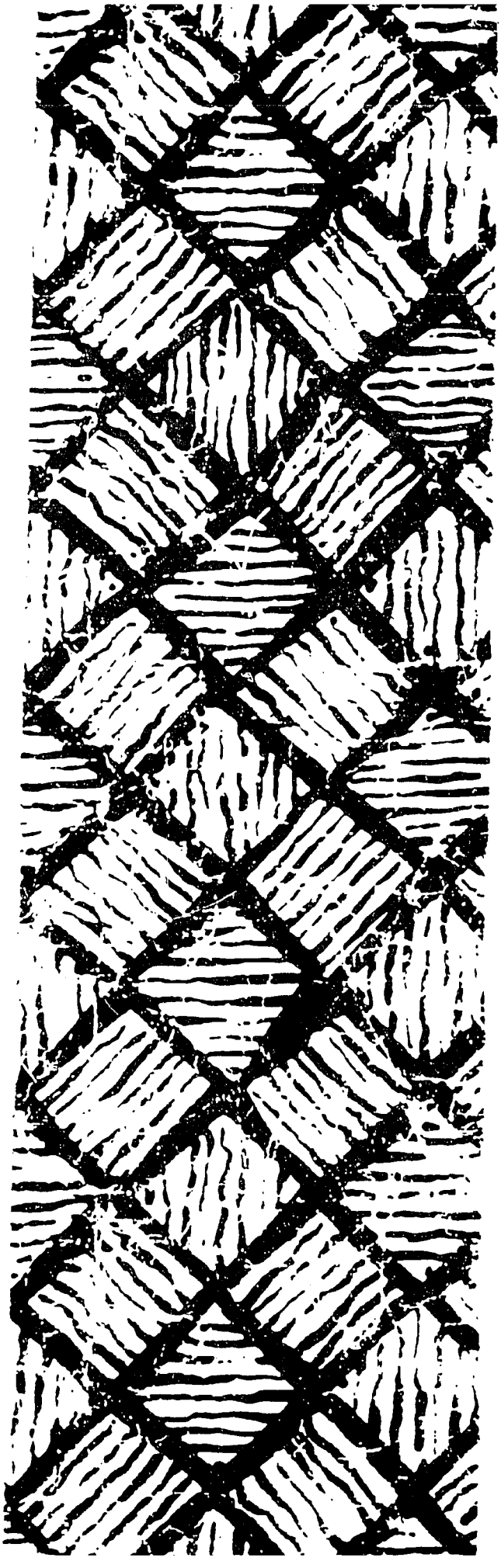


CONTENTS

Commentary and Guide for
VITAMIN A SUPPLEMENTATION DISTRIBUTION PROGRAMS

VITAL SLIDE PRESENTATION

Commentaires pour diapositives
PROGRAMMES DE DISTRIBUTION DE SUPPLEMENTATION DE VITAMINE A

DIAPORAMA VITAL

Texto para diapositivas
PROGRAMAS DE DISTRIBUTION DE SUPLEMENTOS DE VITAMINA A

PRESENTATION DE DIAPOSITIVAS VITAL

1

PROGRAMMES DE DISTRIBUTION DE COMPLEMENTS VITAMINIQUES A

DIAPORAMA VITAL

NOTE : Cette présentation a été préparée à partir d'informations récentes sur l'efficacité de diverses activités de distribution de compléments vitaminiques, qui ont été publiées depuis la parution en 1988 du guide du groupe de travail de l'OMS/UNICEF/IVACG. VITAL transmet ses remerciements aux Dr. John McKigney, Jose Mora, Hernando Flores et, en particulier, Barbara Underwood pour leur analyse technique et leurs commentaires.

VITAL est un programme de l'office de la Nutrition de l'Agence du gouvernement américain pour le développement international.

2 QUAND LES COMPLEMENTS SONT-ILS NECESSAIRES ?

- ALIMENTS RICHES EN VITAMINE A

- non cultivés ou

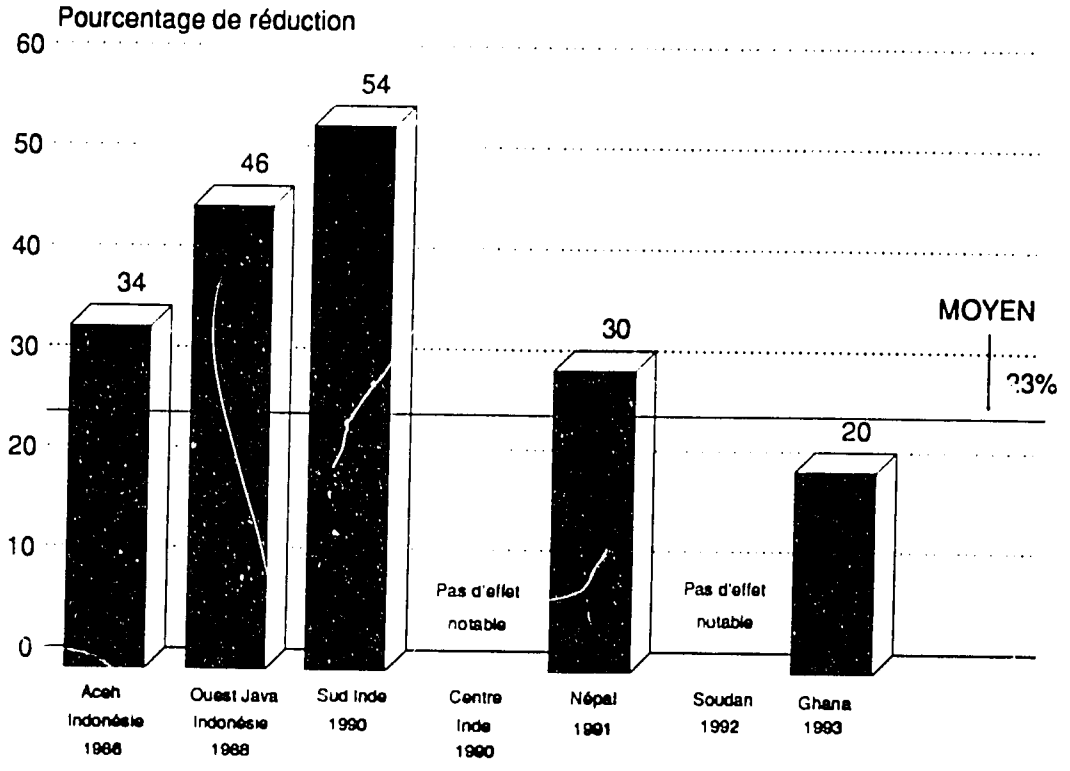
- trop coûteux ou → carences vitaminiques A → mortalité, morbidité, cécité

- pas dans les habitudes alimentaires

La distribution de compléments vitaminiques est considérée comme une intervention de court terme mise en oeuvre lorsqu'il est urgent d'agir pour protéger un groupe exposé au risque de carence vitaminique A. Pour veiller à ce que l'état en vitamine A d'importants groupes de population se maintienne à un niveau normal, il est essentiel de prendre des mesures plus complètes qui mettent plus longtemps à donner des résultats. Il s'agit de l'enrichissement, de l'éducation en nutrition, de la culture de potagers et de la conservation des aliments, autant d'activités qui visent à accroître le contenu en vitamine A des rations alimentaires.

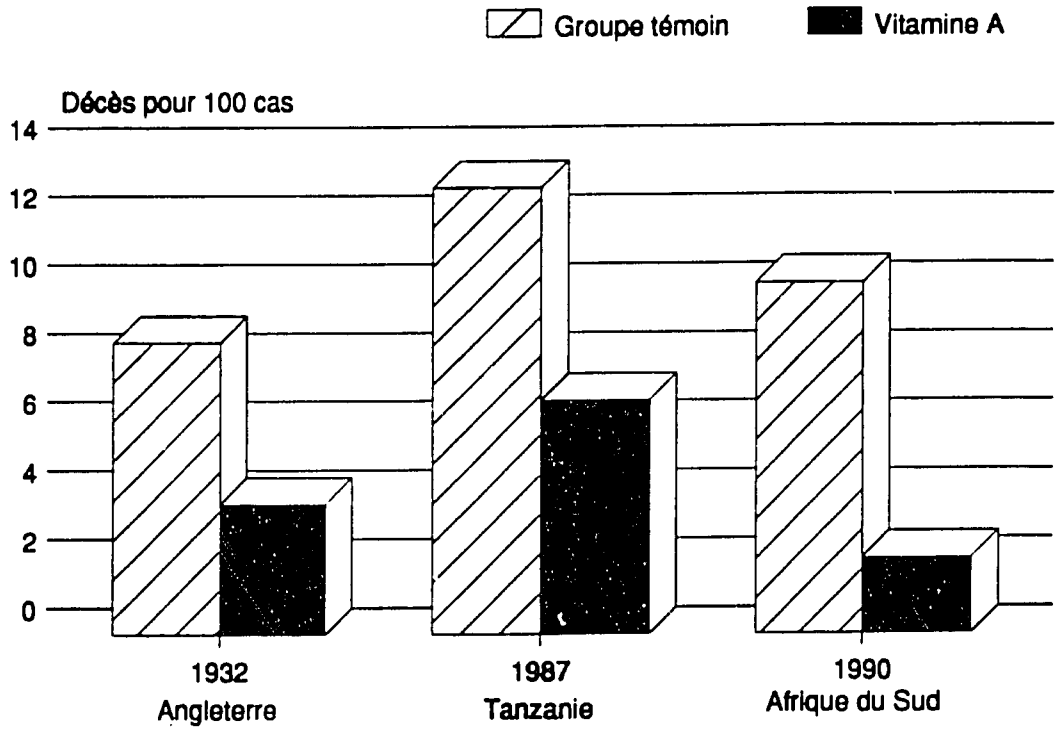
Dans plusieurs régions du monde, les aliments riches en vitamine A ne sont pas cultivés par les populations rurales, sont trop coûteux pour la plupart des familles urbaines ou ne sont que rarement consommés par les femmes enceintes, celles qui allaitent, ou les jeunes enfants. Lorsque la ration alimentaire présente des carences en vitamine A et que les enfants sont exposés à des maladies infectieuses graves et fréquentes, les carences vitaminiques A peuvent accuser une grande acuité. Les enfants courent alors de plus gros risques de morbidité et de mortalité, de xérophtalmie et, partant, de cécité. Les compléments vitaminiques A, autrement dit, la distribution périodique de fortes doses de vitamine A à des personnes accusant des carences sont une intervention efficace et immédiate.

3 EFFET SUR LA MORTALITE JUVENILE



Les études ont démontré une réduction spectaculaire de la mortalité dans les régions à forte prévalence des carences en vitamine A. Dans la plupart des études une dose de 200 000 UI était administrée tous les 4 à 6 mois à des enfants de 1 à 6 ans. Dans bon nombre d'entre elles, on administrait une dose de 100 000 UI à des nourrissons de 6 à 12 mois. Dans l'une des études, les sujets recevaient une faible dose journalière, et dans une autre, de faibles doses hebdomadaires simulant la consommation nutritionnelle. Dans l'ensemble, les diverses études réalisées dans les pays ci-dessus montrent que les interventions de vitamine A ont permis une réduction de 23 % de la mortalité infantile et juvénile.

EFFET SUR LA ROUGEOLE



Des études ont démontré que même dans les régions où la prévalence des carences vitaminiques A n'est pas étendue, les complications et la mortalité causées par la rougeole aiguë peuvent être réduites. Les compléments vitaminiques pour les cas de rougeole sont aujourd'hui considérés comme un élément fondamental du traitement de la rougeole dans le monde entier. Le dosage recommandé de vitamine A pour les enfants d'un an ou plus souffrant de rougeole est de 200 000 UI dès le diagnostic et de 200 000 UI le lendemain. Le dosage recommandé pour les nourrissons de 6 à 11 mois et ceux pesant moins de 8 kilos est de 100 000 UI dès le diagnostic et de 100 000 UI le lendemain.

5 STRATEGIE DE DISTRIBUTION

	TOUTE REGIONS	REGIONS A HAUT RISQUE
• QUI ?	XEROPHTALMIE, DIARRHEE CHRONIQUE, ROUGEOLE, MALNUTRITION PROTEINO-ENERGETIQUE	ENFANTS DE 6-72 MOIS FEMMES POST-PARTUM < 4 SEMAINES
• QUOI ?	TRAITEMENT	PREVENTION+TRAITEMENT
• COMMENT ?	SERVICES DE SANTE	SERVICES DE SANTE COMMUNAUTAIRES

Xérophtalmie = Signe oculaire de carence en vitamine A.

Le choix de la stratégie de distribution dépend de la prévalence des carences et des ressources disponibles. Toutes les régions couvertes par le programme de vitamine A devront, au minimum, inclure la distribution de compléments comme pratique courante dans le traitement de la xérophtalmie, de la rougeole, de la malnutrition protéino-énergétique et de la diarrhée persistante. Ce faisant, on pourra réduire immédiatement les décès, les complications et la cécité, autant de conséquences courantes de la maladie.

En outre, les pays et les districts qui souffrent d'une forte prévalence de carences et qui disposent d'une infrastructure et des ressources nécessaires pour entreprendre la distribution de compléments vitaminiques A au moins tous les six mois, peuvent commencer une opération de distribution de compléments comme mesure à court terme en attendant que des solutions plus durables, telles que l'éducation en nutrition, la culture de potagers et le séchage solaire, commencent à donner des résultats.

6 DANS TOUTES LES REGIONS

Compléments pour le traitement des troubles suivants :

QUI ?	QUOI ?
• XEROPHTALMIE	• 3 DOSES
• ROUGEOLE	• 2 DOSES
• MALNUTRITION PROTEINO-ENERGETIQUE/ DIARRHEE CHRONIQUE	• 1 DOSE

COMMENT ?

- HOPITAUX MALADIES INFECTIEUSES
- HOPITAUX/DISPENSAIRES OPHTALMOLOGIQUES
- HOPITAUX/DISPENSAIRES PEDIATRIQUES
- CENTRES/AGENTS DE SANTE
- SERVICES CHARGES DE LA MALNUTRITION

Quelle que soit la portée des carences vitaminiques A, des protocoles de traitement devront être inclus dans le traitement courant de la xérophtalmie, de la rougeole, de la malnutrition protéino-énergétique et de la diarrhée persistante dans tout le pays et dans toutes les régions.

7 DANS LES REGIONS A FORTE PREVALENCE

Compléments pour la prévention

QUI ?	QUOI ?
• ENFANTS : 6-72 MOIS	• 1 DOSE tous les 4-6 mois
• MERES POST-PARTUM : <4 SEMAINES	• 1 DOSE

COMMENT ?

• ACTIVITES DE VACCINATION	• GROUPES DE FEMMES
• ACCOUCHEUSES TRADITIONNELLES	• ECOLES

• A chaque contact avec un enfant malade (malnutrition protéino-énergétique, diarrhée, etc.) il devrait y avoir un intervalle d'un mois entre doses.

Dans les régions à forte prévalence, les protocoles de traitement et de prévention devront être inclus parmi les autres services -notamment de santé - retenus comme supports de distribution.

S'agissant des protocoles de prévention, tous les enfants de 6-72 mois et toutes les femmes post-partum, indépendamment de leur état en vitamine A, devront être inclus dans le programme. Ce type de distribution est dite "universelle" ; elle est déterminante pour assurer au moins un taux de couverture de 65 %. Un certain nombre d'autres canaux de distribution peuvent être utilisés. L'un des plus courants est celui du Programme élargi de vaccination (PEV) car il offre une couverture élevée dans la plupart des pays, ainsi qu'un système de livraison, formation et supervision bien développé. Bien sûr le dosage de la vitamine A est bien plus simple que celui de la vaccination et il n'est pas nécessaire de disposer d'une chaîne de froid. Dans un certain nombre de pays, les taux de couverture de vaccination ont connu une augmentation sensible lorsque la vaccination était accompagnée d'activités de distribution de vitamine A. Dans la région du projet HOPE au Guatemala, la demande de services d'accoucheuses traditionnelles a augmenté lorsque ces dernières ont commencé à distribuer de la vitamine A aux femmes ayant accouché.

8 DEFINIR LES REGIONS A HAUT RISQUE

• DONNEES DE PREVALENCE	• UTILISATION DES FACTEURS DE RISQUE
- Enquêtes auprès des ménages	- Retard de croissance, régions arides des zones écologiques, camps de réfugiés, groupes à faible revenu
- Registres des dispensaires	

Comme il est difficile de mettre au point et de maintenir des programmes à large couverture permettant d'intervenir auprès des jeunes enfants et des femmes post-partum de manière courante au moins tous les 6 mois, beaucoup de pays ont limité la distribution universelle aux régions à haut risque. La définition des régions à forte prévalence est une première étape essentielle dans la planification de programmes universels de distribution de compléments. Si l'on ne dispose pas de données sur la prévalence ou que ces dernières ne sont pas suffisamment bien ventilées et ne permettent pas de délimiter certaines zones en particulier, les facteurs de risque de carence vitaminique A peuvent servir à définir des priorités et à cibler. Dans certains pays et certaines régions, des groupes de population donnés courent plus de risques que d'autres. Durant cette étape, il importe de définir les sous-groupes de population pouvant être exposés à un risque élevé. Par ailleurs il convient également de définir tout profil saisonnier de pénurie alimentaire ou de forte morbidité pouvant exister. La distribution de compléments peut alors être programmée avant les saisons en question.

La malnutrition (retard de croissance et émaciation) est souvent liée à une carence de vitamine A. Par exemple, dans le cas de l'Ouganda, on a confirmé que les retards de croissance constituaient un facteur de risque dans le district de Kamuli. Comme il n'existe pas de données nationales sur la prévalence des carences de vitamine A, on pourrait recenser les régions à haut risque en Ouganda à partir de la prévalence élevée des retards de croissance. La faible couverture de

8 (suite)

vaccination pourrait également constituer un autre critère de ciblage des activités de distribution universelle, et ce pour deux raisons : tout d'abord, les régions à faible couverture présentent probablement des risques élevés de carences vitaminiques A (car les infections fréquentes épuisent les réserves de vitamine A) et par ailleurs la participation accrue grâce à la vitamine A peut avoir des retombées positives en contribuant à accroître les taux de vaccination.

9 CALENDRIER DE PREVENTION

(Applicable uniquement aux régions à haut risque)

• Enfants 12-72 mois	200 000 UI tous les 4-6 mois
• Enfants 6-11 mois pesant moins de 8 kg	100 000 UI tous les 4-6 mois
• Mères qui allaitent	200 000 UI à l'accouchement ou durant les quatres semaines post-partum

* Les enfants de moins de 6 mois qui ne sont pas nourris aux sein devrait recevoir 50 000 UI tous les 4 à 6 mois.

Comme la vitamine A est emmagasinée dans le foie puis libérée progressivement selon les besoins, il n'est pas nécessaire de consommer des compléments de façon journalière. Le calendrier ci-dessus est recommandé par l'OMS/IVACG pour la prévention dans les régions ou les groupes à risque de carence en vitamine A. Il convient de noter que les femmes en âge de procréer ne devraient pas consommer de fortes doses de vitamine A compte tenu du risque que cela représente pour le foetus. Il est une exception à cette règle qui consiste à donner une forte dose aux mères juste après l'accouchement ou pendant les quatre premières semaines post-partum lorsque la probabilité de grossesse est quasiment nulle. En outre, les nourrissons de 6-11 mois ou ceux qui pèsent moins de 8 kg ne doivent recevoir que la moitié de la dose. En général les nourrissons de moins de 6 mois ne présentent pas de signes de carences en vitamine A, en principe parce que le lait maternel en offre suffisamment. Cependant, dans les communautés où l'allaitement maternel n'est pas répandu durant les 6 premiers mois de vie, les nourrissons de moins de 6 mois devraient participer au programme et ne recevoir qu'un quart de la dose.

CALENDRIER DE TRAITEMENT

. . (Applicable à toutes les régions quel que soit le risque de carence vitaminique A)

• 3 DOSES	XEROPHTALMIE
• 2 DOSES	ROUGEOLE
• 1 DOSE	MALNUTRITION PROTEINO-ENERGETIQUE/ DIARRHEE > 14 JOURS

POUR LES ENFANTS DE 12-72 MOIS ET LES ADULTES, EXCEPTION FAITE DES FEMMES EN AGE DE PROCREER

1ERE DOSE : DES LE DIAGNOSTIC 200 000 UI*
2E DOSE : LE LENDEMAIN 200 000 UI*
3E DOSE : 4 SEMAINES PLUS TARD 200 000 UI*, SI POSSIBLE

* Demi-dose ou 100 000 UI pour les nourrissons de 6-11 mois ou pesant moins de 8 kg. Un quart de la dose, soit 50 000 UI pour les nourrissons de 0 à 6 mois.

L'OMS/IVACG ont recommandé un calendrier de traitement pour les enfants souffrant de carences vitaminiques A et les adultes présentant des signes oculaires (ou xérophtalmie). Ce calendrier consiste à administrer une dose dès l'établissement du diagnostic, à en administrer une autre le lendemain et à fournir une troisième dose de 200 000 UI au bout de quatre semaines s'il est possible d'avoir un contact à ce moment là. Tous les cas de rougeole devraient recevoir au moins les deux premières doses ; par ailleurs, mieux vaut une dose qu'aucune. Tous les cas de diarrhée présentant des symptômes pendant plus de 14 jours devraient recevoir la première dose. Exclure cependant ceux qui ont reçu une dose durant le dernier mois.

11 UTILISATION DES CAPSULES

NOMBRE DE GOUTTES PAR CAPSULE = 6 A 8

CHAQUE CAPSULE = 200 000 UI, SOIT UNE DOSE

POUR LES PETITS ENFANTS, OUVRIR LA CAPSULE ET VERSER LA MOITIE DES GOUTTES DIRECTEMENT DANS LA BOUCHE, CE QUI EQUIVAUT A 100 000 UI OU UN QUART DU NOMBRE DE GOUTTES, CE QUI EQUIVAUT A 50 000 UI.

...On peut également utiliser des flacons avec des compléments liquides et des distributeurs...

La distribution de compléments vitaminiques peut s'adapter à de nombreux programmes de soins de santé primaires car elle présente plusieurs avantages : les compléments peuvent être facilement administrés par voie orale et aucune piqûre n'est nécessaire, les produits n'ont pas besoin d'être réfrigérés et leur durée de vie est relativement longue (2 ans si le flacon n'a pas été ouvert ou 6 mois s'il l'a été). Il convient de noter que la capsule de gélatine peut durcir à l'air, les récipients doivent donc être bien fermés.

Le nombre de gouttes dans une capsule de vitamine A varie de 6 à 8. Lorsque chaque lot de capsule est déballé, il faut calculer le nombre de gouttes en ouvrant une capsule et en la vidant de son contenu. Chaque capsule contient 200 000 UI. Pour les petits enfants, ouvrir la capsule et ne donner que la moitié des gouttes, en les plaçant directement dans la bouche. Cela équivaut à 100 000 UI. On peut également administrer de la sorte le complément aux nourrissons et aux jeunes enfants trop malades pour avaler une capsule.

Chez les enfants plus âgés, placer la capsule sur la langue et vérifier que l'enfant l'avale. Chez les nourrissons et les enfants malades, ouvrir la capsule et la vider de son contenu dans la bouche de l'enfant avec la main droite en tenant sa tête avec l'autre main.

INTEGRATION

- DEFINITION ET DIFFUSION DE PROTOCOLES ET DIRECTIVES
- DEFINITION DE COUVERTURES CIBLES
- AFFECTATION DE RESPONSABILITES : FOURNITURES, FORMATION
- ESTIMATION ET ACQUISITION DES FOURNITURES
- CONCEPTION ET MISE EN OEUVRE DE LA FORMATION
- SURVEILLANCE ET EVALUATION

La distribution de compléments vitaminiques A est difficile à maintenir comme programme vertical indépendant. Elle doit par conséquent être intégrée à d'autres activités. Une fois que les systèmes de distribution et les programmes ont été définis, un certain nombre de mesures doivent être mises en oeuvre pour assurer l'intégration . Ces mesures sont énumérées ci-dessus et elles sont toutes essentielles. C'est ainsi qu'il ne suffit pas de définir un mécanisme de distribution approprié parmi les programmes existants sans s'assurer de l'existence d'un système de formation et d'une méthode fiable d'approvisionnement régulier.

13 PLAN DE FORMATION

OBJECTIFS

- Motivation du personnel
- Amélioration des connaissances
- Développement des aptitudes

MESURES

1 : Combien de personnes ?
2 : Où et comment ?
3 : Qui sera responsable ?
4 : De quelles ressources doit-on disposer ?

Les trois objectifs principaux de la formation sont la motivation du personnel, l'amélioration de ses connaissances et le développement de ses aptitudes dans la réalisation de son travail.
Dans un premier temps, il faut définir les catégories de personnel qui participeront à la distribution de vitamine A, à la supervision ou à la gestion. La description de leur fonction et des protocoles devra être révisée et une formation spéciale devra être assurée. En outre, des cursus appropriés devront être mis au point pour les facultés de médecine et les écoles d'infirmières en tenant compte des dernières connaissances sur la vitamine A.

14 APPROVISIONNEMENT

- AJOUTER LA VITAMINE A A LA LISTE DE MEDICAMENTS ESSENTIELS
- IL CONVIENT D'ESTIMER LES QUANTITES NECESSAIRES
- S'APPROVISIONNER ET STOCKER
- APPROVISIONNER LES POINTS DE DISTRIBUTION ET LES REALIMENTER

L'une des causes les plus courantes d'échec dans les programmes de distribution est l'interruption du flux d'approvisionnement. Même après le démarrage du programme, il est nécessaire d'assurer un suivi systématique et de veiller à ce que les points de distribution soient effectivement ravitaillés. Les mesures énoncées ci-dessus sont nécessaires pour veiller à une bonne distribution. Mais sans système fiable de réapprovisionnement, le flux de distribution peut s'interrompre après un ou deux cycles. Même une fois que le programme aura démarré, les ravitaillements devront être soigneusement surveillés et les points de distribution effectivement réapprovisionnés.

15 SURVEILLANCE ET EVALUATION

- COUVERTURE
  - % D'ENFANTS ET DE MERES RECEVANT DES DOSES
  - % DE CAS TRAITES
- APPROVISIONNEMENT
  - NOMBRE REÇU ET STOCK RESIDUEL EN LE COMPARANT AVEC LA POPULATION A COUVRIR
  - % DE SITES DE DISTRIBUTION CONSTAMMENT RAVITAILLES PENDANT CHAQUE PERIODE DE 12 MOIS
- FORMATION
  - % DU PERSONNEL DE DISTRIBUTION FORME
  - % DE RESPONSABLES FORMES
  - % D'INDIVIDUS FORMES PAR RAPPORT AU % PROJETE

Pour assurer une bonne couverture de distribution de vitamine A, il faut notamment tenir à jour un registre simple mais complet des principaux indicateurs et faire régulièrement le point des résultats des évaluations avec tous les principaux agents concernés. La liste ci-dessus en donne certains exemples.

...PEUT ACCROITRE LES EFFETS DE LA DISTRIBUTION DE COMPLEMENTS DE LA MANIERE SUIVANTE...

- PROMOTION DE LA PARTICIPATION AU PROGRAMME DE DISTRIBUTION DE COMPLEMENTS
- ENCOURAGE UNE AMELIORATION DES PRATIQUES ALIMENTAIRES

Les activités de distribution de compléments peuvent donner davantage de résultats avec un travail éducation en nutrition, en informant les communautés de l'importance de la participation et en encourageant l'adoption de pratiques alimentaires meilleures afin d'accroître la consommation d'aliments riches en vitamine A disponibles localement. La promotion des aliments locaux est d'autant plus importante dans les régions où l'approvisionnement en vitamine A peut être interrompu de temps à autres. Des études ont en outre démontré que l'efficacité de la distribution de compléments deux fois par an peut être considérablement accrue par une amélioration de la ration alimentaire.

17 MISE AU POINT D'UN PROGRAMME

- DETERMINER LA PREVALENCE ET LA REPARTITION DES CARENCES
- RECENSER LES LACUNES QUI POURRAIENT EXISTER DANS LA COUVERTURE DES PROGRAMMES EXISTANTS DE VITAMINE A
- RECENSER LA POPULATION CIBLE A COUVRIR
- DEFINIR LES CANAUX DE DISTRIBUTION ET AFFECTER LES RESPONSABILITES

Les mesures ci-dessus doivent être prises pour la planification d'un programme de distribution de vitamine A (nouveau ou élargi).

18 MISE AU POINT D'UN PROGRAMME (suite)

- METTRE AU POINT UN SYSTEME D'APPROVISIONNEMENT
- DEFINIR LES BESOINS EN FORMATION
- FORMULER ET APPLIQUER DES NORMES TECHNIQUES
- EVALUER ET MODIFIER LE PROGRAMME

On trouvera ci-dessus d'autres mesures de planification et de mise en oeuvre. La distribution de compléments à fortes doses est l'une des stratégies d'amélioration de l'état en vitamine A. Elle peut bénéficier des effets complémentaires des autres, à savoir l'enrichissement, l'amélioration de la ration alimentaire et la lutte contre les maladies infectieuses. Dans la plupart des cas, il faudra procéder à une combinaison de plusieurs stratégies. Les compléments vitaminiques peuvent être introduits parallèlement à des améliorations durables et permanentes des solutions aux problèmes, ainsi que l'on envisage de le faire en Ouganda. Dans d'autres cas, l'enrichissement peut constituer la base du programme de lutte contre les carences vitaminiques A, avec comme corollaires des petites programmes clairement ciblés de compléments et d'amélioration de la ration alimentaire dans des communautés spécifiques, ainsi que cela se fait au Guatemala.

Par-delà l'utilisation universelle des compléments de vitamine A dans le cadre de la lutte contre la xérophtalmie, la rougeole, la malnutrition protéino-énergétique et la diarrhée persistante, le rôle et l'ampleur des activités de compléments vitaminiques A dans un ensemble complet d'interventions dépendra des besoins et des ressources des groupes visés.

SUPPLEMENT DISTRIBUTION PROGRAMS

Introduction

In several areas of the world, where children are at high risk of vitamin A deficiency, vitamin A supplementation - that is, the periodic administration of the vitamin to deficient persons - is an effective, immediate intervention to prevent morbidity, mortality and blindness. Supplements are considered a short-term measure which is initiated when urgent and immediate action is deemed necessary to protect groups at risk of vitamin A deficiency.

The choice of strategy for distribution will depend upon the prevalence of deficiency and resources available. At a minimum, all areas within the vitamin A program will need to integrate vitamin A supplementation as a routine practice in case management of xerophthalmia, measles, PEM and prolonged diarrhea. The purpose of this slide/overhead presentation is to provide a basic set of guidelines for the development of a supplement distribution program.

The enclosed material can be used as part of a formal training course or an informal refresher/orientation session for field workers, managers or policy makers interested in obtaining an overview of the components of vitamin A supplement distribution. It is suitable for both, health professionals and para-professionals. Slides or overheads can be made from the charts; photographic material can be added or replaced.

The presentation contains an overview of the program options available for distributing vitamin A supplements, treatment and prevention protocols, and steps needed to implement a supplement program. Material in this presentation is based on recent information on the effectiveness of various supplementation activities which has become available since the publication of the WHO/UNICEF/IVACG Task Force guide in 1988.

The contents of this package are:

- **Charts:** Printouts of 18 slides which can be used as hand-outs, overheads or converted to slides for presentations at meetings, training courses or conferences.
- **Text:** Text for each of the slides
- Effectiveness of Vitamin A Supplementation in the Control of Young Child Morbidity and Mortality in Developing Countries by G.H. Beaton et al, University of Toronto, 1992.
- **Other Publications:**

  - Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality by Dr. David Ross et al, The Lancet, July 3, 1993, Vol. 342 at 7.
  - High Dose Vitamin A Supplementation of Breast-feeding Indonesian Mothers: Effects on the Vitamin A Status of Mother and Infant by Rebecca J. Stoltzfus et al, Journal of Nutrition, Vol. 123 at 666.
  - Cost of vitamin A supplementation: the opportunity for integration with immunization in Ghana by Dyna C. Arhin et al, Health Policy and Planning; 8(4):339-348.
  - Efficacy of vitamin A in reducing preschool child mortality in Nepal by Keith West, et al, The Lancet, July 13, 1991, Vol. 338, No. 8759 at 67.
  - Reduced Mortality among children in Southern India receiving a small weekly dose of vitamin A by Laxmi Rahmathullah et al, New England Journal of Medicine, Oct. 4, 1990, 323:929-935.

CREDITS:

"SUPPLEMENT DISTRIBUTION PROGRAMS" is part of a slide presentation series of the Vitamin A Field Support Project - VITAL - of the U.S. Agency for International Development and International Science and Technology Institute, Inc. (ISTI). This publication was made possible by support from the Office of Nutrition, Bureau for Research and Development, U.S. Agency for International Development under contract No. DAN-5116-C-00-9114-00. Send inquiries, comments, and requests for additional copies to: Dr. Frances R. Davidson, Deputy Director, USAID Office of Nutrition, Washington D.C. or OMNI, 1616 N. Fort Myer Drive, Suite 1100, Arlington, VA 22209, U.S.A.

Author: Tina G. Sanghvi, PhD

USAID Project Officer: Dr. Frances R. Davidson

Translators: French — Joelle De Laplace
Spanish — Alicia Agnese

Reviewers:
Dr. John McKigney
Dr. Jose Mora, MD
Dr. Hernando Flores, MD
Dr. Penelope Nestel
Mr. Robert Pratt
Dr. Barbara Underwood

Editors:
Karen Canova
Katarina Paddack
Dahlia Hayles

Permission is granted to reproduce this material for distribution.

1

ViTAL is a program of the Office of Nutrition,
U.S. Agency for International Development.

vital slide presentation

Supplement Distribution Programs

2

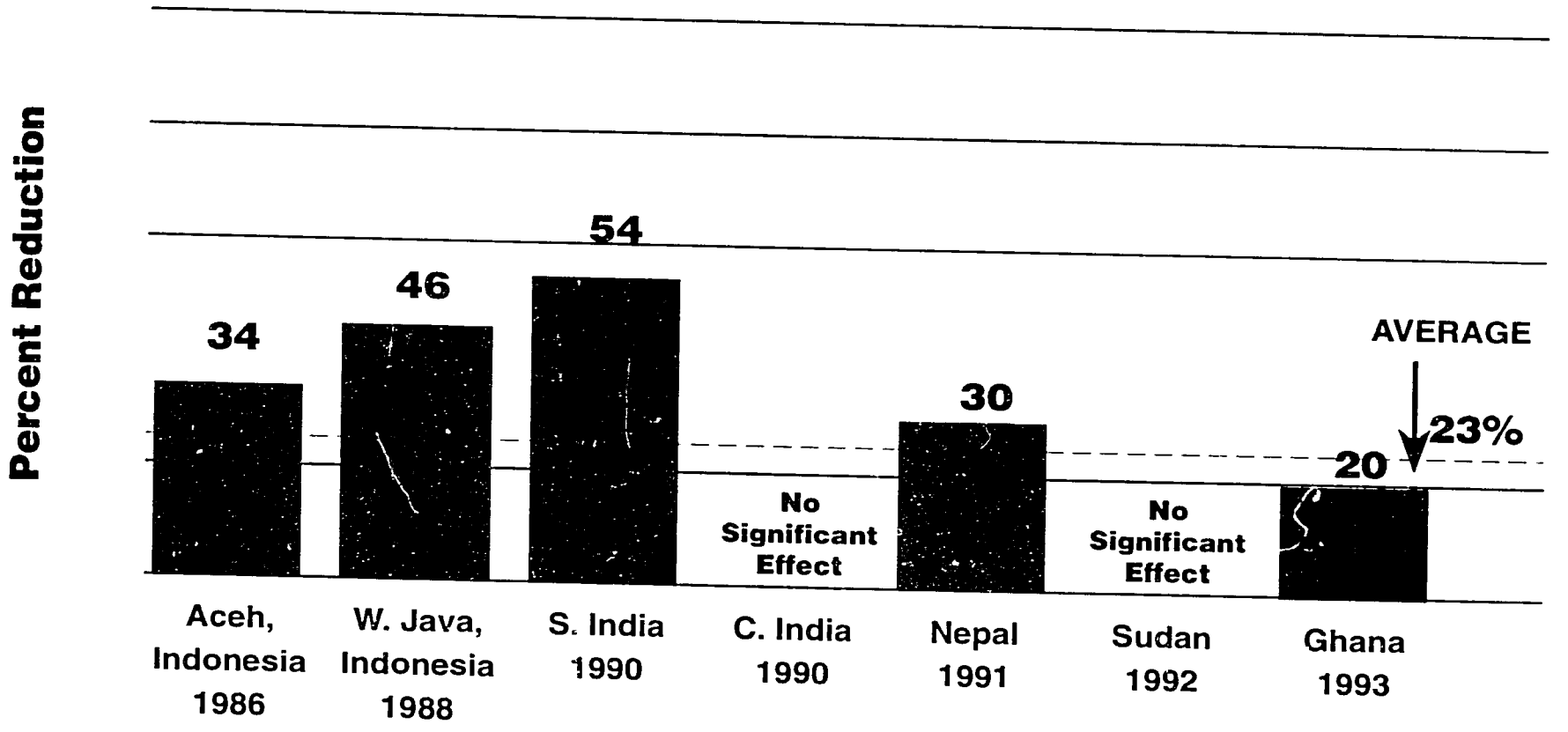
When Are Supplements Needed?

- **Vitamin A Rich Foods**
  - Not grown, or
  - Too expensive, or
  - Not part of food habits

→ Vitamin A deficiency → Mortality, Morbidity, Blindness

3

Impact on Child Mortality

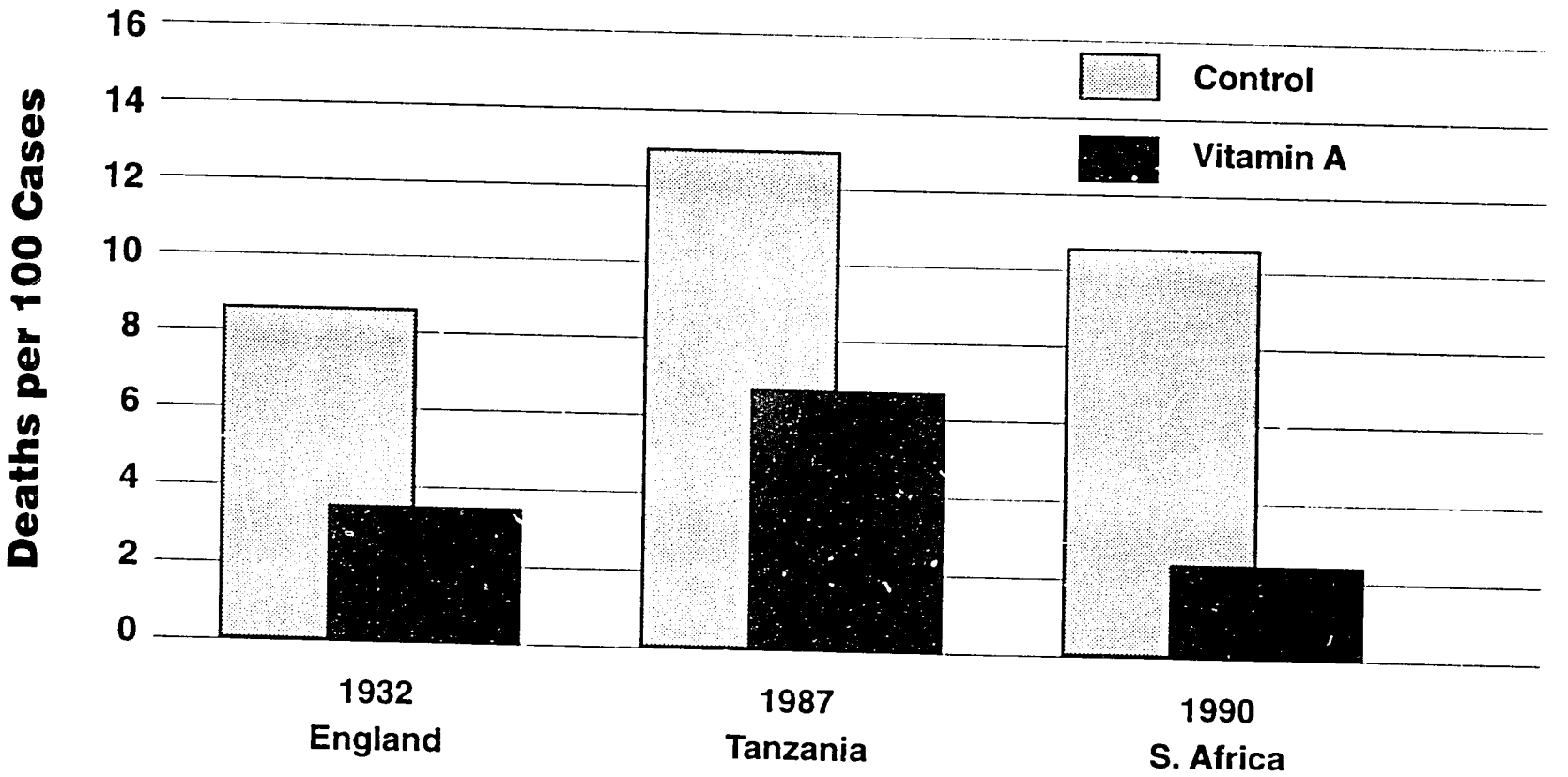


BEST AVAILABLE COPY

23

4

Impact on Measles



BEST AVAILABLE COPY

24

5

Strategies for Distribution

	All Areas	High Risk Areas
● Who?	Xerophthalmia, Measles, PEM, Chronic Diarrhea	Children 6-72 mths Postpartum women < 4 wks
● What?	Treatment	Prevention + Treatment
● How?	Health Services	Community-Based Health Services

Xerophthalmia= Eye signs of vitamin A deficiency.

6

In All Areas

Include supplements in the treatment of the following conditions:

Who?

- PEM/Chronic Diarrhea
- Measles
- Xerophthalmia

How?

What?

- 1 Dose
- 2 Doses
- 3 Doses

– Infectious disease hospitals

– Pediatric hospitals/clinics

– Malnutrition wards

– Ophthalmologic hospitals/clinics

– Health centers/ workers

BEST AVAILABLE COPY

26

In High Prevalence Areas

Use Supplements for Prevention

Who?

- Children: 6-72 months
- Postpartum Mothers: < 4 weeks

What?

- 1 Dose: every 4-6 months
- 1 Dose

How?

- Immunization activities
- Traditional birth attendants
- At every contact with a sick child (Diarrhea, etc.), there should be a one month interval between dosing.
- Women's groups
- Schools

Identifying Areas of High Risk

- **Prevalence data**
  - Household surveys
  - Clinical records
- **Using risk factors:**
  - Stunting, ecological zones, arid regions, refugee camps, low income groups

Prevention Schedule

(Applicable in high risk areas only)

● Children 12-72 months	200,000 IU every 4-6 months
● Infants 6-11 months old and who weigh less than 8 kg	100,000 IU every 4-6 months
● Lactating mothers	200,000 IU once at delivery or during the following 4 weeks

* Infants below 6 months who are not breastfed should receive 50,000 IU every 4-6 months

Treatment Schedule

(Applicable in all areas regardless of vitamin A deficiency risk)

3 Doses: Xerophthalmia

2 Doses: Measles

1 Dose: PEM/Diarrhea > 14 days

For children 12-72 months old and adults, except women of childbearing age

1st Dose: Immediately on diagnosis 200,000 IU*
2nd Dose: The following day 200,000 IU*
3rd Dose: 4 weeks later 200,000 IU*, if possible

* Half dose or 100,000 IU for infants 6-11 months or less than 8 kg
Quarter dose or 50,000 IU for infants 0-6 months of age.

Using Capsules

- Number of drops per capsule = 6 to 8
- Each capsule = 200,000 IU, one dose

For small infants, cut open and squeeze out half the number of drops directly into child's mouth. This equals 100,000 IU or one-fourth the number of drops, which equals 50,000 IU.

..... bottles with liquid supplements and dispensers can also be used....

Integration

- Develop and issue protocols and directives
- Set coverage targets
- Assign responsibilities appropriately
- Estimate and procure supplies
- Design and conduct training
- Monitor and evaluate

13

Training Plan

Objectives:

- Motivating staff
- Improving knowledge
- Developing skills

Step 1: How many people?
Step 2: Where and when conducted?
Step 3: Who will take responsibility?
Step 4: What resources needed?

14

Procurement and Supplies

- Add vitamin A to essential drugs list
- Estimate amounts needed
- Procure and store supplies
- Supply distribution points initially and re-supply

Monitoring and Evaluation

- **Coverage**
  - % Children and mothers dosed
  - % Cases treated
- **Supplies**
  - Numbers received & balances compared with eligible population
  - % distribution sites with uninterrupted supplies for each 12 month period
- **Training**
  - % distribution staff trained
  - % supervisors trained
  - % trained compared with plans

Nutrition Education

- Promote participation in supplements program
- Encourage improvements in dietary habits

BEST AVAILABLE COPY

17

Program Development

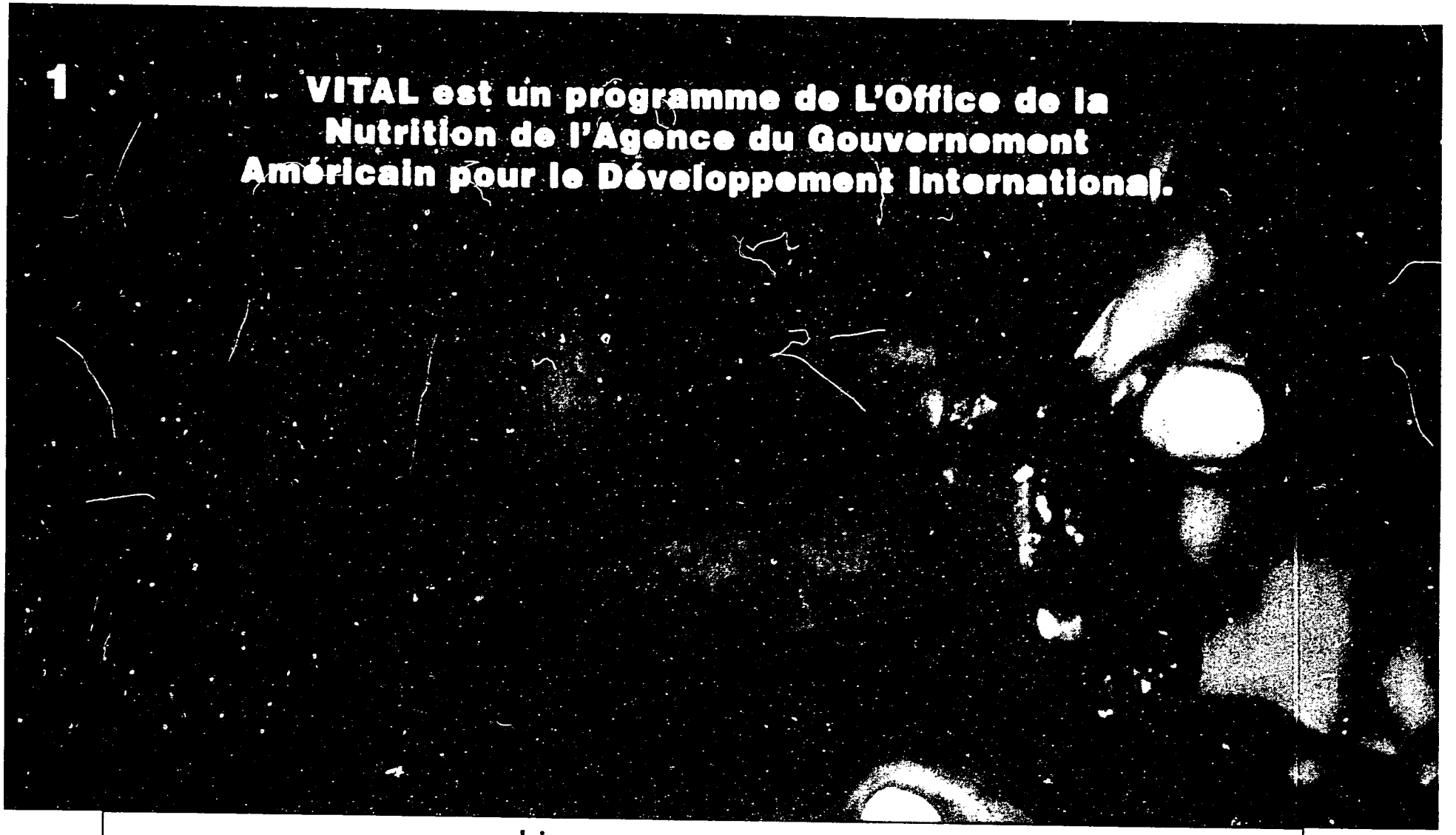
Steps

- Establish prevalence and distribution of deficiency
- Identify gaps in existing program coverage for vitamin A
- Determine who and how many are in the target population for supplements
- Identify channels of distribution and assign responsibility

Program Development (continued)

Steps

- Develop a procurement and supply system for supplements
- Determine training needs
- Formulate and implement technical norms
- Evaluate and modify program



diaporama vital

Programmes de Distribution de Compléments Vitaminiques A

2

Quand Les Compléments Sont-Ils Nécessaires?

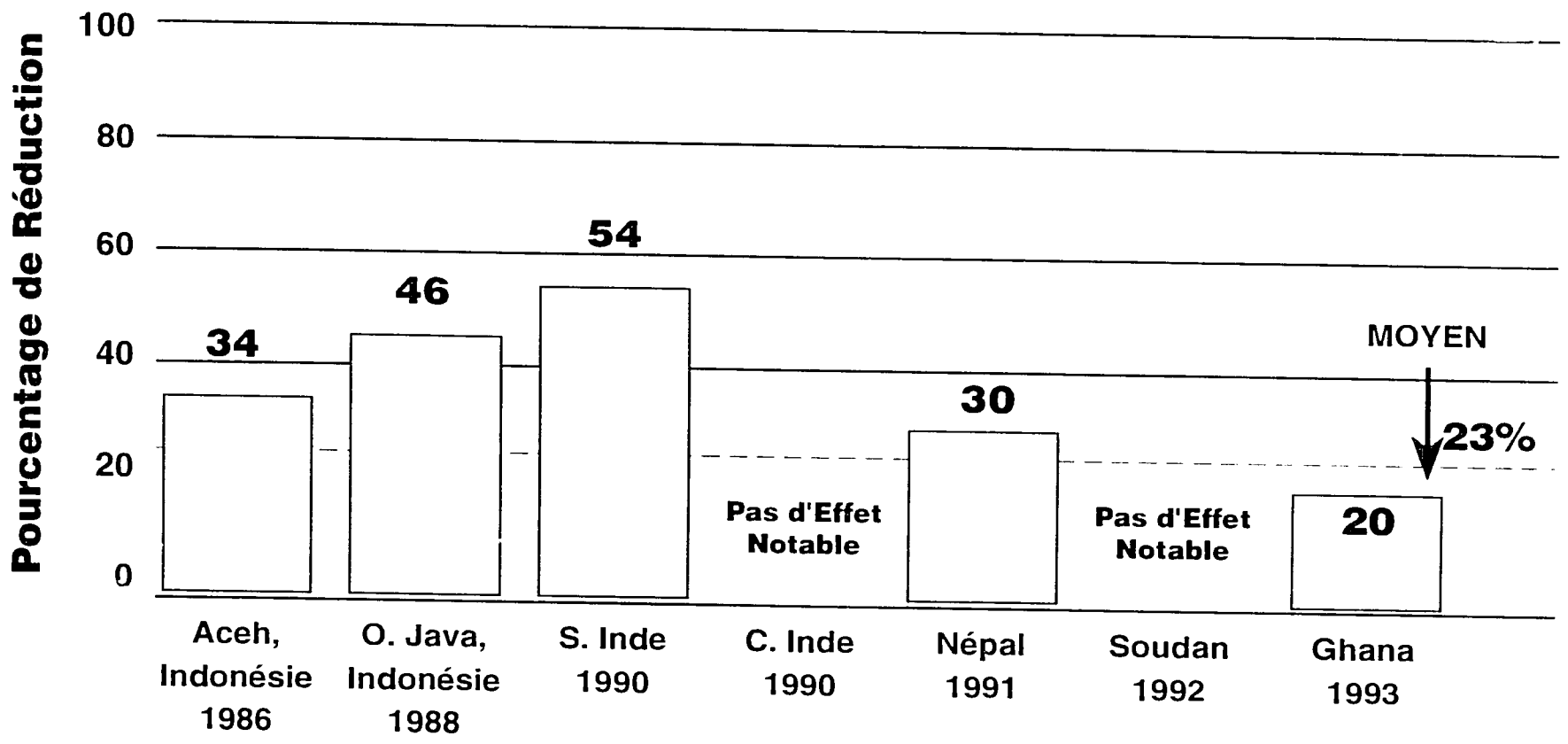
- **Aliments Riches en Vitamine A**

  - Non cultivés ou
  - Trop coûteux ou
  - Pas dans les habitudes alimentaires

→ Carences Vitaminiques A → Mortalité Morbidité Cécité

3

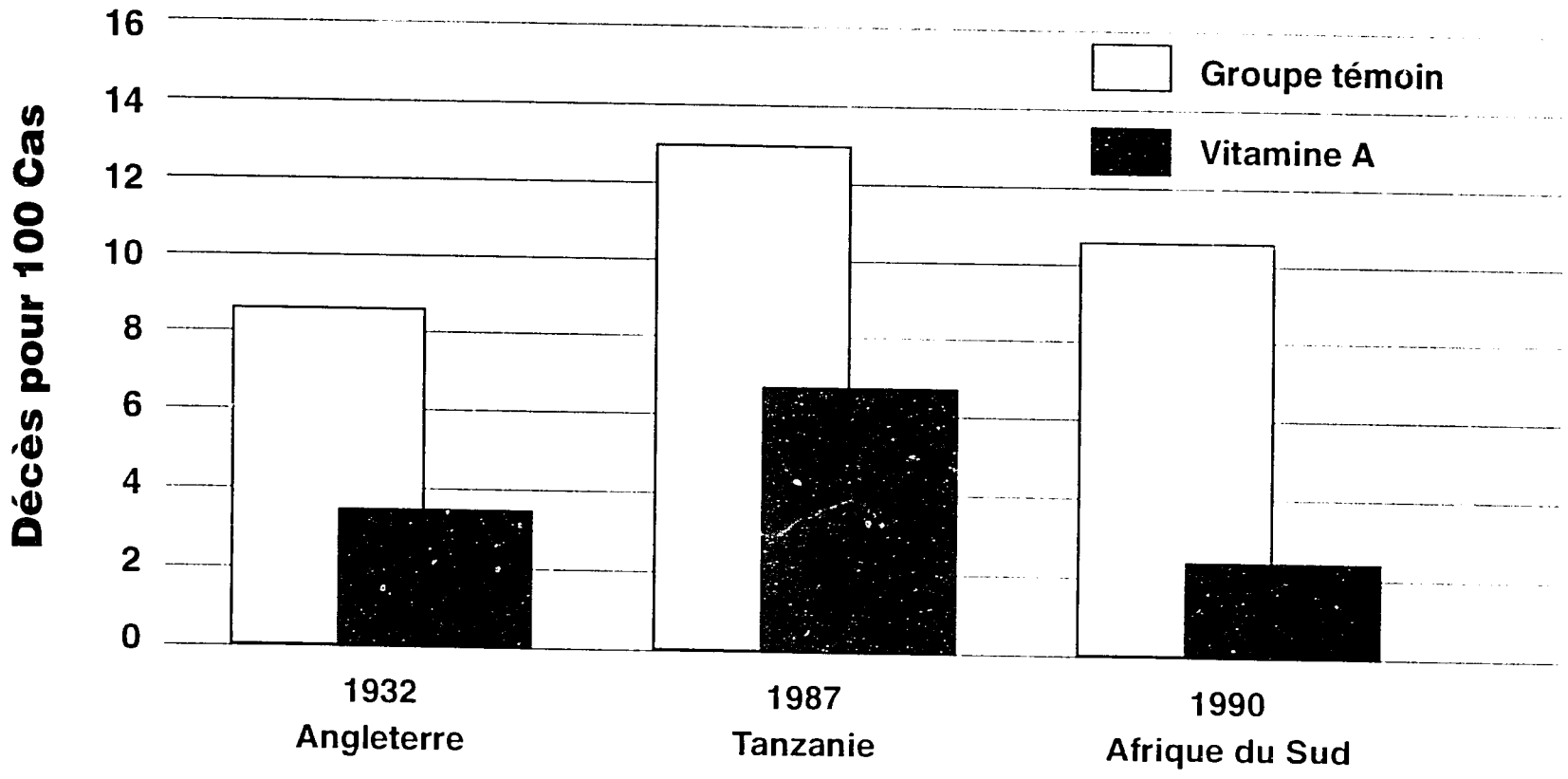
Effet Sur La Mortalité Juvénile



11

4

Effet Sur La Rougeole



BEST AVAILABLE COPY

42

5

Stratégie de Distribution

	Toutes Régions	Régions à Haut Risque
● Qui?	Xérophtalmie, Diarrhée Chronique, Rougeole, Malnutrition Protéino-énergétique	Enfants de 6-72 Mois Femmes Post-Partum < 4 Semaines
● Quoi?	Traitement	Prévention+Traitement
● Comment?	Services de Santé	Services de Santé Communautaires

Xérophtalmie= Signe oculaire de carence en vitamine A.

Dans Toutes Les Régions

Compléments pour le traitement des troubles suivants:

Qui?

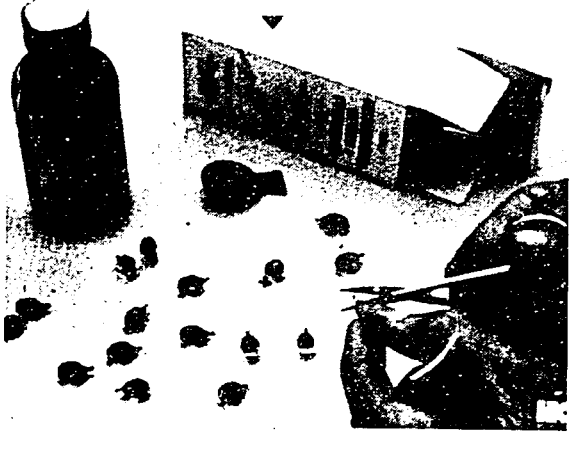
- Xérophtalmie
- Rougeole
- Malnutrition Protéino-Energétique/ Diarrhée Chronique

Quoi?

- 3 Doses
- 2 Doses
- 1 Dose

Comment?

- Hopitaux maladies infectieuses
- Hopitaux/ dispensaires pédiatriques
- Services chargés de la malnutrition



- Hopitaux/ dispensaires ophtalmologiques
- Centres/agents de santé

BEST AVAILABLE COPY

7

Dans Les Régions A Forte Prévalence

Compléments pour la prévention

Qui?

- Enfants: 6-72 mois
- Mères post-partum: <4 semaines

Quoi?

- 1 Dose: tous les 4-6 mois
- 1 Dose

Comment?

- Activités de vaccination
- Accoucheuses traditionnelles
- Groupes de femmes
- Ecoles
- A chaque contact avec un enfant malade (malnutrition protéino-énergétique, diarrhée, etc.) il devrait y avoir un intervalle d'un mois entre doses.

8

Définir Les Régions A Haut Risque

- **Données de prévalence**
  - Enquêtes auprès des ménages
  - Registres des dispensaires
- **Utilisation des facteurs de risque**
  - Retard de croissance, régions arides des zones écologiques, camps de réfugiés, groupes à faible revenu

46

Calendrier De Prévention

(Applicable uniquement aux régions à haut risque)

● Enfants 12-72 mois	200 000 UI tous les 4-6 mois
● Enfants 6-11 mois ou pesant moins de 8 kg	100 000 UI tous les 4-6 mois
● Mères qui allaitent	200 000 UI à l'accouchement ou durant les quatres semaines post-partum

*Les enfants de moins de 6 mois qui ne sont pas nourris aux sein devraient recevoir 50 000 UI tous les 4 à 6 mois

47

Calendrier De Traitement

(Applicable à toutes les régions quel que soit le risque de carence vitaminique A)

3 Doses: **Xérophtalmie**

2 Doses: **Rougeole**

1 Dose: **Malnutrition Protéino-Energétique/Diarrhée > 14 jours**

Pour les enfants de 12-72 mois et les adultes, exception faite des femmes en âge de procréer

1ère Dose: Dès le diagnostic 200 000 UI*
2e Dose: Le lendemain 200 000 UI*
3e Dose: 4 semaines plus tard 200 000 UI*, si possible

* Demi-dose ou 100 000 UI pour les nourrissons de 6-11 mois ou pesant moins de 8 kg. Un quart de la dose, soit 50 000 UI pour les nourrissons de 0 à 6 mois

Utilisation Des Capsules

- **Nombre de gouttes par capsule = 6 à 8**
- **Chaque capsule = 200 000 UI, soit une dose**

Pour les petits enfants, ouvrir la capsule et verser la moitie des gouttes directement dans la bouche, ce qui equivaut à 100 000 UI ou un quart du nombre de gouttes, ce qui equivaut à 50 000 UI.

... On peut également utiliser des flacons avec des compléments liquides et des distributeurs ...

12

Intégration

- Définition et diffusion de protocoles et directives
- Définition de couvertures cibles
- Affectation de responsabilités: fournitures, formation
- Estimation et acquisition des fournitures
- Conception et mise en oeuvre de la formation
- Surveillance et évaluation

Plan De Formation

Objectifs:

- Motivation du personnel
- Amélioration des connaissances
- Développement des aptitudes

Mesures

1: Combien de personnes?

2: Où et comment?

3: Qui sera responsable?

4: De quelles ressources doit-on disposer?

5

Approvisionnement

- Ajouter la vitamine A à la liste de médicaments essentiels
- Il convient d'estimer les quantités nécessaires
- S'approvisionner et stocker
- Approvisionner les points de distribution et les réalimenter

Surveillance Et Evaluation

- **Couverture**
  - % D'enfants et de mères recevant des doses
  - % De cas traités
- **Approvisionnement**
  - Nombre reçu et stock résiduel en le comparant avec la population à couvrir
  - % De sites de distribution constamment ravitaillés pendant chaque periode de 12 mois
- **Formation**
  - % Du personnel de distribution formé
  - % De responsables formés
  - % D'individus formés par rapport au % projeté

Education En Nutrition

... Peut accroître les effets de la distribution de compléments de la manière suivante ...

- Promotion de la participation au programme de distribution de compléments
- Encourage une amélioration des pratiques alimentaires

17

Mise au Point D'un Programme

Etapes

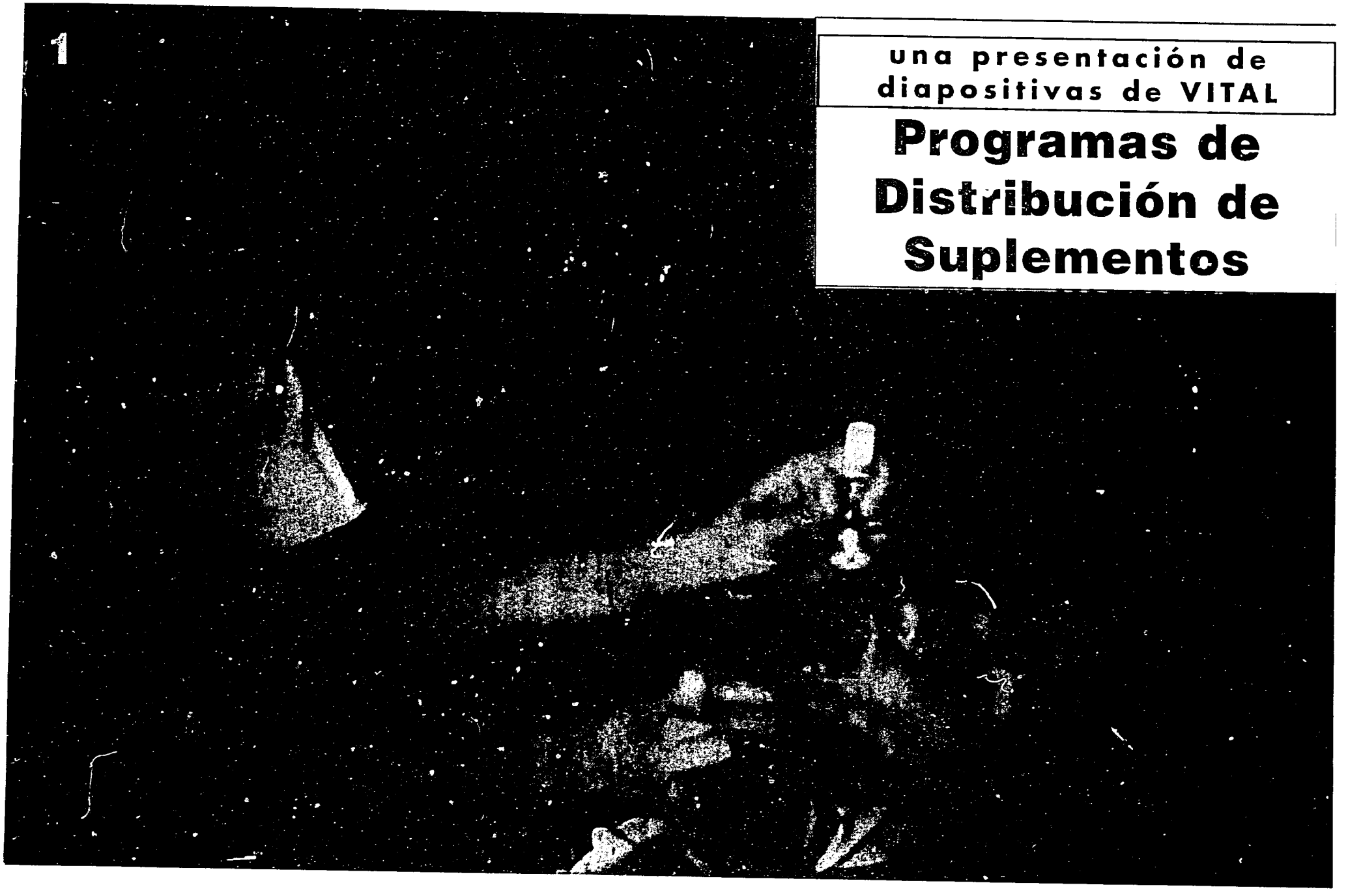
- Déterminer la prévalence et la répartition des carences
- Recenser les lacunes qui pourraient exister dans la couverture des programmes existants de vitamine A
- Recenser la population cible à couvrir
- Définir les canaux de distribution et affecter les responsabilités

55

Mise au Point D'un Programme (suite)

Etapes

- Mettre au point un système d'approvisionnement
- Définir les besoins en formation
- Formuler et appliquer des normes techniques
- Evaluer et modifier le programme



1

una presentación de diapositivas de VITAL

Programas de Distribución de Suplementos

2

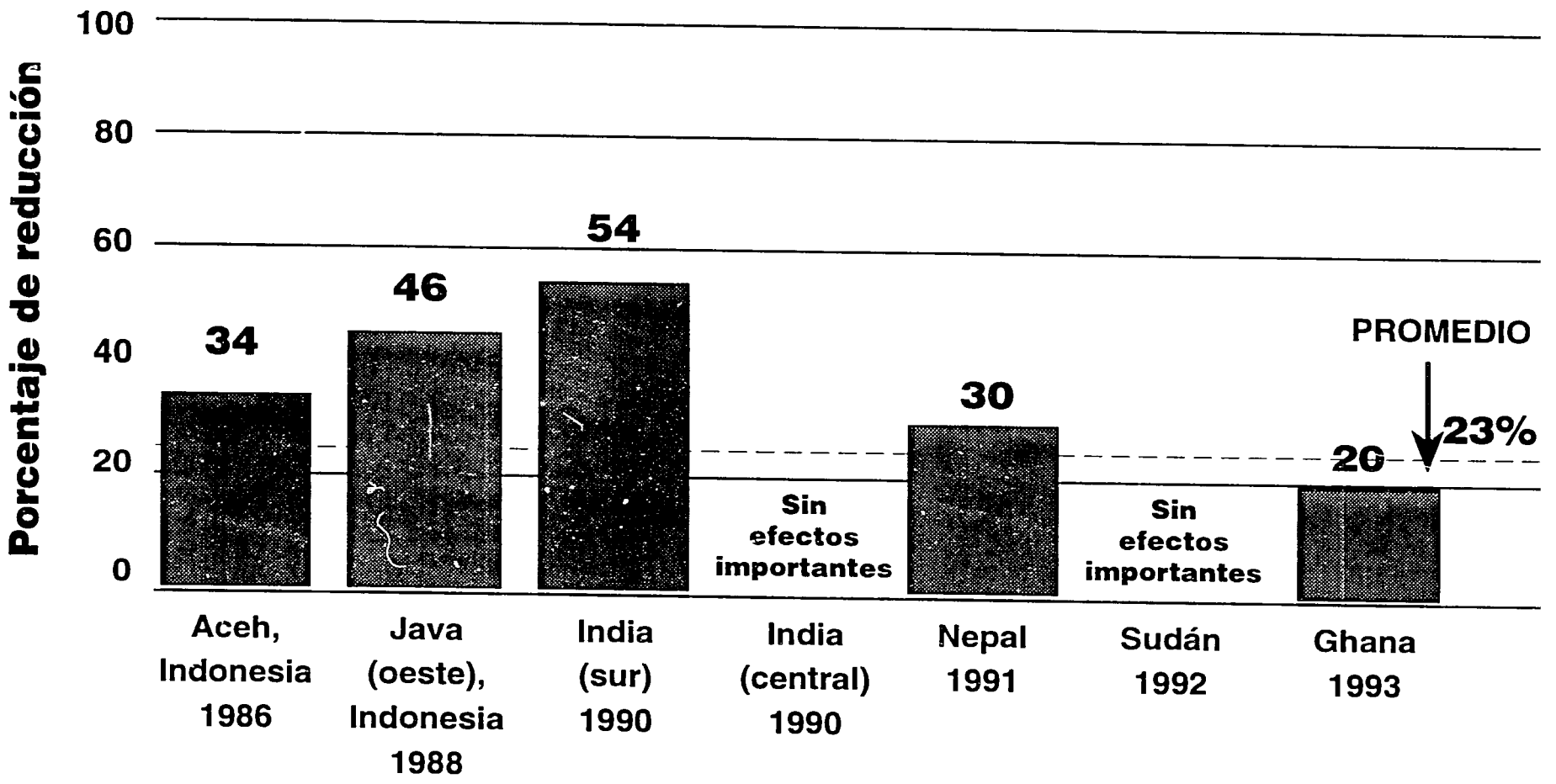
¿Cuándo son necesarios los suplementos?

- **Alimentos ricos en vitamina A**
  - No se cultivan, o
  - Son muy caros, o
  - No forman parte de los hábitos alimentarios

→ **Carencia de vitamina A** → **Mortalidad Morbilidad Ceguera**

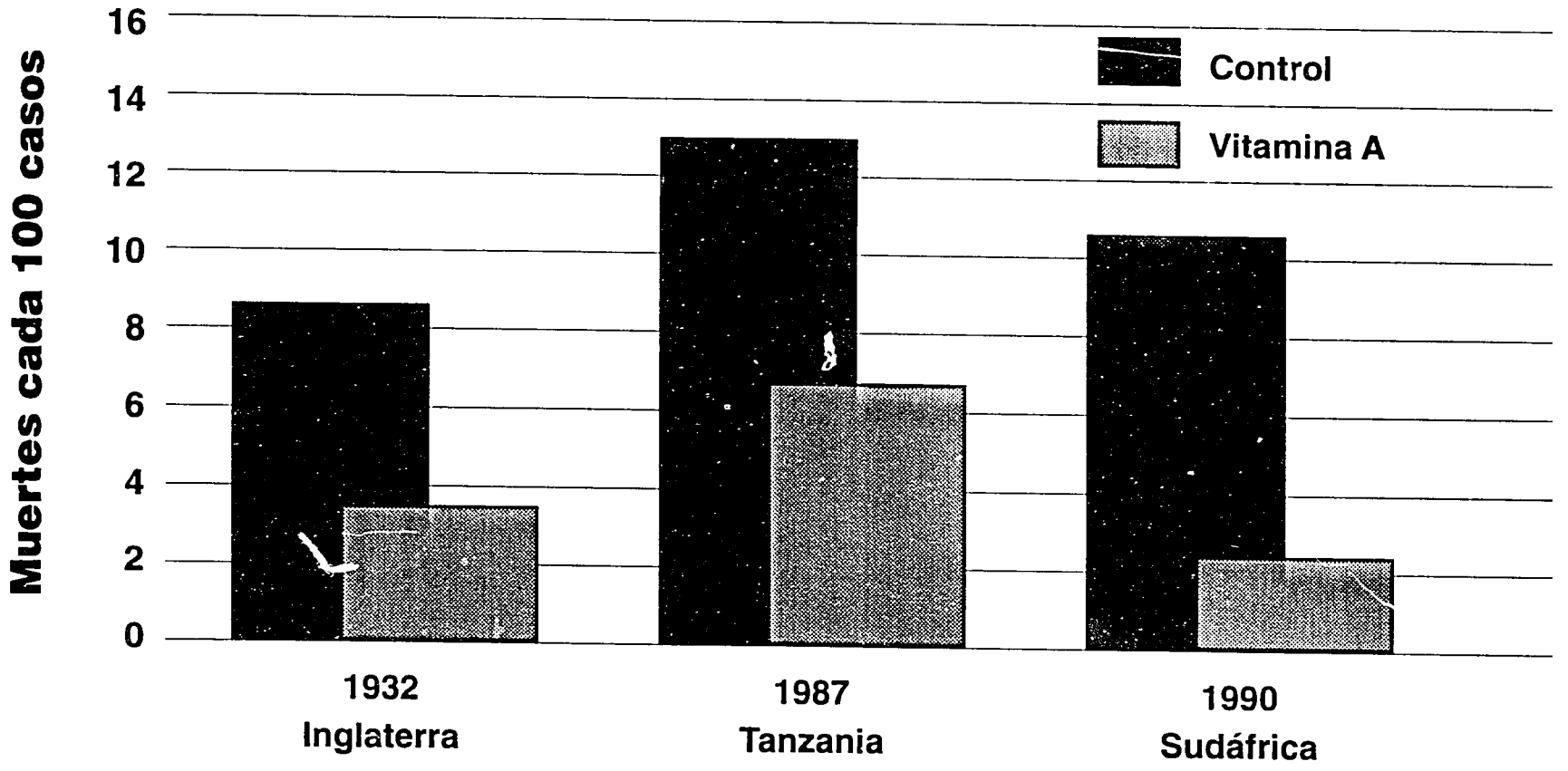
3

Repercusión sobre la mortalidad infantil



4

Repercusión sobre el sarampión



60

5

Estrategias para la distribución

	Todas las regiones	Regiones de alto riesgo
● ¿Quién?	Xeroftalmia, sarampión, DPE, diarrea crónica	Niños de 6-72 meses mujeres en las primeras 4 semanas después del parto
● ¿Qué?	Tratamiento	Prevención + tratamiento
● ¿Cómo?	Servicios de salud	Servicios de salud comunitarios

Xeroftalmia= Síntomas oculares de carencia de vitamina A.

6

En todas las regiones

Incluir suplementos en el tratamiento de las siguientes enfermedades:

¿Quién?

- DPE/Diarrea crónica
- Sarampión
- Xeroftalmia

¿Cómo?

¿Qué?

- 1 dosis
- 2 dosis
- 3 dosis

– Hospitales de enfermedades infecciosas

– Hospitales/ Clínicas pediátricas

– Salas de desnutridos

– Hospitales/servicios Oftalmológicos

– Centros/Trabajadores de salud

62

7

En las regiones de gran prevalencia

Usar suplementos para prevención

¿Quién?

- Niños: 6-72 meses
- Madres en el puerperio: menos de 4 semanas

¿Qué?

- 1 dosis: cada 4-6 meses
- 1 dosis

¿Como?

– Actividades de inmunización
– Parteras tradicionales
– En todos los contactos con un niño enfermo (diarrea, etc.), debe proporcionarse un intervalo de un mes entre dosis
– Grupos de mujeres
– Escuelas

63

8

Identificación de las regiones de alto riesgo

- **Datos de prevalencia**
  - Encuestas en domicilios particulares
  - Historias clínicas
- **Utilización de los factores de riesgo:**
  - Desnutrición, zonas ecológicas, regiones áridas, campos de refugiados, grupos de bajos ingresos.

64

Esquema de prevención

(Corresponde a las regiones de alto riesgo únicamente)

● Niños de 12-72 meses	200.000 UI cada 4-6 meses
● Niños de 6-11 meses o que pesan menos de 8 kg	100.000 UI cada 4-6 meses
● Madres en lactancia	200.000 UI una vez después del parto o dentro de las siguientes 4 semanas

Los niños menores de 6 meses que se amamantan deben recibir 50.000 UI cada 4-6 meses.

Esquema de tratamiento

(Corresponde a todas las regiones, independientemente del riesgo de deficiencia de vitamina A)

- 3 dosis: xeroftalmia
- 2 dosis: sarampión
- 1 dosis: PEM/diarrea > 14 días

Para los niños de 12-72 meses y adultos, con excepción de las mujeres en edad reproductiva

1ra. dosis: al diagnóstico 200.000 UI*
2da. dosis: al día siguiente 200.000 UI*
3ra. dosis: 4 semanas más tarde: 200.000 UI*, si es posible.

* Media dosis ó 100.000 UI para los niños de 6-11 meses o que pesan menos de 8 kg. Un cuarto de dosis ó 50.000 UI para los niños de 0-6 meses de edad.

El uso de cápsulas

Cantidad de gotas en una cápsula = 6 a 8 gotas

Cada cápsula = una dosis de 200.000 UI.

Para los niños más pequeños, abrir la cápsula y extraer la mitad del número de gotas directamente sobre la boca del niño. Esto equivale a una dosis de 100.000 UI. Un cuarto de la cantidad de gotas, lo que equivale a 50.000 UI.

... también se pueden utilizar frascos con suplementos líquidos y dosificadores...

Integración

- Preparar y publicar esquemas e instrucciones
- Establecer objectivos de cobertura
- Asignar responsabilidades en la forma adecuada
- Estimar cantidades y adquirir la vitamina
- Preparar y realizar cursos de capacitación
- Controlar y evaluar

13

Plan de adiestramiento

Objectivos:

- Motivar al personal
- Mejorar los conocimientos
- Capacitar

Pasos

1: ¿Cuántas personas?
2: ¿Dónde y cuándo se lleva a cabo?
3: ¿Quién estará a cargo?
4: ¿Cuántos recursos son necesarios?

14

Aquisición y suministro de suplementos

- Agregar vitamina A a la lista de medicamentos esenciales
- Estimar las cantidades necesarias
- Adquirir y almacenar los suministros
- Abastecer inicialmente los puntos de distribución y reabastecerlos.

70

Supervisión y evaluación

- **Cobertura**
  - % de niños y madres que recibieron dosis
  - % casos tratados
- **Suministros**
  - Cantidades recibidas y saldos en comparación con la población elegible
  - % de lugares de distribución con suministros ininterrumpidos para cada período de 12 meses
- **Capacitación**
  - % de personal de distribución capacitado
  - % de supervisores capacitados
  - % de personas capacitadas en comparación con los planes

Educación sobre nutrición

... puede aumentar el impacto de los suplementos de la siguiente manera...

- Fomenta la participación en los programas de suplementos
- Estimula mejoras de los hábitos alimentarios

BEST AVAILABLE COPY

Desarrollo del programa

Pasos:

- Determinar la prevalencia y distribución de la deficiencia
- Identificar la discontinuidad en la cobertura de los programas existentes para la vitamina A
- Determinar qué personas y cuántas conforman la población objectivo para la distribución de suplementos
- Identificar los canales de distribución y asignar las funciones

Desarrollo del programa (continuación)

Pasos:

- Desarrollar un sistema de adquisición y abastecimiento de los suplementos
- Determinar las necesidades de capacitación
- Formular y poner en práctica las normas técnicas
- Evaluar y modificar el programa

REDUCED MORTALITY AMONG CHILDREN IN SOUTHERN INDIA RECEIVING A SMALL WEEKLY DOSE OF VITAMIN A

LAXMI RAHMATHULLAH, M.B., B.S., D.T.P.H., BARBARA A. UNDERWOOD, PH.D., RAVILLA D. THULASIRAJ, M.B.A., ROY C. MILTON, PH.D., KALA RAMASWAMY, M.SC., RAHEEM RAHMATHULLAH, AND GANEESH BABU, B.COM.

Abstract *Background.* Clinical vitamin A deficiency affects millions of children worldwide, and subclinical deficiency is even more common. Supplemental vitamin A has been reported to reduce mortality among these children, but the results have been questioned.

Methods. We conducted a randomized, controlled, masked clinical trial for one year in southern India involving 15,419 preschool-age children who received either 8.7 μmol (8333 IU) of vitamin A and 46 μmol (20 mg) of vitamin E (the treated group) or vitamin E alone (the control group). Vitamin supplements were delivered weekly by community health volunteers who also recorded mortality and morbidity. Weekly contact was made with at least 88 percent of the children in both study groups. The base-line characteristics of the children were similar and documented a high prevalence of vitamin A deficiency and undernutrition.

Results. One hundred twenty-five deaths occurred, of which 117 were not accidental. The risk of death in the group treated with vitamin A was less than half that in the control group (relative risk, 0.46; 95 percent confidence interval, 0.30 to 0.71). The risk was most reduced among children under 3 years of age (6 to 11 months — relative risk, 0.28; 95 percent confidence interval, 0.09 to 0.85; 12 to 35 months — relative risk, 0.46; 95 percent confidence interval, 0.26 to 0.81) and among those who were chronically undernourished, as manifested by stunting (relative risk, 0.11; 95 percent confidence interval, 0.03 to 0.36). The symptom-specific risk of mortality was significantly associated with diarrhea, convulsions, and other infection-related symptoms.

Conclusions. The regular provision of a supplement of vitamin A to children, at a level potentially obtainable from foods, in an area where vitamin A deficiency and undernutrition are documented public health problems contributed substantially to children's survival; mortality was reduced on average by 54 percent. (N Engl J Med 1990; 323:929-35.)

TWENTY to 40 million children worldwide are estimated to have at least mild vitamin A deficiency, and nearly half are said to reside in India.[1] Controlled field trials in an area of endemic vitamin A deficiency in Indonesia revealed a reduction of 34 percent in mortality among infants and young children given high-dose vitamin A supplements,[2] and a reduction of up to an estimated 75 percent[3] after periodic mass treatment with large-dose (209 μmol [200,000 IU]) vitamin A. Reductions in mortality of 11 to 45 percent were reported after the normal marketing of vitamin A–fortified monosodium glutamate.[4] The results of these studies and an earlier observational trial in Indonesia[5] have been questioned because of aspects of the study designs[6] and because the mortality data provided no cause-specific information and were obtained retrospectively, assuming compliance.[4]

Clarifying the role of vitamin A deficiency in child health and survival and defining successful, sustainable control measures have broad public health, public policy, and programmatic importance. For this reason, we conducted a randomized, placebo-controlled, masked clinical trial among 15,419 preschool-age children using a small, weekly dose of vitamin A (8.7 μmol [8333 IU]) given directly to the children by community health volunteers. We monitored morbidity and mortality weekly for one year. The dose of vitamin A was meant to simulate the amount that could be obtained from food, if food consumption was near the level recommended by international groups (approximately 1 to 1.4 μmol [300 to 400 μg] of vitamin A daily[7,8]).

METHODS

The study was carried out in three drought-prone, economically and environmentally deprived *panchayat* unions (local-government areas) in the Trichy district of Tamil Nadu in southern India. The people of the area had been underserved by child-care programs, including the national program of administering a large-dose (209

From the Aravind Children's Hospital and Aravind Eye Hospital, Madurai, India (L.R., R.D.T., K.R., R.R., G.B.); the Office of International Programs (B.A.U.) and the Biometry and Epidemiology Program (R.C.M.), National Eye Institute, Bethesda, Md. Address reprint requests to Dr. Underwood at the National Eye Institute, Bldg. 31, Rm. 6A-17, 9000 Rockville Pike, Bethesda, MD 20892.

Supported by a grant from the Ford Foundation, New Delhi, India.

Reprinted from the *New England Journal of Medicine* 323:929-935 (October 4), 1990

μmol) supplement of vitamin A every six months. A survey of all children under 60 months of age in the study area revealed that only 1 percent had participated in this program.

The study was reviewed and approved by the human-subjects internal review boards of the Indian Council of Medical Research and the Aravind Eye Hospital. Informed consent was obtained from the leaders of the *panchayat* unions and then from the individual families at the time of the base-line survey.

Survey Personnel and Procedures

All the communities within the areas selected for study were mapped by locally recruited enumerators. A house-by-house demographic and socioeconomic survey was carried out by specially trained local workers, who also obtained from each mother a five-year history of mortality among her preschool-age children. Households with children under 60 months of age were identified and assigned a census number.

Two medical-examination teams were formed, consisting of a medical officer, nurses, and child-care and social workers. The child-care and social workers were trained to undertake ocular examinations, anthropometric measurements, and a morbidity history. The ocular examination was checked by the medical officer who conducted the medical examination and verified the morbidity history. The ocular examination was repeated by the same trained fieldworkers after six months of intervention, and all the indexes measured at base line were reassessed by the medical teams at the end of the study.

A finger-prick blood sample and a dietary history detailing the frequency of intake of locally available foods containing vitamin A[7] were obtained from a randomly selected 2 percent of the children by specially trained community workers.

At the base-line medical examination, all the children with symptoms of xerophthalmia, including night blindness, were treated with a large-dose combination of vitamin A (209 μmol) and vitamin E (46 μmol), and they continued to be followed as part of the study. The data were analyzed both including and excluding them. Children with symptoms of xerophthalmia at the six-month and final ocular examinations were treated in a similar manner. All the children were given the large-dose supplement during their final medical examination at the end of the study.

The children's height (or length for those under 24 months) was measured to the nearest centimeter with a calibrated board. Weight was determined to the nearest 0.1 kg with a hanging Salter scale.

The ocular examination was performed with the classification criteria of the World Health Organization.[8] A history of night blindness was obtained by interviewing the mother about the incidence in her children of *malai ken*, a term used in Tamil Nadu to describe the commonly recognized symptom of "evening eyes," the inability to see well in dim light. The same term was subsequently used by the community health volunteers to monitor the occurrence of night blindness on a weekly basis.

Fieldworkers were aware that they were involved in a study to determine the effect on morbidity of giving vitamins, but they were not told that the study was specifically one of vitamin A or that mortality was an outcome variable.

Randomization

Because of the varied population density in the *panchayat* unions, we used a cluster-sampling design. From the 15,419 children identified and examined at base line, 206 clusters were formed on the basis of the minimal and maximal workloads that could be expected from the community health volunteers. The majority of clusters consisted of 50 to 100 children 6 to 60 months of age. The clusters were arranged according to population size; after a random start, they were assigned alternately to the treated or control groups. The adequacy of randomization in achieving matching according to base-line data was checked for the following characteristics: age and sex distribution, one-month history of diarrhea and respiratory disease, anthropometric indexes of nutritional status, xerophthalmia status, five-year retrospective history of mortality of children under five, household economic and hygienic status, and serum retinol levels. Matching was satisfactory at base line for all the variables examined.

Implementation and Management

Community health volunteers were trained to dispense the supplement, collect morbidity data, and record mortality according to a standard procedure. The volunteers visited each home assigned to them every week for 52 weeks. During the visits they recorded illnesses according to symptoms and duration and checked for any deaths. They dispensed the appropriate liquid supplement directly into the mouth of the study child from a calibrated, color-coded amber bottle. Community health volunteers knew that they were responsible for dispensing from one color-coded bottle, but they were unaware of what it contained other than vitamins.

Trained supervisors were each assigned to oversee seven or eight community health volunteers. The supervisors were responsible for weekly meetings with the volunteers to verify the completeness of the morbidity-data forms for the previous week and to review their proper use. The supervisors also collected the dispensers each week and distributed refilled bottles. In addition, they checked the accuracy of the data gathered from a random 5 percent of the households weekly.

A block officer met every week with the supervisors to review the forms and procedures, discuss problems, and provide refilled bottles for delivery to the community health volunteers. The supervisors were informed weekly of the performance — in terms of rates of contact and accuracy in data recording — of the community health volunteers for whom they were responsible. Evidence of problems was sought and the difficulties were remedied within a two-week period. Unannounced spot checks on households were conducted by block officers and headquarters staff.

Data were verified and then recorded on diskettes with use of portable computers in the field offices. The diskettes were sent weekly to the headquarters office, where they were again checked for completeness and accuracy. The procedures for personnel and data management allowed close surveillance and a two-week feedback to the field staff regarding their performance, thus giving them time to correct any possible errors.

Supplements

Liquid supplements (kindly provided by Hoffmann-LaRoche, Basel, Switzerland) were provided in color-coded aluminum cans containing approximately 1 liter each. The appearance and taste of the solutions were identical. The solution containing vitamin A was prepared to contain approximately the following: 8.7 μmol (8333 IU or 2500 μg) of vitamin A palmitate and 46 μmol (20 mg) of vitamin E per milliliter dissolved in peanut oil. The placebo solution contained approximately 46 μmol (20 mg) of vitamin E per milliliter dissolved in peanut oil.

The stability of the solutions was checked by Hoffmann-LaRoche initially and after 1, 3, 6, and 12 months of storage, at room temperature, 35°C, and 45°C, in both the dispenser bottles and the aluminum flasks. In the flasks there was no loss of vitamin A and about a 10 percent loss of vitamin E, and in the bottles there was a loss of less than 5 percent of vitamin A after one year or less at room temperature and at 35°C. Stability was also checked by randomly withdrawing dispensers from the study areas halfway through and at the end of the study. The field-laboratory analyses, done approximately 18 to 24 months after the supply had been received in India and used under the conditions of storage prevailing in the field, revealed a vitamin A loss of approximately 25 percent.

Data Monitoring

Six months after the weekly distribution began, a data-monitoring committee reviewed the data, summarized according to dose color code only. No one associated with the study was aware of the color code, which was held by Hoffmann-LaRoche until the study ended. Although differences were evident in the mortality trends of the study groups after six months, they could not be associated

76

unambiguously with the incidence, severity, or duration of morbidity. The committee concluded that the study should continue.

Statistical Analysis

Randomization according to cluster rather than according to child introduced a moderate increase (about 30 percent) in the variance of the estimators of the relative risk of death in the treated group as compared with the control group. Relative risks, significance, and confidence intervals were therefore calculated according to the cluster design.[7] The risk of death among the controls was used as the reference value for relative risk of death: a relative risk of 0.5 means that the risk in the treated group was half that among the controls, or conversely, that the risk among the controls was twice that in the treated group. All ages were adjusted to reflect age at the start of the intervention, which began on the same date for all the children.

Nutritional status was assessed with use of the CASP anthropometric software package (version 3.0) provided by the U.S. Centers for Disease Control. Values more than 2 SD below the reference value were considered abnormal.

Results

Mortality data and associated morbidity are reported here. An analysis of morbidity in the 15,419 children is currently under way.

Contact with the Children

During each of the 52 weeks of the study, at least 88 percent of the children were contacted. There was no difference in rates of contact between the treated and control groups. The reasons for lack of contact (of which some children had more than one) included moving from the study area (10 percent), temporary absence (13 percent), refusal to participate (28 percent), sickness (29 percent), and other reasons (30 percent). Table 1 summarizes the study contact and compliance in terms of the number of weeks the dose was missed. Nearly 42 percent of the children received all the doses. For those in the treated group, this was equivalent to more than 453 μmol (433,000 IU) of vitamin A, or approximately the amount available in the commonly used large-dose supplement (209 μmol every six months). More than 90 percent of the children received at least 322 μmol (307,000 IU), which is equivalent to more than 70 percent of what they would have received in a large-dose supplement.

Base-Line Characteristics

Sex, age, xerophthalmia status, serum retinol level, and nutritional status at base line are shown in Table 2. There were no substantial differences in these indexes between the control and treated groups. Although the study was meant to include only children from 6 to 60 months of age, birth records were unavailable, and our recall records include a small number of younger (1.8 percent) and older (5.4 percent) children.

The base-line prevalence of xerophthalmia was 11 percent. The risk of xerophthalmia did not differ according to sex, except for a slight predominance among boys after three years of age. Thirty-seven percent of the serum retinol values from the randomly sampled subgroup (n = 280) were ≤0.70 μmol per liter, and 21 percent were ≤0.35 μmol per liter. The prevalence of vitamin A deficiency in each of the clinical and biochemical categories thus exceeded the World Health Organization's criteria for a public health problem.[9] Seven cases of active corneal involvement (category X2, X3A, or X3B) were seen

Table 1. Doses Missed and Minimal Amount of Vitamin A Received during 52 Weeks of Intervention.

No. of Doses Missed	Percent of Children (N = 15,419)	Minimal Amount Received*
		μmol (IU)
0	41.8	453 (433,000)
1–5	38.7	410 (390,000)
6–10	6.9	366 (349,000)
11–15	3.2	322 (307,000)
16–20	2.0	279 (266,000)
21–26	1.7	227 (216,000)
27–31	0.7	183 (174,000)
>31	5.0	

*The minimal amount received was calculated with the following equation: 453 μmol − (maximal number of doses missed × 8.7 μmol) = minimal amount received.

Table 2. Base-Line Characteristics of the Study Population.

Characteristic	Percentage of Children
Sex	
Male	52
Female	48
Age (mo)*	
≤5	1.8
6–11	7.1
12–23	20.0
24–35	21.2
36–47	22.1
48–60	22.4
61–71	5.4
Xerophthalmia status†	
XN	3.7
X1B	7.2
X2, X3A, X3B	0.05
XS	0.07
Serum retinol (μmol/liter)	
≤0.35	21.4
0.351–0.70	16.1
0.701–1.05	16.4
>1.05	46.1
Nutritional status‡	
Stunted	31
Wasted	23
Stunted and wasted	18
Normal	25
Unknown	3

*Age at the start of intervention.

†XN indicates night blindness, X1B Bitôt's spot, X2 corneal xerosis, X3A corneal ulceration or keratomalacia of less than one third of the corneal surface, X3B corneal ulceration or keratomalacia of one third or more of the corneal surface, and XS corneal scar.

‡As determined with the CASP anthropometric software package. Stunted indicates height for age < the mean minus 2 SD and weight for height ≥ the mean minus 2 SD; wasted indicates height for age ≥ the mean minus 2 SD and weight for height < the mean minus 2 SD; stunted and wasted indicates height for age < the mean minus 2 SD and weight for height < the mean minus 2 SD; and normal indicates height for age ≥ the mean minus 2 SD and weight for height ≥ the mean minus 2 SD.

11

(four in the control group and three in the treated group). Night blindness accounted for about one third and Bitôt's spots for about two thirds of the milder cases of xerophthalmia.

Seventy-two percent of the children were classified by anthropometry as undernourished (defined as more than 2 SD below the reference mean). Approximately one third of the children were stunted, 18 percent stunted and wasted, and 23 percent wasted (Table 2). Stunting thus affected a somewhat larger proportion of the children than wasting, indicating that prolonged malnutrition was more common than acute undernutrition among the study children.

The five-year history of mortality among children under five years of age taken at base line was not significantly different between families of control and families of treated children (data not shown).

Mortality Outcome

There were 125 deaths in the study population during the 52 weeks of surveillance, for an overall mortality rate of 8.1 per 1000. Eight of these deaths, however, involved accidents unrelated to symptoms that could have been associated with the intake of vitamin A: animal bite (two deaths), drowning (three), poisoning (one), and falling (two). Five of the accidental deaths were in the treated group and three in the control group.

Figure 1 shows the cumulative deaths according to study group. Regardless of treatment, girls were at somewhat higher risk of death than boys, but not significantly so (relative risk, 1.5 in the control group and 1.2 in the treated group). Vitamin A significantly reduced the risk of death for both sexes, the effect being somewhat larger for girls (relative risk, 0.41 for girls [$P<0.01$] and 0.52 for boys [$P<0.05$]).

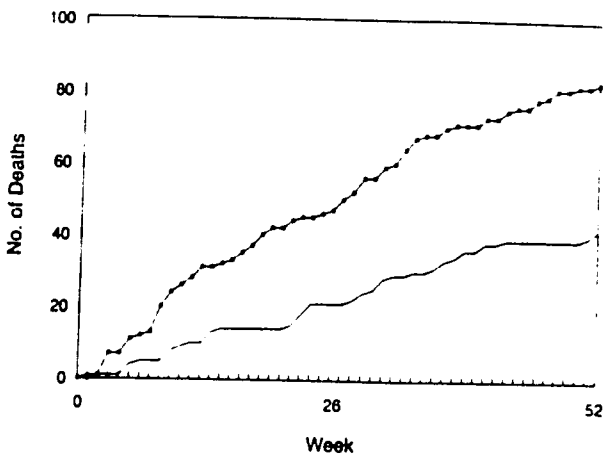


Figure 1. Cumulative Deaths Monitored Weekly, According to Study Group.

The solid line represents the group treated with vitamin A, and the line broken by squares the control group. Children who died in accidents (five in the treated group and three in the control group) are included.

Table 3 shows the mortality according to age and study group for the 117 nonaccidental deaths. The risk of death in the group receiving vitamin A was 46 percent of that in the control group. The relative risk was reduced most for infants (relative risk, 0.28; 95 percent confidence interval, 0.09 to 0.85) and those 12 to 35 months of age (relative risk, 0.46; 95 percent confidence interval, 0.26 to 0.81); it was less than 1.0 in all age groups. Excluding the children who had received the high-dose supplement at any time or who received it only at base line did not substantially change the age-specific relative risks shown in Table 3. In addition, these relative risks were not significantly changed by excluding those who did not receive the study supplements for more than seven consecutive weeks (n = 1863) or those who did not receive the supplements for more than four weeks on four occasions (n = 11). These exclusions were designed to minimize any possible confounding due to a differential participation effect or missing the supplements for a prolonged period.

Among the nonaccidental deaths, 18 occurred among children with xerophthalmia at base line. All 18 occurred in children over 12 months of age (12 children in the control group and 6 in the treated group). The death rate among children with xerophthalmia was 10.6 per 1000, as compared with 7.2 per 1000 among the children without xerophthalmia.

Table 4 shows the symptom- and disease-specific relative risk of death in the treated and control groups. According to the "verbal autopsy," there were too few deaths specifically associated with the symptoms of respiratory disease and malnutrition to provide a reliable relative risk. Excluding these two categories of symptoms, the relative risk was consistently lower for the treated group — and significantly so, except for deaths associated with measles. More than 40 percent of the deaths were associated with diarrhea, 16 percent with measles, and the remainder with symptoms suggesting other infections.

Table 5 shows the mortality according to treatment group and base-line nutritional status. Data on nutritional status were missing for 469 children (3 percent), among whom 7 died (6 in the control group and 1 in the treated group). Among the children not treated with vitamin A (the control group), the death rate of those who were both stunted and wasted was 1.5 to 2 times higher than the death rate of those who were either stunted or wasted, and it was 2.7 times higher than the rate of normal children. Thus, the risk of death was increased by acute undernutrition superimposed on chronic malnutrition. But the effect of treatment with vitamin A was pronounced (relative risk, 0.11; $P = 0.01$; 95 percent confidence interval, 0.03 to 0.36) among stunted children, whereas it was not significant among wasted, stunted and wasted, or normal children.

A hierarchical log-linear model was used to assess the multivariate relation among death, treatment, age,

18

sex, and nutritional status. The significant association between treatment and death persisted when adjusted simultaneously for age, sex, and nutritional status.

Discussion

The results of this community-based, masked controlled field trial clearly indicate that in an area where clinical vitamin A deficiency and chronic undernutrition are common, ensuring a constant consumption of vitamin A at least equivalent to the recommended dietary allowance enhanced children's survival. In Indonesia, somewhat similar effects among preschool-age children (a 45 percent reduction in mortality) were reported with vitamin A–fortified monosodium glutamate when it was a consistent part of the food supply.[1]

For the one-year follow-up period the overall mortality rate among children 6 to 60 months of age was 8.1 per 1000 in our study, comparable to the 7.8 per 1000 for the 12- to 71-month age group reported by the Aceh, Indonesia, study.[2] It was higher, however, than the 5 per 1000 reported from an area near Hyderabad, India, where a placebo-controlled, blinded trial with a high-dose supplement has also been performed.[12] These rates are considerably below the 20 per 1000 reported as the national average for India.[12] We monitored infant mortality in the study area for a one-year period in 1988 and 1989 and obtained a rate of 64 per 1000, a figure somewhat lower than the 83 per 1000 reported for Tamil Nadu in 1982[13] and the 98 per 1000 for India generally.[14] The mortality rate among infants less than 6 months old was 42 per 1000 live births, and among those 6 to 11 months old it was 22 per 1000. We were unable to find any reliable information on mortality rates among one-to-five-year-olds in Tamil Nadu. The lower mortality figures we report undoubtedly reflect in part the well-recognized effect of the frequent contact of households with trained fieldworkers.[12,15] Nonetheless, because the contact was comparable in our two study groups, the efficacy of vitamin A supplementation at the level of the recommended dietary allowance in reducing mortality by 54 percent remains evident; mortality rates were 10.5 per 1000 in the control group as compared with 4.8 per 1000 in the treated group.

We found an insignificant sex-related difference in the risk of death without regard to treatment. Treatment with vitamin A reduced the risk of mortality in both sexes, but the reduction was somewhat greater among girls. This finding contrasts with that reported from Indonesia, in which a significant treatment effect of large-dose supplementation was found only in boys, among whom the prevalence of xerophthalmia was also higher.[2] In our study, the prevalence of xerophthalmia at base line was not significantly different between the sexes until after three years of age, whereas the effect on mortality of treatment with vitamin A was pronounced among the younger groups.

The efficacy of our low-dose supplementation was considerably higher than the 34 percent reduction in mortality reported after high-dose supplementation in Indonesia as determined by intention-to-treat analy-

Table 3. Mortality, According to Age and Study Group.

Age and Study Group	No. of Children	No. of Deaths	Cumulative Mortality Rate	Relative Risk*
0–11 Mo				
Control	678	14	0.021	0.28 (0.09, 0.85)†
Treated	689	4	0.006	
12–35 Mo				
Control	3185	52	0.016	0.46 (0.26, 0.81)‡
Treated	3179	24	0.008	
≥36 Mo				
Control	3792	14	0.004	0.63 (0.26, 1.50)
Treated	3896	9	0.002	
Total				
Control	7655	80	0.010	0.46 (0.29, 0.71)‡
Treated	7764	37	0.005	
Age-adjusted total				0.46 (0.30, 0.71)‡

*Relative risk for the treated group, as compared with the control group. Values in parentheses are 95 percent confidence limits.
†P = 0.05
‡P = 0.01

Table 4. Symptom- and Disease-Specific Mortality, According to Treatment Group.

Symptoms or Disease	Control Group	Treated Group	Relative Risk*
	No. of children		
Measles	12	7	0.58 (0.17, 1.92)
Diarrhea	33	16	0.48 (0.24, 0.96)†
Respiratory	3	2	—
Malnutrition	1	3	—
Convulsions	12	3	0.25 (0.07, 0.85)†
Other	19	6	0.31 (0.12, 0.78)†
Total deaths	80	37	

*Relative risk for the treated group, as compared with the control group. Values in parentheses are 95 percent confidence limits.
†P = 0.05.

Table 5. Mortality, According to Nutritional Status.*

Nutritional Status and Study Group	No. of Children	No. of Deaths	Cumulative Mortality Rate	Relative Risk†
Unknown				
Control	201	6	0.030	0.13 (0.01, 1.14)
Treated	268	1	0.004	
Stunted				
Control	2385	27	0.011	0.11 (0.03, 0.36)‡
Treated	2418	3	0.001	
Wasted				
Control	1806	14	0.008	0.72 (0.30, 1.72)
Treated	1798	10	0.006	
Stunted and wasted				
Control	1373	22	0.016	0.65 (0.30, 1.41)
Treated	1340	14	0.010	
Normal				
Control	1890	11	0.006	0.80 (0.32, 2.00)
Treated	1940	9	0.005	

*The categories of nutritional status are defined in Table 2.
†Relative risk for the treated group, as compared with the control group. Values in parentheses are 95 percent confidence limits.
‡P = 0.01.

79

sis,[2] but lower than the estimated 75 percent reduction reported with an analysis based on actual receipt of the capsules.[3] The estimate based on receipt of the capsules was derived from a total of only 18 deaths over a four-month follow-up period. As the authors noted, its validity awaits verification by a study that ensures consistent, periodic verification of compliance in taking the large-dose supplement, which has not been a feature of most large-scale programs to date.[16]

Vitamin A was most efficacious in children under three years of age, most prominently in infants. This finding contrasts with reports from Indonesia. In the Aceh study the effect of treatment was most marked among those 60 to 71 months old,[2] and in the study involving vitamin A–fortified monosodium glutamate, mortality was reduced by 11 percent among infants and 45 percent among preschoolers.[4] In the monosodium glutamate study the infants probably received a considerable portion of their food as breast milk, and the effect of the program would therefore be expected to be less. The reasons for the discrepancy between our results and those of the Aceh study are less clear but may be related to the relative level of underlying malnutrition in the two study populations. Our base-line prevalence of xerophthalmia was 11 percent, as compared with about 1 to 2 percent in Indonesia, and only 25 percent of the Indian children had normal anthropometric features, whereas at least 40 to 69 percent of the Indonesian children were classified within 10 percent of the median standards of the U.S. National Center for Health Statistics.

In accordance with many reports from developing countries where vitamin A deficiency is endemic, diarrhea was associated with the highest number of deaths, followed by measles and symptoms associated with other infections — convulsions, jaundice, and encephalitis, for example. The protective effect of vitamin A was significant for all these conditions except measles. This finding contrasts with hospital-based case–control reports from Africa, in which the protective effect of very large doses of vitamin A was exceptionally high in measles.[17,18] Previous studies suggest that measles is a less severe disease in India than in Africa, and that factors other than vitamin A — the severity of concurrent malnutrition, for example — may be a more critical determinant of measles-associated morbidity and mortality.[19,20] It may also be that a large dose of vitamin A is required to prevent a fatal outcome in severe measles complicated by vitamin A deficiency.

Prolonged undernutrition, as evidenced by stunting, characterized nearly one third of the children in our study at base line, and a continuous supply of vitamin A reduced the risk of dying to one-ninth that of the controls. The protective effect of vitamin A was unremarkable in children with wasting, an indicator of acute malnutrition, and in those with normal anthropometric features. Stunting reflects — in addition to an inadequate food supply — many characteristics of social deprivation that are frequently found in poor households. Our data suggest that these persistent ecological and physiologic insults undermine the ability of a child who is deficient in vitamin A to ward off a fatal outcome when confronted by an infection. The programmatic implication of this is that maximal reductions in mortality can be expected from vitamin A prophylaxis targeted to children who are chronically undernourished and to those with superimposed acute malnutrition.

Children with xerophthalmia are reported to be at 4 to 12 times the risk of death of neighboring children with normal eyes, and the risk increases with the increasing severity of symptoms.[5] The mortality rate among children with xerophthalmia in our study was about 50 percent higher than among children without the condition (7.2 vs. 10.6 per 1000). When we adjusted for those who received a large dose of vitamin A because of xerophthalmia, the treatment effect of the continued small dose persisted — that is, half as many died among those who continued to receive the weekly supplement as among those who did not.

Sommer et al.[2] noted that daily consumption of the recommended dietary allowance was the ideal approach to vitamin A prophylaxis, but considered it to be impractical from a programmatic point of view and chose distribution of the large-dose capsule every six months instead. Sommer et al. subsequently commented that the single most important limitation to achieving the maximal effect with large-dose capsules was inadequate contact and verification of compliance[3]; the large-dose approach requires careful monitoring of distribution channels to avoid possible overdosing. In contrast, our approach involving frequent low doses showed that when the supplement is provided at a safe dosage level in an easily dispensed form, community workers can be effective in attaining high rates of contact and verification if there is also an appropriate managerial and supervisory system. Importantly, the efficacy of supplementation at the level of the recommended dietary allowance suggests that a similar effect could be achieved by an equivalent supply of vitamin A from foodstuffs, an approach that would potentially address other nutritional deficiencies as well.

References

1. United Nations Administrative Committee on Coordination–Subcommittee on Nutrition. First report on the world nutrition situation. Geneva: United Nations, 1987:36.
2. Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. Lancet 1986; 1:1169-73.
3. Tarwotjo I, Sommer A, West KP Jr, Djunaedi E, Mele L, Hawkins B. Influence of participation on mortality in a randomized trial of vitamin A prophylaxis. Am J Clin Nutr 1987; 45:1466-71.
4. Muhilal, Permesih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. Am J Clin Nutr 1988; 48:1271-6.
5. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. Lancet 1983; 2:585-8.

80

6. Subcommittee on Vitamin A Deficiency Prevention and Control. Food and Nutrition Board, National Research Council. Vitamin A supplementation: methodologies for field trials. Washington, D.C.: National Academy Press, 1987.
7. Requirements of vitamin A, iron, folate and vitamin B_{12}: report of a Joint FAO/WHO Expert Consultation. No. 23 of FAO food and nutrition series. Rome: Food and Agricultural Organization of the United Nations, 1988.
8. Subcommittee on the Tenth Edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. Recommended dietary allowances. 10th ed. Washington, D.C.: National Academy Press, 1989.
9. Underwood BA, Chavez M, Hankin J, et al. Guidelines for the development of a simplified dietary assessment to identify groups at risk for inadequate intake of vitamin A. In: Report of International Vitamin A Consultative Group (IVACG)®. Washington, D.C.: International Life Sciences Institute–Nutrition Foundation, 1989.
10. Control of vitamin A deficiency and xerophthalmia: report of a joint WHO/UNICEF/USAID/Helen Keller International/IVACG meeting. WHO Tech Rep Ser 1982; 672:1-64.
11. Cochran WG. Sampling techniques. 2nd ed. New York: John Wiley, 1963:65.
12. Gopalan C. Vitamin A and child mortality. Nutr Found India Bull 1990; 11:1-3.
13. UNICEF. 1988 Asian and Pacific atlas of children in national development. Thailand: Viscom Center Ltd., 1987.
14. The state of the world's children 1990. New Delhi, India: Oxford University Press for UNICEF, 1990:76.
15. Gopalan C. Vitamin A deficiency and child mortality. Nutr Found India Bull 1986; 7:1-2.
16. Underwood BA. Vitamin A prophylaxis programs in developing countries: past experiences and future prospects. Nutr Rev 1990; 48:265-74.
17. Barclay AJG, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomised clinical trial. BMJ 1987; 294:294-6.
18. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. N Engl J Med 1990; 323:160-4.
19. Reddy V, Bhaskaram P, Raghuramulu N, et al. Relationship between measles, malnutrition, and blindness: a prospective study in Indian children. Am J Clin Nutr 1986; 44:924-30.
20. Markowitz LE, Nzilambi N, Driskell WJ, et al. Vitamin A levels and mortality among hospitalized measles patients, Kinshasa, Zaire. J Trop Pediatr 1989; 35:109-12.

©Copyright, 1990, by the Massachusetts Medical Society
Printed in the U.S.A.

81

THE NEW ENGLAND JOURNAL OF MEDICINE is published weekly in the English language by the Massachusetts Medical Society (Waltham, MA, USA). Material printed in the *Journal* is covered by copyright. No part of this reprint may be reproduced or transmitted in any form without written permission. All rights reserved. Direct permission requests to the Permissions Department at the USA subscription office. Editorial office: 10 Shattuck Street, Boston, MA 02115, USA. **SUBSCRIPTIONS:** Subscription offices: 1440 Main Street, Waltham, MA 02154-1649, USA; P.O. Box 1123, Commerce Court Postal Station, Toronto, Ontario M5L 1K1, Canada; and Saxon Way, Melbourn, Royston, Herts SG8 6NJ, UK. Subscription prices: USA: $79 per year (interns, residents $47 per year; students $41 per year). Outside USA: Canadian dollars drawn on a Canadian bank: C$122 per year (interns, residents C$88 per year; students C$73 per year). Pounds sterling drawn on a UK bank: £75 per year (interns, residents, and students £51 per year). US dollar payments accepted at current rate of exchange pro rata to the pound. Payments and correspondence for all subscriptions delivered to Japan should be sent directly to Nankodo Co., Ltd., 42-6, Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan. Rates are subject to change without notice. Sample copies available on request.

HEALTH POLICY AND PLANNING; 8(4): 339-348 © Oxford University Press 1993

Costs of vitamin A supplementation: the opportunity for integration with immunization in Ghana

DYNA C ARHIN[1,2] DAVID A ROSS[1,3] AND FRANCISCA KUFOUR[2]

[1]London School of Hygiene and Tropical Medicine, UK, [2]Planning Unit, Ministry of Health, Accra, Ghana and [3]Ghana Vitamin A Supplementation Trials (VAST), Navrongo, Ghana

Health service information intended for the planning and/or monitoring of district health programmes should be up to date, precise and obtained by judicious use of available resources. Employing a rapid assessment type of design, this study quickly and inexpensively investigated the cost implications of integrating vitamin A supplementation with immunization. It also assessed its potential for achieving adequate supplementation coverage. The study was conducted in the Bolgatanga-Frafra district of northern Ghana in 1991. The average health service cost per child for full immunization plus vitamin A supplementation was US$6.47. The additional cost of providing vitamin A to a fully immunized child in Bolgatanga-Frafra district, using a mobile clinic approach that provided integrated curative and preventive maternal and child health care, including immunization, was US$0.02. There was no additional monetary cost to the patient and an average additional indirect cost to the patient of two minutes in waiting time. The study concluded that the pattern of utilization of immunization services in the district presented an opportunity for achieving significant vitamin A supplementation coverage.

Introduction

Based on WHO's recommended minimum prevalence criteria,[1] xerophthalmia (which literally means 'dry eye' and applies to all the ocular manifestations of vitamin A deficiency) is an established public health problem in more than 20 countries. These countries are mainly in the tropical and subtropical regions of Asia, Africa and central and south America.[2] Large inter- and intra-country variations in the pattern of deficiency exist and are a reflection of the ecological, economic and cultural differences between the areas. Consequently, control measures and outcome expectations need to be specific to localities. In communities that have significant levels of deficiency, the long-term aim will be to ensure adequate dietary vitamin A by promoting the production and consumption of vitamin A rich foods (e.g. milk products, eggs, liver) and foods rich in vitamin A precursors (e.g. dark green leafy vegetables and orange non-citrus fruits). This will require strategies that improve relevant agricultural production, food storage and distribution and feeding practices. The target groups for dietary improvements are women and children, the groups most at risk of vitamin A deficiency. In the short term, however, WHO advocates vitamin A supplementation for children, and for mothers within four weeks after delivery, as an initial step in the control of vitamin A deficiency.[3]

Five recent community trials in Asia have shown significant reductions in child mortality to result from vitamin A supplementation.[4,5,6,7,8] Although two other trials have not confirmed these findings,[9,10] these results in conjunction with the evidence from observational studies[11,12,13,14] and clinical and community trials in Africa,[15,16,17,18] have led to calls for vitamin A programmes to be used as a child survival strategy, along with other child survival programmes.[19,20]

To justify the claim of vitamin A supplementation programmes to scarce health resources, the benefits of vitamin A supplementation relative to the cost of provision need to be comparable to, or higher than, those of competing child survival strategies. Economic evaluation techniques such as cost-benefit and cost-effectiveness analysis can be used to evaluate these alternatives. Economic analysis of different strategies for the delivery of vitamin A (using cost-effectiveness analysis) can also be undertaken in specific

83

operational settings to determine which approach is most cost-effective.

Where the strategy for supplementation involves integration with other existing health care programmes, the relevant measure of the opportunity cost for decision making is the marginal cost of expanding the activities to include vitamin A supplementation. For example, WHO's Expanded Programme on Immunization has proposed accelerating the delivery of vitamin A supplements by using immunization programmes.[21] For countries following the current WHO recommended childhood immunization schedule for developing countries,[22] the easiest way to implement this is to give vitamin A capsules with measles immunization at nine months. The other immunizations are scheduled to be given before 6 months of age and vitamin A supplementation dosage regimes for babies under 6 months have not yet been adequately tested in field trials. In WHO's proposals, however, it is noted that, in practice, some children do not receive some of the other immunizations (BCG, DPT and Polio) until after 6 months of age. The proposal suggests, therefore, that it may be possible to link supplementation to any of these immunizations when given after the child reaches 6 months of age.

To decide which immunization(s), if any, should be linked to supplementation and to be able to appraise the effectiveness of different linkages and different modes of integration, at least two types of information are necessary. Firstly, the percentage of target children being reached by the immunization programme should be assessed, and, secondly, the ages of contact with the immunization programme for the different vaccines established. It will then be possible to determine whether a specific immunization programme and its resulting utilization pattern provides the opportunity for vitamin A supplementation; that is, the extent of the 'window of opportunity'.

Study background and objectives

By early 1990, the health providers in the Bolgatanga-Frafra District had epidemiological evidence suggesting vitamin A deficiency was an important local public health problem. In 1989 a study of 16 568 children under six years of age in Kassena-Nankana District of the Upper East Region estimated a xerophthalmia prevalence rate of just over 1%.[23] This confirmed earlier reports from this region,[24] and suggested that the results of the five supplementation trials in Asia might be relevant to this area. In addition, information specific to northern Ghana was being collected in a controlled trial in the Kassena-Nankana District, which borders Bolgatanga-Frafra District. Once the results of this trial become available, district health planners will need to decide whether to institute routine supplementation for children in the district and, if so, to decide how to integrate this activity with the current routine health services. Information on the resource implications of such a policy would be required to make this decision rationally. It was also judged that additional information on which to base the coverage projections for integrated programmes of supplementation would be required to assist the decision making process. The study reported in this paper was therefore a response to these local planning concerns. It was undertaken in March 1991 by the government health services in Bolgatanga-Frafra District and the Upper East Region, the Ghana Vitamin A Supplementation Trials (VAST) Project, Navrongo, and the Health Economics and Financing Programme of the London School of Hygiene and Tropical Medicine.

The study had three short-term objectives. The first was to estimate the marginal cost of vitamin A supplementation to the health service and to the consumer, if supplementation was integrated with outreach child health activities, particularly immunization. The second short-term objective was to determine the percentage of children that would receive vitamin A supplementation between 6–11 and 6–23 months of age, if supplementation was linked with immunizations received during this period. These percentages would therefore represent the 'window of opportunity' for delivering vitamin A supplementation linked with immunization in the district. The final short-term objective was to provide up-to-date health service information for monitoring the district's immunization programmes.

The long-term objective was to provide the cost data for a cost-effectiveness analysis of vitamin A supplementation. The cost information from the study will be combined with the effectiveness findings of the controlled trials in the Kassena-

Nankana District to estimate the cost per death prevented by supplementation.

This paper reports the findings on immunization coverage, the age of immunization, and patient and health service costs that relate to integration of vitamin A supplementation with immunization activities. The estimated cost per death prevented by vitamin A supplementation will be reported elsewhere.

The study area

The Bolgatanga-Frafra District is in the guinea savannah woodland area of northern Ghana. The population was 237 393 in 1984 (National Population Census) with an annual growth rate of 2.0%, and a density of 124.7 per km^2. Most of the population are poor, subsistence farmers living in dispersed extended family 'compounds'. Access to vitamin A rich foods is relatively low. Western-type health care is provided by the government, Groups Outside the Government (GOG) and private practitioners. There is a government hospital (the regional hospital at Bolgatanga), 2 health posts, 2 private clinics, 1 Nutrition Rehabilitation Centre, 2 Maternal and Child Health units, and 2 mobile clinics (one run by the Catholic Church and the other by the Presbyterian Church).

Immunization of children in the district is provided by the Ministry of Health facilities (the hospital and health centres) and by the church health facilities, consisting mainly of mobile clinics. In addition, annual mass campaigns had been carried out by the Ministry of Health in the years preceding the study. Its 1990 mass campaign continued for several months and became known as the 'Out-reach EPI Service'. This EPI service only provided immunizations and the staff had not been trained or equipped to give curative care.

The Presbyterian Rural Health (PRH) team has been involved in health care activities in the district since 1978. The health work consists of training and supervision of village health workers, traditional birth attendants and community health worker trainers; mobile clinics for child health care and promotion, antenatal care and eye care; and a latrine programme. The mobile clinics are conducted either monthly or fortnightly in 14 villages, and weekly in Bolgatanga. During these clinics, a health team provides curative care, growth monitoring, nutrition education and immunization. In addition, capsules of vitamin A are given to children aged 6–59 months. The capsules contain 200 000 IU of vitamin A. Children under 12 months receive half a capsule and the older children one full capsule. The minimum interval between doses is six months and these are recorded in the child's Immunization/Road to Health chart which is retained by the mother. The Presbyterian Mobile Eye Clinic also gives out vitamin A, but only to treat xerophthalmia cases, and some of the village health workers trained and supported by the PRH programme also give prophylactic vitamin A.

Study methods

Household survey

Two-stage sampling was carried out using a cluster sampling technique.[25] The procedure used was based on that recommended by the EPI/WHO for assessing immunization coverage.[26] Sixty communities were selected at random from the 478 communities in the District. In each selected community, interviewers randomly selected the first compound and then advanced to the next closest compound until at least 7 children aged 6–23 months and at least 19 children 6–59 months were sampled for immunization and vitamin A histories respectively.

The guardians of children who were identified from their Immunization/Road-to-Health charts as having received either a vaccination and/or a vitamin A supplement within six months of the survey, were interviewed. Information was obtained about travel and waiting times, the monetary costs arising from the most recent clinic attendance and about their knowledge of the local foods rich in vitamin A. They were also asked questions to determine whether they associated low dietary intake of local foods rich in vitamin A with eye problems. The interviewers were 10 post-secondary school students, some of whom had previously been involved in similar district studies. They all spoke the local language and were supervised by a social scientist and a health worker, both Ministry of Health staff members.

85

Health services study

Observations of the staff time use, in relation to immunization and vitamin A supplementation of children, were made by the study team during outreach clinics by the PRH teams.

Records on clinic attendances, immunizations given and the 1990 expenditure accounts of the PRH programme were consulted. Interviews with staff of the programme provided additional information on expenditure and the allocation of personnel time to different activities. The immunization returns of the Ministry of Health, Bolgatanga District, were also obtained.

Analysis

Epi Info, version 5 (a public domain software programme developed by WHO, Geneva, and Centres for Disease Control, Atlanta, Georgia) was used to analyze the community survey data. In addition, life table analyses were done using SPSS/PC Version 4.0. The costing of PRH immunization and vitamin A activities was done using a computer spreadsheet package Quattro Pro Version 3.0.

Results: coverage and the 'window of opportunity'

The immunization and vitamin A supplementation histories of 443 and 1209 children, respectively, were obtained. The former group consisted of children aged 6–23 months, 388 (87.6%) of whom had their immunization information transcribed from their Immunization/Road-to-Health charts. Those without a valid chart were recorded as not having received any immunizations. The frequency and percentage coverage of BCG, 1–3 DPT, 1–3 oral polio and measles among children aged 12–23 months are shown in Table 1, without adjustments for immunizations given incorrectly according to the EPI schedule; for example measles given before the age of nine months.

At the end of 23 months, the probability of having dropped out between 1st and 2nd doses, and between 1st and 3rd doses of DPT was low. Full immunization with the EPI vaccines was delayed in a significant proportion of the children; 23% had achieved all the standard vaccines before the age of 12 months compared with 69% before 24 months. Cumulative proportions of children given polio vaccines were not estimated, because, in many cases, polio vaccinations were recorded in the Road-to-Health chart without dates, presumably because they were usually given at the same time as the equivalent dose of DPT.

Table 1. Immunization coverage

Vaccine		Coverage in children 12–23 months of age (Total = 305)		Cumulative proportion of children vaccinated before X months o age[a] (Total = 443)	
		n	%	X = 12	X = 24
BCG		267	87.5	0.78	0.94
DPT	1st	265	86.9	0.78	0.94
	2nd	239	78.4	0.65	0.92
	3rd	202	66.2	0.51	0.89
OPV	1st	260	85.2		
	2nd	240	79.5		
	3rd	205	67.2		
Measles		265	86.9	0.35	0.83
All standard vaccines received		198	64.9		0.69

[a] estimated by follow-up life table technique in SPSS/PC

The cumulative proportions of children vaccinated before each month of age are shown in Figure 1. Each cumulative proportion vaccinated is an estimate of the probability of being vaccinated before that age, and is estimated from follow-up life tables.[27] The proportion of children vaccinated between two ages is the difference between the two cumulative proportions.

The number of contacts at which an immunization was given between the ages of 6–11 months inclusive, was calculated for each child. Only children aged 12 months or older were included in this analysis (n = 302), since younger children could still have future contacts that would fall within this age range. The result is shown in Figure 2. Fifty five per cent of the children aged 12–23 months had had one or more contacts with the health services between the ages of 6 and 11 months that resulted in an immunization.

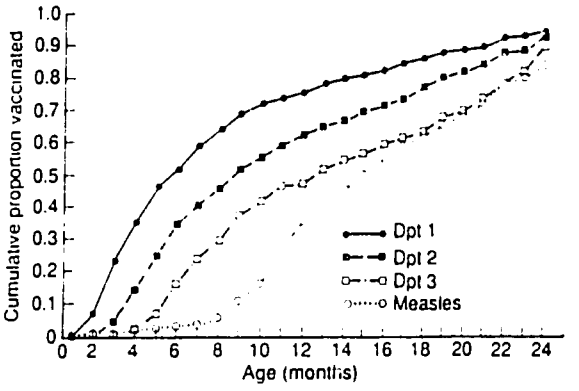


Figure 1. Probability of vaccination before a certain age[a]

[a] estimated by follow-up life table technique in SPSS+PC

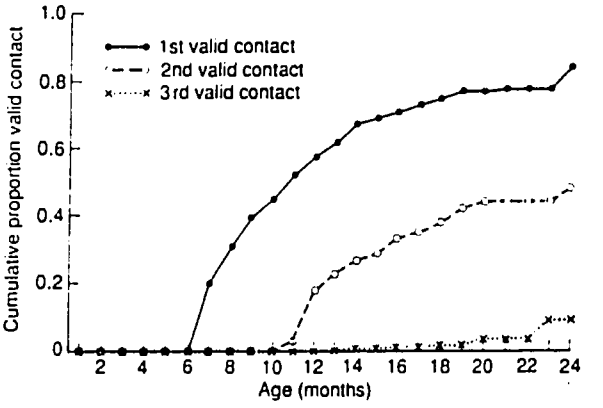


Figure 3. Probability of having a valid contact before a certain age

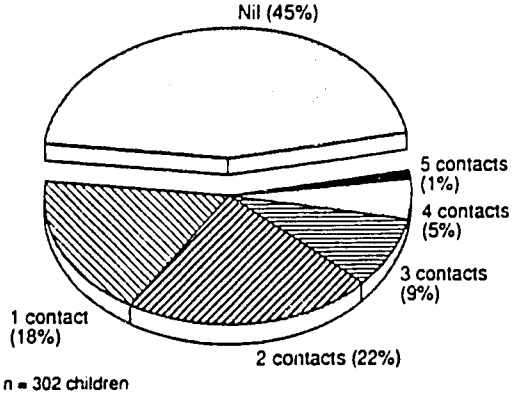


Figure 2. Immunization contacts between the ages of 6–11 months

Figure 3 shows the cumulative proportion of children who had had 1, 2 and 3 valid contacts before each month of age. Valid contacts were either first immunization contacts at 6 months of age or more, or subsequent contacts at intervals of 4 months or more: these are assumed to be equated to opportunities for vaccine-linked vitamin A supplementation. By the end of the second year of life, 84% had had one, 48% two and 9% three valid contacts. The cumulative proportion of 2nd valid contacts before the age of 12 months was only 18%. Although twice as many (37%) had had two or more immunization contacts between the ages of 6–11 months (Figure 2), the interval between many of these contacts was less than 4 months. These results suggest that although the opportunity to deliver one vitamin A supplement linked to immunization in the first year of life was high, the opportunity to deliver a second supplement was very limited.

Results: reason for visit, knowledge of vitamin A and costs

Reason and knowledge

A total of 194 guardians were interviewed about visits by their children to health facilities in the district that resulted in immunization and/or vitamin A supplementation. Only visits made within the six months preceding the interview were included. The guardians were also asked about their knowledge of vitamin A. The main reason for the visit for 15% was reportedly to receive immunization whereas it was to seek care for illnesses in 57% (Table 2). No guardian who gave immunization as the main reason travelled for more than 2 hours, whereas 25% of those whose main reason was seeking care for illness did (Table 2).

About half of those interviewed recognized the samples of vitamin A capsules shown to them as having been given to their child, but only 7% said that they were used to help prevent blindness.

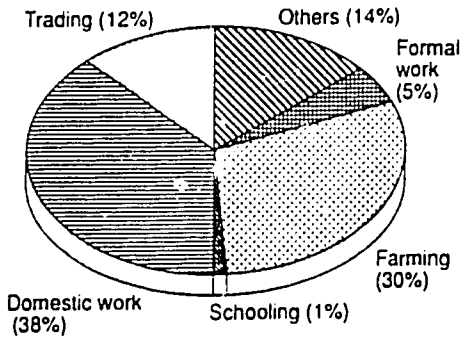
Indirect patient costs

In over 90% of the visits, the children were taken by their mothers who had foregone a variety of activities (Figure 4). Seventy three per cent walked a mile or less to reach the health facility. Travelling and waiting times at the health facilities ranged from less than half a hour to four hours (Figure 5). These reported waiting times were consistent with the times observed in the clinic. They were made up of the time

87

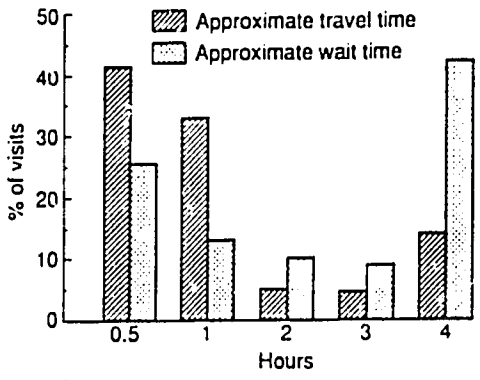
Table 2. Reasons for visiting health services among those children with a recent immunization and/or vitamin A supplementation history in relation to travel times

Reason	Approximate travel time (hours) <1	1	2	3	4	Total	(%)
Check-up	13	8	0	2	3	26	13.4
Illness	41	35	7	6	21	110	56.7
Immunization	22	6	1	0	0	29	14.9
Growth monitoring	4	15	1	1	1	22	11.3
Vitamin A	0	3	1	0	0	4	2.1
Other	0	1	1	1	0	3	1.5
Total	80	68	11	10	25	194	
(%)	41.2	35.1	5.7	5.1	12.9		100



n = 194

Figure 4. Main activities foregone by the child's guardian because of visits to health facilities



n = 194

Figure 5. Patient time costs of visiting health facilities

patients said they waited for the clinic team to arrive, where applicable, plus the observed time required for patients to complete their consultations and collect treatments (including immunizations and/or vitamin A capsules). The time spent with a health worker in the clinic that was solely attributable to receiving a vitamin A capsule was less than two minutes in all cases. This time included the time taken for the health worker to determine from the child's Road-to-Health chart whether he/she was eligible for supplementation during the current visit plus the time taken to collect the capsule from the dispenser. This additional time was therefore insignificant compared to the total time spent visiting the clinic.

Direct patient costs

Twenty per cent of the guardians did not walk to the health facility, and they paid an average transport fare of twenty two cedis (US$0.06). The fee paid per visit among those interviewed ranged from 50–150 cedis (US$0.13–0.40), and it covered consultation and all medications received, including immunizations and vitamin A supplements.

Health service costs

The part of the total cost of the PRH programme in 1990 which was related to immunization activities was US$15 975, computed at 1992 prices. The cost profile of the PRH programme's immunization activities showed that vaccines and supplies accounted for 12.0% of input costs (US$1917), salaries for 12% (US$1917), vehicles and fuel for 37.8% (US$6039), and buildings and equipment for 38.2% (US$6102). The salary component of the cost was lower than in several other immunization programmes.[28]

This was probably due to three main reasons: 1) health workers' salaries are very low in Ghana and probably do not reflect the true opportunity cost of labour; 2) the time of only two community health nurses was fully devoted to immunization while the screening of children to determine their immunization status and requirements was done by consulting nurses who were primarily providers of curative care; and 3) immunizations accounted for only about a third of outreach activities and therefore less than the full cost of support staff, such as the driver, was apportionable to immunization activities.

The average cost per immunization was US$0.65 and the average cost per fully immunized child was US$6.45 (Table 3).

Discussion

Integration of vitamin A supplementation with immunization after the age of 6 months could be achieved by linking capsule delivery to one specific immunization. Alternatively, a policy could be implemented in which health workers, either those trained only to immunize or those trained to provide integrated child health care, assess children for eligibility for supplementation independent of the particular immunization that may also be required.

Linkage with a single vaccine

There was the opportunity to deliver vitamin A linked to DPT3 between the ages of 6 and 11 months, to approximately 30% of the children. The corresponding percentages for DPT1 and DPT2 were 27% and 25%. A proportion of children (approximately 16%), received all their DPT vaccinations before 6 months and the number of children in this category is likely to increase as immunization services improve. If vitamin A supplementation was linked to DPT1, DPT2 or DPT3 approximately 18%, 30% and 42% respectively of children aged between 12–23 months would receive one dose of vitamin A (Figure 1). Given that the trials of vitamin A supplementation which have suggested a positive impact of vitamin A supplementation have all been based on repeated doses throughout childhood, the likely impact of one or two doses between 6–23 months of age is low.

The proportion of children vaccinated against measles by the end of their 23rd month was high

Table 3. Presbyterian rural health programmes 1990: costs of integrated immunization and vitamin A supplementation

	No.	(US $)
Total cost of immunizations		15 974.72
No. of immunizations	24 405	
No. of fully immunized children	2 478	
Average cost per immunization		0.65
Average cost per fully immunized child		6.45
Total cost of immunizations and vitamin A supplementation		16 034.52
Average cost per fully immunized and vitamin A supplemented child		6.47
Additional cost per supplement to a fully immunized child		0.02

Assumptions used in the analysis of the economic costs of the immunization activities of the Presbyterian Rural Health programme are:

- Sufficient slack exists in the staff time of those engaged in immunization to permit incorporation of vitamin A supplementation without employment of additional staff.
- The appropriate discount rate by which the cost of immunization activities are discounted to produce present value is 6%.
- The market wage/salary of programme staff, being scarce, reflects skilled labour's marginal productivity in alternative use.
- The official exchange rate is a true reflection of the value of foreign currency in terms of domestic currency.
- The cost of freight, insurance and local transport to Bolgatanga is equal to 30% of the Free on Board (fob) price.
- The number of children fully immunized by the programme in the year is equivalent to the mean number of 3rd DPT and 3rd Polio vaccinations delivered by the programme in the year.

(84%), but the proportion receiving it between 6–11 months was only 49% (Figure 1). This suggested that the pattern of immunization service utilization in Bolgatanga-Frafra offered the opportunity for delivering one vitamin A supplement with measles vaccine to approximately 84% of children before the 24th month, but only about half of these opportunities occurred before the age of 12 months. Were vitamin A supplementation linked to measles vaccination, the majority of children would be given only one dose between 6 and 23 months and, as in the case of DPT-linked supplementation the expected impact would be low.

Linkage with eligible immunization contacts

Over three quarters (84%) of children had contacts with the immunization staff of the PRH programme that could have been used to deliver a vitamin A supplement and about a quarter (23%) had subsequent contacts suitable for delivery of a second supplement. Only 8%, however, would have had the opportunity to receive a third supplement before they were two years old. It is important to stress that these estimates of eligible contacts are based on the age distribution of immunizations received (Figure 3) and therefore are minimal estimates, since not all contacts with the immunizations staff would have resulted in an immunization.

The core assumption here is that an alternative approach is adopted in which immunization staff give vitamin A supplements to children at the time of the first contact at 6 months or above and at all subsequent contacts at intervals of 4 months or more. Such a strategy would require health workers to use discretion in prescribing supplementation similar to that required of them to ensure that DPT and polio vaccinations are given at least 4 weeks apart. They would, therefore, need adequate guidelines and education on the use and dangers of vitamin A. It may also be necessary to redesign the Road-to-Health chart to include spaces for recording dates of supplementation. This option would be more costly to implement in terms of training and supervision than one in which supplementation is linked to a particular vaccine but could potentially provide more than a single dose per child before they reach two years of age.

Conclusions

We conclude that there was not a substantial 'window of opportunity' for vitamin A supplementation linked to a single dose of an immunization, such as with a delayed third dose of DPT or measles immunization in Bolgatanga district during the period of investigation. The data on coverage by age in this district strongly suggests that it would be difficult to ensure reasonable vitamin A coverage within the first year of life and acceptable levels of inappropriately early supplementation (i.e. before 6 months) by linking supplementation with any particular immunization dose. Linkage of supplementation with any immunization contact, with at least a four month interval between doses, would be more effective, ensuring that at least 84% of children would receive at least one dose before they reached two years of age, 27% at least two doses and 8% at least three doses. This could be achieved at minimal additional cost either to the health service (approximately US$0.02 per dose of supplement to a fully immunized child) or to the patient.

The relatively high rate of immunization coverage and potential coverage of vitamin A in the district studied appears to be due to the integration of immunization services with curative care by the PRH programme. This inference is supported by the finding that of children who had received immunizations, for only 15% was seeking immunization the main reason for the visit to the health facility. Given that a significant proportion of contacts with the immunization services in the district are incidental to receiving curative care, vitamin A supplementation given as part of a vertical immunization programme such as a mass immunization campaign, where health workers do not provide curative care, is likely to achieve a much lower coverage.

On the other hand, expansion of outreach child clinics similar to those provided by PRH to more communities in the district, either on a mobile or static basis, would increase immunization coverage and permit an integrated vitamin A supplementation strategy to reach a high percentage of young children. Integrating vitamin A supplementation with broad child health activities would not increase patient time costs. The patient costs in terms of travelling and waiting

times were high in the district (75% of the patients sampled waited 2 or more hours at the health centre and 56% spent an hour or more in reaching the health facility). These time costs would be reduced significantly by such an expansion. Any reduction in the opportunity cost to carers in taking children for health care is likely to increase those visits made to health services mainly for immunization, and so increase the total opportunities for both immunization and vitamin A supplementation.

In the light of the study findings, two measures are proposed to integrate vitamin A supplementation with immunization, should the initial decision be made by the Ministry of Health to institute routine supplementation in the district in the near future:

1 The formation of 'child health care teams' that will provide comprehensive care, that is curative and preventive care including immunization and vitamin A supplementation, through mobile and static clinics.

2 The training of team members to give vitamin A capsules to children with the first contact at 6 months or above, and then repeated with a minimum interval of 4 months.

The first measure is intended to increase the number of contacts between health care providers and children in the target group and, in effect, integrates vitamin A supplementation with child health services rather than only with immunization activities. The second is considered the best option to ensure appropriate and adequate levels of vitamin A supplementation coverage.

The results of this study, apart from providing the basis for the above recommendation, also have wider policy implications. Firstly, they demonstrate the need to know the immunization coverage and age at vaccination of a population when designing an immunization-linked vitamin A control programme. The proportion of children who could receive one dose of vitamin A between the ages of 6–11 months if this dose was linked to only one of the DPT vaccines or to the measles vaccine, will vary considerably depending on the coverage and age at vaccination in the population. In theory, if the supplement was linked only to measles vaccination, for example, the proportion could approach 100% in a near perfect situation, where all children are vaccinated with measles between 9–11 months of age. However, the actual situation is usually very different from this, with many children receiving their measles vaccine well into their second year of life, if at all.

Secondly, the study suggests that, at least in some countries, the additional cost of providing a dose of vitamin A when a supplementation programme is integrated with existing child health services, will not be significantly different from the average cost of a dose of vitamin A and its transportation. This is likely to be the case in sub-Saharan countries that have health service structures, and therefore recurrent costs, similar to Ghana. As additional costs have been shown to be very low, this suggests that a vitamin A control programme is likely to be a cost-effective child survival strategy in these countries.

References

1 World Health Organization. 1976. *Vitamin A deficiency and xerophthalmia.* Technical Report Series 590, Geneva.

2 McLaren DS. 1986. Global occurrence of Vitamin A. In: Bauernfeind JC (ed). *Vitamin A deficiency and its control.* London, London Academic Press Inc. 1–18.

3 WHO/International Vitamin A Consultative Group/UNICEF. 1988. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.* Geneva, WHO.

4 Sommer A, Tarwotjo I, Djunaedi E et al. 1986. Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. *Lancet* i: 1169–73.

5 Muhilal, Permeisih D. Idjradinata YR, Muherdiyantiningsih and Karyadi D. 1988. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *American Journal of Clinical Nutrition* 48: 1271–6.

6 Rahmathullah L, Underwood BA, Thulasiraj RD et al. 1988. Reduced mortality among children in Southern India receiving a small weekly dose of Vitamin A. *New England Journal of Medicine* 323: 929–35.

7 West KP, Pokhrel RP, Katz J et al. 1991. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 338: 67–71.

8 Daulaire NMP, Starbuck ES, Houston RM, Church MS, Stukel TA and Pandey MR. 1992. Childhood mortality after a high dose of vitamin A in a high risk population. *British Medical Journal* 304: 207–10.

9 Vijayaraghavan K, Radhhaiah G, Prakasam BS, Sarma KVR and Reddy V. 1990. Effect of massive dose of vitamin A on morbidity and mortality in Indian children. *Lancet* 336: 1342–5.

[10] Herrera MG, Nestel P, El Amin A, Fawzi WW, Mohamed KA and Weld L. 1992. Vitamin A supplementation and child survival. *Lancet* 340: 267-71.

[11] Sommer A, Tarwotjo I, Hussaini G and Susanto D. 1983. Increased mortality in children with mild vitamin A deficiency. *Lancet* II: 585-8.

[12] Sommer A, Katz J and Tarwotjo I. 1984. Increased risk of respiratory disease and diarrhoea in children with pre-existing mild vitamin A deficiency. *American Journal of Clinical Nutrition* 40: 1090-5.

[13] Milton RC, Reddy V and Naidu AN. 1987. Mild vitamin A deficiency and childhood morbidity - an Indian experience. *American Journal of Clinical Nutrition* 42: 827-9.

[14] Bloem MS, Wedel M, Egger RJ et al. 1990. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhoea in preschool and school children in Northeastern Thailand. *American Journal of Epidemiology* 131: 52-9.

[15] Ghana VAST Study Team. Vitamin A supplementation in Northern Ghana effects on clinic attendances, hospital admissions, and child mortality. *Lancet* (in press - expected date of publication, July 1993).

[16] Barclay AJG, Foster A and Sommer A. 1987. Vitamin A supplements and mortality related to measles: a randomised clinical trial. *British Medical Journal* 294: 294-6.

[17] Hussey GD and Klein M. 1990. A randomized, controlled trial of vitamin A in children with severe measles. *British Medical Journal of Medicine* 323: 160-4.

[18] Coutsoudis A, Broughton M and Coovadia HM. 1991. Vitamin A supplementation reduces measles morbidity in young African children: a randomized placebo-controlled, double-blind trial. *American Journal of Clinical Nutrition* 54: 890-5.

[19] World Health Organization/United States Agency for International Development/National Eye Institute. 1992. *Vitamin A mortality and morbidity studies.* Report of a joint WHO/USAID/NEI consultation of principal investigators, Geneva, Switzerland. Arlington, USA, VITAL.

[20] Helen Keller International. 1992. *Bellagio brief: vitamin A deficiency and childhood mortality.* New York, Helen Keller International.

[21] Cohen N. 1991. Accelerating delivery of vitamin A supplements by using immunization programmes. Unpublished conference paper. Geneva, WHO. June.

[22] Expanded Programme on Immunization. 1985. Report of the Expanded Programme on Immunization Global Advisory Group meeting, 21-25 October, Alexandria. EPI/GEN/85/1. Geneva, WHO.

[23] Ghana Vitamin A Supplementation Trials (VAST). 1990. Report of Activities July 1989 - June 1990. Unpublished report. Ghana VAST, Navrongo, Ghana.

[24] Rossler H. 1977. Vitamin A deficiency and eye disease in Northern Ghana: report of the survey carried out in April-May 1977. Unpublished report. Geneva, WHO.

[25] Frerichs RR and Tar Tar K. 1989. Computer-assisted rapid surveys in developing countries. *Public Health Reports* 104: 14-23.

[26] Henderson JM and Sundaresan T. 1982. Cluster sampling to assess immunization coverage: a review of the experience with simplified methods. *Bulletin of the World Health Organization* 60 (2): 253-60.

[27] Norusis JM. 1990. *SPSS/PC+ Advanced Statistics 4.0 for the IBM PC/XT/AT and PS/2.* Chicago, SPSS Inc. B-219.

[28] Barnum HN, Tarantola D and Setiady EF. 1980. Cost-effectiveness of the Expanded Programme of Immunization in Indonesia. *Bulletin of the World Health Organization* 58 (3): 499-503.

Acknowledgements

This study was undertaken as part of the activities of the British Overseas Development Administration (ODA) funded Health Economics and Financing Programme at the London School of Hygiene and Tropical Medicine. We are grateful to Anne Mills and Moses E K Adibo for their guidance and to Saul S Morris for his advice on aspects of the data analysis. The staff of the Ghana Vitamin A Supplementation Trials (VAST) made helpful comments on drafts of this paper for which we are indebted. We also thank Gerdy A van Noort of the Presbyterian Rural Health and her staff as well as staff of the Ministry of Health in Bolgatanga for their assistance, without which the study would not have been possible.

Biographies

Dyna Arhin is a research fellow on the Health Economics and Financing Programme at the London School of Hygiene and Tropical Medicine, and a PhD candidate at the London School of Economics. She graduated from Ghana Medical School in 1982 and then obtained postgraduate degrees from the Nuffield Institute, University of Leeds and University of York in health administration and planning, and health economics. She worked as a clinician in Ghana and Nigeria and later as a Senior Health Planner in the Ministry of Health in Ghana. Her main interests are community health insurance and economic evaluation of health programmes.

David A Ross, MA, MSc, BMBCh, is a senior lecturer in Epidemiology at the London School of Hygiene and Tropical Medicine. He spent much of his childhood in West Africa, qualified as a doctor in 1980, and joined the LSHTM in 1983, initially working in the Evaluation and Planning Centre for Health Care and more recently in the Maternal and Child Epidemiology and Tropical Health Epidemiology units in which he has a joint appointment. From late 1988 to mid-1992 he was based in northern Ghana as Director of the Ghana Vitamin A Supplementation Trials. His current research interests include vitamin A and child mortality and morbidity, health risks associated with attendance at child care facilities outside the home, and methods to measure cause-specific mortality rates in areas where death certification systems are weak (including use of verbal autopsy questionnaires).

Francisca Kufour, BSc, is Assistant Health Planning Officer in the Ministry of Health, Ghana. After graduating from the University of Science and Technology in 1987, she has worked in the Policy, Planning, Monitoring and Evaluation Division of the MOH, collaborating in five research works including Public/Private Mix, Vitamin A Supplementation Trials and Strategies for Health Insurance in Ghana. She was also on the team of authors of the Health Planning Guidelines.

92

Articles

Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality

*Ghana VAST Study Team**

Summary

Although most studies on the effect of vitamin A supplementation have reported reductions in childhood mortality, the effects on morbidity are less clear. We have carried out two double-blind, randomised, placebo-controlled trials of vitamin A supplementation in adjacent populations in northern Ghana to assess the impact on childhood morbidity and mortality.

The Survival Study included 21 906 children aged 6–90 months in 185 geographical clusters, who were followed for up to 26 months. The Health Study included 1455 children aged 6–59 months, who were monitored weekly for a year. Children were randomly assigned either 200 000 IU retinol equivalent (100 000 IU under 12 months) or placebo every 4 months; randomisation was by individual in the Health Study and by cluster in the Survival Study. There were no significant differences in the Health Study between the vitamin A and placebo groups in the prevalence of diarrhoea or acute respiratory infections; of the symptoms and conditions specifically asked about, only vomiting and anorexia were significantly less frequent in the supplemented children. Vitamin-A-supplemented children had significantly fewer attendances at clinics (rate ratio 0 88 [95% CI 0 81–0 95], p=0 001), hospital admissions (0 62 [0 42–0 93], p=0 02), and deaths (0 81 [0 68–0 98], p=0 03) than children who received placebo. The extent of the effect on morbidity and mortality did not vary significantly with age or sex. However, the mortality rate due to acute gastroenteritis was lower in vitamin-A-supplemented than in placebo clusters (0 66 [0 47–0 92], p=0 02); mortality rates for all other causes except acute lower respiratory infections and malaria were also lower in vitamin A clusters, but not significantly so.

Improving the vitamin A intake of young children in populations where xerophthalmia exists, even at relatively low prevalence, should be a high priority for health and agricultural services in Africa and elsewhere.

Lancet 1993; **342:** 7–12.

***Child survival study** Dr David A Ross, Dr Fred N Binka, Ms Nicola Dollimore, Prof Peter G Smith, Prof Hutton A Addy, Prof Andrew M Tomkins. **Child Health Study** Dr Ross, Ms Betty R Kirkwood, Dr Paul Arthur, Mr Saul S Morris, Dr John O Gyapong, Professor Tomkins.

London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (D A Ross BM, N Dollimore MSc, P G Smith DSc, B R Kirkwood MSc, P Arthur MPH, S S Morris MSc); **University of Science and Technology, Kumasi, Ghana** (Prof H A Addy PhD); **Ministry of Health, Ghana** (Fred N Binka MPH, P Arthur, J O Gyapong MB); **and Institute of Child Health, London, UK** (Prof A M Tomkins FRCP).

Correspondence to: Dr David A Ross.

Introduction

An association between vitamin A deficiency and an increased risk of childhood morbidity[1-4] and mortality[5] has been reported in observational studies, and intervention trials in Asia have reported reductions in mortality ranging from 6% to 54%.[6-11] By contrast, a study in Sudan reported a small increase in overall mortality.[12] In the three studies that reported large reductions in mortality and listed causes of death, mortality rates for diarrhoea and measles fell but the rate for acute respiratory infections (ARI) did not change.[8-10] Two of three studies reporting on morbidity and mortality found no effect on the prevalence of any illness studied despite substantial falls in mortality[6,8,13,14] (the other reported no significant effect on morbidity or mortality[11]). Clinical trials have shown that treatment with vitamin A reduces the severity of illness and mortality in children with measles,[15-17] even in areas where eye signs of vitamin A deficiency are rare.

We have carried out two randomised, double-blind, placebo-controlled trials to assess the effect of 4-monthly large doses of vitamin A on childhood mortality (the Ghana Vitamin A Supplementation Trials [VAST] Survival Study) and morbidity (the VAST Health Study) in northern Ghana.

Subjects and methods

The trials took place in the guinea savannah area of Ghana in the Kassena-Nankana District, on the border with Burkina Faso (figure 1). The area has a sub-Sahelian climate and the mean annual rainfall was 852 mm during 1981 to 1990, with 90% of the rain falling between April and September.[18]

The study populations were exclusively rural. Extended families live in a group of houses (a compound) connected by a single outer wall, and surrounded by their farmland. The main staple foods are millet, sorghum, and groundnuts, and the diet is deficient in carotenoids and vitamin A. Red palm oil, a major source of carotenoids in coastal West Africa, was found in only 2% of compounds during baseline surveys. However, about a third of compounds owned at least one mango tree, and about 10% one or more pawpaw (papaya) trees. Vitamin A deficiency and xerophthalmia are recognised as problems locally; words exist for night blindness in all the local languages and cases of xerophthalmia are reported by local ophthalmological services. There was no vitamin A supplementation programme within the study area.

The district is underserved by health services; one hospital and three health centres, with limited outreach services, serve about 180 000 people. Immunisation coverage and access to other maternal and child health services are correspondingly low.

All compounds in the study areas were included in the trials. They were listed and marked on specially prepared maps (1/5000 scale) and a full census of all residents was carried out shortly before the start of each trial. All children living in compounds within the

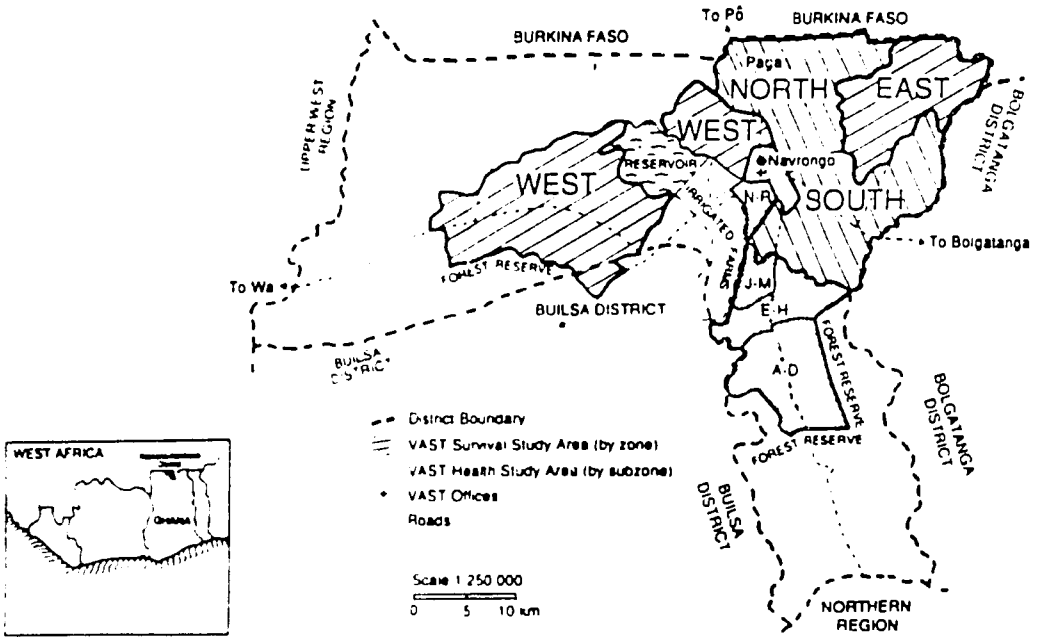


Figure 1: **Kassena-Nankana district**

study areas were eligible to enter the trials at any of the 4-monthly dosing points, once they had reached the age of 6 months. Children born from 1984 onwards were included in the Survival Study, but the Health Study restricted admission to children born from 1986 onwards. The Survival Study trial was carried out between September, 1989, and December, 1991, and the Health Study trial between June, 1990, and August, 1991.

At enrolment, the dates of birth of the children and their mothers were assessed by means of detailed local events calendars, supplemented by any written documentation available. Other information collected included an illness history, vaccination history, and anthropometric measurements on the child, the survival status of siblings, parental education, and mother's age. For each compound, data were collected on the type of house, possessions, animals, and access to vitamin-A-rich foods.

At the start of each trial, blood samples were collected to establish baseline serum retinol concentrations. In the Health Study, all children had serum retinol measurements at baseline and then a different, randomly chosen one-third sample was tested at each of the three subsequent dosing rounds. In the Survival Study, a random, stratified sample of 520 compounds was selected and blood samples were taken from all the children living in these compounds at baseline and at the end of the trial.

A fingerprick blood sample was taken into a 1 mL amber microtube with serum separator gel (Becton Dickinson, Oxford, UK). Samples were stored on ice and centrifuged within 12 h. The serum was stored at −40°C in foil-covered tubes, then transported on dry ice to the Nutritional Biochemistry Laboratory in the Institute of Child Health in London, where the serum retinol content was measured by high-performance liquid chromatography (Spectraphysics, Hemel Hempstead, UK) with a 10 cm ODS2 column (Pharmacia, Milton Keynes, UK) and an ultraviolet detector (Phillips, Cambridge, UK).

The Survival Study area was divided into 185 geographical areas (clusters) based on boundaries such as roads, paths, or streams, with 30–77 compounds in a cluster (mean 51); the cluster was used as the unit of randomisation. Overall, 92 clusters were assigned vitamin A and 93 placebo treatment. In the Health Study, individual children were randomly assigned either vitamin A or placebo. Randomisation was blocked in both studies to ensure similar numbers of children in each group in each part of the study area. Randomisation was carried out in London by an independent statistician, who held the randomisation code and who also did an interim analysis of the mortality results from the Survival Study for the trial's data-monitoring committee after a year of follow-up.

Vitamin A and placebo were supplied by Hoffmann-La-Roche's Sight and Life Programme, and were similar in taste and colour. In the Survival Study, liquid vitamin A or placebo was supplied in opaque 150 mL bottles containing 20 IU/mL vitamin E alone (placebo) or plus 100 000 IU/mL retinol equivalent as retinyl palmitate (vitamin A) in purified peanut oil. Each bottle had a unique number, and was labelled with a cluster code before despatch to Ghana. In the Health Study, vitamin A and placebo were supplied in gelatin capsules, individually packaged in opaque envelopes labelled with one child's unique identification number. The capsules contained 200 000 IU retinol equivalent as retinyl palmitate (vitamin A) or peanut oil only (placebo).

Supplements were stored in sealed bottles at room temperature. Random samples of the vitamin A bottles and of the capsules were returned for testing of retinol content by Hoffmann-La-Roche's laboratories in Basel; there was less than 20% loss of potency, even in vitamin A stored for up to 2 years.

In both trials, at each dosing round, children aged less than 6 months were not eligible, children 6–11 months old received 100 000 IU retinol equivalent or placebo, and children 12 months or older were given 200 000 IU retinol equivalent or placebo. Vitamin A was given to all children during the final dosing round of each trial.

In the Survival Study, children were visited and dosed by trained fieldworkers every 4 months for 2 years in seven survey rounds. At each visit each child was recorded as being present, temporarily absent, moved away, or dead. A child was classified as being temporarily absent if he or she was not in the compound when visited at least three times during a week. The parents of children found to be suffering from any illness at a fieldworker's visit were advised to take them to the nearest health facility for diagnosis and treatment.

In the Health Study, morbidity surveillance was based on weekly home visits by fieldworkers. At each visit, a detailed interview was conducted about the occurrence on each day of the week of 21 listed symptoms, signs, and conditions, using locally defined terms where appropriate. Recall was aided by use of a pictorial daily health diary, on which mothers were taught to record that the child was healthy or to mark the occurrence of diarrhoea, cough, or any other illness. Further questions and observations were made to assess the severity of any diarrhoeal or respiratory illnesses reported (to be published elsewhere).

The Health Study area had no static health facility, but weekly mobile clinics were held, at which study children were offered a highly subsidised service. At their weekly visits, fieldworkers were

instructed to refer ill children to the clinics, according to specified criteria. All study children who attended the clinic were seen by a physician, who recorded the diagnoses and treatment. A standard, detailed clinical assessment was also carried out on a subsample of these children. Children presenting with acute respiratory infections were referred to the district hospital for chest radiography, and severely ill children were admitted to hospital, where they were treated by standard protocols, and monitored daily by the study physician. Direct admissions of study children to the district hospital were also notified to the physician for assessment, monitoring, and treatment by the same standard treatment protocols.

Children were screened for signs of xerophthalmia every 4 months. In the Survival Study, fieldworkers at their 4-monthly home visits screened children for suspected night blindness, Bitot's spot, or corneal abnormality, and referred affected children for further assessment by a study physician. In the Health Study, each child was examined every 4 months by a physician.

All children with confirmed active xerophthalmia or its sequelae (corneal scars) were withdrawn from the trial at diagnosis. They were given three large doses of vitamin A over a week, and received vitamin A in all subsequent survey rounds. Because of the frequent follow-up in the Health Study, we could detect and treat cases of measles with vitamin A. These children were also excluded from the trial from that point.

Child deaths were identified at the time of the home visits, and also through a network of about 100 key informants—members of the study community who were asked to record all pregnancies, births, and child deaths in their area. Information was collected from the informants every 2 weeks. Specially trained staff interviewed the parents or the nearest relative of any study child who died. They recorded information on the circumstances of the death and the symptoms and signs that preceded it on a form that included both an open history of the final illness and screening questions for the presence of common symptoms, followed by the application of appropriate modules with precoded answers. More than 90% of interviews were done within 7 months of the child's death (median interval 2·9 months).

Verbal autopsy questionnaires were examined independently by three physicians who assigned the cause of death to one of eleven categories, which included "miscellaneous" and "unknown". If at least two of the three physicians assigned the death to the same category, it was taken as the cause, otherwise the cause was classified as "unknown".

Several methods were used both to promote and to check on data quality. These included weekly visits to each fieldworker by a supervisor, who observed interviews, revisited compounds, and either conducted full re-interviews or checked a more limited set of information on a sample of recently completed interview forms. Meetings were held weekly between supervisors and headquarters field and data-processing staff, and at least once every 2 weeks between groups of fieldworkers and their supervisors to ensure good two-way communication. Both fieldworkers and supervisors received regular training courses.

Completed forms were checked manually by the supervisors, before independent data entry into computers by two clerks. After typing errors had been corrected, the data were checked for range and consistency. Any discrepancies that could not be resolved in the headquarters led to a revisit to the child's home and checking of information on the relevant variables.

Regular computer analyses of the results reported by each fieldworker were done to identify workers whose results differed substantially from those of their colleagues; they were given extra supervision and, where necessary, retraining.

All data entry and processing were done in the study headquarters in Navrongo with IBM PS 2 computers and dBase III+ software. Analyses were carried out in Navrongo and London with dBASE III+, Epi Info 5·00, SPSS PC+ 4·0, and GLIM 3·77. Two-tailed significance tests were used throughout, and continuity corrections applied where appropriate. Preliminary results were reported to the study communities, the district and regional health services, and the Ministry of Health of Ghana within 4 months of the end of data collection.

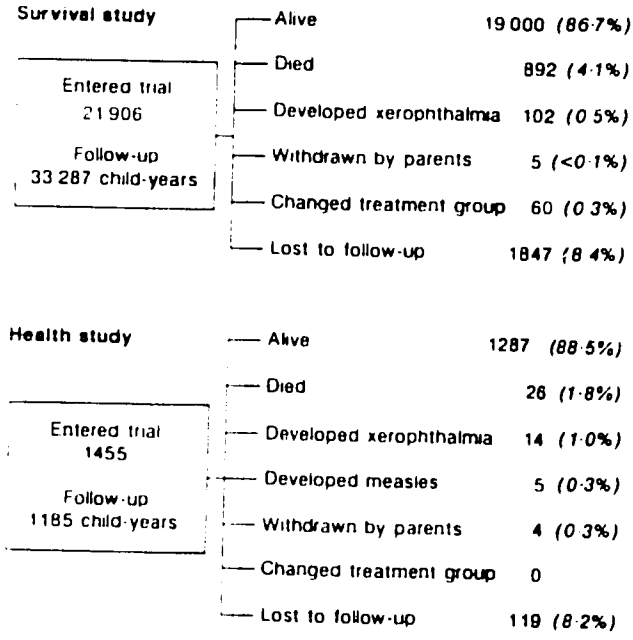


Figure 2. **Follow-up of study children**

Children who were at least 6 months old entered the trials at the first dosing round or at a subsequent round and left at the last dosing round, or when they moved out of the study area, died, or were withdrawn from the trial. Confirmed xerophthalmia cases were excluded from the date of diagnosis. In the Survival Study, children could move from one treatment group to the other by moving between clusters with different treatment assignments. Such children were excluded from the date they received their first dose of the different treatment.

Since children were randomised to treatment group by cluster in the Survival Study, the results, both of the baseline comparisons and the mortality rates, were analysed by a comparison of the mean of the results in each of the 92 vitamin A clusters against the mean of the results in each of the 93 placebo clusters. Each cluster's mortality rate was calculated by dividing the number of deaths by the child-years of follow-up. The ratio of the mean mortality rate in the vitamin A and placebo clusters was used to measure the mortality impact of vitamin A supplementation, with 95% CI calculated by the method of Armitage and Berry.[18]

An independent data-monitoring committee reviewed the mortality results from the first 12 months of follow-up in the Survival Study, and recommended the continuation of the trial to the end of the planned 24 months of follow-up. The results of this interim analysis were not revealed to the members of the study team until after the trial.

In comparing mean daily prevalence rates of morbidity between vitamin A and placebo groups in the Health Study, separate daily prevalence rates were calculated for each child for each of the intervals between dosing points. These were then averaged to give overall mean rates for each treatment group. The CIs for the rate ratios were calculated by means of a formula for determining the confidence interval of the ratio of two normal means.[19]

Ethical approval for both trials was obtained from the Ministry of Health of Ghana, and from the ethics committee of the London School of Hygiene and Tropical Medicine. The trials were explained in detail to all the local, regional, and district authorities and paramount chiefs, who gave their approval. Efforts were made to keep the communities informed of the studies' purposes, and of any new developments, through meetings open to all community members, and by announcements at market places. The trial was also explained and consent was sought from the head of each compound and the parents or guardians of each eligible child before enrolment.

Results

The prevalence of xerophthalmia at baseline was 0·7% in the Survival Study children and 1·5% in the Health Study children. In each study, the rates in the vitamin A and placebo groups were similar. The proportions of children with low baseline serum retinol concentrations were substantial in both trial populations. In the Survival Study, 14·4% were severely deficient (< 0·35 μmol/L) and 42·5% moderately deficient (0·35–0·69 μmol/L); the equivalent rates were 15·8% and 57·6% among the Health Study children. The treatment groups were compared at baseline with respect to more than fifty characteristics. In both trial populations, the treatment groups were significantly different ($p < 0·05$) for only two variables, which is the number expected by chance.

No parent refused permission for a child to enter the trials. Losses to follow-up were less than 10% in both trials (figure 2) and similar in the treatment groups.

The 21 906 children who entered the Survival Study were followed up for 33 287 child-years (16 508 vitamin A group, 16 779 placebo group). Dosing compliance was similar in the two groups; an average of 89·5% of eligible children were successfully treated in each round. The commonest reason for missing a dose was absence from home at the time of the fieldworker's visit. Dosing errors were rare (less than 0·7% of all doses given). Most were due to mislabelling of bottles.

1455 children entered the Health Study and were followed up for 1185 child-years (596 vitamin A group, 589 placebo group). Morbidity information was missing for 5·7% of the weekly follow-up visits owing to temporary absences of the study children or their mothers, but the missing data were equally distributed between the treatment groups. At each dosing point, an average of 94·7% of eligible children received the supplement or placebo.

Symptom/condition	Mean daily prevalence (%)		Prevalence ratio†	p
	Vitamin A	Placebo		
Specifically asked about				
Diarrhoea	15·5	15·9	0·98	0·55
Daytime cough	13·2	13·0	1·02	0·67
Blocked nose	11·5	11·3	1·01	0·82
"Tied ribs"*	1·1	1·1	0·98	0·86
Difficulty breathing	1·2	1·2	0·96	0·70
Rapid breathing	1·1	1·3	0·81	0·11
Ear pain	0·7	0·9	0·82	0·40
Ear discharge	0·7	0·8	0·91	0·72
Measles	0·1	0·1	1·10	0·79
Skin rash	5·0	4·8	1·04	0·61
Pus*	2·2	2·0	1·08	0·30
"Hot body"*	16·7	16·7	1·00	0·89
Vomiting	2·0	2·3	0·84	0·02
Refusing food/breastmilk	1·3	1·6	0·84	0·03
Reported but not asked about				
Skin ulcers/boils	1·3	1·6	0·84	0·13
Red/painful/discharging eyes	1·6	1·8	0·91	0·39
"Sore anus"*	0·8	0·9	0·93	0·62
Other‡	1·6	1·8	0·91	0·29

* Locally defined symptoms: tied ribs = severe respiratory illness, Pus = febrile illness including symptoms of malaria; hot body = raised body temperature.
‡Included convulsions, worms, headache, stomach pains.
†Vitamin A/placebo.

Table 1: **Mean daily prevalence of symptoms/conditions in health study during follow-up**

	No of deaths (% of total)	No of deaths		Ratio of mean mortality rates† (95% CI)
		Vitamin A clusters (n=92)	Placebo clusters (n=93)	
Deaths with established cause*				
Acute gastroenteritis	180 (25·8%)	69	111	0·66 (0·47–0·92)
Malaria	161 (23·1%)	76	85	1·03 (0·74–1·43)
Measles	134 (19·2%)	61	73	0·82 (0·48–1·40)
Acute lower respiratory infection	92 (13·2%)	47	45	1·00 (0·61–1·64)
Chronic diarrhoea or malnutrition	58 (8·3%)	22	36	0·67 (0·38–1·18)
Injury	20 (2·9%)	10	10	0·85 (0·34–2·07)
Meningitis	11 (1·6%)	4	7	0·66 (0·18–2·49)
Other	41 (5·9%)	19	22	0·73 (0·38–1·41)
Cause not known		89	106	0·81 (0·59–1·13)
Total		397	495	0·81 (0·68–0·98)

*Total with established cause = 697. †Vitamin A/placebo.

Table 2: **Total and cause-specific mortality in Survival Study**

There were only two significant differences between the vitamin A and placebo groups in the mean daily prevalence of the symptoms/conditions investigated at the weekly visits in the Health Study (table 1)—prevalence of vomiting and refusal of food or breastmilk.

In the Health Study clinic attendance rates were significantly lower in the vitamin A group than in the placebo group (1193 *vs* 1341 attendances, rate ratio 0·88 [95% CI 0·81–0·95], $p < 0·001$). A child in the vitamin A group was significantly less likely than a placebo-treated child to have made several clinic visits ($p = 0·019$), for example children in the vitamin A group were 27% (95% CI 4–45%) less likely to have attended the clinic 3 or more times during a 4-month dosing interval. Similarly, hospital admission rates were significantly lower in the vitamin A group than in the placebo group (36 *vs* 57 admissions, rate ratio 0·62 [0·42–0·93], $p = 0·02$). The rate ratio for admission was similar when only the first admission of each child was counted (27 *vs* 42, rate ratio 0·65 [0·41–1·04], $p = 0·09$).

There were 892 deaths among the children in the Survival Study, which gave an overall mean mortality rate for all clusters of 27·1 per 1000 child-years of follow-up. 397 of the deaths were in vitamin A clusters (mean mortality rate 24·4 per 1000 child-years) and 495 in placebo clusters (29·9 per 1000 child-years). The ratio of the mean mortality rates was 0·81 (95% CI 0·68–0·98, $p = 0·03$, table 2). The ratio of mean mortality rate was smaller in boys than in girls (0·73 [0·59–0·92] *vs* 0·90 [0·71–1·15]) but the difference was not significant ($p = 0·3$). A protective effect of vitamin A was apparent in five of seven age groups, but there was no consistent trend in the size of the ratio by age.

A probable cause of death was established for 697 (78·1%) of the 892 deaths (table 2). The mortality rate due to acute gastroenteritis was significantly lower in the vitamin A clusters than in the placebo clusters. Mortality rates for all the other causes of death except acute lower respiratory infections and malaria were lower in the vitamin A group but none was significant at $p < 0·05$, and, overall, the difference in the size of the effect of vitamin A supplementation by cause was not statistically significant.

There were 26 deaths among trial children in the Health Study, 6 in the vitamin-A-supplemented group and 20 in the placebo group.

Discussion

These trials broke new ground in several ways. The two trials were carried out in adjacent populations in West Africa; one looked in detail at the effect of vitamin A supplementation on morbidity and the other at its effect on mortality. We assessed the effect of vitamin A supplementation on the care sought for illness (clinic attendances and hospital admissions). The trials were carried out in a population with xerophthalmia rates that were very close to the threshold used by WHO to define a population as having a xerophthalmia problem of public health significance (1%);[20] previously reported studies were done in populations with substantially higher rates of xerophthalmia.

Our results may explain the puzzling results from at least two previous trials, which failed to find an impact on morbidity[13,14] even in the presence of a large effect on mortality.[6,8] Those studies collected data on a limited number of symptoms/conditions, without detailed information on their severity or the care-seeking provoked. We also found no effect on reported morbidity, though there was a suggestion that the prevalence of vomiting and refusal of food or breastmilk, both of which tend to be associated with severe episodes of illness, were lower in the supplemented children. However, we did find a strong influence on the occurrence of episodes severe enough to lead the mother to take the child to a clinic, and those that subsequently resulted in the child being admitted to hospital, as well as an effect on mortality. Thus, it seems that vitamin A supplementation reduced the frequency of severe and lethal illnesses without decreasing the frequency of less severe illnesses.

Vitamin A has two main effects on the immune system—enhancement of non-specific immunity by maintaining the physical and biological integrity of epithelial tissue as the first barrier to infection,[21-24] and increasing the effectiveness of the immune response to infection once the epithelial barrier has been breached.[25-27] The first should result in a lower incidence of infections, possibly in combination with decreased severity due to a lower average "dose" of pathogens crossing the mucosal barrier, whereas the second will tend towards a decreased severity, but not incidence of infection. The overall observed impact of supplementation will depend on the relative enhancement of these two components of the immune system in the population. Our results imply that the effects of vitamin A supplementation on the immune response to infection after the epithelial barrier has been breached are of greater functional significance than the effects on the integrity of the epithelial barrier itself.

The trials are the first to show an effect of prophylactic vitamin A supplementation on morbidity or mortality in Africa. The only other similar trial in Africa (in Sudan[12]) did not show an effect of vitamin A supplementation on child survival (relative risk = 1·06 [95% CI 0·82–1·37]). The investigators speculated that the lack of effect in their study population was due to the 6-monthly rather than 4-monthly dosing schedule, the low mortality rate in the control group, or the postulated lack of other nutrients, such as fat or zinc, in the diet.

Our findings of a 19% reduction in all-cause mortality with vitamin A supplementation and the substantial reductions in clinic attendance rates and hospital admissions are consistent with the results of five large trials in Asia,[6-10] and observational studies in Asia.[1-5] Only one trial in Asia did not find significantly lower child mortality with vitamin A supplementation;[11] however, even in that trial, the lower 95% confidence interval on the ratio of the mortality rates was below 0·81.

The all-cause mortality results of our trials are important for two reasons. Firstly, they showed that improving the vitamin A intake of at least some populations of young African children can substantially reduce their mortality. Secondly, this effect on all-cause mortality was in a population that had a vitamin A deficiency problem of marginal public health importance;[20] baseline xerophthalmia rates were substantially higher in the Asian trials.[6-11] Nonetheless, there was evidence that vitamin A supplementation reduced the incidence of xerophthalmia.

Our study found a rate ratio of 0·66 for acute gastroenteritis deaths and of 0·67 for deaths due to chronic diarrhoea, malnutrition, or both. A reduction of at least 30% in child mortality due to diarrhoeal diseases has now been found by all trials that have found a significant effect on overall mortality and have also examined causes of death.[8-10] By contrast, we found no reduction in deaths attributed to acute lower respiratory infections in the vitamin-A-supplemented group. The effect of vitamin A supplementation on such deaths has not been consistent in previous trials,[8-10,12] though none has found a significant change. Similarly, we found no reduction in deaths due to malaria. Malaria was probably a much more important immediate and underlying cause of death in this population than in any other trial population, with the possible exception of the Sudan, where "fever" was the second commonest symptom associated with death.[12] The other major cause of death in our trial was measles, in which the ratio of the mortality rates was 0·82, though this ratio did not significantly differ from 1·0.

The results of this study have important health policy implications. They show that improving the vitamin A intake of young children in areas where xerophthalmia exists, even at low prevalence, should be a high priority for both health and agricultural services. If routine interventions can be devised that effectively improve vitamin A status, the burden of xerophthalmia, other severe illness, and mortality in children will be substantially reduced. As well as these direct benefits to the population, there will be substantial indirect benefits owing to substantial reductions in clinic attendances and hospital admissions. Health services appropriate a significant proportion of national budgets, and the economic and social costs incurred by the family of an ill child are also large.

Since the impact of improvements in vitamin A status is likely to be related to the extent of deficiency in the population, there is an urgent need for surveys of the prevalence of vitamin A deficiency and xerophthalmia. Remarkably little is known about the extent of the problem in most countries in Africa, the Middle East, Asia, and Latin America. It will then be important to gather information on local dietary and agricultural practices and beliefs to assess the feasibility of improving the production, storage, and consumption of local vitamin-A-rich foods, the introduction of new foods, or fortification of a locally consumed food. Other potential strategies include the provision of vitamin A supplements to at-risk groups. Although likely to be the least cost-effective strategy for the improvement of vitamin A status in the long term, even this approach is a highly cost-effective child survival intervention.[28]

The Ghana Vitamin A Supplementation Trials (VAST) were a collaborative research project between the London School of Hygiene and Tropical Medicine and the School of Medical Sciences of the University of Science and Technology, Kumasi, Ghana, with support from the Ministry of Health of Ghana. The project was funded by the Health and Population Division of the UK Overseas Development Administration. Preliminary exploratory studies were supported by the Wellcome Trust and Save the Children Fund (UK). Hoffmann-La-Roche's Sight and Life programme supplied the vitamin A and placebo.

We thank all the VAST field, laboratory, computer centre, and administrative staff, especially Mr Martin Adjuik, Mr Azumah Amidini, Mr J Kwabena Badu, Ms Margaret Gyapong, Mr Eric Kasise, Mr Ogyebre Owusu-Agyei, and Mr David Pendlebury; the population of Kassena-Nankana District and their leaders; the Regional and District Administration and Health Services; Dr Moses Adibo and Dr Sam Adjei, (Ministry of Health of Ghana) for support and encouragement; Prof Patrick Vaughan and other colleagues at the LSHTM for support and advice; Ms Nina Saroi for administrative and secretarial support in London; Dr Sandra Saenz de Tejada and the WHO-ARI Programme for preliminary study of local concepts and terminology of illness; Ms Gilly Maude for the randomisation and interim analysis; Ms Sharon Huttly, Mr Ben Amenuvegbe, and the late Mr Steve Tulloch for helping to design the data management system; Dr Hazel Inskip and Mr Jerry Wheeler for advice on data processing; Ms Penny Fennell for help with the training of the computing and secretarial staff; Ms Rebecca Abbott and Dr Suzanne Filteau (Institute of Child Health, London) for measuring serum retinol; Dr Andy Hall for helping to code the cause of death questionnaires; and the members of the data monitoring committee for reviewing the interim results.

References

1 Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhoea in children with pre-existing vitamin A deficiency. *Am J Clin Nutr* 1984; 40: 1090–95.

2 Milton RC, Reddy V, Naidu AN. Mild vitamin A deficiency and childhood morbidity—an Indian experience. *Am J Clin Nutr* 1987; 46: 827–29.

3 Bloem MW, Wedel M, Egger RJ, et al. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhea in preschool and school children in Northeastern Thailand. *Am J Epidemiol* 1990; 131: 332–39.

4 El Bushra HE, Ash LR, Coulson AH, Neumann CG. Interrelationship between diarrhea and vitamin A deficiency: is vitamin A deficiency a risk factor for diarrhea? *Pediatr Infect Dis J* 1992; 11: 380–84.

5 Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. *Lancet* 1983; ii: 585–88.

6 Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. *Lancet* 1986; i: 1169–73.

7 Muhilal, Permesih D, Idjradinata YR, et al. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *Am J Clin Nutr* 1988; 48: 1271–76.

8 Rahmathullah L, Underwood BA, Thulasiraj RD, et al. Reduced mortality among children in Southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; 323: 929–35.

9 West KP Jr, Pokhrel RP, Katz J, et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; 338: 67–71.

10 Daulaire NMP, Starbuck ES, Houston RM, et al. Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; 304: 207–10.

11 Vijayaraghavan K, Radhaiah G, Prakasam BS, et al. Effect of massive-dose vitamin A on morbidity and mortality in Indian children. *Lancet* 1990; 336: 1542–45.

12 Herrera HG, Nestel P, El Amin A, et al. Vitamin A supplementation and child survival. *Lancet* 1992; 340: 267–71.

13 Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC. Diarrhea, respiratory infections, and growth are not affected by a weekly low-dose vitamin A supplement: a masked, controlled field trial in children in Southern India. *Am J Clin Nutr* 1991; 54: 568–77.

14 Abdeljaber MH, Monto AS, Tilden RL, et al. The impact of vitamin A supplementation on morbidity: a randomized community intervention trial. *Am J Publ Health* 1991; 81: 1654–56.

15 Barclay AJG, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomised clinical trial. *BMJ* 1987; 294: 294–96.

16 Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990; 323: 160–64.

17 Coutsoudis A, Broughton M, Coovadia HM. Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-controlled, double-blind trial. *Am J Clin Nutr* 1991; 54: 890–95.

18 Irrigation Company of Upper Regions (ICOUR). Monthly rainfall statistics, 1981–90. Tono, Ghana, 1991.

19 Armitage P, Berry G. Statistical methods in medical research, 2nd ed. Oxford: Blackwell, 1987: 92.

20 Sommer A. Field guide to the detection and control of xerophthalmia, 2nd ed. Geneva: WHO, 1982.

21 Wolbach SB, Howe PR. Tissue changes following deprivation of fat-soluble vitamin A. *J Exp Med* 1925; 42: 753–77.

22 Blackfan KD, Wolbach SB. Vitamin A deficiency in infants: a clinical and pathological study. *J Pediatr* 1933; 3: 679–706.

23 Olson JA. The biological role of vitamin A in maintaining epithelial tissues. *Israel J Med Sci* 1972; 8: 1170–78.

24 Chandra RK. Increased bacterial binding to respiratory epithelial cells in vitamin A deficiency. *BMJ* 1988; 297: 834–35.

25 Mohanram M, Reddy V, Mishra S. Lysozyme activity in plasma and leucocytes in malnourished children. *Br J Nutr* 1974; 32: 313–16.

26 Bhaskaram C, Reddy V. Cell mediated immunity in iron and vitamin deficient children. *BMJ* 1975; 3: 522.

27 Friedman A, Sklan D. Antigen-specific immune response impairment in the chick as influenced by dietary vitamin A. *J Nutr* 1989; 119: 790–95.

28 West KP, Sommer A. Delivery of oral doses of vitamin A to prevent vitamin A deficiency and nutritional blindness: a state-of-the-art review. Rome, Italy; United Nations Administrative Committee on Coordination, Subcommittee on Nutrition, Nutrition Policy Discussion Paper No. 2, 1987.

C-18

THE LANCET

Vol 338 Saturday 13 July 1991 No 8759

ORIGINAL ARTICLES

Efficacy of vitamin A in reducing preschool child mortality in Nepal

KEITH P. WEST, JR R. P. POKHREL JOANNE KATZ
STEVEN C. LECLERQ SUBARNA K. KHATRY
SHARADA R. SHRESTHA ELIZABETH K. PRADHAN
JAMES M. TIELSCH M. R. PANDEY ALFRED SOMMER.

Community trials of the efficacy of vitamin A supplementation in reducing preschool childhood mortality have produced conflicting results. To resolve the question, a randomised, double-masked, placebo-controlled community trial of 28 630 children aged 6–72 months was carried out in rural Nepal, an area representative of the Gangetic flood plain of South Asia. Randomisation was carried out by administrative ward; the vitamin-A-supplemented children received 60 000 retinol equivalents every 4 months and placebo-treated children received identical capsules containing 300 retinol equivalents. After 12 months, the relative risk of death in the vitamin-A-supplemented compared with the control group was 0·70 (95% confidence interval 0·56–0·88), equivalent to a 30% reduction in mortality. The trial, which had been planned to last 2 years, was discontinued. The reduction in mortality was present in both sexes (relative risk for boys 0·77; for girls 0·65), at all ages (range of relative risks 0·83–0·50), and throughout the year (0·76–0·67). The reduction in mortality risk was not affected by acute nutritional status, as measured by arm circumference. Thus, periodic vitamin A delivery in the community can greatly reduce child mortality in developing countries.

Lancet 1991; **338**: 67–71.

Introduction

Vitamin A deficiency is associated with an increased risk of childhood morbidity[1-3] and mortality[4] in developing countries. Community trials of vitamin A supplementation in Indonesia[5,6] and India[7] reported annual reductions in preschool child mortality of 34% to 54%. However, another field trial in India failed to confirm a reduction in child mortality with vitamin A;[8] thus, concern was raised about the potential impact of improved vitamin A nutrition on child survival across different cultures.[9-11]

As a follow-up to the original large-dose vitamin A trial in Indonesia,[5] a community trial in rural Nepal was undertaken to assess the efficacy of vitamin A supplementation every 4 months in reducing preschool child mortality. Such supplementation is recommended by the World Health Organisation for prevention of xerophthalmia[12] and may represent an achievable delivery schedule for child survival.

Study population and methods

A randomised, double-masked, placebo-controlled vitamin A supplementation trial was carried out from September, 1989, to December, 1990, in the rural, plains (Terai) district of Sarlahi. This area was selected because it has endemic vitamin A deficiency,[13] no previous vitamin A supplementation programme, and ecological, cultural, and demographic similarities to the Gangetic floodplain communities of South Asia, with which it is continuous; the factor enhances the general applicability of the findings.

29 local development units, each containing 9 administrative wards, were selected for the trial. In 1988 the area had a population of 144 000 with about 28 000 children (19·0%) under 5 years of age (Census Report of the District Public Health Office, Sarlahi, Nepal,

ADDRESS: **Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, The Johns Hopkins Schools of Medicine and Public Health, Baltimore, Maryland, USA** (K. P. West, Jr, DrPH, J. Katz, MS, S. C. LeClerq, BS, E. K. Pradhan, BA, J. M. Tielsch, PhD, Prof A. Sommer, MD); **National Society for the Prevention of Blindness and World Health Organisation Prevention of Blindness Programme, Kathmandu, Nepal** (R. P. Pokhrel, FRCS, S. K. Khatry, FRCS, S. R. Shrestha, MPH); **and the Ministry of Health of His Majesty's Government, Kathmandu, Nepal** (M. R. Pandey, FRCS). Correspondence to Dr K. P. West, Jr, Dana Center for Preventive Ophthalmology, Wilmer Eye Institute 120, 600 North Wolfe Street, Baltimore, Maryland 21205, USA

TABLE I—BASELINE CHARACTERISTICS OF STUDY CHILDREN

—	No (%)	
	Control (n = 12 264)	Vitamin A (n = 12 541)
Sex		
Male	6265 (51·1)	6479 (51·7)
Female	5999 (48·9)	6062 (48·3)
Age (mo)		
6–11	1290 (10·5)	1356 (10·8)
12–23	2806 (22·9)	2827 (22·5)
24–35	2696 (22·0)	2827 (22·5)
36–47	2624 (21·4)	2595 (20·7)
48–60	2848 (23·2)	2936 (23·4)
*Measles during previous 4 mo**	759 (6·2)	639 (5·1)
Morbidity ≥ 1 day during previous week†		
Diarrhoea	1214 (11·0)	1244 (11·0)
Dysentery	506 (4·6)	508 (4·5)
High fever	1882 (17·0)	1936 (17·1)
Persistent cough	1609 (14·5)	1720 (15·2)
Arm circumference (cm)		
< 11·5	420 (3·8)	380 (3·4)
11·5–12·4	1032 (9·4)	1109 (9·9)
12·5–13·4	2859 (26·1)	2836 (25·3)
≥ 13·5	6652 (60·7)	6890 (61·4)
Total‡	10 963	11 215
Xerophthalmia§	66 (3·5)	52 (2·6)

*Data missing for 69 controls and 42 vitamin A children
†Assessed only for children reported to be at home for all of the previous 7 days (about 90% of children)
‡Not measured on 2627 (11%) children at baseline
§Nightblindness, Bitot's spots, corneal xerosis, keratomalacia, assessed in a random 15% sample of 40 wards (n = 4274 children: 1871 control, 2024 vitamin A, 379 not examined). There were 2 corneal cases, 1 in each group

TABLE II—HOUSEHOLD CHARACTERISTICS AT TIME OF ENTRY

—	No (%)	
	Control	Vitamin A
Mother's age (yr)		
< 20	860 (8·6)	873 (8·7)
20–29	5586 (55·9)	5662 (56·1)
≥ 30	3540 (35·4)	3551 (35·2)
Total	9986	10 086
Mother's education (any)	912 (9·1)	1018 (10·1)
History of ≥ 1 child death	4177 (41·9)	4200 (42·0)
Occupation of head of household		
Farmer	5218 (58·0)	5288 (58·1)
Labourer	2250 (25·0)	2174 (23·9)
Other	1536 (17·0)	1636 (18·0)
Total	9004	9098
Household owns radio	1832 (20·3)	1942 (21·3)
Preschool child/infant death in previous year	355 (3·9)	374 (4·1)

1989). Signed statements of consent were obtained from all 29 chairmen on behalf of their communities. Participation of wards, households, and children in the trial was voluntary at all times.

The ward served as the unit of treatment allocation. Local development units were ordered by geographic areas and wards by population size within each local development unit. After a random start, each of the 261 wards was systematically allocated to one of four coded batches of supplements. Two codes contained a standard 60 000 μg retinol equivalent (200 000 IU) dose of vitamin A and two served as control, containing 300 retinol equivalents (1000 IU) of vitamin A (retinyl palmitate in arachis oil; Roche, Basel, Switzerland). All supplements contained 40 IU vitamin E as an antioxidant. The supplements were given as single-dose gelatin capsules of identical taste and appearance. Every 4 months two capsules of each code, sampled from the study area, were analysed for vitamin A potency by a local laboratory unaware of their code. The mean retinol contents were 53 300 (SD 3513) and 246 (27) retinol equivalents, which is equivalent to 89% and 82% potency for the vitamin A (n = 19) and control (n = 20) capsules, respectively.

All households in a ward were visited by trained field staff every 4 months for a year. At baseline, children of 60 months and younger were enrolled; at follow-up visits only infants born during the study were later enrolled. Birth dates of children were determined by means of local events and Nepali astrological calendars. At each visit infants aged 6–11 months received half the contents of a capsule (6 drops of oil), equivalent to either 30 000 or 150 retinol equivalents, respectively, and children of 12 months and older received the whole contents of the capsule. After repeated household visits when children were absent, capsules were left in the home and the parents were asked to administer them. Families and children who moved within a ward were followed at each visit; those who moved out of a ward (less than 2% per round) were declared withdrawn at the next household visit. At each visit, a child's capsule receipt and vital status were recorded, left mid-upper arm circumference was measured with an insertion tape[14] and 7-day morbidity and 4-month measles histories were taken. Children of 12 months and older with an arm circumference below 11·5 cm were referred to local health posts. At the time of enrolment household and demographic indicators were assessed, including maternal histories of previous child mortality by the Brass method.[15]

At baseline an ocular survey was carried out in a 15% random sample of wards (n = 40). Children were examined for xerophthalmia at a central site by an ophthalmologist (S. K. K.) or a senior ophthalmic assistant. Chance-corrected inter-observer agreement,[16] based on 1001 independent replicates, was excellent (κ = 0·93). A history of night blindness ("ratandho ratauni") was elicited from parents for children of 12 months and older. All xerophthalmic and severely ill children were treated with vitamin A and referred to local health posts for follow-up, as indicated. These children are included in the analysis. Full details of this substudy will be published elsewhere.

Child deaths were identified by means of the regular 4-monthly census and by an independent vital events surveillance every 2 months in every ward. A "verbal autopsy" interview was carried out, usually within 2 months of death, for all children who died. Data were reviewed and probable causes of death were assigned independently by two physicians. Differences in assignment were discussed and a consensus cause of death assigned.

Capsule codes were broken and the four groups merged into control and vitamin A treatment groups. Baseline differences were tested by chi-square.[17] All analyses were carried out on an intention-to-treat basis. Computed mortality rates were based on child-years of observation. Relative risks were derived with all variance and 95% confidence interval estimates[17] adjusted to account for the design effect[18]—ie, the ward rather than individual serving as the unit of treatment allocation. Mortality rates and

TABLE III—INTERVAL-SPECIFIC AND ANNUAL MORTALITY OF CHILDREN 6–72 MONTHS OF AGE

	Time interval (x to x + 4)			
	0–4 mo	4–8 mo	8–12 mo	0–12 mo
No entered at x	24 805	1807	2018	28 630
Control	12 264	834	1045	14 143
Vitamin A	12 541	973	973	14 487
Withdrawals				
Control	174	207	152	533
Vitamin A	154	201	214	569
Child deaths				
Control	62	72	76	210
Vitamin A	48	51	53	152
*Child-years**				
Control	4049	4241	4505	12 795
Vitamin A	4147	4395	4633	13 175
Mortality (per 1000 child-years)				
Control	15·3	17·0	16·9	16·4
Vitamin A	11·6	11·6	11·4	11·5
Relative risk	0·76	0·68	0·67	0·70
(95% CI)	(0·50–1·15)	(0·45–1·00)	(0·45–0·99)	(0·56–0·88)

*Children who were withdrawn or who died during an interval were assigned 2 months of observation

TABLE IV ANNUAL MORTALITY OF CHILDREN AGED 6–72 MONTHS BY AGE AND SEX

	Control			Vitamin A			Relative risk (95% CI)
	Child-years	Deaths	MR	Child-years	Deaths	MR	
Sex							
Male	6531	89	13·6	6821	72	10·6	0·77 (0·55–1·09)
Female	6263	121	19·3	6354	80	12·6	0·65 (0·48–0·89)
Age (mo)							
6–11	1315	47	35·8	1393	39	28·0	0·78 (0·49–1·25)
12–23	2725	75	27·5	2790	53	19·0	0·69 (0·47–1·01)
24–35	2592	31	12·0	2724	27	9·9	0·83 (0·47–1·50)
36–47	2633	28	10·6	2657	18	6·8	0·64 (0·33–1·24)
48–59	2573	25	9·7	2649	13	4·9	0·51 (0·24–1·07)
60–72	956	4	4·2	964	2	2·1	0·50 (0·08–3·29)

MR = mortality rate (per 1000 child-years)

TABLE V ANNUAL MORTALITY OF CHILDREN AGED 6–72 MONTHS BY NUTRITIONAL STATUS AND AGE

Arm circumference (cm)	Control			Vitamin A			Relative risk (95% CI)
	Child-years	Deaths	MR	Child-years	Deaths	MR	
Children aged 6–11 mo							
<11·5	132	14	106·3	126	12	94·9	0·89 (0·37–2·12)
11·5–12·4	261	12	45·9	267	6	22·5	0·49 (0·17–1·41)
12·5–13·4	392	8	20·4	432	10	23·1	1·13 (0·40–3·16)
≥13·5	346	6	17·3	387	6	15·5	0·89 (0·25–3·11)
Unknown	184	7	38·0	179	5	27·9	0·73 (0·20–2·62)
Children 17–72 mo							
<11·5	208	61	293·3	191	33	172·6	0·59 (0·39–0·90)
11·5–12·4	721	15	20·8	759	24	31·6	1·52 (0·75–3·08)
12·5–13·4	2132	30	12·9	2371	16	6·7	0·52 (0·27–1·00)
≥13·5	6986	35	5·0	7159	29	4·1	0·82 (0·48–1·41)
Unknown	1232	22	17·9	1310	11	8·4	0·47 (0·21–1·03)

MR = mortality rate (per 1000 child-years)

relative risks were calculated across strata of age, sex, and nutritional status. A Poisson regression model[19] was fitted to estimate the effect of vitamin A on mortality with simultaneous adjustment for each of these factors.

The study protocol was approved by the Nepal Health Research Council in Kathmandu, Nepal, and by the Joint Committee on Clinical Investigation at the Johns Hopkins University School of Medicine in Baltimore, USA.

Results

24 805 children aged 6–60 months entered the trial at baseline (12 264 in the control group and 12 541 in the vitamin A group), which represented more than 96% of all children of eligible age in the study area. The two groups of children were very similar in their distributions of demographic and clinical characteristics (table I). The pooled prevalence of xerophthalmia in the random subsample of wards was 3·0%.

Treatment groups were also practically identical on more than 25 characteristics assessed in all participating households, including risk factors commonly associated with preschool child mortality (table II). In both treatment groups, at least one of the liveborn children of 42% of mothers had died, and 4% of households reported at least one preschool child death during the previous year. During the year before the trial in both treatment groups, the estimated infant mortality rate was 82 per 1000 livebirths and the 1–4-year-old mortality rate was 12–13 per 1000 children per year. Thus, the two groups showed no differences in many risk factors for mortality and by reported past mortality at the outset and were taken to represent the same population.

Capsule coverage remained high and equal in each group throughout the trial—about 88% of children in each group received the capsule contents from the staff at each visit. Capsules were left in the home for about 10% of children at each visit, of whom about 65% were estimated (by history on follow-up of a subsample) to have received the capsule contents from the parents. Thus, about 93% of all eligible children in each group received a supplement at each visit. At least 74% of all enrolled children in each group were known to receive their full quota of supplements; only 2% failed to receive any supplement.

The initial 24 805 children plus 3825 infants who entered the 6–11 month age range at the first or second 4-monthly visits (1879 controls, 1946 vitamin A) provided a total of 28 630 children who contributed 25 970 child-years of observation for this analysis (table III). There were 362 deaths during the 12 month period. The annual mortality rate was 16·4 per 1000 child-years in the control group and 11·5 per 1000 child-years in the vitamin A group, which gives a protective relative risk of 0·70 (95% CI 0·56–0·88) for a 30% reduction in child mortality. This CI and all others reflect a 23% increase in the estimated variance due to the design effect. The difference in risk increased from the first to the second interval of dosing and then remained stable during the third interval, which indicates a sustained effect.

The effect of vitamin A was evident across sex and age strata (table IV). There was a slightly greater reduction in mortality in girls than in boys. The excess female:male mortality ratio was somewhat smaller in the vitamin A than in the control group (relative risk 1·19 *vs* 1·42). The protective effect of vitamin A was consistent at each age and, except for children aged 24–35 months, became stronger with age (table IV).

The effect of acute nutritional status on the impact of vitamin A during a subsequent 4-month interval was examined separately in infants and older children (table V). Although arm circumference was measured at least once in 97% of the children, only 89% were measured at each visit, thus reducing by 11% the number of child-intervals for this analysis. In 8 of 10 age-status-specific strata, including the most malnourished and the best nourished children, vitamin-A-supplemented children had lower mortality ($p < 0·05$ by Wilcoxon signed rank test). No trend in the effect was observed with severity of wasting.

Multivariate analysis did not change the effect estimate. The relative risk of death in the vitamin A group, after simultaneous adjustment for the effects of sex, age, and

nutritional status by Poisson regression, was 0·72 (95% CI 0·55–0·95).

Based on 358 completed verbal autopsy reports, vitamin A seemed to reduce mortality ascribed to diarrhoea or dysentery (relative risk 0·61), wasting malnutrition (0·65), uncertain (infectious) causes (0·52), and measles (0·24). These "probable causes" accounted for 28%, 20%, 19%, and 4% of all deaths, respectively, in the combined groups. There was no apparent effect on mortality due to acute lower respiratory infection (1·29) or other miscellaneous causes (1·01), which accounted for 18% and 11%, respectively, of all deaths.

Discussion

Since the initial report from Indonesia on the effectiveness of periodic, large-dose vitamin A supplementation in reducing child mortality,[5] there have been several attempts to clarify the effect of vitamin A on child survival in different populations. Most trials have reported a profound effect, but one trial did not show a significant reduction in child mortality,[8] for reasons which remain unclear.[9-11]

More frequent supplementation of children with vitamin A may have a greater effect on child survival than less frequent dosing—supply of about half of a preschool child's daily requirement by way of fortification reduced mortality by 46% in Indonesia,[6] and weekly vitamin A doses of 2500 retinol equivalents reduced mortality by 54% in south India.[7]

The reduction in mortality was slightly greater in girls than in boys, which accords with the south Indian study.[7] As in Indonesia,[5] the effect of vitamin A in Nepal was stronger with age, reaching a 50% reduction in mortality in the fifth and sixth years of life. By contrast, the south Indian trial found the greatest effect among infants 6–11 months of age.[7] This variability may reflect differences in the age specificity and severity of vitamin A deficiency and other determinants of child mortality in different populations. Given the wide confidence intervals for all age-specific findings in all studies, it may also be chance variation.

A very small arm circumference (less than 11·5 cm) at the start of each interval was associated with a very high risk of mortality (table V), despite referral of such children to local health posts. However, acute nutritional status did not seem to modify the protective effect of vitamin A. A consistent effect of vitamin A across categories of wasting was also observed in south India, although its effect was stronger in stunted children.[7]

It is likely that vitamin A modifies the incidence, duration, or severity of life-threatening infectious illness, as seen with severe measles.[20,21] The verbal autopsy suggested that vitamin A had no effect on mortality attributed to acute lower respiratory infection. This finding is surprising, because there is evidence that vitamin A deficiency is linked to increased risk of respiratory infection.[22] However, the 40% reduction in deaths attributed to diarrhoea and dysentery is consistent with evidence that closely links mild xerophthalmia to risk of protracted diarrhoea.[23-25] The substantial reduction in mortality from measles (76%) is consistent with vitamin A measles intervention trials[20,21] from Africa and the weekly supplementation trial from India.

This trial provides a firm estimate of the efficacy of large-dose vitamin A prophylaxis in an endemically vitamin-A-deficient population. The large sample size, the similarity of the treatment groups, the high coverage while minimising visits to avoid a "contact" effect,[7] the checking of capsule potency, and the high level of ascertainment help to support the validity of the findings. A 30% reduction in preschool child mortality predicts that, in Nepal alone, where 2% or more of preschool children are xerophthalmic,[26] more than 15 000 deaths could be averted each year by adequate nourishment of children with vitamin A. In south Asia 0·7–1·1 million child deaths could probably be prevented annually by adequate vitamin A nourishment in the preschool years (J. Humphrey and colleagues, unpublished).

Although periodic, large-dose delivery may lead to a more modest reduction in child mortality than more frequent, smaller doses, this approach is a feasible strategy for most developing countries seeking to reduce child mortality with vitamin A by means of immediately available and affordable delivery systems.[27]

Periodic dosing should not preclude, or compete with, efforts to improve the local food supply and dietary vitamin A intake by vulnerable groups (eg, by means of gardens, dietary counselling, and fortification). However, there may be a compelling reason, in terms of child survival, to control vitamin A deficiency quickly through periodic supplementation while longer-term solutions are pursued.

This study was carried out under cooperative agreement no DAN 0045-A-5094 between the Office of Nutrition, US Agency for International Development (USAID), Washington, DC, and the Dana Center for Preventive Ophthalmology (DCPO). It was a joint undertaking betwen DCPO and the National Society for the Prevention of Blindness, Kathmandu, Nepal. The study was funded by USAID, with financial and technical assistance from Task Force Sight and Life (Roche, Basel), the United Nations Children's Fund (UNICEF), Nepal, and NIH grant no RR03060.

The Sarlahi Study Group (in addition to the authors) included Dr B. D. Chataut, Dr R. Adhikari, Dr D. Calder, Dr J. Gmunder, Lai-Chu See, J. Humphrey, J. Canner, L. Clement, N. N. Acharya, D. N. Mandal, T. R. Sakya, B. B. Shrestha, U. Khadka, R. K. Shrestha, M. D. Thapa, and S. R. Ranjit. We thank Prof James Tonascia for helpful statistical advice and oversight of the data safety and monitoring committee; the committee's other members, Dr F. Davidson, Dr M. R. Pandey, Dr I. Tarwotjo, and Mr D. Piet; and Y. Vaidya and K. B. Shrestha at the Central Food Research Laboratory in Kathmandu for the analyses of vitamin A supplements.

REFERENCES

1. Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhoea in children with preexisting mild vitamin A deficiency. *Am J Clin Nutr* 1984; **40:** 1090–95.
2. Milton RC, Reddy V, Naidu AN. Mild vitamin A deficiency and childhood morbidity—an Indian experience. *Am J Clin Nutr* 1987; **46:** 827–29.
3. Bloem MW, Wedel M, Egger RJ, et al. Mild vitamin A deficiency and risk of respiratory track diseases and diarrhea in preschool and school children in Northeastern Thailand. *Am J Epidemiol* 1990; **131:** 332–39.
4. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. *Lancet* 1983; ii: 585–88.
5. Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. *Lancet* 1986; i: 1169–73.
6. Muhilal, Permeisih D, Idjradinata YR, et al. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *Am J Clin Nutr* 1988; **48:** 1271–76.
7. Rahmathullah L, Underwood BA, Thulasiraj RD, et al. Reduced mortality among children in Southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; **323:** 929–35.
8. Vijayaraghavan K, Radhalah G, Prakasam BS, et al. Effect of massive dose vitamin A on morbidity and mortality in Indian children. *Lancet* 1990; **336:** 1342–45.
9. Thurnham DI. Vitamin A and childhood mortality. *Lancet* 1991; **337:** 232.
10. Reddy V, Vijayaraghavan K. Vitamin A and childhood mortality. *Lancet* 1991; **337:** 232.
11. Sommer A, West KP Jr. Vitamin A and childhood mortality. *Lancet* 1991; **337:** 925.

12. WHO UNICEF IVACG Task Force. Vitamin A supplements. A guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia. Geneva: World Health Organisation, 1988.
13. Brilliant LB, Pokhrel RP, Grasset NC, et al. Epidemiology of blindness in Nepal. *Bull WHO* 1985; **63:** 375–86.
14. Zerfas AJ. The insertion tape: a new circumference tape for use in nutritional assessment. *Am J Clin Nutr* 1975; **28:** 782–87.
15. United Nations Manual 10. Indirect techniques for demographic estimation. Department of International Economics and Social Affairs. Population Studies no 81. New York: United Nations, 1983.
16. Fleiss JL. Statistical methods for rates and proportions, 2nd ed. New York: Wiley and Sons, 1981.
17. Kahn HA, Sempos CT. Statistical methods in epidemiology. New York: Oxford University Press, 1989.
18. Katz J, Zeger SL, Tielsch JM. Village and household clustering of xerophthalmia and trachoma. *Int J Epidemiol* 1988; **17:** 865–69.
19. McCullagh P, Nelder JA. Generalized linear models, 2nd ed. New York: Chapman and Hall, 1989.
20. Barclay AJG, Foster A, Somme A. Vitamin A supplements and mortality related to measles: a randomized clinical trial. *Br Med J* 1987; **294:** 294–96.
21. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990; **323:** 160–64.
22. West KP Jr, Howard GH, Sommer A. Vitamin A and infection: public health implications. *Annu Rev Nutr* 1989; **9:** 63–86.
23. Stanton BF, Clemens JD, Wojtyniak B, Khair T. Risk factors for developing mild nutritional blindness in urban Bangladesh. *Am J Dis Child* 1986; **140:** 584–89.
24. Stoll BJ, Banu H, Kabir I, Molla A. Nightblindness and vitamin A deficiency in children attending a diarrhoeal disease hospital in Bangladesh. *J Trop Pediatr* 1985; **31:** 36–38.
25. Shahid NS, Sack DA, Rahman M, et al. Risk factors for persistent diarrhoea. *Br Med J* 1988; **297:** 1036–38.
26. West KP Jr. Vitamin A delivery prevention in Nepal: building a natural strategy. Proceedings of the XIII IVACG meeting, Kathmandu, Nepal. Washington, DC: The International Life Sciences Institute Nutrition Foundation, 1990: 11–18.
27. West JP Jr, Sommer A. Periodic large doses of vitamin A for the prevention of vitamin A deficiency and xerophthalmia: a summary of experiences. IVACG Report, Nutrition Foundation, 1984: 25–39.

High Dose Vitamin A Supplementation of Breast-Feeding Indonesian Mothers: Effects on the Vitamin A Status of Mother and Infant[1,2]

REBECCA J. STOLTZFUS,[3] MOHAMMAD HAKIMI,* KEVIN W. MILLER, KATHLEEN M. RASMUSSEN, SITI DAWIESAH,† JEAN-PIERRE HABICHT AND MICHAEL J. DIBLEY**

Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853-6301; *Clinical Epidemiology and Biostatistics Unit and †Biochemistry Laboratory, Faculty of Medicine, Gadjah Mada University, Yogyakarta 55001, Indonesia; and **Division of Human Nutrition, Department of International Health, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD 21205

ABSTRACT For regions where vitamin A deficiency is common, high dose vitamin A supplementation of lactating mothers is currently recommended, but the effects of this intervention have not been carefully evaluated. We conducted a randomized, double-blind trial in which 153 Indonesian mothers 1–3 wk postpartum received either a capsule containing 312 μmol of vitamin A as retinyl palmitate or a placebo. Mothers' serum retinol concentrations in the vitamin A group tended to be lower than in the placebo group at baseline but higher at 3 mo postpartum (1.39 vs. 1.24 μmol/L, $P = 0.03$) and 6 mo postpartum (1.23 vs. 1.08 μmol/L, $P < 0.01$). The milk retinol concentrations of the vitamin A group were higher than those of the placebo group by 0.48 to 1.18 μmol/L at 1–8 mo postpartum ($P < 0.05$). Among the infants at 6 mo of age, the prevalences of low serum retinol concentration (<0.52 μmol/L) were 36 and 15% in the placebo and vitamin A groups, respectively ($P < 0.005$), and the prevalences of low vitamin A stores (assessed by relative dose response) were 23 and 10%, respectively ($P < 0.03$). High dose vitamin A supplementation of lactating mothers is an efficacious way to improve the vitamin A status of both mother and breast-fed infant. J. Nutr. 123: 666–675, 1993.

INDEXING KEY WORDS:

- *vitamin A* • *women* • *lactation*
- *breast milk* • *infants*

Vitamin A deficiency is one of the most prevalent and important nutritional deficiencies among children of less-developed countries (McLaren 1986). Severe vitamin A deficiency causes xerophthalmia, and there is mounting evidence that even mild vitamin A deficiency contributes to increased mortality in childhood (Daulaire et al. 1992, Rahmathullah et al. 1990, Sommer et al. 1986, West et al. 1991). Although pre-school children are at highest risk for vitamin A deficiency (Tielsch and Sommer 1984), it may also be an important public health problem for infants. Most trials have found that vitamin A supplementation reduced mortality in the 6–11-mo age group (Daulaire et al. 1992, Rahmathullah et al. 1990, West et al. 1991), and in two studies (Daulaire et al. 1992, Rahmathullah et al. 1990) supplemental vitamin A had the greatest mortality-sparing effect in that age group.

For regions where vitamin A deficiency is common, supplementation of lactating mothers has been proposed as a way to increase the mother's milk vitamin A content and provide additional vitamin A to the breast-fed infant. Supplementation of lactating mothers in the first month postpartum is currently recommended by the World Health Organization as part of vitamin A capsule distribution programs

[1]Parts of this report were presented at Nutrient Regulation during Pregnancy, Lactation and Infant Growth, a conference of the International Society for Research of Human Milk and Lactation, August 9–12, 1992, Stockholm, Sweden and in abstract form [Stoltzfus, R. J., Hakimi, H., Miller, K. W. and Rasmussen, K. M. (1992) High-dose vitamin A supplementation of lactating women in rural Central Java, Indonesia improves mother's and infant's vitamin A status. FASEB J. 6: A1497 (abs.)].

[2]Supported by a grant from the Thrasher Research Fund and a National Science Foundation Graduate Fellowship to Rebecca J. Stoltzfus.

[3]To whom correspondence should be addressed at the current address: Division of Human Nutrition, Department of International Health, School of Hygiene and Public Health, Johns Hopkins University, 615 N. Wolfe St., Baltimore, MD 21205.

0022-3166/93 $3.00 © 1993 American Institute of Nutrition. Received 11 August 1992. Accepted 9 December 1992.

103

(WHO/UNICEF/IVACG Task Force 1988). However, insufficient evidence has been available regarding the efficacy of maternal supplementation and the importance and extent of vitamin A deficiency in infancy to enable policymakers to evaluate the importance of maternal supplementation in the face of other program demands.

Other epidemiologic studies of high dose vitamin A supplementation of lactating women have been conducted, but they have not been randomized and placebo controlled (Roy et al. 1989, Thanangkul et al. 1974). A previous trial in Indonesia (Muhilal et al. 1985) was adequately designed, but the mothers were supplemented later in lactation (mo 1–5) than is currently recommended, and the effect on the mother's vitamin A status was not measured.

For these reasons, we conducted a randomized, placebo-controlled, double-masked trial in rural Central Java, Indonesia, to measure the effects of supplementing mothers postpartum with 312 μmol of vitamin A. We hypothesized that *1*) the decrease in mothers' vitamin A status over the first 6 mo of lactation would be less in the vitamin A group than in the placebo group, *2*) the concentration of vitamin A in the breastmilk at mo 1–6 of lactation would be at least 0.17 μmol/L higher in the vitamin A group than in the placebo group, and *3*) the vitamin A status of infants at 6 mo of age would be higher in the vitamin A group than in the placebo group.

MATERIALS AND METHODS

Study population. The study was conducted in 12 villages in the subdistrict of Prembun in Central Java, Indonesia. This rural, agricultural area consists of both fertile rice plains and foothills, in which fruits, vegetables, lumber and spices are grown. The subdistrict is served by one Community Health Center (Puskesmas) and by a system of Integrated Health Posts (Posyandu) at the sub-village level. In addition to other services, the public health system provides prenatal care and immunizations, and semiannually distributes vitamin A capsules to children age 1–5 y.

We attempted to recruit into the study all mothers who delivered live infants between August 1 and December 1, 1990. Each week, field workers contacted the village clerks (to whom families must report births) as well as all midwives and traditional birth attendants who served the study area to obtain a list of the mothers who delivered infants in the past week. The numbers of mothers who were excluded, refused to join, or dropped out of the study are shown in **Figure 1**. Two pairs of twins were recruited into the study, but in both cases only one infant remained in the family for more than 1 mo. (In one case, one baby died; in the other, one baby was given to another family.) Only data from the remaining infant were used.

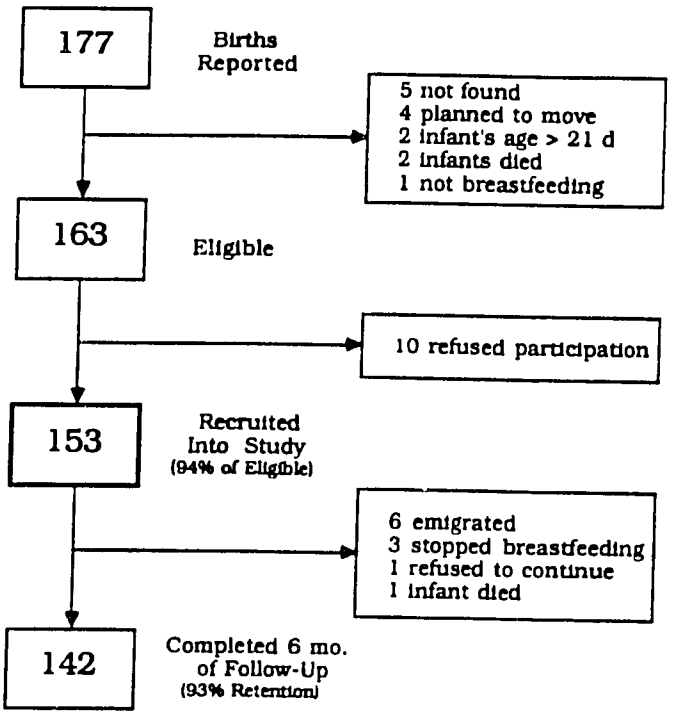


FIGURE 1 Casefinding, recruitment and retention of study participants. Of those recruited into the study, 77 received vitamin A and 76 received placebo. Of the 11 who did not complete follow-up, 8 were in the vitamin A group, and 3 were in the placebo group. Rates of loss to follow-up in the two treatment groups were not statistically significantly different ($P > 0.10$ by χ^2 test).

Before beginning data collection, a number of meetings were held in the villages during which the consent and cooperation of the village leaders and the Community Health Center physician were obtained. Written informed consent was obtained from all study participants. The study was approved by the Cornell University Committee on Human Subjects and the Committee on Ethics in Human Biomedical Research of the Faculty of Medicine, Gadjah Mada University.

Randomization and supplementation. When we learned of a birth, the family was visited by an anthropologist (and usually a local village staff person) who explained the purpose and procedures of the study and obtained written informed consent (unless the mother refused). At 2 wk postpartum (acceptable range, 7–21 d), the mother was visited by several field workers who obtained baseline data and then administered the intervention.

Individual randomization to treatment codes A and B was done in blocks of eight according to the Moses-Oakford assignment algorithm (Meinart 1986). We chose not to stratify randomization on key variables because with a sample size greater than 50 per group, the benefit from stratified randomization is small compared with the logistical complexity of conducting it (Meinart 1986). The allocation of treatment

104

codes A and B to vitamin A or placebo capsules was done by the Sight and Life Task Force, Hoffmann-LaRoche (Basel, Switzerland), who prepared the capsules. All investigators, field and laboratory staff and study participants were blinded to the randomization code until field work was completed.

Three gelatin capsules, each containing either 104 μmol of retinyl palmitate plus 46 μmol of all-*rac*-α-tocopherol in oil, or oil alone, were packaged in foil envelopes with labels bearing identification numbers from 001 to 200, according to the randomization scheme. The placebo and vitamin A capsules looked practically identical. The mothers swallowed the capsules in the presence of field staff. One half of the label from the capsule envelope, bearing the identification number, was removed and attached to a data form.

Data collection regime. Mother's vitamin A status was assessed by serum retinol, conjunctival impression cytology (CIC) and relative dose response (RDR) at baseline, 3 mo and 6 mo postpartum. Infant's vitamin A status was assessed by serum retinol and RDR at 6 mo. A breast milk sample was obtained at baseline and mo 1–6 postpartum and was analyzed for fat content (data not presented) and vitamin A. Mother's dietary intake of vitamin A was assessed using a food frequency method based on the IVACG guidelines (IVACG 1989) at baseline, 3 mo and 6 mo postpartum. Infant's non-breast milk food intake was assessed by 1-wk recall at baseline and mo 1–6. The diets of mothers and infants in the two treatment groups were not found to differ at any time in the study (data to be presented elsewhere). Mother's weight was measured at baseline and 6 mo postpartum, and height at 3 mo postpartum. Infant's weight was measured at baseline, 3 mo and 6 mo, and length at 6 mo.

After the study was in progress, an ancillary study of mother's and infant's iron status was begun. This study was observational; no iron intervention was conducted. For this purpose, a follow-up visit at 8 mo was added to the design, at which time another breast milk sample was obtained. At 8 mo, a milk sample was obtained from 137 (90%) of the mothers. The milk vitamin A data at 8 mo are presented here; however, iron status will be presented elsewhere.

All infants were supplemented with 104 μmol of retinyl palmitate at the conclusion of the study.

Field methods. All data and samples were collected in the mother's home (or occasionally at her workplace). Anthropometric meaurement techniques were standardized as described by Habicht (1974). Mother's height was measured to the nearest 0.1 cm using a portable stadiometer. Mother's weight was measured to 0.1 kg with a Seca Integra digital scale (Seca Corp., Columbia, MD). Infant's weight was measured to the nearest 0.1 kg with a hanging Salter scale (Salter Industrial Measurement Limited, West Midlands, England).

Breast milk samples were collected using a manual breast pump (Model 500, White River, Laguna Hills, CA). Six local village women were trained to collect all the milk from one breast until no more milk could be obtained either by pump or by the mother's hand. (If the mother was still able to manually express milk, the worker continued to use the pump.) Samples were collected between 0900 and 1100 h from a breast that had not been nursed for at least 1 h. The entire sample was stored in a dark glass bottle on ice, then transported to the field office, where it was stored at 4°C for 4 to 30 h. Before being transported to the laboratory, the samples were warmed to room temperature, swirled gently to homogenize, and 200-μL aliquots stored in yellow polypropylene screw-cap tubes (12 × 75 mm, Baxter Healthcare, Edison, NJ).

Capillary blood samples were obtained from the mothers by fingerprick and from the infants by fingerprick or heelprick. Blood was collected into a Microtainer serum separator tube (Becton Dickinson and Co., Rutherford, NJ). Blood samples were transported in coolers to the field office, where they were centrifuged and stored at 4°C for 24 to 48 h before being transported to the laboratory.

The RDR procedure was performed by taking a morning blood sample, then placing 1.75 μmol of vitamin A in aqueous solution (Aquasol A, Rorer Pharmaceutical, Fort Washington, PA) on the subject's tongue. We used a dose 10% higher than the dose of 1.57 μmol that has been recommended based on clinical studies to ensure that the full test dose would be delivered even if a drop remained on the syringe. This slightly greater dose is within the variation in RDR dosages used successfully by previous investigators. After receiving the dose, the subject was urged to drink water or tea (or breast-feed, if the subject was an infant). A second blood sample was taken 5 h after the dose was given.

Specimens for CIC were obtained using the method of ICEPO (1988). Briefly, a small strip of cellulose acetate filter paper (pore size 0.45 μm, Millipore, Bedford, MA) was applied to the inferior-temporal portion of the conjuctiva, then peeled away from the conjunctiva using a blunt forceps. A specimen from each eye was stored at room temperature in fixative for up to 3 mo until processed in the laboratory.

Laboratory procedures. Serum in 100-μL (occasionally 50-μL) aliquots was stored in test tubes at −20°C until analyzed. For analysis, samples were thawed, and all-*trans*-retinyl acetate internal standard was added. The sample was mixed with ethanol, extracted into hexane, then redissolved in methanol. Retinol was determined by HPLC, with methanol-water (95:5) as eluent, using a 15-cm C18 Resolve column (Waters, Milford, MA).

Pre-dose and post-dose RDR specimens were analyzed in the same batch. The RDR was calculated as $((A_5 - A_0)/A_5)\cdot 100$, where A_0 and A_5 are the pre-dose and post-dose serum retinol values, respectively.

Milk samples were capped with nitrogen gas and stored at −20°C until analysis. For analysis, samples were thawed, hydrolyzed at room temperature with alcoholic KOH, washed with 100 g/L NaCl, and extracted in hexane. All-*trans*-retinyl acetate internal standard was added, the extract was washed again with water, then redissolved in methanol. Retinol was determined by HPLC as described for serum.

The CIC specimens were stained with periodic acid-Schiff reagent and Harris hematoxylin and mounted on slides. All specimens were interpreted by one of us (KWM) using a light microscope, following the algorithm of ICEPO (1988).

Data management and statistical analysis. All data were recorded onto pre-coded forms, reviewed by a supervisor in the field, then entered in blind duplicate into the computer. Data were entered and cleaned using the software dSURVEY (Corner 1989). Statistical analyses were conducted using SYSTAT statistical software (Wilkinson 1990). Crude treatment effects were tested using Student's *t* test for continuous outcomes and χ^2 or Fisher's exact test for categorical outcomes. For mother's serum retinol and milk retinol concentrations, the distribution of values in the two groups and the frequency of values <1.05 μmol/L were compared. Logistic regression was used to adjust for the influence of modifying variables on the association between treatment and infant's vitamin A status. Significance levels for tests of treatment effects (i.e., post-intervention, between-group comparisons) are one-tailed, in accordance with our hypotheses; all other significance levels are two-tailed. A probability level of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics. The baseline characteristics of the mothers and their infants are shown in **Table 1**. The age distributions of the two groups differed, with the placebo group being more centered in the 20–29-y category. Mothers who received vitamin A were of higher parity and had less schooling, although these differences were not statistically significant. Other socio-economic data (not shown) confirm that the vitamin A group tended toward characteristics usually associated with poorer health and nutritional status. The infants' characteristics were similar in the two groups, with the exception of sex: only 38% of infants in the vitamin A group were boys, compared with 52% in the placebo group.

Mother's vitamin A status. Mother's vitamin A status was assessed by three methods: serum retinol concentration, RDR and CIC. In accord with other baseline characteristics, the vitamin A group tended to have lower serum retinol concentrations before supplementation (**Table 2**). The beneficial effect of supplementation was evident in two ways. First, at both 3 and 6 mo postpartum, the serum retinol concentrations of the vitamin A group were significantly higher than those of the placebo group. The intervention effectively shifted the distribution of serum retinol concentrations for the vitamin A group toward higher values. For example, at 6 mo postpartum the 25th, 50th and 75th percentiles for the vitamin A group were 1.01, 1.18 and 1.43 μmol/L, respectively, compared with 0.84, 1.05 and 1.29 μmol/L for the placebo group. Also, at 6 mo postpartum, 30% of the vitamin A group had serum retinol concentrations of <1.05 μmol/L, compared with 47% of the placebo group (χ^2 test, $P = 0.02$). Second, the vitamin A group ended 6 mo of lactation with slightly but not significantly higher serum retinol concentration than they began it, whereas the placebo group experienced a significant decline over the same period.

In contrast to serum retinol, mother's RDR values were not significantly affected by supplementation. The percentages of mothers with RDR >20% at baseline, 3 mo and 6 mo postpartum were 9.2, 10.3

TABLE 1

Baseline characteristics of study participants by treatment group[1]

	Vitamin A treatment group	Placebo treatment group	Significance level[2]
Mothers' characteristics			
Age, *y*			0.027
10–19	8 (10.4%)	4 (5.3%)	
20–29	37 (48.1%)	54 (71.1%)	
30–39	28 (36.4%)	14 (18.4%)	
40–49	4 (5.2%)	4 (5.3%)	
Total pregnancies			0.126
1	21 (27.3%)	22 (28.9%)	
2–4	30 (39.0%)	39 (51.3%)	
>4	26 (33.8%)	15 (19.7%)	
Weight, *kg*	47.4 ± 5.8	47.8 ± 6.1	0.654
Height,[3] *cm*	150.9 ± 5.1	149.8 ± 4.8	0.186
Education level			0.133
<6 y	29 (37.7%)	20 (26.3%)	
≥6 y	48 (62.3%)	56 (73.7%)	
Infants' characteristics			
Sex			0.089
Male	29 (37.7%)	39 (51.3%)	
Female	48 (62.3%)	37 (48.7%)	
Weight, *kg*	3.4 ± 0.4	3.4 ± 0.5	0.917

[1]For mothers' age and total number of pregnancies and for infants' sex, values are counts of individuals in the category. For mothers' weight and height and for infants' weight, values are means ± SD. For vitamin A group, $n = 77$; for placebo group, $n = 76$.

[2]From *t* test for weight and height, otherwise χ^2 test.

[3]Measured at 3 mo postpartum.

TABLE 2

Mothers serum retinol concentrations at baseline, 3 mo and 6 mo postpartum in the vitamin A and placebo treatment groups[1]

Time postpartum	Vitamin A treatment group: Mean ± SD (n)	Median	Frequency <1.05 μmol/L	Placebo treatment group: Mean ± SD (n)	Median	Frequency <1.05 μmol/L
	μmol/L		%	μmol/L		%
0.5 mo	1.17 ± 0.45 (69)	1.07	45	1.31 ± 0.51 (71)	1.25	31
3 mo	1.39 ± 0.49[2] (70)	1.42	21	1.24 ± 0.43 (69)	1.13	33
6 mo	1.23 ± 0.34[3] (67)	1.18	30[4]	1.08 ± 0.37[5] (72)	1.05	47

[1]Treatment was administered immediately following the 0.5-mo postpartum (baseline) evaluation. Comparisons of mean values were tested by *t* test; frequencies tested by χ^2 test. *P* values for tests of treatment effect are one-tailed, in accord with stated hypotheses.
[2]Vitamin A group significantly different from placebo group, $P < 0.05$.
[3]Vitamin A group significantly different from placebo group, $P < 0.01$.
[4]Vitamin A group significantly different from placebo group, $P < 0.02$.
[5]For placebo group, 6 mo value significantly different from baseline value, $P < 0.01$.

and 3.0%, respectively, for the vitamin A group, and 4.4, 9.0 and 1.5% for the placebo group. Differences between the groups at each time and trends within each group over time were not statistically significant.

Using abnormal CIC in both eyes as the criterion for vitamin A deficiency (the standard definition), there was no clear trend in the placebo group over time (**Table 3**). In the vitamin A group, there was a decreasing trend, which was not statistically significant. Using the more liberal criterion of one or both eyes abnormal, the decreasing trend in the vitamin A group was statistically significant (Table 3). The placebo group showed no significant change over time.

Breast milk vitamin A. The vitamin A group tended to have lower milk vitamin A concentrations at baseline, but following supplementation this group had significantly higher levels for the duration of the study (**Table 4**). For each point in time, supplementation shifted milk retinol concentrations up by 0.48 to 1.18 μmol/L. In the vitamin A group, only one mother's milk vitamin A was <1.05 μmol/L at 1 mo postpartum compared with 16 mothers (24%) in the placebo group ($P < 0.0001$), and at all other times milk vitamin A concentrations of <1.05 μmol/L were significantly less frequent in the vitamin A group than in the placebo group.

Infants' vitamin A status. Infants' vitamin A status at 6 mo was assessed by serum retinol and RDR. Although the range of serum retinol concentrations for the two treatment groups was similar, low values were more common in the placebo group (**Fig. 2, Table 5**). Mean serum retinol concentrations in the two groups differed in the expected direction, but the difference was not significant. However, serum retinol concentrations of <0.52 μmol/L were more than twice as common in the placebo group than in the vitamin A group ($P < 0.005$).

The frequency of abnormal RDR was significantly greater among infants in the placebo group (Table 5). Because of the difference in sex distribution between the groups, we used logistic regression to adjust for the influence of sex and other variables on the treatment effect. The final model included the covariates sex, mother's total number of pregnancies, and a sex by total pregnancies interaction term. This yielded an odds ratio of 0.30 (95% confidence limits, 0.11, 0.84) for abnormal RDR (>20%) in the vitamin A group relative to the placebo group. This is a larger treatment effect than the unadjusted odds ratio, which is 0.38 (95% confidence limits, 0.14, 1.01).

TABLE 3

Abnormal conjunctival impression cytology (CIC) over time by treatment group[1]

Time postpartum	Vitamin A treatment group	Placebo treatment group
	both eyes abnormal[2]	
0.5 mo	7/77 (9.1%)	4/76 (5.3%)
3 mo	5/74 (6.8%)	7/74 (9.5%)
6 mo	2/69 (2.9%)	3/73 (4.1%)
	one or both eyes abnormal[3]	
0.5 mo	25/77 (32.5%)	21/76 (27.6%)
3 mo	17/74 (23.0%)	17/74 (23.0%)
6 mo	9/69 (13.0%)	17/73 (23.3%)

[1]Treatment was administered immediately following 0.5-mo (baseline) assessment.
[2]Numbers are proportion abnormal in each group.
[3]For vitamin A group, χ^2 test for trend over time, $P < 0.006$.

TABLE 4

Mothers' milk retinol concentrations at baseline and during 8 mo follow-up in the vitamin A and placebo groups[1]

Time postpartum	Vitamin A treatment group: Mean ± SD (n)	Median	Frequency <1.05 μmol/L	Placebo treatment group: Mean ± SD (n)	Median	Frequency <1.05 μmol/L
	μmol/L		%	μmol/L		%
0.5 mo	2.30 ± 1.42 (70)	1.98	10	2.69 ± 1.53 (66)	2.35	8
1 mo	3.10 ± 1.77[2] (64)	2.75	2[2]	1.92 ± 1.20 (67)	1.66	24
2 mo	2.61 ± 1.48[2] (64)	2.34	13[3]	1.76 ± 1.30 (69)	1.33	32
3 mo	2.45 ± 1.23[2] (57)	2.29	11[3]	1.82 ± 1.28 (60)	1.47	32
4 mo	2.80 ± 1.61[2] (67)	2.42	6[2]	1.81 ± 1.13 (71)	1.59	28
5 mo	2.38 ± 1.34[2] (65)	2.11	6[2]	1.68 ± 1.01 (73)	1.41	30
6 mo	2.36 ± 1.17[2] (66)	2.24	9[3]	1.77 ± 0.97 (70)	1.75	24
8 mo	2.04 ± 1.19[3] (63)	1.91	16[4]	1.56 ± 0.99 (65)	1.40	28

[1]Treatment was administered immediately following the 0.5-mo post-partum (baseline) evaluation. Comparisons of mean values were tested by *t* test; frequencies tested by χ^2 test. *P* values are one-tailed, in accord with stated hypotheses.
[2]Vitamin A group significantly different from placebo group, $P < 0.005$.
[3]Vitamin A group significantly different from placebo group, $P < 0.01$.
[4]Vitamin A group significantly different from placebo group, $P < 0.05$.

DISCUSSION

Study population. Despite random allocation to treatment groups, baseline characteristics of the two groups were not identical. The probability that differing characteristics between the groups caused the observed differences in outcome measures is included in the significance levels of the treatment effects (Pocock 1983), i.e., that probability is <5%. By chance, the vitamin A group had lower vitamin A status at baseline as assessed by mother's serum retinol concentration, RDR, CIC and milk vitamin A concentration. Thus the true improvement in mother's vitamin A status due to supplementation is likely to be even larger than is apparent from simple comparisons of the vitamin A group with the placebo group. Similarly, for the effect of treatment on infants' vitamin A status, adjusting for other characteristics resulted in larger treatment effects.

Mother's vitamin A status. There are relatively little data on the vitamin A status of women during lactation, and therefore no normative values are available with which to evaluate the degree of vitamin A deficiency in our study population. Recently, reference serum vitamin A distribution curves for children have been published (Flores et al. 1991), but these curves are inappropriate for adults because normal serum vitamin A concentrations increase as

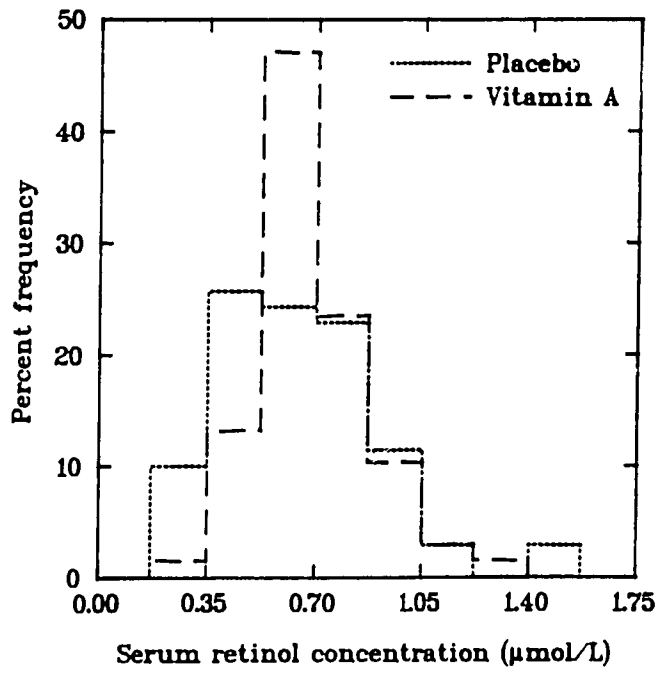


FIGURE 2 Frequency distribution of infants' serum retinol concentrations at 6 mo of age by treatment group. For vitamin A group, $n = 68$; for placebo group, $n = 70$.

TABLE 5

Infants' vitamin A status at 6 mo of age by treatment group

Measure of vitamin A status	Vitamin A treatment group	Placebo treatment group
Serum retinol concentration,[1] μmol/L	0.670 ± 0.192	0.651 ± 0.260
Serum retinol category[2]		
<0.52 μmol/L	10 (15%)	25 (36%)
≥0.52 μmol/L	58 (85%)	45 (64%)
Relative dose response (RDR)[3]		
<20%	60 (90%)	49 (77%)
≥20%	7 (10%)	15 (23%)

[1]Values are means ± SD, n = 68 for vitamin A group, n = 70 for placebo group. Data from four infants (one vitamin A, three placebo) are missing due to laboratory error.

[2]For each cutoff, numbers are counts of infants in each category; χ^2 test for association between treatment group and serum retinol category, $P < 0.005$.

[3]Chi-square test for association between treatment group and RDR status, $P < 0.03$. Data from 11 infants (two vitamin A, nine placebo) are missing due to laboratory error.

children age (Lewis et al. 1990). In the First National Health and Nutrition Examination Survey (NHANES I) (Pilch 1987), 3.9% of adult women had serum vitamin A concentrations of <1.05 μmol/L. In contrast, in this study population 33% of placebo group mothers at 3 mo postpartum and 47% at 6 mo postpartum had values below this cutoff. Even among mothers in the vitamin A group, the proportion of serum retinol values <1.05 μmol/L was 21% at 3 mo postpartum and 30% at 6 mo postpartum.

Because serum retinol concentration is homeostatically controlled over the range of adequate liver stores, an increase in serum retinol concentration following high dose supplementation is considered evidence of vitamin A deficiency (Underwood 1990). Typically, a 30-d period (pre-dose to post-dose) has been used (Flores et al. 1984 and 1991). In this study, mother's serum retinol concentrations were still significantly higher 3 mo post-supplementation. On this basis, this population of lactating women can be said to be vitamin A deficient.

A rise in serum retinol concentration following supplementation is also the basis for the RDR method, and very high agreement has been reported between baseline RDR and 30-d response in children's serum retinol following high dose supplementation (Flores et al. 1984 and 1991). It is therefore surprising that <10% of mothers in this study had low vitamin A status as assessed by RDR. Physiologic factors, such as protein deficiency, that could cause a vitamin A–deficient person to have a normal (i.e., nonresponsive) RDR test would also interfere with the utilization of a high dose of vitamin A. Because of the significant rise in mothers' serum retinol concentrations following high dose supplementation, neither vitamin A sufficiency in the population nor other physiologic characteristics of the population can explain the infrequency of abnormal RDR in this population.

A possible explanation for the insensitivity of RDR to vitamin A deficiency in this study is that the dose of vitamin A used in the RDR test (1.57 μmol or 450 μg) is appropriate for children (and the infants in this study) but too small for adults. This has also been suggested by Solomons et al. (1990), who found surprisingly low rates of abnormal RDR values in a population of Guatemalan adults believed to be mildly vitamin A deficient.

Further evidence of vitamin A deficiency in this population of mothers is the fact that the serum retinol concentrations of the placebo group declined over the first 6 mo of lactation. From our assessments at 3-mo intervals of the dietary vitamin A intake of the mothers, no effect of season was observed (data not shown). We attribute the decline in maternal vitamin A status over lactation to the transfer of a large quantity of vitamin A from the mother's stores to the infant via the mother's milk, coupled with an intake of vitamin A that is not increased sufficiently during lactation to balance the drain on her stores. Similar declines in serum retinol concentration during lactation have been observed in El Salvadoran (Arroyave et al. 1974) and Gambian (Bates 1983) women.

Supplementation with 312 μmol of vitamin A improved mother's vitamin A status and offset the depleting effect of the first 6 mo of lactation; however, it did not increase the mother's stores of vitamin A enough for her to remain vitamin A replete throughout lactation. The decline in serum retinol concentration from 3 to 6 mo postpartum in the vitamin A group was nearly parallel to that in the placebo group. Supplementation seems to have simply raised the starting point for their decline.

To our knowledge, this is the first report of CIC results from a population of mildly vitamin A–deficient adults. Because xerophthalmia is rare in adults (Tielsch and Sommer 1984), one would expect lower prevalences of abnormal CIC in adults than in preschool children. The prevalence of cases with both eyes abnormal was <10%, although about a quarter of the population had one eye abnormal. The trend toward decreasing prevalence of abnormal CIC following supplementation suggests that improved vitamin A status resulted in healthier conjunctivas in these women.

Two points about the CIC data deserve consideration. First, the prevalence of abnormal CIC in the vitamin A group decreased from 3 to 6 mo postpartum as well as from baseline to 3 mo postpartum. If the observed trend is caused by improved vitamin A

status, then the healing process is a relatively slow one. In children, reversion from abnormal to normal CIC following high dose vitamin A supplementation takes from 2 wk to >2 mo (Natadisastra et al. 1987). Second, the serum retinol concentration of the placebo group declined during lactation, but there was no trend toward increasing prevalence of abnormal CIC over the same period. Apparently there is a lag period between the response of biochemical indicators of vitamin A status to vitamin A supplementation and response of CIC.

Although mothers' serum retinol, RDR and CIC were not measured after 6 mo postpartum, the fact that the milk retinol concentration of supplemented mothers was significantly higher at 8 mo postpartum is evidence that the effect of supplementation on the mother's vitamin A status persisted for at least 8 mo.

Breast milk vitamin A. The mean breast milk vitamin A concentrations for both groups are in the range measured in American (Kim et al. 1990, Vaisman et al. 1985) and Swedish (Gebre-Medhin et al. 1976) women. Mean breast milk vitamin A concentrations in populations in less developed countries vary widely. In studies of mothers' serum and milk vitamin A concentrations in Thailand (Thanangkul et al. 1974), Bangladesh (Roy et al. 1989), El Salvador (Arroyave et al. 1974) and The Gambia (Bates 1983), mean serum retinol concentrations were 1.15, 1.32, 1.08 and 1.11 μmol/L, respectively, whereas mean milk vitamin A levels (at mo 3–4 of lactation) were 1.50, 1.11, 0.63 and 1.84 μmol/L. These divergent milk vitamin A levels in areas with similar serum concentrations may reflect variation in methods for sampling and determining milk vitamin A as much as they reflect biological variation among the populations—milk is a much more heterogenous fluid than serum. The mean milk vitamin A levels in our placebo group (~1.75 μmol/L) are nearly triple the mean level of 0.61 μmol/L recently reported in West Java (Muhilal et al. 1988). (Mothers' serum retinol levels in West Java were not measured.) This could be due to differences in the vitamin A status of the study populations or differences in methods. In the West Java study, milk samples were collected in the middle of a feeding, and vitamin A was analyzed by the trifluoroacetic acid method.

In contrast to serum concentrations, milk vitamin A levels in both groups were relatively constant from mo 2 to mo 8 of lactation. It is generally true that during the first 2 mo of lactation, milk vitamin A concentrations decline from the high levels of colostrum to the lower levels of mature milk and then remain relatively constant (Wallingford and Underwood 1986). Among the studies mentioned above, in Thailand (Thanangkul et al. 1974) and Bangladesh (Roy et al. 1989) milk vitamin A levels were fairly stable after mo 2 of lactation, but in El Salvador (Arroyave et al. 1974) milk levels declined from mo 2 to mo 4 of lactation.

Infants' vitamin A status. Breast-feeding has been shown to protect against vitamin A deficiency in infancy (Tarwotjo et al. 1982, West et al. 1986); nonetheless, breast-fed infants of mothers with marginal vitamin A status may be vitamin A deficient. Nearly one-fourth of infants in the placebo group had RDR values >20% at 6 mo of age indicating critically low liver stores. Infants are born with low reserves of vitamin A even if the mother is not vitamin A deficient (Wallingford and Underwood 1986) and are dependent on vitamin A–rich breast milk to build up stores of the vitamin. In this study, vitamin A supplementation of the mother protected infants from serum retinol concentrations of <0.52 μmol/L and decreased the odds of low liver stores by about two-thirds at 6 mo of age.

It is possible that the difference in vitamin A status between the vitamin A and placebo groups was even larger later in infancy. Because the mothers' milk vitamin A was still elevated until at least 8 mo postpartum, the effect of the intervention on the infants' vitamin A stores may have continued to accumulate into late infancy. As supplementary foods (which are often low in vitamin A) gain importance in the infant's diet, the infant will become more dependent on its vitamin A stores. Thus the health benefits to the infants from this intervention may be reaped in late infancy or the second year of life.

Other studies of maternal vitamin A supplementation. Several epidemiologic studies of vitamin A supplementation during lactation have been conducted using vitamin A–rich or fortified foods as the form of supplement. In a trial of the effects of vitamin A fortification of sugar in El Salvador (Arroyave et al. 1974), mothers' serum and milk vitamin A concentrations at 4 mo postpartum were significantly greater than in mothers who consumed nonfortified sugar. Infants' serum retinol concentrations were higher in the intervention group, but not significantly so. Vitamin A fortification of monosodium glutamate increased mothers' milk vitamin A levels in West Java (Muhilal et al. 1988). However, in a relatively vitamin A–replete population of Filipino mothers, consumption of vitamin A–fortified monosodium glutamate improved vitamin A concentrations in serum but not milk (Bongga 1982). Provision of a vitamin A–rich food supplement to Gambian mothers did not raise mothers' serum retinol concentrations (Bates 1983), but this study was not randomized and was inadequately controlled.

Three other studies of high dose vitamin A supplementation to lactating women in less developed countries have been reported. In a randomized, placebo-controlled trial in West Java, supplementation of mothers at 1–5 mo postpartum with 416 μmol of vitamin A increased milk vitamin A levels at 3 mo post-supplementation by 0.35 μmol/L and significantly increased infants' serum retinol concentrations at 6 mo post-supplementation (Muhilal et al.

110

1985). In a nonrandomized study in Thailand (Thanangkul et al. 1974), supplementation of mothers at delivery with 312 μmol of vitamin A raised serum retinol concentrations in the mothers through mo 9 postpartum, raised milk levels by ~0.17 μmol/L through mo 7 postpartum and raised infants' serum retinol concentrations at mo 1–7 of age, relative to a group that received no intervention. Finally, in Bangladesh (Roy et al. 1989), supplementation of mothers at delivery with 208 μmol of vitamin A raised mothers' serum concentrations for at least 1 mo postpartum and raised milk vitamin A levels by 0.2–0.7 μmol/L for more than 6 mo. This study was randomized, but not placebo controlled, and the infants' vitamin A status was not assessed.

In summary, all trials conducted in populations with marginal to low vitamin A status found that mothers' serum and milk vitamin A concentrations increase in response to vitamin A supplementation. Effects on the infant's vitamin A status have been more equivocal, with statistically significant effects found in the Indonesian (Muhilal et al. 1985) and Thai (Thanangkul et al. 1974) studies but not in the El Salvadoran study (Arroyave et al. 1974). In the present study, maternal supplementation had a small impact on the mean serum retinol concentration of the infants but significantly protected infants from serum retinol concentrations of <0.52 μmol/L. This is the first study in which infants' liver stores of vitamin A were assessed using the RDR method. The RDR results confirm that maternal vitamin A supplementation improved the vitamin A status of the infants.

Comparison with other supplementation strategies. Vitamin A supplementation of lactating mothers as a way to improve infants' vitamin A status should be evaluated in light of other interventions, such as direct supplementation of the infant. For this purpose, one can estimate the amount of vitamin transferred to the infants in this study due to supplementation of their mothers. Assuming that breast milk intake was 600 mL during the first half of infancy and 400 mL during mo 7–9, and that the mean milk vitamin A concentration at each measurement point represents the time surrounding it, the breast milk vitamin A intake in the vitamin A group over 9 mo of breastfeeding was 114 μmol higher than in the placebo group. Assuming 90% of vitamin A in human milk is absorbed (ESGPAN Committee on Nutrition 1977), the net supplement to the infant was ~103 μmol. (Using median milk vitamin A values instead of means gives an estimate of 99 μmol.) For the subset of mothers with baseline milk vitamin A of <1.39 μmol/L, the net supplement to the infants is even higher, ~130 μmol.

For comparison, the maximal current recommendations for high dose vitamin A supplementation of infants in vitamin A–deficient regions during the first 9 mo of life are 52 μmol before 6 mo of age and 104 μmol at 6 mo (WHO/UNICEF/IVACG Task Force 1988). Assuming 50% of vitamin A from a high dose is retained (West and Pettiss 1986), the net supplement is 78 μmol. Thus, in this study population, high dose vitamin A supplementation of the lactating mother delivered an amount of vitamin A to the infant similar to what could be provided by direct supplementation of the infant.

For populations in which breast-feeding rates are high, the strategy of maternal supplementation offers several advantages over direct supplementation of the infant. First, supplementing the lactating mother is one of the safest ways to deliver vitamin A to the infant, because it effectively gives the infant a daily low dose supplement for at least 8 mo, in a form that is well absorbed and utilized. When 1- to 6-y-old children are given high dose vitamin A supplements, transient side effect rates of 8.8% are attributable to the supplement (Florentino et al. 1990); side effect rates from high dose vitamin A supplementation of infants have not yet been reported. Second, maternal supplementation requires one contact with a vitamin A delivery system, whereas direct supplementation to the infant requires at least two contacts. Third, two people benefit from maternal supplementation: the mother and the infant. Public health policymakers must weigh the relative feasibility and benefits from these supplementation strategies within their specific programmatic contexts. Where resources permit, it may be appropriate to conduct a combination of maternal and infant vitamin A supplementation.

ACKNOWLEDGMENTS

The authors wish to thank Kenneth Brown for his help as a field consultant and Jean Humphrey for providing training in CIC. We also thank Suharto, Prembun Community Health Center, Kebumen, Central Java, who provided us with local support and advice. Finally, the competent and enthusiastic help of the ASIVITA field staff and the support of our colleagues at the Clinical Epidemiology Unit of Gadjah Mada University are warmly acknowledged.

LITERATURE CITED

Arroyave, G., Beghin, I., Flores, M., Soto de Guido, C. & Ticas, J. M. (1974) Efectos del consumo de azucar fortificada con retinol, por la madre embarazada y lactante cuya dieta habitual es baja en vitamina A. Estudio de la madre y del nino. Arch. Latinoam. Nutr. 24: 485–512.

Bates, C. J. (1983) Vitamin A in pregnancy and lactation. Proc. Nutr. Soc. 42: 65–79.

Bongga, D. C. (1982) Vitamin A Supplementation of Lactating Women in The Philippines: Its Effect on Milk and Serum Vitamin A. Doctoral thesis, Cornell University, Ithaca, NY.

Corner, G. (1989) dSURVEY User Manual. Helkorn Pty. Ltd., Pearce, ACT 2607, Australia.

Daulaire, N.M.P., Starbuck, E. S., Houston, R. M., Church, M. S., Stukel, T. A. & Pandey, M. R. (1992) Childhood mortality after a high dose of vitamin A in a high risk population. Br. Med. J. 304: 207–210.

ESGPAN Committee on Nutrition (1977) Guidelines on infant nutrition. I. Recommendations for the composition of an adapted formula. Acta Paediatr. Scand. Suppl. 262: 8–10.

Florentino, R. F., Tanchoco, C. C., Ramos, A. C., Mendoza, T. S., Natividad, E. P., Tangco, J.B.M. & Sommer, A. (1990) Tolerance of preschoolers to two dosage strengths of vitamin A preparation. Am. J. Clin. Nutr. 52: 694–700.

Flores, H., Azevedo, M.N.A., Campos, F.A.C.S., Barreto-Lins, M. C., Cavalcanti, A. A., Salzano, A. C., Varela, R. M. & Underwood, B. A. (1991) Serum vitamin A distribution curve for children aged 2–6 y known to have adequate vitamin A status: a reference population. Am. J. Clin. Nutr. 54: 707–711.

Flores, H., Campos, F., Araujo, C.R.C. & Underwood, B. A. (1984) Assessment of marginal vitamin A deficiency in Brazilian children using the relative dose response procedure. Am. J. Clin. Nutr. 40: 1281–1289.

Gebre-Medhin, M., Vahlquist, A., Hofvander, Y., Uppsall, L. & Vahlquist, B. (1976) Breast milk composition in Ethiopian and Swedish mothers. I. Vitamin A and β-carotene. Am. J. Clin. Nutr. 29: 441–451.

Habicht, J-P. (1974) Estandardizacion de methodos epidemiologicos cuantitativos sobre el terreno. Boletin Of. Sanit. Panam. 76: 375–384.

ICEPO (1988) Assessment of Vitamin A status by Impression Cytology: Training Manual. ICEPO, Dana Center for Preventive Ophthalmology, The Wilmer Institute and School of Hygiene and Public Health of The Johns Hopkins University, Baltimore, MD.

International Vitamin A Consultative Group (IVACG) (1989) Guidelines for the Development of a Simplified Dietary Assessment to Identify Groups at Risk for Inadequate Intake of Vitamin A. International Life Sciences Institute-Nutrition Foundation, Washington, DC.

Kim, Y., English C., Reich, P., Gerber, L. E. & Simpson, K. L. (1990) Vitamin A and carotenoids in human milk. J. Agric. Food Chem. 38: 1930–1933.

Lewis, C. J., McDowell, M. A., Sempos, C. T., Lewis, C. L. & Yetley, E. A. (1990) Relationship between age and serum vitamin A in children aged 4–11 y. Am. J. Clin. Nutr. 52: 353–360.

McLaren, D. S. (1986) Global occurrence of vitamin A deficiency. In: Vitamin A Deficiency and Its Control (Bauernfeind, J. C., ed.), pp. 1–18. Academic Press, Orlando, FL.

Meinart, C. L. (1986) Clinical Trials: Design, Conduct, and Analysis. Oxford University Press, New York, NY.

Muhilal, Murdiana, A., Azis, I., Saidin, S., Jahari, A. B. & Karyadi, D. (1988) Vitamin A-fortified monosodium glutamate and vitamin A status: a controlled field trial. Am. J. Clin. Nutr. 48: 1265–1270.

Muhilal, Permaesih, D., Saidin, M., Murdiana, A., Wiramihardja, K. K. & Karyadi, D. (1985) Dampak pemberian vitamin A dosis tinggi pada ibu menyusui terhadap status vitamin A anak. Penelitian Gizi dan Makanan 8: 5–19.

Natadisastra, G., Wittpenn, J. R., West, K. P., Muhilal & Sommer, A. (1987) Impression cytology for detection of vitamin A deficiency. Arch. Ophthalmol. 105: 1224–1228.

Pilch, S. M. (1987) Analysis of vitamin A data from the health and nutrition examination surveys. J. Nutr. 117: 636–640.

Pocock, S. J. (1983) Clinical Trials. John Wiley & Sons, New York, NY.

Rahmathullah, L., Underwood, B. A., Thulasiraj, R. D., Milton, R. C., Ramaswamy, K., Rahmathullah, R. & Babu, G. (1990) Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. N. Engl. J. Med. 323: 929–935.

Roy, S. K., Islam, A., Molla, A. & Akramuzzaman, S. M. (1989) Dynamics of vitamin A levels in the breastmilk of mothers of low socio-economic status in Bangladesh. Paper presented at IVACG meeting, November 5–10, 1989, Kathmandu, Nepal.

Solomons, N. W., Morrow, F. D., Vasquez, A., Bulux, J., Guerrero, A-M. & Russell, R. M. (1990) Test-retest reproducibility of the relative dose response for vitamin A status in Guatemalan adults: issues of diagnostic sensitivity. J. Nutr. 120: 738–744.

Sommer, A., Tarwotjo, I., Djunaedi, E., West, K. P., Jr., Loeden, A. A., Tilden, R., Mele, L. & the ACEH Study Group. (1986) Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. Lancet 1: 1169–1173.

Tarwotjo, I., Sommer, A., Soegiharto, T., Susanto, D. & Muhilal (1982) Dietary practices and xerophthalmia among Indonesian children. Am. J. Clin. Nutr. 35: 574–581.

Thanangkul, O., Promkutkaew, C., Wanivapong, T. & Damrongsak, D. (1974) Comparison of the effects of a single high dose of vitamin A given to mother and infant upon plasma levels of vitamin A in the infant. Presented at a joint WHO/USAID meeting: The Control of Vitamin A Deficiency: Priorities for Research and Action Programmes. NUT/WP/74.114. November 25–29, 1974, Jakarta, Indonesia.

Tielsch, J. M. & Sommer, A. (1984) The epidemiology of vitamin A deficiency and xerophthalmia. Annu. Rev. Nutr. 4: 183–205.

Underwood, B. A. (1990) Methods for assessment of vitamin A status. J. Nutr. 120: 1459–1463.

Vaisman, N., Mogilner, B. M. & Sklan, D. (1985) Vitamin A and E content of preterm and term milk. Nutr. Res. 5: 931–935.

Wallingford, J. C. & Underwood, B. A. (1986) Vitamin A deficiency in pregnancy, lactation, and the nursing child. In: Vitamin A Deficiency and Its Control (Bauernfeind, J. C., ed.), pp. 101–152. Academic Press, Orlando, FL.

West, K. P., Chirambo, M., Katz, J., Sommer, A. & the Malawi Survey Group (1986) Breast-feeding, weaning patterns, and the risk of xerophthalmia in Southern Malawi. Am. J. Clin. Nutr. 44: 690–697.

West, K. P. & Pettiss, S. T. (1986) Control of vitamin A deficiency by the vitamin A periodic oral dosing approach. In: Vitamin A Deficiency and Its Control (Bauernfeind, J. C., ed.), pp. 325–357. Academic Press, Orlando, FL.

West, K. P., Jr., Pokhrel, R. P., Katz, J., LeClerq, S. C., Khatry, S. K., Shrestha, S. R., Pradhan, E. K., Tielsch, J. M., Pandey, M. R. & Sommer, A. (1991) Efficacy of vitamin A in reducing preschool child mortality in Nepal. Lancet 338: 67–71.

WHO/UNICEF/IVACG Task Force (1988) Vitamin A Supplements: A Guide to Their Use in the Treatment and Prevention of Vitamin A Deficiency and Xerophthalmia. World Health Organization, Geneva, Switzerland.

Wilkinson, L. (1990) SYSTAT Version 5.02. SYSTAT Inc., Evanston, IL.

112

SUMMARY
REPORT TO
CIDA

Revised to Jan 5/93

Effectiveness of Vitamin A Supplementation in the Control of Young Child Morbidity and Mortality in Developing Countries

SUMMARY REPORT

G.H. Beaton, R. Martorell, K.A. L'Abbé, B. Edmonston,
G. McCabe, A.C. Ross and B.Harvey

A project of the
International Nutrition Program
Department of Nutritional Sciences
Faculty of Medicine, University of Toronto
Toronto, Ontario, Canada M5S 1A8

Funded by the
Canadian International Development Agency
Contract: 8714, RC: 871/11109
Commitment: 127333, Supplier S30854

January 7, 1993

This project was financially supported by the Canadian International Development Agency. However the views expressed herein do not necessarily represent the views of either CIDA or the Government of Canada.

© University of Toronto, 1992

113

This document presents a summary of the main findings, and their interpretation, of a review of controlled studies of the effect of vitamin A supplementation on young child morbidity and mortality. The analyses and arguments supporting these findings and interpretations are presented in the Final Report to CIDA and are not presented here. In presenting interpretations, special emphasis has been placed on findings and interpretations that appear particularly relevant to policy development and programme design.

The full report gives emphasis to an important disclaimer offered by the authors. It is repeated here for perspective. While most of the studies available for review involved the periodic administration of high potency doses of vitamin A, the reviewers have interpreted the analyses and conclusions to relate to effects of improvement of vitamin A status and suggest that such benefits are likely to be achieved in any programme approach that is as effective as, or more effective than, the reviewed studies in improving vitamin A status. Thus, the specific disclaimer was that the final report, and this summary, should not be taken as an evaluation or endorsement of a particular approach to improvement of vitamin A status.

Specific Goals of the Review of Experience:

Under the original contractual agreement, there were three goals specified. These are set forth below.

- *to review and assess the available experience with regard to the effect of vitamin A supplementation on young child morbidity and mortality.*
- *to advise CIDA on the apparent effectiveness of vitamin A supplementation in young children in developing countries*
- *to estimate, to the extent possible, the range of effects for mortality and morbidity outcomes expected under various nutritional and ecological circumstances and for various subgroups of the population.*

These goals were to be addressed in the connotation of informing policy decisions but the review , assessment and formulation of policy was not included in the assigned mandate. It is understood that another group, with different composition and with additional background documents, will address policy implications of the report. The following summary is presented under the headings of the three specific objectives, rephrased as questions that were addressed.

Identify and Review Controlled Trials

We were able to identify and examine 10 mortality trials and 19 morbidity trials (including morbidity results from the 10 mortality trials). This included both published and

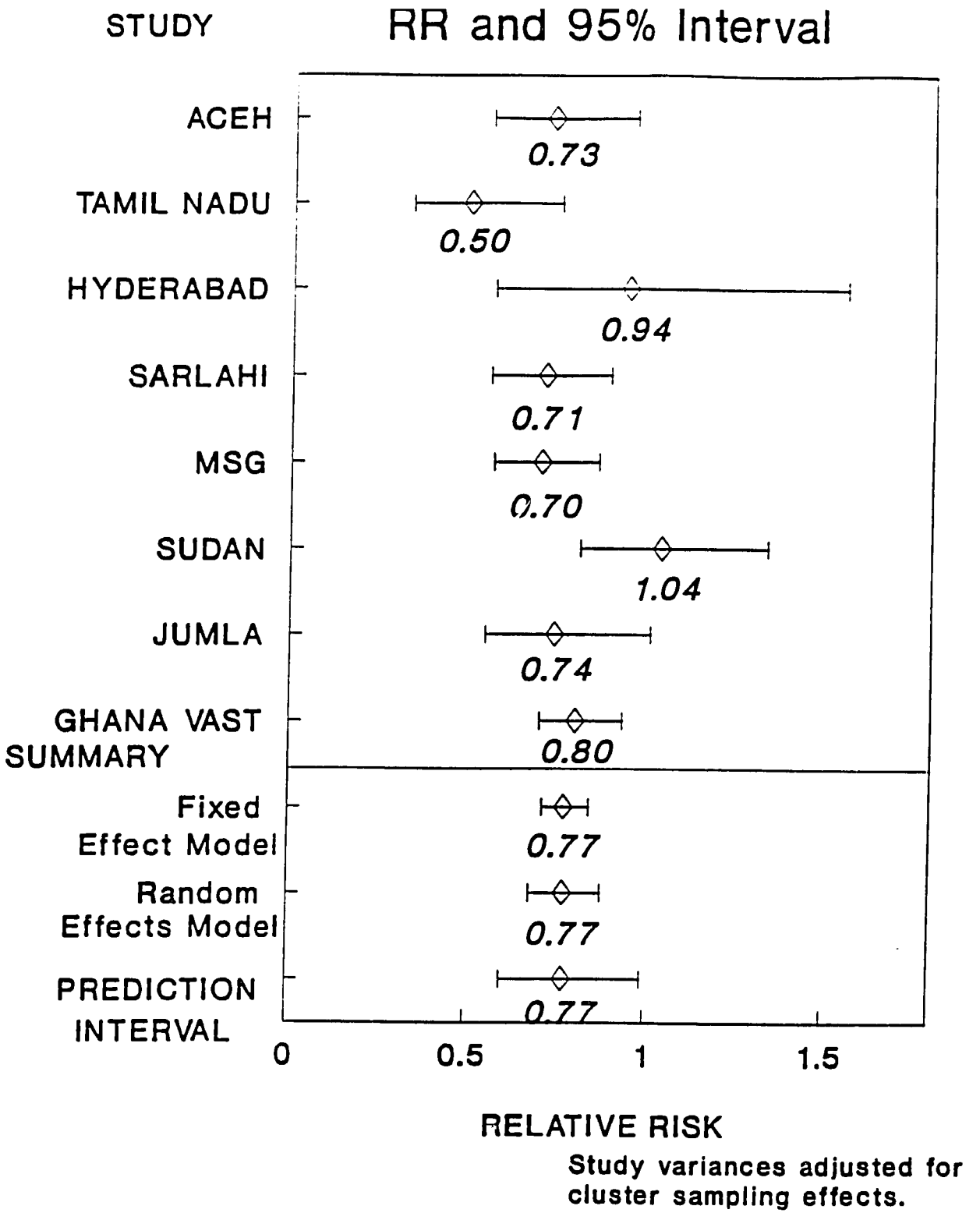


Fig. 1. Impact of Vitamin A Supplementation on Mortality of Infants and Children 6 months to 5 years. Shown are the point estimates and 95% Confidence Intervals for the eight original studies reviewed in detail. Also shown are two summary estimates for the relative effect, taking into account all 8 studies. These have the same point estimates, a 23% reduction in mortality, but differ in the estimated Confidence Intervals. The second estimate (SUMMARY2) takes into account the between study variation that we believe exists. Technically it is derived from a random effects model. The Prediction Interval for a future programme or study is also presented. Again the predicted average effect is 23% but the interval describing possible actual effects is greatly expanded (see text for explanation).

115

What can be Expected in Future Programs?

The third goal specified in the contract is perhaps the most important. It addresses the important planning question of what should we expect in a new programme in a new setting? Below we divide our response to the third goal into two sub-questions: Where (in what population setting(s)) can one expect vitamin A to be effective? and What is the range of effect to be expected?

Where is Improvement of Vitamin A Status Most Likely to Affect Morbidity and Mortality?

The obvious answer to this question is "Where vitamin A deficiency is now a serious problem." For the mortality trials, all of which had been conducted in settings where it had been assumed vitamin A was a public health problem under the WHO definition, we attempted to ask about population-level predictors of the relative effect. For these analyses we had only 8 studies and with such a small sample, subtle effects might go undetected. However, any major effects should have been seen.

We found no relationship between the baseline prevalence of xerophthalmia and the relative effect of vitamin A. Thus we have to conclude that while the existence of clinically apparent deficiency was a marker for all programmes, the actual prevalence added very little additional information in predicting outcome. One very important question is unanswered. There were no studies conducted in populations with biochemical evidence of vitamin A depletion but without associated evidence of clinical manifestations of deficiency (Ghana came closest to this situation). Thus we can reach no firm conclusion about the impact of vitamin A to be expected in populations where there is evidence of depletion but not evidence that depletion is severe enough to produce clinical lesions in at least a small proportion of individuals. This, unfortunately leaves as judgemental the potential impact of programmes in a very substantial part of the developing world.

We found no impact of the prevalence of stunting or wasting or of the interaction with xerophthalmia prevalence on the prediction of the relative effect of vitamin A. We note however that all of the population groups studied exhibited a high prevalence of stunting and shared the common feature of representing the poorer segments of the population exhibiting the stigmata of early deprivations and undoubtedly also a common social/biological environment favouring high morbidity and mortality. Thus, stunting was seen more as a marker of the environment of early growth and development than as an index of current

We suggest, in keeping with conclusions reported by the Sudan study, that it may be timely to review with care the evidence supporting the existing guidelines for high potency periodic dosing. It may be that the combination of dose (200,000 IU after one year) and frequency (6 months interval) was inadequate in the Sudan setting although apparently adequate in other studies following a similar dosing schedule.

What is the Range of Expected Effects for Future Programmes?

Given that we were unable to explain the variation in reported results among the 8 mortality trials, we must base any prediction on the total experience. In Fig 1, we included a portrayal of the Prediction Interval applicable to a new study but based on the review of past experience. This interval includes the possibility that a new study will have no effect on mortality (such was a part of the experience). It includes also the possibility that a new study might have an effect much greater than the average 23% reduction expected. In the main report we developed this concept further and actually developed probabilities that could be attached to various levels of effect. These are portrayed in Table 1. These might be interpreted in the following manner. If justification of a vitamin A control programme requires that there be a mortality reduction of at least 10%, then we suggest that there are about 9 chances in 10 (probability = 0.89) of an effect at least this large being present in a programme that does improve vitamin A status to a degree comparable to the reviewed programs. If a 20% reduction is needed, then the probability of achievement is 0.6 (3 chances in 5). However if reductions of 30% and 40 % are sought, the probabilities fall to 0.2 and 0.03. All of these may be contrasted to the probability of better than 97% that *some* effect will be produced.

Table 1. Probability That a Vitamin A Effect of Specified Magnitude Will be Present in a Future Study.

MORTALITY REDUCTION	*Probability*
Any effect	*0.98*
≥ 10%	*0.89*
≥ 20%	*0.62*
≥ 30%	*0.23*
≥ 40%	*0.03*

Estimates assume a cluster effect (DEFF = 1.3). No new study sampling variance included in this model of the expected true effect.

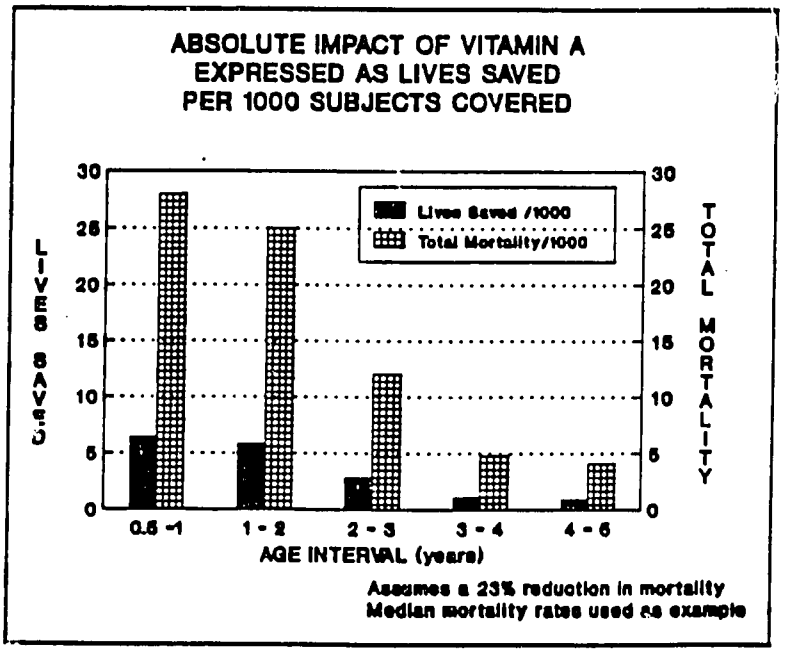
We also cautioned, in our main

117

directly estimated by the research project). We did not have opportunity to test these hypotheses and warn only that we do not *know* whether vitamin A treatment is equally effective in children that might have been excluded - hence we do not *know* whether the predicted effect of vitamin A (23% reduction in mortality) is applicable to true baseline mortality rates. From those studies in which the baseline and control group mortalities appeared comparable, the reported effect of vitamin A appeared comparable. Therefore we *think* the relative effect is applicable to true baseline mortality rates. It was also reported in the Tamil Nadu study that inclusion or exclusion of children treated for xerophthalmia (and then left in their original treatment group assignments) did not change the estimated relative effect of vitamin A. Thus, although that type of exclusion of a high risk group might alter apparent mortality rates (in both control and treated groups) without influencing the estimate of effect of vitamin A. What the planner must recognize is that in a programme setting, without a concurrent control group, reductions from baseline mortality attributable to any of these causes might *appear* to be results of the intervention. In this sense our estimates of the real effect could be smaller than the apparent effect seen in an operating programme. Offsetting this, of course, would be lower 'compliance' rates expected in an operational programme as compared to a research study.

The Distinction Between Relative and Absolute Effects of Vitamin A on Mortality

All of the results described above refer to the relative effects of vitamin A, the proportional reduction in mortality. We have shown from those analyses that there was no apparent effect of gender, age or mortality rate. However, it is to be recognized that if the relative effect is unchanged, then the absolute effect (number of lives saved) must be directly proportional to the baseline mortality rate:



118

environment and associated early growth failure

- *presence of clinical manifestations of vitamin A deficiency at least sufficiently prevalent to meet the WHO criteria of a public health problem.*

A very important unanswered question is whether such populations, lacking evidence of clinical manifestations of vitamin A deficiency, but presenting biochemical evidence of major vitamin A depletion, would also be responsive to improvement of vitamin A status.

Programme Approaches

This analysis of experience was not designed to compare programme approaches, nevertheless some interesting observations relevant to the topic can be offered. First, it was demonstrated, without doubt, that daily (through fortification of monosodium glutamate, MSG) and weekly intakes of physiological levels of vitamin A (Tamil Nadu) were just as effective as periodic high potency dosing. It follows, in the judgement of the reviewers that any approach to improving vitamin A status that effectively controlled xerophthalmia would have beneficial impact on mortality comparable to that reported. We noted also a recent report from an Indonesian study that one time dosing of women shortly after birth was effective in raising breast milk vitamin A levels and improving the vitamin A status of the infant for at least 6 months. This might be a strategy worthy of exploration if the target group is young infants.

Finally it must always be remembered that vitamin A is potentially toxic and may be teratogenic during pregnancy. In the studies reviewed there was some evidence of transient side effects of high potency dosing (e.g reports from Ghana VAST) but no evidence of actual toxicity. Conversely, there was some suggestion (Sudan, and perhaps also Hyderabad) that the 200,000 IU x 6 month interval for children over one year may have been inadequate to evoke a beneficial response. That would be in keeping with an earlier review of oral dosing with vitamin A in the control of xerophthalmia. That review suggested that while the suggested dose level appeared adequate to prevent xerophthalmia, it did not appear adequate to sustain blood and tissue levels over 6 months. It is suggested that there is need for continuing review of the norms for periodic high potency vitamin A dosing if that approach to intervention is chosen. Such review might focus upon the dose x frequency combination required to sustain blood levels (and presumably tissue stores) without necessarily having to document a mortality effect.

EFECTIVIDAD DE LA SUPLEMENTACION CON VITAMINA A EN EL CONTROL DE LA MORBI-MORTALIDAD DE LOS NIÑOS EN PAISES EN DESARROLLO

Extracto del Informe Resumido

G.H. Beaton, R. Martorell, K.A. L'Abbé, B. Edmonston
G. McCabe, A.C. Ross and B. Harvey
Extracción y Traducción: David P. Nelson

120

EFECTIVIDAD DE LA SUPLEMENTACION CON VITAMINA A EN EL CONTROL DE LA MORBI-MORTALIDAD DE LOS NIÑOS EN PAISES EN DESARROLLO

Extracto del Informe Resumido

Aclaración: En la mayoría de los estudios revisados, se administró dosis de vitamina A de alta potencia. Los revisores interpretaron los análisis y conclusiones en relación con los efectos del mejoramiento del estado de vitamina A en general y sugieren que tales beneficios se esperarían de cualquier programa que consiga el mismo nivel o mejore el estado de vitamina A. No se debe interpretar este estudio como una evaluación o recomendación para una acción particular de mejoramiento del estado de vitamina A.

Objetivos Específicos de la Revisión de Experiencias

- revisar y ponderar las experiencias disponibles respecto al efecto de la suplementación con vitamina A en la morbi-mortalidad de los niños
- informar a CIDA (Agencia Canadiense de Desarrollo Internacional) sobre la efectividad aparente de la suplementación con vitamina A a los niños en países en desarrollo
- en la medida de lo posible, estimar el rango de efectos sobre la morbi-mortalidad que se puede esperar bajo diferentes condiciones nutricionales y ecológicas en los varios subgrupos de población

Identificación y Revisión de Estudios Controlados

Se pudo identificar y estudiar 10 investigaciones de mortalidad y 19 de morbilidad (incluyendo el estudio de impacto sobre la morbilidad de las 10 investigaciones de mortalidad). Estas incluyeron tanto estudios publicados como no publicados para los cuales se pudo obtener descripciones del investigador principal. Se tuvo conocimiento de otras investigaciones de morbilidad aún en fase de estudio o análisis; sin embargo, no se conoció de otro estudio de mortalidad actual o futuro. Por lo tanto, aparte de dos investigaciones - una en Bombay, India y otra en Haiti - que no se incluyeron en el análisis formal por falta de información detallada, se cree haber abarcado la experiencia total existente.

Los estudios en proceso arrojarán resultados en los próximos dos o tres años que complementarán este análisis de las experiencias a la fecha.

¿Tuvo Efecto la Suplementación con Vitamina A en la Morbi-Mortalidad de los Niños?

Efecto en Mortalidad

Contestamos esta pregunta con un SI definitivo con respecto a mortalidad. La suplementación con vitamina A produjo una disminución promedia de 23% en las tasas de mortalidad infantil y de niños entre 6 meses y 5 años de edad, Gráfica 1. El efecto fue altamente significativo bajo los dos modelos conceptuales estudiados: uno de efecto fijo (SUMMARY1 RR) y uno de efecto aleatorio (SUMMARY2 RR), aunque los intervalos de confianza de 95% fueron algo más amplios en el segundo. La Gráfica también muestra el Intervalo de Predicción del efecto esperado en un estudio futuro.

Para niños menores de 6 meses de edad, el efecto estimado fue también una reducción de 23%. Sin embargo, debido al reducido tamaño de la muestra, el intervalo de confianza fue muy amplio y no se alcanzó validez estadística. Por lo tanto, no se pudo contestar la pregunta para niños menores de 6 meses en forma definitiva.

Para niños mayores de 6 meses, el efecto de la vitamina A en la reducción de mortalidad no fue diferente por sexo ni edad. Vale decir que se esperaría disminuciones similares en niños y niñas de 6 meses hasta 5 años de edad.

El efecto es pronunciado para enfermedades diarréicas pero mínimo (o quizás ausente) en muertes atribuídas a enfermedades respiratorias; además, se lo puede demonstrar en muertes por sarampión aunque el número de casos es muy reducido.

Un hallazgo muy importante fue que la disminución de la mortalidad no dependió de la dosis; un estudio se basó en el consumo de glutamato monosódico fortificado y otro en la administración de dosis semanales que llenaban la recomendación internacional de consumo alimentario.

Efecto sobre Morbilidad

Se concluyó que el mejoramiento del estado de vitamina A no afecta la incidencia, duración o prevalencia de las enfermedades diarréicas o respiratorias. Parece probable que el mejoramiento en el estado de vitamina A, impida el empeoramiento de las infecciones y su desenlace fatal. Este impacto sobre la severidad se documentó recientemente en el estudio VAST de Ghana en el que se observó una reducción en las remisiones y admisiones hospitalarias así como en la incidencia de morbilidad severa. También se observó el mismo fenómeno en niños con sarampión que recibieron vitamina A; se redujo tanto la severidad de los casos como la letalidad. Las investigaciones en proceso arrojarán más información sobre misiones y admisiones hospitalarias, la misma que puede confirmar esta conclusión preliminar.

Como corolario a esta conclusión, para el control de la morbilidad en niños, la vitamina A no es una panacea. Tan solo permite que el niño responda adecuadamente una vez infectado; la reducción en la incidencia de infecciones requiere acciones de inmunización y saneamiento ambiental.

El análisis de morbilidad reveló que la reducción en la severidad y letalidad del sarampión ocurrió aún cuando la vitamina A fue administrada despues de iniciada la enfermedad. Los autores infieren que lo importante es el estado de vitamina A durante la infección pero que éste puede mejorarse antes o después del inicio de la enfermedad.

¿Que se puede esperar de los Programas Futuros?

La respuesta a esta pregunta puede ser la más importante. Se la divide en dos: ¿donde (en qué poblaciones) será efectiva la vitamina A? y ¿cuán efectiva será la vitamina A en la reducción de la mortalidad?

¿Dónde se puede esperar que el mejoramiento del estado de vitamina A mostrará efecto sobre la morbi-mortalidad?

La respuesta obvia es "donde la deficiencia de vitamina A es un problema serio." Todos los estudios de mortalidad se realizaron en áreas en donde la deficiencia de vitamina A es considerada como problema de salud pública según la definición de la OMS; en 8 de ellos se analizó predictores de nivel poblacional.

No se encontró relación entre la prevalencia inicial de xeroftalmía y el efecto relativo de la vitamina A. Por lo tanto, a pesar de que se encontraron signos clínicos en todos los estudios, se concluyó que la prevalencia de éstos no predecía los resultados. Sin embargo, en ninguno de los estudios se conoció el estado bioquímico de las poblaciones en relación a las manifestaciones clínicas. En consecuencia, no se puede predecir el impacto de la vitamina A en poblaciones depletadas pero sin signos oculares, ie. Latinoamérica y grandes extensiones del mundo en desarrollo.

Tampoco se encontró relación entre la prevalencia de desnutrición aguda o crónica y el efecto de la vitamina A Se observó que, en todas las poblaciones estudiadas, hubo alta prevalencia de desnutrición crónica (enanismo nutricional), lo cual se consideró más como un indicador de las condiciones de crecimiento y desarrollo anteriores que como un indice del estado nutricional actual.

No se encontró asociación entre las tasas de mortalidad (que variaron entre 5 y 120 por mil) de los grupos control y la efectividad de la vitamina A.

La única variable que tuvo valor predictivo fue la causa de muerte. Se concluye que el mayor efecto de la vitamina se esperaría donde la diarrea y el sarampión predominan como causas de muerte; sería menor donde las infecciones respiratorias predominan.

En dos de los estudios no se observó efecto de suplementación (en Hyderabad, India, se encontró una reducción de 6% y en Sudán, un aumento del 4%, sin que ninguno de los dos alcanzara significancia estadística. Además, los intervalos de confianza incluyeron el efecto promedio calculado para todos los estudios en conjunto. En ambos casos, los tratamientos no produjeron diferencias en el estado de vitamina A entre los grupos tratados y los controles en términos de prevalencia de xerortálmia. En Sudán, parece que el producto de vitamina A no tuvo actividad biológica; en Hyderabad, se encontró una mejoría inesperada en el estado de vitamina A del grupo control. Se concluye que cualquier programa futuro tendrá que demostrar que la suplementación ha cambiado el estado de vitamina A del grupo tratado en relación al control, mediante exámenes clínicos periódicos o la titulación de retinol en sangre.

Los autores concuerdan con una recomendación del estudio de Sudán en el sentido que se revisen los criterios que fundamentan las normas actuales de dosificación, tanto en cantidad (200.000 UI para mayores de un año) como en periodicidad (cada 6 meses), ya que este esquema no bastó para producir un cambio en el estado de vitamina A en Sudán (aunque sí lo hizo en los demás estudios).

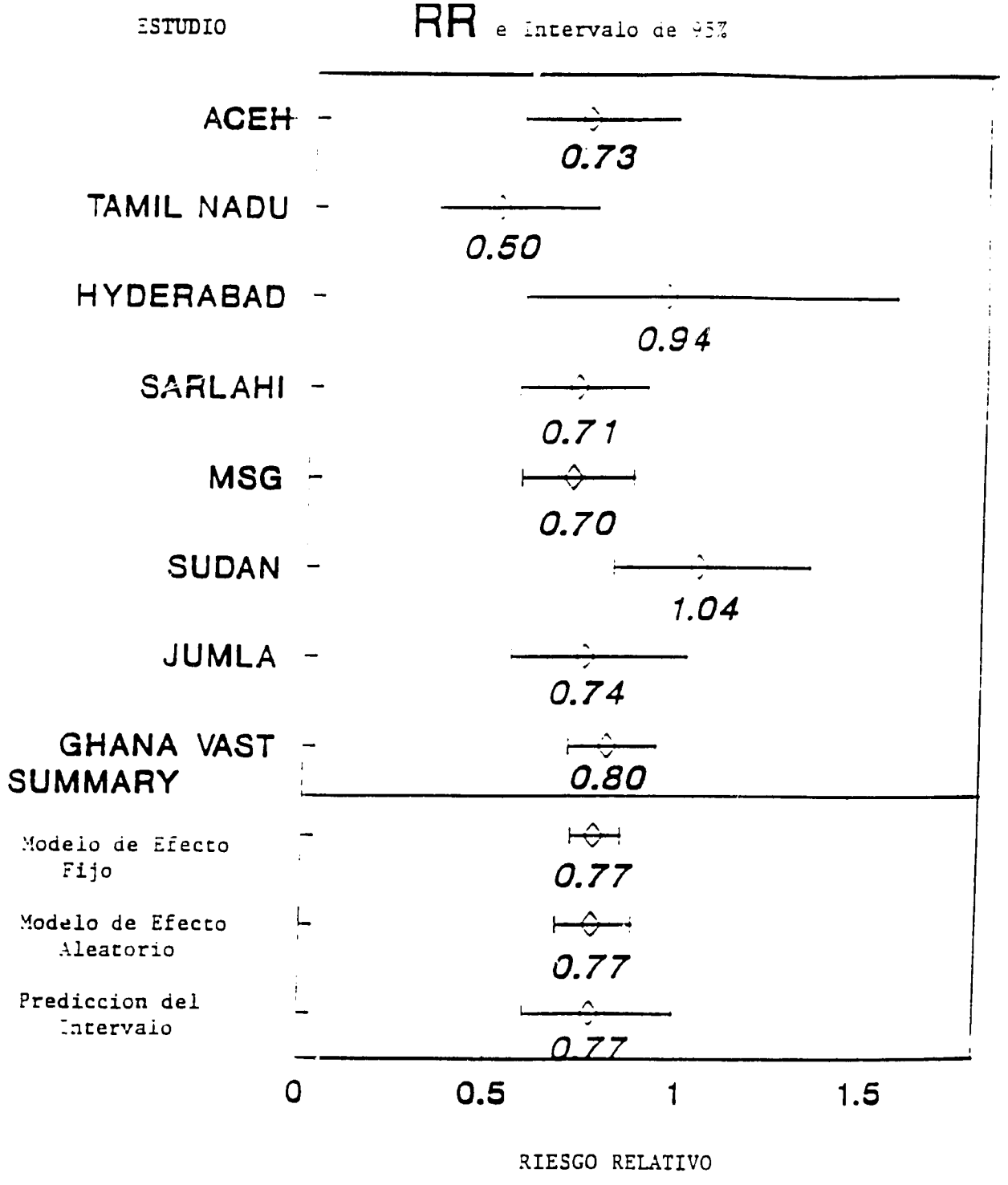
¿Cuál sería el Rango de Efectos esperados en Programas Futuros?

La Gráfica I presenta un Intervalo de Predicción derivado de la experiencia pasada y que se puede aplicar a nuevos estudios. Este intervalo incluye la posibilidad de que un estudio nuevo no muestre ningún efecto sobre la mortalidad, así como la posibilidad que muestre un efecto mucho mayor que el promedio esperado de 23%. El Cuadro I muestra las probabilidades de observar diferentes niveles de efectos. Se podría interpretar el cuadro de la siguiente manera. Si un programa de mejoramiento del estado de vitamina A requiere mostrar una disminución del 10% o mas en mortalidad, habría una probabilidad de 0,9 (nueve en diez) de observar tal efecto si el programa alcanza niveles de mejoramiento en vitamina A comparables a los de los estudios revisados. Si se requiere una reducción de 20%, la probabilidad de alcanzarla bajaría a 0.6 (tres en cinco) y si se requiere reducciones de 30% o 40%, las probabilidades disminuyen a 0,2 y 0,03. En cambio, existe una probabilidad de 0,98 de que se producirá algún efecto.

Cuadro I. Probabilidad de que la vitamina A produzca efecto en un estudio futuro.

REDUCCION MORTALIDAD	PROBABILIDAD
Cualquier efecto	0,98
≥ 10%	0,89
≥ 20%	0,62
≥30%	0,23
≥ 40%	0,03

Las estimaciones suponen un efecto de muestreo por conglomerados (DEFF = 1.3)



Gráfica I. Impacto de la suplementación con vitamina A en la mortalidad de infantes y niños de 6 meses a 5 años de edad. Se muestran los estimados puntuales e intervalos de confianza de 95% para los ocho estudios. También se muestran los dos estimados de resumen (SUMMARY) que tienen el mismo estimado puntual (23%) pero difieren en el intervalo de confianza. El segundo de estos (SUMMARY2) toma en consideración la varianza entre estudios que los revisores calculan a partir de un modelo de efectos aleatorios. El Intervalo de Predicción ("Prediction Interval") estima el efecto que se esperaría observar en un estudio futuro; parte del mismo estimado puntual, pero el intervalo de posibles efectos es mucho más amplio.

También existe cierta probabilidad de no observar ningún efecto aunque lo hubiera en verdad. Este resultado puede preverse en grupos de estudio pequeños y en condiciones de baja mortalidad inicial debido a los efectos de errores de muestreo. El Cuadro II muestra la probabilidad de no observar efecto como función del tamaño del grupo de estudio y la tasa inicial de mortalidad. En un estudio piloto que se lleva a cabo en una población pequeña (en términos de estudios de mortalidad) y, de baja mortalidad, la probabilidad es alta de no observar ningún efecto aunque éste sí este presente. Aparentemente, el estudio en Hyderabad representa un ejemplo de este caso.

Los autores advierten que la estimación de los efectos futuros se basa en la comparación de grupos tratados con grupos control, y comentan que, en los estudios revisados, las tasas de mortalidad iniciales fueron bastante inferiores a las que se suponían. Algunas explicaciones posibles son: (i) un efecto no-específico que se hace presente en ambos grupos, sin relación a la vitamina A; (ii) un efecto secundario al tratamiento con vitamina A a los niños que presentaban xeroftalmía (en ambos grupos); (iii) un fenómeno relacionado a la exclusión del estudio de niños de alto riesgo (ya sea por diseño o por auto-selección); (iv) la población de estudio no es representativa de la población para la cual se calcula la tasa de mortalidad (quizás como resultado de haber seleccionado el área porque tiene mejores servicios o infraestructura); o (v) simplemente porque la estimación de mortalidad tiene errores (en los casos en que ésta no haya sido estimada por la investigación). Ya que los autores no pudieron evaluar estas hipótesis, no se sabe si la vitamina A tiene igual efecto en los grupos estudiados que en los niños que fueron excluídos en el estudio. Lo importante para un programa es que, a falta de un grupo control, la reducción de mortalidad que se observa pudiera atribuírse a cualquiera de las causas indicadas, y de esa manera, se sobre-estimaría el efecto de la vitamina A.

Cuadro II. Probabilidad de no observar un efecto de la vitamina A, como función del tamaño de grupo y tasa de mortalidad inicial.

TAMAÑO DE GRUPO	TASA DE MORTALIDAD/1000			
	5	15	25	45
5.000	0.239	0.135	0.096	0.064
10.000	0.172	0.085	0.060	0.042
50.000	0.061	0.034	0.029	0.025
100.000	0.041	0.028	0.025	0.023
250.000	0.029	0.024	0.023	0.022

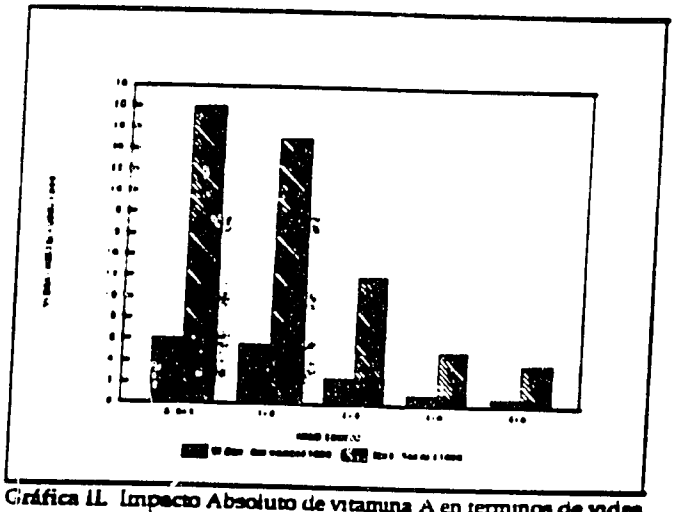
Las estimaciones suponen un efecto de muestreo por conglomerado (DEFF = 1.3) y una reducción promedio de mortalidad de 23%

La Diferencia entre Efectos Absolutos y Relativos de la Vitamina A en Mortalidad

Todos los resultados descritos arriba se refieren a efectos relativos de la vitamina A, o sea la disminución proporcional de la mortalidad. A pesar de que las condiciones de edad, sexo o tasa de mortalidad inicial no tuvieron relación con los efectos relativos de la vitamina A, el número de vidas salvadas en cada grupo de edad o sexo puede variar en relación a la tasa de mortalidad específica de cada uno, como se muestra en la Gráfica II. Ya que las tasas de mortalidad disminuyen a mayor edad y pueden variar según el sexo, se podría esperar un impacto diferenciado en el efecto absoluto con más vidas salvadas en las edades menores.

Algunas Implicaciones para el Enfoque de los Programas

El estudio tiene implicaciones para la orientación de programas preventivos y curativos. En términos de los efectos relativos de la vitamina A en la prevención de mortalidad, el único factor que influye es la causa de muerte. Como ya se demonstró, hay mayor impacto en las poblaciones donde predomina la mortalidad por enfermedades diarréicas o por sarampión en comparación con las respiratorias.



Gráfica II. Impacto Absoluto de vitamina A en terminos de vidas salvadas por 1000 sujetos cubiertos

La efectividad de la vitamina A en la disminución de las complicaciones y muertes por sarampión tiene implicaciones para los esquemas de tratamiento primario y secundario despues de iniciada la enfermedad. Sugiere, también, la conveniencia de investigar si el mismo fenómeno ocurre en el caso de enfermedades diarréicas y otras infecciones. Podría incidir en las recomendaciones para la terapia de éstas, siempre y cuando existan los servicios médicos capaces de detectarlas y efectuar el tratamiento.

En cuanto al número absoluto de vidas salvadas por mil niños cubiertos, las siguientes poblaciones se beneficiarían más:

- las que tienen altas tasas de mortalidad, especialmente por causa de diarrea o sarampión (posiblemente, a raíz de bajas coberturas de inmunización antisarampionosa).
- las de menor edad (ya que la mortalidad en el primer año de vida es mucho mayor que la de los años posteriores).

Desde luego que el análisis se refirió a poblaciones caracterizadas por:

- pobreza general
- alta prevalencia de desnutrición crónica que sugiere un ambiente social y biologicamente empobrecido
- prevalencia de manifestaciones clínicas de deficiencia de vitamina A que indican un problema de salud pública segun OMS.

Queda sin contestar la pregunta sobre la eficacia de la vitamina A en poblaciones depletadas según indicadores bioquímicos pero carentes de signos clínicos.

Enfoques Programáticos

La revisión no tuvo como propósito el evaluar los enfoques programáticos. No obstante, resulta interesante observar lo siguiente. Primero, se demonstró, sin lugar a duda, que la dosificación fisiológica diaria (mediante el glutamato monosódico fortificado) o semanal (Tamil Nadu, India) tuvo igual efecto que la administración de dosis de alta potencia. Por lo tanto, a juicio de los revisores, cualquier método que controle la xeroftalmía mediante el mejoramiento del estado de vitamina A, tendrá igual efecto en la mortalidad. También se observó que la administración de una dosis única de vitamina A a mujeres parturientas aumentó la concentración de ésta en la leche materna y mejoró el estado de la vitamina en los niños por lo menos hasta los 6 meses de edad. Esta medida debe ser investigada y aplicada con mayor intensidad.

Finalmente, se recuerda que, en dosis excesivas, la vitamina A es tóxica y, durante el embarazo, tiene efecto teratogénico. A pesar de algunos pocos casos de efectos colaterales por las dosis de alta potencia (reportados en el estudio VAST de Ghana), no se observaron casos de toxicidad en ninguno de los estudios. Por el contrario, hubo evidencias (en Sudán y, posiblemente, Hyderabad) de que el régimen de una capsula de 200.000 UI cada seis meses puede ser insuficiente para provocar una respuesta en la mortalidad, a pesar de su efectividad en controlar la xeroftalmía. Por lo tanto, se sugiere estudiar alternativas de dosificación que puedan mantener las reservas sanguíneas y corporales, sin que, necesariamente, se demuestren efectos en la mortalidad.