09/09/95 09:19 ICDDR.B. 003116 → 0012050752330 NO.560 P002

Attachment 1.
(FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date ~~Aug 29,~~ 1995
Sept 30, 1995

Principal Investigator George Fuchs, MD
Co-PI: C.M. Makris, MD
Application No. 95-021
Title of Study Effects of Recurrent Infections in Children with Adequate Vitamin A Levels

Trainee Investigator (if any)
Supporting Agency (if Non-ICDDR,B) UAB

Project status:
(X) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects Yes (No)
   (b) Non-ill subjects (Yes) No
   (c) Minors or persons under guardianship (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects Yes (No)
   (b) Social Risks Yes (No)
   (c) Psychological risks to subjects Yes (No)
   (d) Discomfort to subjects (Yes) No
   (e) Invasion of privacy Yes (No)
   (f) Disclosure of information damaging to subject or others Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) Yes (No)
   (b) Use of fetal tissue or abortus Yes (No)
   (c) Use of organs or body fluids Yes (No)
4. Are subjects clearly informed about:
   (a) Nature and purposes of study (Yes) No
   (b) Procedures to be followed including alternatives used NA Yes No
   (c) Physical risks (Yes) No
   (d) Sensitive questions NA Yes No
   (e) Benefits to be derived (Yes) No
   (f) Right to refuse to participate or to withdraw from study (Yes) No
   (g) Confidential handling of data (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure NA Yes No

5. Will signed consent form be required:
   (a) From subjects NA Yes No
   (b) From parent or guardian (if subjects are minors) (Yes) No
6. Will precautions be taken to protect anonymity of subjects (Yes) No
7. Check documents being submitted herewith to Committee:
   ✓ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ___ Protocol (Required)
   ___ Abstract Summary (Required)
   ___ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ___ Informed consent form for subjects
   ___ Informed consent form for parent or guardian
   ___ Procedure for maintaining confidentiality
   ___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

[signature]
Principal Investigator

Trainee

EFFECT OF RECURRENT INFECTIONS ON VITAMIN A STORES IN CHILDREN WITH ~~ADEAU~~ ADEQUATE VITAMIN A LEVELS.

GEORGE FUCHS
AND OTHERS

Project Proposal Application, ICDDR,B

1). Principal Investigator: George Fuchs, MD, Director Clinical Investigation Division, ICDDR,B.

Co-Principal Investigator: Christopher M. Makris, MD, Fellow, Pediatric Pulmonary Division, University of Alabama at Birmingham.

2) Other Investigators: KMA Aziz, MD, ICDDR,B; Md Yunus, MD, ICDDR,B; M.A. Wahed, MS, ICDDR,B; DS Alam, MD, ICDDR,B; Jose O. Alvarez, Ph.D. Director and Chairman Department of International Health, School of Public Health, University of Alabama at Birmingham; Charles Stephensen, Ph.D., Department of International Health, UAB.

3) Project Title: Effect of recurrent infections on Vitamin A stores in children with adequate Vitamin A levels.

4) Starting Date: October 15, 1995

5) Date of Completion: February 4, 1996

6) Total Budget: 59,765.00 (Funds to be transferred to ICDDR,B prior to start of project, 56,900).

7) Head of Program: George Fuchs, MD, Director Clinical Investigation Division, ICDDR,B.

8) Aims of Project:

a) General aim: This project is designed as a pilot project to gather preliminary data regarding the effects of recurrent infections on Vitamin A stores in children in a developing country.

b) Specific aim: The goal of this study is to examine the effect of recurrent infections on Vitamin A stores in children recently treated with therapeutic doses of Vitamin A. A cohort of children given a therapeutic dose of vitamin A will be followed over a period of 12 weeks and clinical episodes of infection will be documented. At the end of the study period Vitamin A stores will be measured using the RDR test. Our hypothesis is that those children experiencing multiple infections during the study period will have significantly lower Vitamin A stores than those children experiencing very few infections. We will attempt to show that children living in an area with a high incidence of infection lose their Vitamin A stores in as little as three months and that urinary excretion of retinol plays a key role in this process.

c) Significance: Strategies regarding Vitamin A supplementation in developing countries are currently based on the notion that Vitamin a stores are maintained for 4-6 months following supplementation. If in fact Vitamin A stores are depleted in children experiencing recurrent infections in as little as three months supplementation strategies will need to be altered as it is these children who are at highest risk of adverse outcome related to Vitamin A deficiency.

9) Ethical implications: This study involves minimal risk to the participants as the only risk the participants are exposed to is 4 peripheral vein blood draws. The benefits obtained from this study by the participants include Vitamin A supplementation and physical exam with treatment for any identified illness by a pediatrician on 2 separate occasions.

This study will help to identify those children at highest risk of developing Vitamin A deficiency and may alter current strategies of Vitamin A supplementation in developing countries. This may result in a decrease in the morbidity and mortality which is known to occur in children with Vitamin A deficiency.

10) Background: The association between Vitamin A deficiency, increased susceptibility to infections and increased mortality is now well accepted (1.2). It has been estimated that Vitamin A supplementation can decrease mortality from diarrheal disease, respiratory disease and measles by 35-50% in areas where Vitamin A deficiency is common (3,4,5,6,7(). Recurrent infections will reduce Vitamin A stores in the liver below critical levels through several mechanisms (8). Gastrointestinal illnesses may alter mucosal surfaces resulting in impaired absorption (9), anorexia may lead to decreased intake, infections may alter mobilization and transport of liver stores and urinary excretion of Vitamin A may increase several folds during acute infections (10,11).

Campos et al noted that following an outbreak of varicella almost 75% of preschoolers previously treated with high dose Vitamin A had a positive relative dose response (RDR) test indicating Vitamin A depletion due to their varicella infection (12,13). Less than half of malnourished children 5-36 months of age with an abnormal modified relative dose response test (MRDR) had a normal test result six weeks following high dose Vitamin A supplementation (14). This was felt to be due to either poor absorption or to increased excretion of Vitamin A secondary to infections. In addition infants in Bangladesh with febrile illnesses were found to have inadequate Vitamin A stores even after high dose Vitamin A supplementation (15). The postulation that increased urinary excretion of retinol is responsible for decreased Vitamin A stores has recently been supported in the literature. Stephensen et al showed that Vitamin A and retinol binding protein were excreted in large amounts in the urine of patients with pneumonia and sepsis (10). Children in Peru with diarrhea, particularly when associated with fever, were also found to excrete large quantities of Vitamin A in their urine (11).

Currently strategies for Vitamin A supplementation in areas where malnutrition and micronutrient deficiencies are common are not clearly defined. If. as we will attempt to demonstrate in this study, Vitamin A stores are depleted in as little as three months in children with recurrent infections this will dramatically impact the design of supplementation programs.

Research Plan : *Population.* A group of 100 children living in Matlab of Bangladesh between the ages of 1-3 years, with an approximately equal number of males and females, will be enrolled into the study. This population has been studied in the past and found to have a high incidence of acute infectious events. The incidence of diarrhea is approximately 0.4-0.5 cases/child/month (16). The incidence of acute respiratory infection (ARI) is also approximately 0.4-0.5 cases/child/month (17). There is a wide range in the incidence of ARI with =16% of children not experiencing any episodes of ARI and =14% experiencing 10 or more episodes over a twelve month period of time. This results in an average of 0.9-1.0 acute infections/child/month with a range of 0.4-1.5 acute infections/child/month. In addition this population is known to have a high incidence of both subclinical and clinical Vitamin A deficiency (18).

Experimental design: The aim of this study is to examine the effect of recurrent infections on Vitamin A status in children at risk for Vitamin A deficiency. To examine this relationship a cohort of 1-3 year olds will be given a therapeutic dose of Vitamin A. To ensure that all children have adequate Vitamin A stores following the therapeutic dose, RDR tests will be performed one week later. Each child will then be followed by a pediatrician or community health worker (CHW) on a weekly basis to assess the child for evidence of recurrent infections. At the end of the 12 week study period a repeat RDR test will be performed to assess Vitamin A stores. Children will be grouped into quintiles based on the number of infectious episodes they experience during the study period. The Vitamin A status of those in quintile #1 (children experiencing the greatest number of infections) will be compared to that of children in quintile #5 (those with the fewest infections). In addition urinary retinol levels will be followed during the study period in an effort to determine if excessive urinary losses of Vitamin A account for the changes in Vitamin A stores.

At the time of enrollment all children will be assessed for acute infection, xerophthalmia or recent (<3 months) history of Vitamin A supplementation, all of which will be grounds for exclusion. After informed consent, either verbal or written, those children eligible will be enrolled into the study. At the time of enrollment complete physical exam including height and weight will be performed. Those children found eligible, as well as those excluded because of clinically apparent xerophthalmia, will be given 200,000 IU of retinol palmitate and 40 IU of Vitamin E (Sight and Life, Basel, Switzerland) orally. One week following the therapeutic dose of Vitamin A the child will be fasted overnight and a RDR test will be performed the following morning. This test consists of a fingerstick sample of blood taken at the beginning of the test termed A_o. A 450 RE dose of retinol palmitate is given with a high fat snack to increase Vitamin A

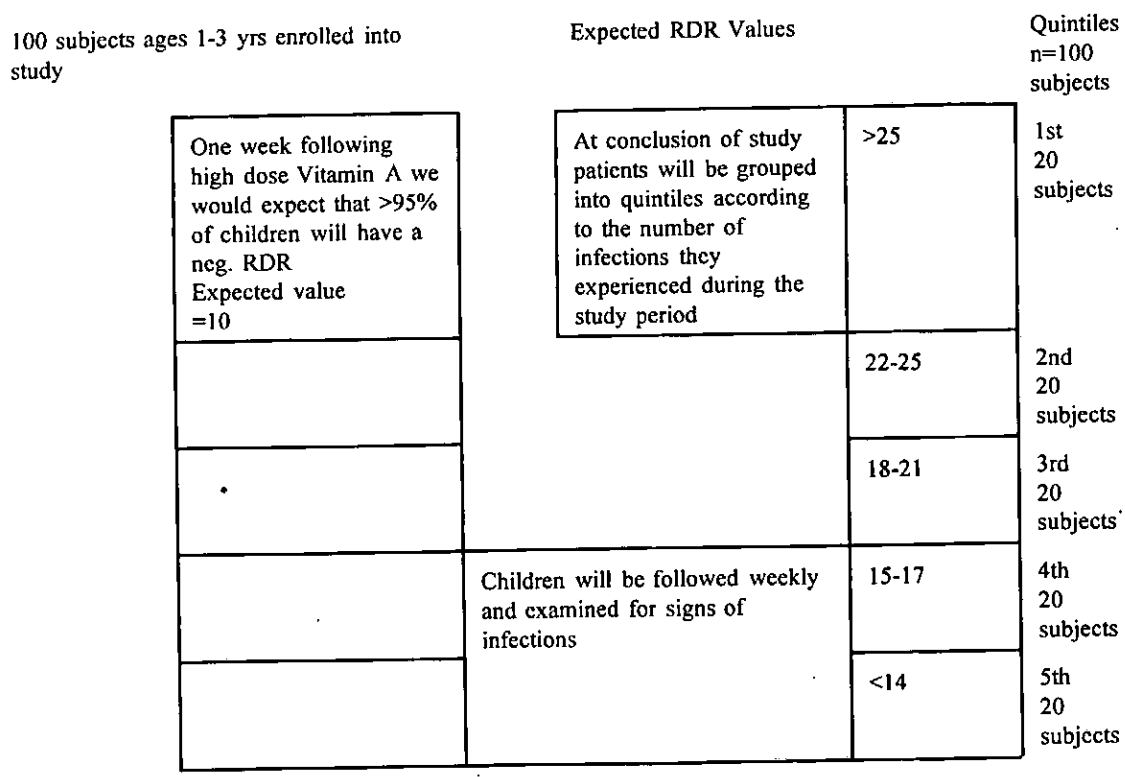
absorption. Five hours after the Vitamin A is given a repeat fingerstick sample, A_5, is obtained. An RDR is calculated using the following formula:

$$[(A_5-A_0)/A_5]X100$$

A value of <20 is considered negative and is a strong indication that liver stores of Vitamin A are adequate. In addition all participants in the study will have serum retinol, retinol binding protein and c-reactive protein levels. Each study participant will be visited weekly by either a CHW and/or a pediatrician. Emphasis will be placed on history and physical signs of ARI (acute respiratory tract infection) or diarrhea. Episodes of ARI will be defined as either upper respiratory tract infections (coughing for 24 hours or nasal discharge or purulent otorrhea) or as lower respiratory tract infection (cough for 24 hours with retractions). Diarrhea will be defined as three or more watery stools in 24 hours or any loose bloody stool. An episode of diarrhea or ARI will end when the illness is followed by three or more symptom-free days. During these exams urine samples from a few (1-2 per day, 60-100 total) will be obtained for retinol levels and acute phase reactants.

At the end of the 12 week study period complete physical exam, including height and weight will be obtained. A RDR test will be repeated as will serum retinol, retinol binding protein and acute phase reactants.

SCHEMATIC OR STUDY DESIGN



Time 0 Vitamin A 2000,000 IU given orally	RDR	3 months	Conclusion of study Repeat RDR

Serum retinol values will be measured using standard HPLC analysis (Waters, Millipore, USA at the ICDDR,B. Serum and urine samples will be frozen and returned to UAB where serum RBP, C-reactive protein and urinary retinol levels will be measured.

Statistical analysis: In this study we will be comparing the results of the RDR test (either positive >20 or negative <20) between quintile number 1 and quintile number 5. A two by-two table can be constructed and chi-square analysis of the data carried out to test for a significant difference between the two quintiles.

We will also be able to retrospectively compare each child's RDR results at the beginning of the study to their RDR value at the conclusion of the study (ARDR). We would expect there to be a difference in RDR values with the RDR value obtained at the conclusion of the study being greater than that at the beginning of the study. However, the ARDR for those children in quintile # 1 would be greater than those in quintile # 5; i.e., children with the greatest number of infections would have a larger difference in RDR values. Testing for statistically significant differences between RDR values for each child in quintile # 1 and quintile #5 will be done using a paired t-test.

By grouping study participants into quintiles at the conclusion of the study based on the number of infections they experienced a "dose response" may be seen. We would expect that the mean RDR value for quintile 1 would be greater than that for quintile 2; mean RDR value for quintile 2 would be greater than that for quintile number 3 and so forth. This would strengthen our assertion that it is repeated infections that reduce Vitamin A stores. We will also examine the excretion of retinol in the urine of children enrolled in the study. We would expect that the urine of children in quintile # 1 would contain the highest concentration of retinol. The children in each subsequent quintile would have lower concentrations of retinol in their urine with the children in quintile #5 having the lowest levels. It is expected that there will be a correlation between the level of retinol excretion in the urine and depletion of Vitamin A stores as measured by the RDR.

Human subjects: One-hundred children between the ages of 1-3 with no preference to sex will be enrolled into the study. All children will be examined at the beginning of the study for current illnesses and signs of xerophthalmia. Those children who are ill or have signs of Vitamin A deficiency will be treated and excluded from the study. Those children enrolled in the study will be followed during the study period. At the conclusion of the study all participants will once again have a complete physical exam and treated appropriately for any on going infections.

Specimens obtained during the study period will include 4 blood draws of a small volume

of blood (3-5cc's) from a peripheral vein. Urine will be collected by means of an external collection bag. Risk to the participant will be negligible as collection of blood will be from peripheral veins with new, sterile needles using aseptic technique. The administration of Vitamin A at a dose of 200,000 IU has been shown to be safe in children >1 year of age and associated with minimal side effects. Benefits to those children studied and to those children excluded include evaluation and treatment of infectious diseases and Vitamin A deficiency.

References

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11) Flow Chart of Tasks and Time Frame:

Week 1	Week 2	Weeks 3-15	Week 16
Enrollment period Visit villages with CHW and enroll 20 subjects per day for a total enrollment of 100 subjects. At the time of enrollment all subjects will have H & P and will be given Vitamin A 200,000 IU orally	**Initial Vitamin A** Twenty subjects per day brought to the clinic in Matlab for RDR test. In 5 days all 100 subjects will have had initial RDR test. Serum from sample #1 frozen and returned to UAB for RBP and C-Reactive Protein levels.	**Morbidity Assessment** Each subject visited weekly (20 per day) by CHW and/or Pediatrician. History and physical obtained to assess morbidity during the previous 7 days. Urine from 1-2 subjects per day (a total of 60-100 urine samples) collected via external urine bag to assess urinary losses of Vitamin A. Urine will be frozen and returned to UAB.	**Final Vitamin A assessment using RDR test.** Twenty subjects per day brought to the clinic in Matlab for RDR test. Serum from sample #1 frozen and returned to UAB for RBP and C-Reactive Protein levels

12. Budget

Project Title: Effects of recurrent Infections in Children with Adequate Vitamin A Levels.

Date of Project: October 15, 1995 - February 4, 1996.

EXPENSES

A. Personnel		
Staff, Local Hire		
Two community health workers	$150.00/mo/worker	1200.00
Living Expenses in Matlab for PI		
Housing	4 months @ $100.00/mo	400.00
Meals	120 days @ $5.00/day	600.00
B. Operating Costs		
Laboratory Expenses in Bangladesh		
Retinol levels, serum	400 @ $6.25ea	2500.00
Travel to villages for morbidity surveillance PI and CHW travelling 5 days/week for 12 weeks		900.00
Office supplies, photocopying etc.		300.00
Supplies for blood draws; syringes, needles, etc.		500.00
Compensation for Families Travel to and from clinic for RDR test Meals for the day during the RDR test	 200 @ $2.50ea 200 @ $2.50ea	500.00 500.00
C. Capital equipment		
None		
D. Travel		
Airfare : Birmingham-Dhaka-Birmingham		$1835.00
Local: Dhaka-Matlab-Dhaka		30.00
E. Computing		
None		
F. Miscellaneous		500.00
	TOTAL	$9765.00

MORBIDITY ASSESSMENT

Definitions

Episode of Diarrhea
≥ 1 day in which ≥ 3 stools of watery or loose consistency, *or* any loose stool with blood.

Episode of Upper Respiratory Infection (URI)
≥ 1 day of cough or nasal discharge or purulent ear drainage.

Episode of Lower Respiratory Infection (LRI)
≥ 1 day of combination of cough with indrawing of the lungs.

Three or more symptom-free days differentiate episodes of diarrhea or respiratory tract infections.

Subject N°: _____

Visit N°: _____

Today's Date ___/___/__
dd mm yr

Date of last visit ___/___/__
dd mm yr

DIARRHEA MORBIDITY

1. Watery or loose stool? Yes No

2. Any loose stool with blood? Yes No

If answer to both 1 and 2 is No: go to #7.

If answer to either 1 or 2 is Yes:

3. How many times per day?

1 2 3 >3

4. For how many days?

1 2 3 4 5 6 7

5. Days with normal stool between days with diarrhea?

Yes No

If answer to 5 is No: Go to #7.

If answer to 5 is Yes:

6. If yes, normal stool for how many days?

1 2 3 >3

Number of episodes diarrhea past week _____

RESPIRATORY MORBIDITY

7. Any cough? Yes No

If answer to 7 is No: Go to #12.

If answer to 7 is Yes:

8. Several times during the day or night? Yes No

9. Night only? Yes No

10. Cough for how many days?

1 2 3 4 5 6 7

11. Any indrawing of lungs? Yes No

12. Any nasal discharge? Yes No

13. Any purulent ear drainage? Yes No

If answer to either 12 or 13 is Yes:

14. How many days with nasal discharge *or* ear drainage?

1 2 3 4 5 6 7

If answer to either 7 or 12 or 13 is Yes:

15. Any days *without* cough, nasal discharge, or ear drainage between days of respiratory symptoms?

Yes No

If answer to 15 is No: Go to #17.

If answer to 15 is Yes:

16. If yes, no cough, nasal discharge, or ear drainage for how many days?

1 2 3 >3

Number of URI episodes past week _____

Number of LRI episodes past week _____

OTHER

17. Any medications? Yes No

If yes, what type? _____

_____

_____