22

Date 13-12-85

ETHICAL REVIEW COMMITTEE, ICDDR,B

Principal Investigator J R HARRIS FAFOA
Trainee Investigator (if any) _____

Application No. 85-043P
Supporting Agency (if Non-ICDDR,B) _____

Title of Study Mortality Following Shigellosis in Matlab

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)
   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)
   (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 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 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.

Jeffrey R. Harris M.D.
(PTO)

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

Jeffrey R. Harris, M.D.
Principal Investigator

_____
Trainee

85-043
19-12-85

SECTION I - RESEARCH PROTOCOL (PILOT)

1. Title: MORTALITY FOLLOWING SHIGELLOSIS IN MATLAB

2. Principal Co-investigators: Dr. N. Huda
Dr. J. Harris

Co-investigators: Dr. K. Zaman
Dr. B. Wojtyniak
Dr. M. Yunus

3. Starting Date: January 1, 1985

4. Completion Date: June 30, 1985

5. Total Direct Cost: $605

6. Scientific Program Head: This protocol has been approved by the Disease Transmission Working Group

Scientific Program Head's Signature [signature] Date 27 Nov 1985

7. Abstract Summary:

At the ICDDR,B, we are attempting to design interventions for reduction of mortality among children under the age of 5 years. One group of children shown to be at high risk for mortality are children who present to the Matlab treatment center with diarrhea. Of these, children with shigellosis may be at exceptionally high risk for mortality, particularly during the current multiply antibiotic-resistant S. dysenteriae type 1 epidemic, which began in 1983. We propose here a retrospective review of 1983 and 1984 records to allow us to calculate species-specific mortality following shigellosis, to compare this mortality to that following other diarrheal illnesses, and to determine risk factors for post-shigellosis mortality. With this information, we hope to guide intervention efforts aimed at decreasing mortality among young children.

8. Reviews: a) Ethical Review Committee_____ Date_____

b) Director_____ Date_____

SECTION II - RESEARCH PLAN

INTRODUCTION

Objectives

To determine the mortality following shigellosis during an epidemic of S. dysenteriae type 1, compare this mortality to that following other diarrheal illnesses, and determine risk factors for post-shigellosis mortality.

Background

At the ICDDR,B, we are attempting to design interventions for reduction of mortality among children under the age of 5 years. One group of children shown to be at high risk for mortality are children who present to the Matlab treatment center with diarrhea (1). Mortality rates for children discharged from the treatment center exceed those of children of the general population and, for discharged children in the third year of life, are 5 times the expected. Unfortunately, about half of the 4,000 to 6,000 Demographic Surveillance System (DSS) residents who present to the Matlab treatment center each year are children under the age of 5 years, so this is probably too large a group for effective intervention. Further identification of risk factors for mortality among this group would be useful. One such risk factor is severe malnutrition. Severely malnourished children discharged from the treatment center have mortality rates which are 14 times higher than those of discharged well-nourished children (1).

Shigellosis may well be another risk factor. Shigella are the fourth most commonly isolated diarrheal pathogens from persons who present to the treatment center (2). All of the three more commonly isolated pathogens, rotavirus, enterotoxigenic Escherichia coli, and Vibrio cholerae 01, cause an acute watery diarrhea that would be expected to result in death primarily by dehydration before or during hospitalization. Shigella, on the other hand, frequently causes grossly bloody dysentery (3) which can be prolonged and may cause or exacerbate malnutrition and result in post-discharge mortality.

Among the Shigella species, S. dysenteriae type 1 causes the most severe illness. In Stoll et al.'s study of shigellosis at the Dhaka treatment center, bloody diarrhea was a symptom at presentation of 83% of S. dysenteriae type 1 patients and only 47% of patients with other Shigella species. This severe illness may lead to death. In the Central American multiply antibiotic-resistant S. dysenteriae type 1 outbreak of the early 1970's, case-fatality ratios of 10% to 15% were seen (4)..

Bangladesh and Matlab are in the midst of a similar outbreak. Figure 1 shows the marked increase in the incidence of Matlab treatment center-diagnosed S. dysenteriae type 1 diarrhea in 1983 and 1984. Similar increases have been seen in northern Bangladesh and West Bengal (5, 6). Multiply antibiotic-resistant isolates have been documented in all these locations (5-7), and case-fatality ratios as high as 12% have been documented in the 6 months following illness in northern Bangladesh (6).

Rationale

We propose here a retrospective analysis of mortality following Matlab treatment center presentation with shigellosis in 1983 and 1984, the first 2 years of the current S. dysenteriae type 1 outbreak. We plan to calculate species-specific mortality to determine if mortality following S. dysenteriae type 1 illness is higher than that following other Shigella illness as well as compare mortality following shigellosis to that following non-Shigella diarrheal illness. In addition, we will attempt to determine other risk factors for post-shigellosis mortality. With this information, we hope to guide intervention efforts aimed at decreasing mortality among young children.

SPECIFIC AIMS

1. To determine the species-specific mortality following shigellosis during an epidemic of S. dysenteriae type 1.
2. To determine if the mortality following shigellosis is higher than that following other diarrheal illness.
3. To determine risk factors for post-shigellosis mortality.

METHODS OF PROCEDURE

Post-shigellosis mortality

To ascertain DSS residents who presented to the Matlab treatment center with culture-proven shigellosis in 1983 or 1984, we will simultaneously review the Matlab treatment center and microbiology logbooks. For each of the

approximately 1,400 DSS residents who presented to the treatment center and had a stool culture positive for Shigella, we will list the name, registration number, hospital number, date of admission, Shigella species isolated, age, and sex. We will then verify the registration number, age, and sex of these persons with updated 1982 DSS census volumes and enter the data on a Kaypro microcomputer.

To determine the mortality following shigellosis, we will use the microcomputer to link the list of DSS residents with culture-proven shigellosis to lists of DSS residents who died or out-migrated in 1983, 1984, or the first half of 1985. We will then calculate age-, sex-, cause-, and species-specific mortality rates for the first 3 months and first 6 months after presentation with shigellosis.

Mortality among a comparison group of treatment center attendees

To determine the mortality following presentation to the treatment center with an illness other than shigellosis, we will again simultaneously review the Matlab treatment center and microbiology logbooks and list a sub-sample of DSS residents who presented to the treatment center in 1983 or 1984 on dates similar to the dates of admission of the shigellosis patients, and who were culture-negative for Shigella. We will list these persons, verify their information, and use the microcomputer to determine post-treatment center presentation mortality rates exactly as above. While controlling for age and sex, we will then compare mortality rates following shigellosis and following non-Shigella diarrheal illness.

The exact number of non-shigellosis controls necessary will be calculated after the post-shigellosis mortality has been determined. However, if there are 1,400 DSS residents with culture-proven shigellosis in 1983 and 1984, and their subsequent mortality is twice the 3% post-discharge rate observed by Roy et al. (3), then a sample of 700 controls (one for every two cases) would, with 80% power, be adequate to detect a statistically significant difference between these groups.

Risk factors for post-shigellosis mortality

After completion of the above analyses, if post-shigellosis mortality rates are found to be higher than mortality following a non-shigellosis diarrheal illness, we will attempt to determine risk factors for death among the patients with shigellosis. To do this, we will compare the demographic and clinical characteristics of persons who had shigellosis and died to those of persons who had shigellosis and survived. We will ascertain the clinical characteristics, including nutritional status (weight-for-age at discharge), duration and character of diarrhea, presence or absence of fever, degree of dehydration, and antibiotic treatment received, from a review of treatment center records. The exact sample sizés of cases and controls will be determined later.

SIGNIFICANCE

This study should provide us with further information about exactly which persons are at risk for death following presentation to our diarrheal treatment centers. With this information, we hope to be able to design more specific interventions for prevention of death. Examples of interventions

based on information that might be gained from this study include, 1) a change in first-line antibiotic therapy for shigellosis in general or for shigellosis caused by specific species, 2) admission to the planned Matlab nutritional rehabilitation center of severely-malnourished children with S. dysenteriae type 1 dysentery, and 3) prolonged hospitalization for patients with dysentery until the etiology can be determined, and more focused antibiotic therapy can be given. In addition, this study may provide an increased impetus to efforts at the ICDDR,B and elsewhere to develop a S. dysenteriae type 1 vaccine. Of course, actual intervention strategies will await the results of the study.

FACILITIES REQUIRED - none

COLLABORATIVE ARRANGEMENTS - none

REFERENCES

1. Roy SK, Chowdhury AKMA, Rahaman MM. Excess mortality among children discharged from hospital after treatment for diarrhoea in rural Bangladesh. Br Med J 1983;287:1097-9.

2. Black RE, Merson MH, Rahman MH, et al. A two-year study of bacterial, viral, and parasitic agents associated with diarrhea in rural Bangladesh. J Infect Dis 1980;142:660-4.

3. Stoll BJ, Glass RI, Huq MI, Khan MU, Banu H, Holt J. Epidemiologic and clinical features of patients infected with Shigella who attended a diarrheal disease hospital in Bangladesh. J Infect Dis 1982;146:177-83.

4. Mata L. Shigellosis in Central America. In: Rahaman MM, Greenough WB III, Novak NR, Rahman S, eds. Shigellosis: a continuing global problem. Proceedings of an international conference. Dhaka: International Center for Diarrhoeal Disease Research, Bangladesh. 1983;26-38.

5. Pal SC. Epidemic bacillary dysentery in West Bengal, India, 1984. Lancet 1984;2:1462.

6. Bennish M, Eusof A, Kay B, Wierzba T. Multiresistant Shigella infections in Bangladesh. Lancet 1985;2:441.

7. Zaman K, Yunus M, Baqui AH, Hossain KMB, Khan MU. Co-trimoxazole-resistant Shigella dysenteriae type 1 outbreak in a family in rural Bangladesh. Lancet 1983;2:796-7.

ABSTRACT SUMMARY

1. The study population will consist of persons who visited the Matlab treatment center in 1983 and 1984 for routine clinical care. No new contacts will be made with these persons, and no consent will be necessary.
2. This study involves no risks.
3. This study involves no risks.
4. In order to preserve confidentiality, after identities are confirmed, persons will be identified only by number. In addition, written records and computer diskettes will be kept in a locked drawer in the office of one of the principal investigators. No person will be identified individually in any published report of this investigation.
5. Since this is a retrospective review of non-sensitive records, no consent will be obtained other than the implied consent already obtained when the patients originally presented for treatment.
6. No interviews will take place.
7. The potential benefit from this study is an increase in our ability to prevent mortality following shigellosis. There is no risk, so the benefit outweighs the risk.
8. The study involves the use of Matlab treatment center records and DSS death records.

SECTION III - BUDGET

SUMMARY BUDGET

Item	1986 Project Cost In Dollars
3100 - LOCAL PERSONNEL	360
3200 - INTERNATIONAL PERSONNEL	0
3300 - CONSULTANTS	0
3500 - LOCAL TRAVEL	125
3600 - INTERNATIONAL TRAVEL	0
3700 - SUPPLIES AND MATERIALS	8
3800 - OTHER COSTS	0
4800 - INTERDEPARTMENTAL SERVICES	112
TOTAL DIRECT COSTS	605

DETAILED BUDGET

3100 - LOCAL PERSONNEL

Name or Title	% Time	Total Person-Months	Monthly Personnel Cost	1986 Project Cost In Dollars
Coding/Data Entry Asst - GS 3	100	3	120	360
Dr. N. Huda	No Incremental Cost			0
Dr. K. Zaman	"			0
Dr. M. Yunus	"			0

3200 - INTERNATIONAL PERSONNEL

Name or Title	% Time	Total Person-Months	Monthly Personnel Cost	1986 Project Cost In Dollars
Dr. J. Harris	No Incremental Cost			0
Dr. B. Wojtyniak	"			0

3500 - LOCAL TRAVEL

Item	1986 Project Cost In Dollars
Per Diem (3.90/day X 4 days/wk X 8 wks)	125

3700 - SUPPLIES AND MATERIALS

Item	1986 Project Cost In Dollars
Xerox (0.03/page X 260 pages)	8

4800 - INTERDEPARTMENTAL SERVICES

Item	1986 Project Cost In Dollars
Matlab trip (14.00/person-round-trip X 8 trips)	112

74	63
75	68
76	176
77	48
78	42
79	75
80	52
81	28
82	28
83	331
84	414

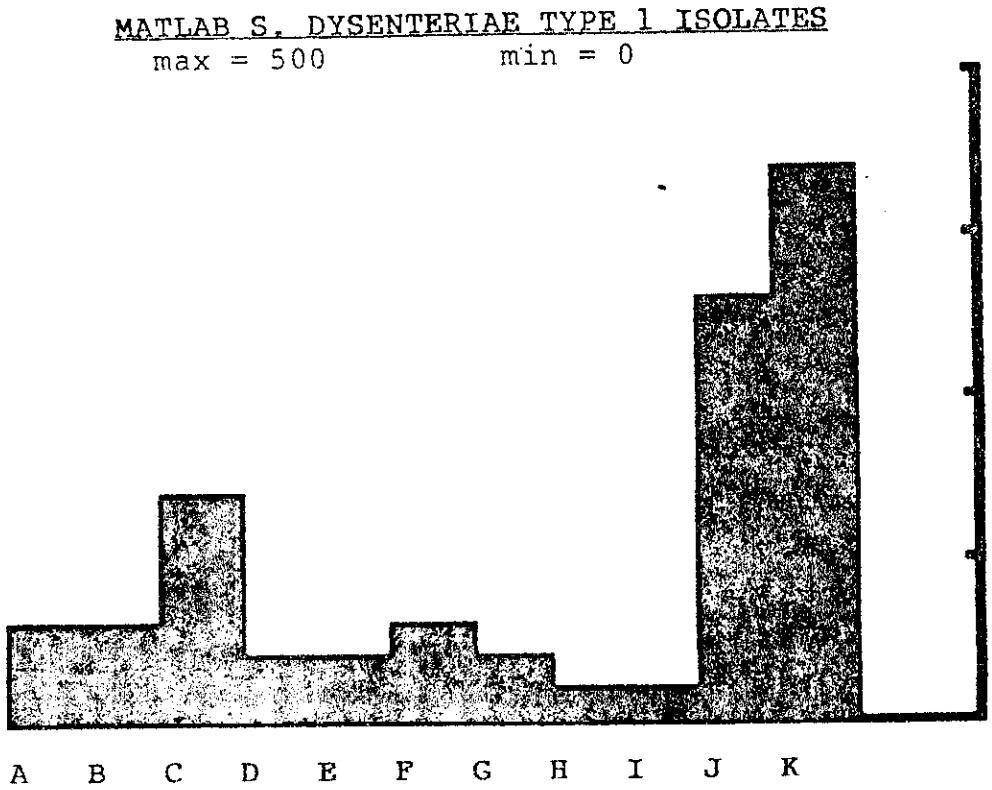

FIGURE 1