementation.

10. Future studies should consider the fact that little is known with regard to vitamin A status and AIDS. In some populations, AIDS morbidity and mortality may obscure effects of vitamin A.

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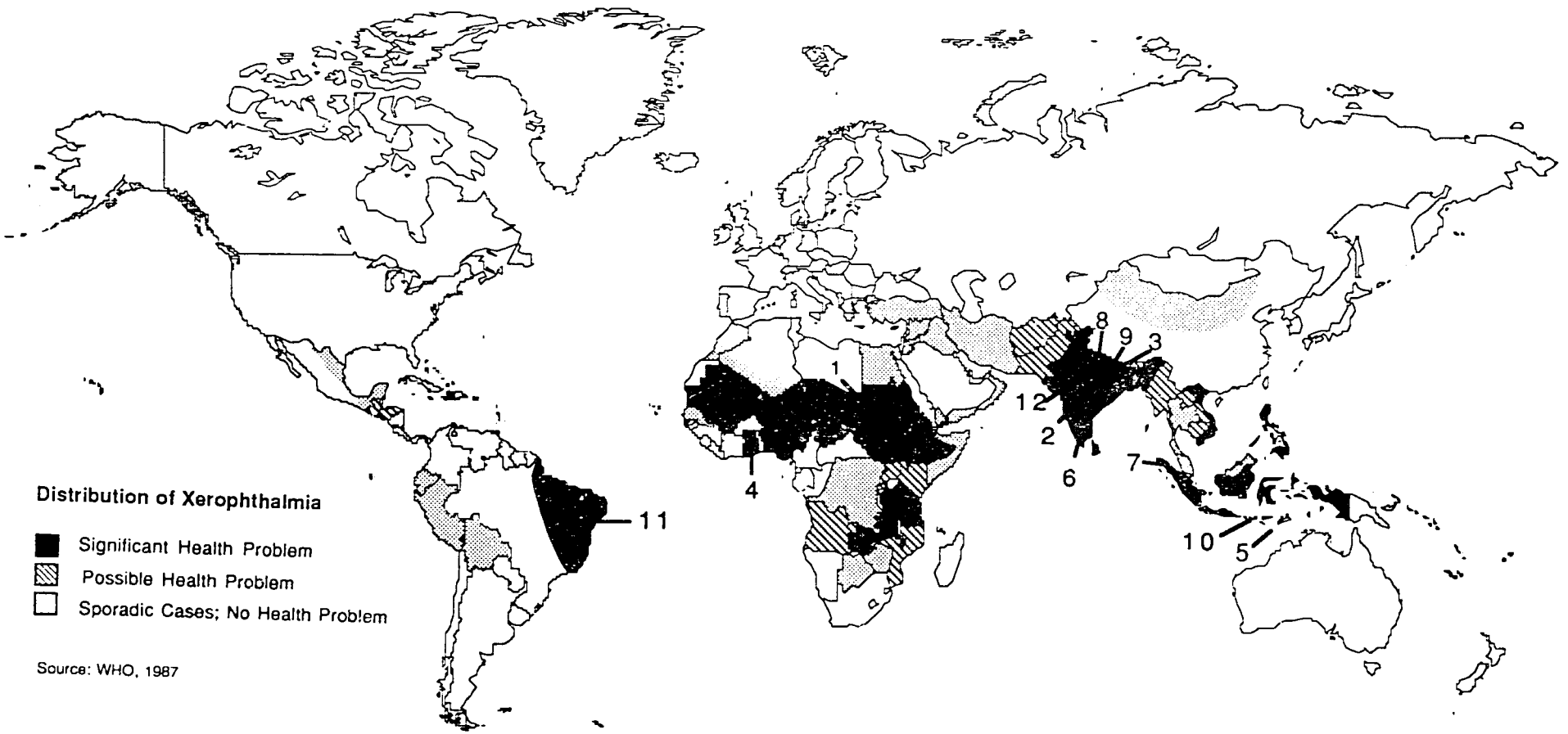
Figure 1: Study Sites and the Geographical Distribution of Xerophthalmia



STUDY SITES

1. Sudan
2. Hyderabad, India
3. Sarlahi, Nepal
4. Ghana
5. Yogyakarta, Indonesia
6. Madurai, India
7. Aceh, Indonesia
8. Jumla, Nepal
9. Bharatpur, Nepal
10. Bogor, Indonesia
11. Bahia, Brazil
12. New Delhi, India

TABLE 1. SUMMARY OF STUDIES REVIEWED

Country/Collaborators/ Current Status	Dosage/ Intervention Period	Outcomes/ Status of Analysis	
A. RANDOMIZED DOUBLE-MASKED, PLACEBO-CONTROLLED TRIALS			
A.1. High-dose/Periodic Supplementation			
i) SUDAN MOH-Sudan/Harvard University Completed 1990	200K every 6 months to children 9-72 months; follow-up time 18 months	Mortality: Morbidity: Xerophthalmia: Growth:	No significant impact in children 9-71 months; treatment group: 8.4/1,000; control group: 7.7/1,000 Decreased over time, but no significant impact of treatment Analysis incomplete Analysis incomplete
ii) INDIA, Hyderabad Nat'l. Institute of Nutrition Completed 1989	200K every 6 months to children 12-59 months; follow-up time 12 months	Mortality: Morbidity Xerophthalmia: Growth:	No significant impact in children 12-59 months; treatment group: 5.5/1,000; control group: 5.8/1,000 No significant impact on incidence Prevalence reduced from 6.0% to 1.3% in treatment group Treatment effect not analyzed
iii) NEPAL, Sarlahi (NNIPS) NNJS/Johns Hopkins Univ. Completed 1991	200K every 4 months to children 6-72 months; follow-up time 12 months	Mortality: Morbidity: Xerophthalmia: Growth:	Significant impact (P<.05; RR=0.7; CI=0.56, 0.88); treatment group: 11.5/1,000; control group: 16.4/1,000 Analysis incomplete Analysis incomplete Analysis incomplete; treatment lowered mortality regardless of nutritional status as measured by AC

TABLE 1. SUMMARY OF STUDIES REVIEWED (*Continued*)

Country/Collaborators/ Current Status	Dosage/ Intervention Period	Outcomes/ Status of Analysis	
iv) GHANA, (VAST)UST-SMS, Ghana/LSHTM, UK To be completed 1991	100K every 5 months to children 6-11 months; 200K every 4 months to children 12-71 months; follow-up time 24 months	Field work to be completed 9/91; results of treatment effect on mortality, morbidity, xerophthalmia, growth, anemia, serum retinol, dietary intake, and CIC expected in early 1992.	
v) INDONESIA (MORVITA)/Johns Hopkins Univ. To be completed 1991	200K every 4 months to children 6-48 months; follow-up time 24 months	Field work to be completed 11/91; results of treatment effect on morbidity, growth, anemia, serum retinol, and dietary intake expected in early 1992.	
vi) INDIA, Madurai Aravind Children's Hosp./NEI Completed 1989	8.3K every week to children 4-59 months; follow-up time 12 months	Mortality:	Significant impact (P<0.01; RR=0.46; CI=0.30, 0.71); treatment group: 4.8/1,000; control group 10.4/1,000; Mortality reduction most significant in children under 3 years of age and those nutritionally characterized as stunted; diarrhea reported (by the mother) to be the major symptom associated with mortality
		Mortality:	No significant impact on incidence or severity of diarrhea and respiratory infection
		Xerophthalmia:	Significant impact on incidence (P<0.5) in children over 12 months of age
		Growth:	No significant impact

B. OTHER TRIALS

B.1. High-dose/Periodic Supplementation

i) INDONESIA, Aceh Johns Hopkins Univ. Completed 1984	200K every 6 months to children 12-71 months; follow-up time 12 months (children under 12 months included)	Mortality:	Significant impact in children over 12 months (P<0.05; RR = 0.7, CI = 0.44, 0.97); treatment group: 4.9/1,000; control group: 7.3/1,000
		Morbidity:	No significant impact
		Growth:	Impact on wt./age and AC males 3-5 years only; no impact on linear growth for either sex
		Xerophthalmia:	Significant impact on incidence in children over 12 months of age (P<.05)

TABLE 1. SUMMARY OF STUDIES REVIEWED (*Continued*)

Country/Collaborators/ Current Status	Dosage/ Intervention Period	Outcomes/ Status of Analysis	
ii) NEPAL, Jumla MMT/INTERCEPT REACH Project, John Snow, Inc. Completed 1990	50K once to children under 6 months; 100K once to children 6-11 months; 200K once to children 12-59 months	Mortality:	Significant impact in children 1-59 months of age. (P<.05). No clear effect in infants <6 months (RR 0.99, but wide CI); most notable effect in infants 6-11 months (RR=0.51), overall mortality figures: treatment group: 93.2/1000; control group: 126.2/1000 (RR=0.74)
		Morbidity:	Analysis incomplete
iii) NEPAL, Bharatpur (NVACSP) NNJS/Univ. Michigan To be completed 1991	100K once to children 6-11 months; 200K every 4-6 months to children 12-59 months; follow-up time 24 months	Ongoing operations research study, analysis not yet completed; expect results on mortality, morbidity, xerophthalmia, growth, and serum vitamin A	
B.2. Low-dose/"Continuous" Supplementation			
iv) INDONESIA MOH/Johns Hopkins Univ. Completed 1987	Marketing of fortified MSG through ordinary marketing channel in limited area; analysis in children under 60 months; follow-up time 12 months	Mortality:	Significant impact in fortified group among children over 12 months (P<0.05; OR=1.45; CI=1.19, 1.76)
		Biochemical Status:	Hemoglobin and serum and breastmilk retinol levels increased in fortified group
		Growth:	Linear growth improved (P<.02) ages 1, 2 years only
		Xerophthalmia:	Prevalence in treated group reduced from 1.2% to 0.2%

TABLE 2. BASELINE CHARACTERISTICS

Country/ Site	Social/ Economic Status	Availability of Health Services	Vitamin A Status/Intake	Mortality (1,000/year)	Morbidity	Nutrition Status	Xerophthalmia Status
A. RANDOMIZED DOUBLE-MASKED, PLACEBO-CONTROLLED TRIALS							
A.1. High-dose Periodic Supplementation							
i) SUDAN	Arid rural area with variable sanitation & water availability; maternal literary about 30%	Scarce government services, no other existing programs; immunization coverage low	Available in future	3.0/1,000 in children aged 9-72 months (control group)	17% diarrhea 14% fever 20% cough 0.3% measles (point prevalence)	38% stunted 6% wasted 6% stunted and wasted 50% normal (NCHS stds.)	0.7% XN 2.7% X1B 2.9% (XN, X1B, X3, XS); all treated and excluded
ii) INDIA Hyderabad	Rural, ag. area with poor sanitation & water available; maternal literacy about 9%; per capita income <US 15c/day	Government health services fairly accessible; no specific feeding programs; immunization avg. about 30%-35% for state	No specific diet surveys, but reported figures are 75-100 μ retinol equivalents in 1-5 year-olds	Info. obtained but not provided	Info. obtained but not provided	6-9% <60% std. wt./age 4-5% >90% std. wt./age (NCHS stds)	2% XN 4% X1B 0.015% X2, X3 only corneal xero. treated & excluded

TABLE 2. BASELINE CHARACTERISTICS *(Continued)*

Country/ Site	Social/ Economic Status	Availability of Health Services	Vitamin A Status/Intake	Mortality (1,000/year)	Morbidity	Nutrition Status	Xerophthalmia Status
iii) NEPAL Sarlahi	Rural, flat plains; fairly good sanitation & water availability; maternal literacy about 10%; poor economic status	Fairly well served; vit. A available for treating xero.; accelerated EPI coverge	No info. reported	IMR about 82/1,000; 1-4 yrs about 12-13/1000	11% diarrhea 14%-15% persistent cough (1 wk. period prev.)	MUAC < 12.5 cm about 13.2% children; ht. & wt. data available on 15% sample but not yet reported	85% children not checked for ocular status; xero. assessed in 15% sample; treated cases but not excluded; about 3%-4% XN, X1B; 0.05% X2, X3
iv) GHANA (VAST)	Mainly rural, small-scale subsistence farming; fairly poor sanitation & available water; maternal literacy=10%	Fairly well served immunization of 12-23 month olds (1989): BCG 60% DPT3 34% OPV3 34% measles 40%	Detailed dietary info. to come; serum retinol levels on a sample of 650 children (result not available); CIC in sample of 656 shows 0%-30.5% to be abnormal	30/1,000 of children aged 6-71 months	53% diarrhea &/or vomit 64% cough 79% fever (1-wk. period prev.)	Ht./age: 46% <2 SD Wt./ht.:17% <2 SD Wt./age: 44% <2 SD [Ht./age & wt./ht. for about 200 <3 year Wt./age for all] (NCHS std.)	Estimated 1.1% XN .02% X1B .02% X2,X3 .09% XS All examined; not excluded but analyzed separately
v) INDONESIA Yogyakarta (MORVITA)	Rural, coastal Java; ample water but not always safe; maternal literacy about 80%, mainly farmers with land, most with a monthly household in income range of US$10-$39	Well served; no feeding progs., but 17% children had received 2 vit. A capsules in the past yr.; 70% unvacc. for measles & 50%-60% unvacc. for OPV1-3	Serum retinol (μ/dl): < 10 6% >10-20 52% >20-30 37% > 30 4% Dietary info. to be analyzed	Not done	Not available at this time	Ht./age: 42% <2 SD Wt./age: 41% <2 SD Wt./ht.: 9% <2 SD (NCHS stds)	Not available at this time; cases treated and followed

TABLE 2. BASELINE CHARACTERISTICS *(Continued)*

Country/ Site	Social/ Economic Status	Availability of Health Services	Vitamin A Status/Intake	Mortality (1,000/year)	Morbidity	Nutrition Status	Xerophthalmia Status
A.2. Low-dose/"Continuous" Supplementation							
vi) INDIA Madurai	Dry & severely drought-prone; rural farmers; poor water & sanitation; maternal literacy about 35%	Poorly served; no regular vit. A distribution; 44% used mid-day feed prog.; 85%-95% unvacc. BCG & measles, 53% unvacc. for DPT/polio	99% had rec'd. vit. A; serum retinol (μ/dl): <10 17-21% 10-19 16-18% 20-30 16-17% >30 46-50%	About 20/1000 children ≤ 5 years.	% with an episode previous month, approximately 12% diarrhea 34% URI 6.5% LRI	31% stunted 23% wasted 17% stunted and wasted (NCHS stds)	3.7% XN 7.2% X1B 0.05% X2,X3 0.07% XS all treated & followed
B. OTHER TRIALS							
B.1. High-dose Periodic Supplementation							
i) INDONESIA Aceh	Predominantly rural; main employment ag. farming, cattle breeding, & fishing; generally poor sanitation & water supply	Well served by govt. health services; minimal existing child feeding and vit. A distrib. progs.; no data on immunization coverage	No dietary or serum retinol information reported	Collected but not reported	32% cough 46% fever 7% diarrhea (1-wk. period prev.)	Weight & height measured in 10% random subsample; 2.1% severely malnourished vs. 5.5% in E. Java	Ocular survey on all children; all xero cases treated, followed, and analyzed separately
ii) NEPAL Jumla	Rural ag., dry; small farmers with per capita income <US$75/month; maternal literacy about 5%; extremely poor sanitation & water availability	Poorly served by govt. health fac. & no other existing progs.; low immununization. coverge (15% measles)	No dietary or serum retinol obtained	IMR about 189/1,000 1-4 about 52/1,000 0-5 about 98/1,000	No info. on diarrhea; pneumonia rate above 1.6 episodes per/child in 1st year of life	MUAC < 12.5 cm in 26% of 1-4 year-olds	4.7% XN 8.2% X1B 0.3% X2,X3 0.5% XS All treated & excluded from analysis

TABLE 2. BASELINE CHARACTERISTICS *(Continued)*

Country/ Site	Social/ Economic Status	Availability of Health Services	Vitamin A Status/Intake	Mortality (1,000/year)	Morbidity	Nutrition Status	Xerophthalmia Status
iii) NEPAL Bharatpur	Terai/mid-hill area of central Nepal, very poor; poor sanitation & water availability; maternal literacy about 9%	Fairly well served with some nutrition progs. ongoing; immunization coverge about 55%-70% fully immunized	Dietary pattern will be available; serum retinol levels (µ/dl) <10 3.9% 10<20 38% 20->30 35% >30 23%	Done, but info. not provided	1.8%-3.5% diarrhea 0.5%-0.9% respiratory infections (point prev.)	"Z" scores (1-60 mo.) Ht./age -2.4 Wt./age -2.5 Wt./ht. -1.2 (60-120 mo.) Ht./age -2.3 Wt./age -2.3 Wt./Ht. -1.3	Xero. cases treated & included: 0.9% XN, 1.3% X1B 0.09% X2, X3 0.2% XS
B.2. Low-dose "Continuous" Supplementation							
INDONESIA MSG Trial	Mainly ag.; fairly good sanitation & water available; maternal literacy about 80%; avg. economic status	Fairly well served by govt. health service & monthly growth monitoring; no other existing progs.; immunization coverge not assessed	Roughly 113 RE/day (trted. area) 131 RE/day (ctl. area); Serum vit A (µ/dl): <10 9-10% 10-19 38% >20 52%	Not available	Diarrhea: 3%-4% 11%-12.5% URI (point prev.)	Ht./age: 51%-54% <2 SD; Wt./age: 33%-40% <2 SD; Wt./ht.: 3%-6% <2 SD (NCHS stds.)	X1B: 0.77%-1.2% all measured & followed up

TABLE 3. STUDY DESIGNS

Study	Unit Random	Masking	Sample	Morbidity/Mortality Surveillance
A. RANDOMIZED DOUBLE-MASKED, PLACEBO-CONTROLLED TRIALS				
i) SUDAN	Households	2 colors	17,031 households 28,754 children	6/6 months 1-week recall
ii) INDIA* Hyderabad	Villages	2 colors	84 villages 15,775 children	3/3 months 1-month recall
iii) NEPAL** Sarlahi	Wards*	4 codes	270 wards 287,630 children	4/4 months 1-week recall
iv) GHANA** (VAST)	Clusters	Coded by cluster	188 clusters 19,730 children	4/4 months 1-week recall
v) INDONESIA** (MORVITA)	Individual	Coded by individual	1,300 children	2-3 times/wk.
vi) INDIA* Madurai	Clusters	2 colors	206 clusters 15,419 children	1/1 week 1-week recall
B. OTHER TRIALS				
i) INDONESIA* Aceh	Villages	No	450 villages 29,430 children	9-13th month 1-week recall
i) NEPAL*** Jumla	Subdistricts	No	16 subdistricts 7,197 children	2/2 weeks 2-week recall
ii) Nepal* (NVACSP)	Wards	No	100 wards 60,000 children	12/12 months ?
v) INDONESIA^	Not random	Yes	2 areas 11,200 children	12 months point prevalence

200,000 IU (100,000 IU for children < 12 mo. age given every six months).
* 200,000 IU (100,000 IU for children < 12 mo. age given every four months).
** 50-, 100-, or 200,000 IU once for < 6 mo., 6-11 mo., ≥12 mo. ages, respectively, in a single dosing.
Weekly low dose of 8,333 IU.
Continuous dose of 210 µg (about 700 IU) daily from fortified MSG potentially available.

TABLE 4. COMPLETENESS OF FOLLOW-UP AND IMPLEMENTATION

Study	Lost to Follow-Up	Did not receive at least 2 doses
Aceh, Indonesia	11%	22%
Sudan	14%	(included in 14%)
Hyderabad	?	42%
Sarlahi (NNIPS)	about 7%	7%
Madurai	about 10%	(about 10% missed 11 - 15 of 52 weekly doses)

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TABLE 5. REQUIRED TOTAL SAMPLE SIZE

Control Mortality rate	Reduction in mortality	
	30%	50%
10/1,000	40,000	13,200
20/1,000	20,000	6,600

These numbers assume the following conditions:

(i) Two-sided test of treated vs. control mortality at level of significance $\alpha=0.05$.

(ii) Power of 0.8 to detect a specified reduction in mortality due to treatment.

(iii) An inflation factor in sample size of 30 percent to account for possible effect of clusters as unit of randomization. (Note: A 30 percent factor does not apply to the Sudan study because the unit of randomization was the household and the required correction factor, therefore, would be smaller.)

(iv) Equal numbers of treated and control children.

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