

22

26 May 1978

Principal Investigator _____ Trainee Investigator (if any) _____

Case No. 78-016 Supporting Agency (if Non-CRL) _____

Title of study amoxicillin Phosphatidylcholine emulsion of refugee children project status:
() New Study
() Continuation with change
() No change (do not fill out rest of form)

Give 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 possibly leading 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 Yes No
 - c) Physical risks Yes No
 - d) Sensitive questions Yes No None
 - 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

5. Will signed consent form be required:
- a) From subjects Yes No
 - b) From parent or guardian (if subjects are minors) Yes No
6. Will precautions be taken to protect confidentiality of subjects: Yes No
7. Check documents being submitted herewith to Committee:
- Umbrella proposal - Initially submit as overview (all other requirements will be submitted with individual studies).
 - Protocol (Required)
 - Abstract summary (Required)
 - Statement given or read to subjects or 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 Board for review.

For approval of the Review Board on Use of Human Volunteers for any change involving the rights and welfare of subjects before making such change.

[Signature]
Principal Investigator

Trainee

78-016
Rec'd 3/5/78


SECTION I - RESEARCH PROTOCOL

- 1) Title: Doxycycline Prophylaxis for Diarrhea of Refugee Children
- 2) Principal Investigator: Dr. Munshi
- 3) Starting Date: 3 June, 1978
- 4) Completion Date: 1 November, 1978
- 5) Total Direct Cost: U.S. \$5,882.87
- 6) Abstract Summary:

One-hundred subjects aged 1-4 years who are residing at Ledha refugee camp near Teknaf, will be included in a double blind comparison of doxycycline 4mg/kg/dose, twice each week, as a prophylaxis against diarrheal disease. The subjects will be treated for three weeks with daily surveillance during the treatment period and for an additional three weeks (total six weeks surveillance). Rectal swabs culture will be obtained at the beginning of the study and with each diarrheal episode to document the pathogens in this epidemiologic setting.

7) Reviews:

- a) Research Involving Human Subjects: _____
- b) Research Committee: _____
- c) Director: _____
- d) BMRC: _____
- e) Controller/Administrator: _____



PILOT STUDY

DOXYCYCLINE PROPHYLAXIS FOR DIARRHEA OF REFUGEE CHILDREN

A. INTRODUCTION

1. Objective: To decrease diarrheal disease related morbidity in groups of people who have a greatly increased risk of diarrheal disease because of a disaster situation.

2. Background: Diarrheal disease, including both watery diarrhea and dysentery, are extremely common in disaster situations which are generally associated with poor water and sanitation facilities. The specific etiologic agents responsible for these diarrheal episodes have never been determined in this epidemiologic setting; however, it would be logical to assume that the usual enteric pathogens (shigella, and enterotoxigenic E. coli) would be most common with cholera occurring in specific defined epidemics.

During the last few months such a disaster situation has occurred in Bangladesh with many refugees (now numbering 150,000) coming from Burma because of persecution. These refugees are being held in camps located between Teknaf and Cox's Bazar, Bangladesh. Two of the camps, Ledha and Nila camps, are located close to Teknaf (eight to eleven miles respectively). Ledha camp is the most primitive in terms of water and sanitation services; that is, there is no well water, and only inadequate trench latrines for a population of 25,000. Water is being trucked from Cox's Bazar in a fire truck daily but much of the water comes from ditches. Housing is extremely congested with several long houses built, a section

of which is assigned to one or two families. The section is about 8' x 8' and normally houses about ten persons. Food supply is mainly wheat flour and is all donated.

The camps appear to be well organized socially with a headman (Maji) responsible for the persons which accompanied him from Burma. Usually 200-300 persons would be in one group associated with one Maji, and these people occupy one section of the camp.

Other relief organizations are attempting to provide well water and sanitation facilities; this will not be available for several days or even weeks.

A brief survey of 30 random families in the camp revealed a mean family size of 7.8 members per family. Twenty-five of 233 (11%) persons were between one and four years and six of these 25 had diarrhea on the day of the interview. Overall, 16 of the 233 (6.9%) persons had diarrhea and twenty of 233 (8.5%) complained of some type of illness.

It has been proposed that a tetracycline drug could be used effectively to decrease diarrhea related morbidity in an acute situation until improved sanitation facilities become available. This is based on the known sensitivities of the major pathogens (E. coli, Vibrio and Shigella (Seven of eight S. flexneri from the camp were tetracycline sensitive)). In previous observations in animals receiving Tetracycline, growth is improved and diarrheal episodes

are decreased. Also in travelers diarrhea, doxycycline has been shown to be an effective prophylactic agent. Doxycycline rather than tetracycline is to be used because of its long half life (about 20 hours) which allows for a less frequent dosage schedule, and because of its unique mode of excretion through the mucosa of the small intestine which places the drug at the site of the infection.

B. SPECIFIC AIMS

1. To determine the incidence and etiology of diarrheal disease in the Burmese refugee population aged 1-4 years.
2. To determine the efficacy of prophylactic doxycycline in the prevention of diarrheal disease in this population.

C. METHODS OF PROCEDURE

Subjects: One-hundred Burmese refugee children aged 1-4 years (less than five years) living in Ledha camp chosen from randomly selected families will be included in the study. Children who are ill at the onset of the study (diarrhea, fever, severe malnutrition) and children who had received antibacterial medication during the previous week and children who are exclusively breast fed will be excluded. Persons allergic to tetracycline will be excluded. Written informed consent will be obtained from the subjects' parents.

Randomization of subjects will take place by listing 120 children, then using a list of random numbers children will be assigned to one of four drugs, two of which are doxycycline, and two of which are placebo.

Methods: The study will be described to the parents of the subjects and if they consent, the children will be entered into the study and a brief identifying questionnaire will be filled out (see form). Patients will be weighed and measured and questioned regarding recent medical illnesses. A rectal swab culture will be obtained. The subjects will then be started on doxycycline or placebo, 4 mg/kg, twice each week for three weeks.

Surveillance (see accompanying form) will be carried out every day during the drug treatment and for an additional three weeks to determine the occurrence and severity of diarrheal symptoms, fever, or other symptoms. Body weight will be determined at the beginning of the study, after three weeks and at the end of six weeks. Diarrheal disease will be treated either by oral fluid if mild or referred to the rehydration center if more severe. Febrile patients or other ill patients will be referred to Dr. Munshi.

Rectal swab cultures will be obtained at the onset of the study and with each visit when there has been diarrhea the day of the visit or the day preceding the visit. If any of the subjects are treated at the rehydration unit, an attempt will be made to secure a rectal swab culture at that time also.

The rectal swab culture will be plated onto MacConkey, S.S., and Monsur's agar for isolation of salmonella, shigella, or vibrio. In addition, five E. coli isolates will be picked from the MacConkey plate for enterotoxin testing using the Y₁ adrenal cell and infant mouse assays. Also a rectal swab will be obtained for rotavirus assay using the elisa assay.

A diarrheal episode will be defined as the occurrence of three or more watery stools per day or the occurrence of blood or mucous in the stool.

Data Analysis: One-hundred patients will be included in this study.

This was based on an assumed attack rate of at least 50% in the placebo group during the three weeks of study and a possible drop our rate of 50% from the study. This will still give sufficient numbers to show a significant difference ($p=0.05$) if the protection rate is at least 80%.

Analysis of data will be by Fisher's exact or Chi Square analysis as appropriate.

D. SIGNIFICANCE

An effective preventative is needed to decrease diarrheal disease morbidity and mortality in disaster situations as a short term measure until effective sanitation and safe water is established.

SECTION III - BUDGET

A. DETAILED BUDGET

1. PERSONNEL SERVICES

<u>Name</u>	<u>Position</u>	<u>% of time</u>	<u>Annual Salary</u>	<u>Project Requirements TAKA</u>	<u>DOLLARS =</u>
Dr. M. Munshi	Investigator	20%	Tk 35,424	7,084.80	
Dr. M.M. Rahman	Investigator	5%	Tk116,736	5,836.90	
Dr. D. Sack	Investigator	5%	\$ 34,750	--	1,737.50
To be named (3)	Field assistants	7 wks		12,000	
To be named	Bacteriology tech.	2 wks		2,000	
Dr. Al-Mahmud	Animal Resources	5%	Tk 43,470	2,373.50	
			Sub Total:	29,295.20	1,737.50
				=====	=====

2. SUPPLIES AND MATERIALS

<u>Items</u>	<u>Unit Cost</u>	<u>Amount Required</u>		
Rectal Swab Culture	Tk 15.00	300	4,500	
Stock Culture Vial	Tk 2.00	1500	3,000	
Y ₁ Assay	Tk 3.00	1500	4,500	
ST Assay (supplies)	\$ 0.11	600		66.00
ST Assay (mice)	Tk 3.00	600	1,800	
Rotavirus (elisa)	Tk 1.50	300	450	
Doxycycline & Placebo	1 liter each		donated	
Paper, pens misc.			3,000	
			Sub Total:	17,250
			=====	66.00
				=====

3. EQUIPMENT

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4. PATIENT HOSPITALIZATION

-- --

5. OUTPATIENT CARE

-- --

		<u>Project Requirements</u>	
		<u>TAKA</u>	<u>DOLLARS</u>
6.	<u>CRL TRANSPORT</u>		
	Dacca/Teknaf/Dacca - 722 miles - 2 trips Tk 3/mile	4,332	
	Teknaf/Cox's Bazaar/T knaf - 6 trips 100 miles, Tk 3/mile	<u>1,800</u>	_____
	Sub Total:	6,132	
		=====	=====
7.	<u>TRAVEL AND TRANSPORTATION OF PERSONS</u>		
	Dacca/Cox's Bazaar/Dacca - 6 trips by air @ Tk 340	<u>2,040</u>	_____
	Sub Total:	2,040	
		=====	=====
8.	<u>TRANSPORTATION OF THINGS</u>		
	Import of Supplies	<u>1,000</u>	_____
	Sub Total:	1,000	
		=====	=====
9.	<u>RENT, COMMUNICATION & UTILITIES</u>		
		<u>1,000</u>	_____
		<u>1,000</u>	_____
		=====	=====
10.	<u>PRINTING AND REPRODUCTION</u>		
	Printing of forms	1,000	
	Publication		<u>300</u>
	Sub Total:	1,000	300
		=====	=====
11.	<u>OTHER CONTRACTUAL SERVICES</u>		
		--	--
12.	<u>CONSTRUCTION, RENOVATION, ALTERATIONS</u>		
		--	--

B. SUDGET SUMMARY

<u>Category</u>	<u>Project Requirements</u>	
	<u>TAKA</u>	<u>DOLLARS</u>
1. Personnel	29,295.20	1,737.50
2. Supplies and Materials	17,250	66.00
3. Equipment		
4. Hospitalization		
5. Outpatients		
6. CRL Transport	6,132	
7. Travel Persons	2,040	
8. Transportation Things	1,000	
9. Rent/Communication	1,000	
10. Printing/Reproduction	1,000	300.00
11. Contractual Service		
12. Construction		
	<u> </u>	<u> </u>
	Total:	57,717.20 2,110.50
		<u> </u>
	Total Dollars:	5,882.87
		=====

Conversion rate \$ 1.00 = Tk 15.3

ABSTRACT SUMMARY

1. The subjects in this study will include 100 children aged 1-4 years who are residing at Ledha refugee camp near Teknaf, Bangladesh. This group is chosen because they are the group at highest risk of diarrheal disease and in whom an episode of severe diarrhea is most likely to be lethal.
2. The risks associated with the administration of doxycycline to this group are very low but include hypersensitivity reactions such as skin rashes, and super infection with resistant organisms. In children all tetracyclines may cause staining of teeth; however, the dosage used is less than that which would be expected to stain teeth and in Bangladesh, where beetle nut chewing is prevalent, teeth staining is not considered to be a significant risk.
3. Surveillance will be carried out daily and any reactions will be reported to a physician who can take necessary action.
4. Patients will be identified by number and at the end of the study, all names will be removed from data sheets, leaving only numbers. Also all records will be kept in a locked file in the investigators office.
5. Signed informed consent will be obtained. No information will be withheld.
6. Subjects will be visited daily during the study to detect any episode of diarrhea.

: 2 :

7. The patients receiving doxycycline should have significant protection from diarrhea. Society may benefit from the development of an effective approach to the problem of diarrhea associated with acute unsanitary conditions such as with newly formed refugee camps. Doxycycline is an established drug with a known low risk.

8. Only stool or rectal swab material will be obtained.

PERMISSION FORM
PROPHYLACTIC DOXYCYCLINE FOR UNSPECIFIED DIARRHEAL DISEASES

The Cholera Research Hospital is carrying out research to determine a method of preventing diarrheal diseases in children aged 1-4 years. We would like your child(ren) to participate in a study to determine whether one dose of doxycycline given two times per week would be effective in the prevention of diarrheal diseases. If this method of treatment is proven effective it would relieve human suffering among disaster stricken populations from diarrhea. If you agree to allow your child(ren) to participate in this study you can expect the following:

1. We will visit your house every day to inquire about diarrhea or other illnesses in your child(ren). Treatment will be available for your child(ren) should any diarrheal disease develop.
2. Your child(ren) will receive either doxycycline or a syrup which looks like doxycycline but has no antibiotic in it. The syrup will be given to your child(ren) in one dose two times per week for three weeks.
3. Your child(ren) will be given some sort of identification for the purposes of the study. At the beginning of the study your child(ren) will be weighed and two rectal swabs will be taken. Rectal swabs will also be taken with each diarrheal episode for the following six weeks.
4. The risk of taking the medicine is extremely small. Side effects might include allergic reactions (such as skin rashes) or infection with another resistant organism. Also, taking the medicine for a very long time may result in some staining of the teeth but this should not occur at this dosage for three weeks of medication that we are planning.

: 2 :

5. Your child(ren)'s medical records will be kept confidential.
6. Your child(ren) does/do not have to participate in this study. If you do allow your child(ren) to enter the study you are free to withdraw them from the study at any time. If you decide not to allow your child(ren) to enter the study or if you withdraw them from the study, you and your children may still be treated by us for diarrheal disease. Your decision regarding the study will not jeopardise you or your child(ren)'s medical care.
7. We will answer any questions you have.

If you agree to allow your child(ren) to participate in the study above, please sign your name here.

(Signed)

(Date)

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 42. 2013-14
 43. 2014-15
 44. 2015-16
 45. 2016-17
 46. 2017-18
 47. 2018-19
 48. 2019-20
 49. 2020-21
 50. 2021-22

(2022)

(2021)

REGISTRATION FORM FOR DOXYCYCLINE PROPHYLAXIS STUDY

Study Number / / / / /
 1 2 3 4

Patient's Name _____ Age / / / years Sex / / /
 5 6

Father's Name _____ Mother's Name _____

Maji's Name _____ Family Size / / / /
 7 8

Date entered camp / / / / day / / / / mo. / / / / year
 9 10 11 12 13 14

Date of filling out form / / / / day / / / / mo. / / / / year
 15 16 17 18 19 20

Breast feeding / / / exclusively=1 half and half=2 no=3
 21

Recent (1 mo.) medical illnesses / / / /
 22 23

None=01	Pneumonia=04
Measles=02	Dysentery=05
Fever=03	Diarrhea=06
Other=07	_____

Any other members with dysentery/diarrhea within 15 days / / /
 24

None=1 Dysentery=2 Diarrhea=3 Both=4

Drinking source / / / Ditch (Y,N)
 25

/ / / Truck (Y,N)
 26

/ / / Tank (Y,N)
 27

/ / / Well (Y,N)
 28

Height / / / / / cm
 29 30 31

Weight / / / / / kg
 32 33 34

Any medicine taken within last week / / / (Y,N)
 35

DOXYCYCLINE PROPHYLAXIS IN LEDHA CAMP FORM

Study Number / / / / /
1 2 3 4

Patient's Name _____ Age / / years Sex / /
5 6

Father's Name _____ Mother's Name _____

Maji's Name _____

24 HOUR HISTORY

Diarrhoea / / Watery=1 Mucoid=2 Time and date of onset:
7 Loose=3 Bloody=4 _____
 Mucoid and Bloody=5

Frequency of diarrhoea / / /
in last 24 hours 8 9

Vomiting in last / / None=1, 5 times=2, More=3 _____
24 hours 10

Fever / / None=1, Mild=2, Mod (102°)=3 _____
11

Abd Pain / / None=1, Occasional=2, Continuous=3 _____
12

Prolaps rectum / / Not present=1, On straining=2, Large=3
13

Convulsion / / None=1, Mild=2, Severe=3 _____
14

Other complaints / / Specify _____
15

Clinical Dx / /
16

Diarrhea form filled out yesterday / / (Y,N)
17

Action taken / / No action needed=1, Oralyte given=2
18 Referred to treatment center=3,
 Taken to treatment center=4,
 Other=5 (specify) _____

Non-Diarrheal disease / / Fever=1, Other=2 _____
19