Attachment 1.

Date 16/10/88
19/10/88

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator C. BONSMANN M. YUNUS

Application No. 88-027

Title of Study INTERVENTION TO REDUCE DEATHS FROM DYSENTERY IN UNDER-FIVE CHILDREN IN THE MATLAB HEALTH PROJECT AREA

Trainee Investigator (if any) _____

Supporting Agency (if Non-ICDDR,B) _____

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 (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 NA 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.

(PTO)

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

Principal Investigator

Trainee

88-027
9/10/88

SECTION I: RESEARCH PROTOCOL.

(1) Title: INTERVENTION TO REDUCE DEATHS FROM DYSENTERY IN UNDER-FIVE-CHILDREN IN THE MATLAB MCH-FP AREA.

(2) Principal investigators: Carine Ronsmans
M Yunus
Co-Investigators: V Fauveau, J Chakraborty
S.A Khan, H. Begum, EH Khan

(3) Starting date: Soon after approval

(4) Completion date: 2 years after starting date

(5) Total cost: 84,597 US $
Probable source of funding : Shigella project

(6) Scientific programme head:
This protocol has been approved by the Community Health Division

Signature of the Scientific Programme Head: ----------
Date: 17/10/88

(7) Abstract summary:

In Bangladesh, dysentery, primarily due to infection with Shigella is one of the major causes of diarrhoeal associated morbidity and mortality in under-five children. Case management by community health workers(CHW), incorporating the use of antibiotics for treatment of bloody diarrhoea, might help reduce the morbidity and mortality from dysentery. This study aims at evaluating the feasability and effectiveness of such an intervention.

During a 2 year period CHW's will provide home treatment for dysentery in 2 blocks of the Matlab MCH-FP area. In the 2 other blocks children with dysentery will be referred to the treatment centre. Impact of the intervention will be measured by comparing the case-fatality rates from dysentery between the 2 areas.

(8) Reviews:

(i) Ethical Review Committee: ----------

(ii) Research Review Committee: ----------

(iii) Director's signature: ----------

SECTION II: RESEARCH PLAN

A. INTRODUCTION

1. Objective

To assess the feasability and effectiveness of an intervention, using home treatment of dysentery with antibiotics, in reducing mortality from dysentery in under-five-children.

2. Background

(1) Definition of dysentery.

Dysentery is defined as loose or watery stool with visible blood. The translation in bangla is "rokto amasha" or "rokto paikana".

(2) Current knowledge about the etiology of dysentery in children under five years of age.

In data collected by household surveillance in 2 villages in rural Matlab, Shigella was isolated in 62% of 188 episodes of dysentery investigated in children under 5 years of age (1). Entamoeba histolytica was associated with 2 episodes and no pathogen could be found for the rest of the dysentery cases. Of children under 5 years of age presenting to the treatment centre in Matlab with gross blood in the stool, 28% had a Shigella spp. identified (J. Clemens, data not published). Information on other pathogens was not available. The difference in isolation rates for Shigella between community and hospital is probably due to the extensive use of antibiotics prior to coming to the hospital.
Compared with other areas in Bangladesh, the one consistent finding seems to be the high proportion of all dysentery associated with Shigella infection (2,3). Given the evidence that the organisms can be retrieved in only 60-70% of symptomatic cases of shigellosis (4), the etiologic fraction of dysentery due to Shigella is probably higher than the isolation rates.
Other pathogens sometimes identified in cases of dysentery are E.Histolytica, Campylobacter jejuni and enteroinvasive E.Coli. There is however not much evidence that these pathogens would be a major cause of dysentery in young children (2,5,6,7,8,9).

(3) Importance of dysentery as a cause of death in under-five children.

One study conducted in the northern area of Bangladesh reported a case fatality rate for dysentery of 0.7 % (2). Patients with bloody diarrhoea were at significantly higher risk of death in

comparison to patients with watery diarrhoea.
According to the "cause of death" reporting in the Matlab DSS area, diarrhoea is the main cause of death in children 1-4 years of age and dysentery is the main cause of diarrhoeal death. In 1986 diarrhoea accounted for 56% (212/380) of all deaths in under-five-children and 74% (156/212) of the diarrhoeal deaths were associated with dysentery (Dr. V.Fauveau,unpublished data). The high association of bloody diarrhoea and risk of death in children aged 6-36 months in the community in Matlab has also been showed by Briend et al (10). Watery diarrhoea was not associated with a higher risk of death.

(4)Effect of dysentery on growth.

Diarrhoea has been found to have an adverse effect on the growth of young children in developing countries. In Bangladesh, dysentery and shigellosis, of all types of diarrhoea, had the greatest effect on linear growth of young children (11,12).

(5)Risk factors for severe or fatal shigellosis.

Several studies have assessed whether there are identifiable risk factors for severe or fatal shigellosis (3,13,14,15). The most commonly identified risk factors are: poor nutritional status, lack of breast feeding and young age (less then one year old).

(6)Drugs for treatment of shigellosis.

The pattern of resistance of all the Shigellae spp. isolated in the Matlab laboratory over the last year (from July 1987 to June 1988) show a 47% resistance to co-trimoxazole, 61% to ampicillin and 7% to nalidixic acid. Treatment with nalidixic acid is thus the most appropriate choice. The second drug of choice would be pivmecillinam.
One important issue has to be addressed: the possible promotion of resistance with more common use of antibiotics for the treatment of dysentery . Over the last two months an increasing number of Shigella dysenteriae type 1 have become resistant to nalidixic acid in Matlab (Table 1).

Table 1: Isolation of strains of S.dysenteriae type 1 resistant to nalidixic acid from july 87 to june 88 in Matlab.

Month	N of isolates	N resistant (%)
July 87	32	3 (9.3)
Aug 87	43	1 (2.3)
Sep 87	72	2 (2.8)
Oct 87	89	0
Nov 87	95	3 (3.2)
Dec 87	151	2 (1.3)

Jan	88	82	5 (6.1)
Feb	88	31	3 (9.7)
Mar	88	28	3 (10.7)
Apr	88	61	5 (7.6)
May	88	70	12 (17.1)
Jun	88	74	15 (20.3)

The mechanism of this resistance is not yet well understood. Previously, resistance to nalidixic acid was believed to be plasmid-mediated (16) but those observations have been questioned recently . An alternative hypothesis is that the nalidixic acid resistant strain of Shigella shiga currently isolated in Matlab has initially been selected through use of nalidixic acid but is now moving through the population independent on the use of antibiotics in the community (personal communication, Dr. B. Kay). Since there is some evidence that emergence of resistant strains follows the introduction of a drug for widespread and uncontrolled use (17); one could reasonably assume that controlled use of antibiotics is less likely to induce resistance then the current irrational use of antibiotics by village practitioners (see under (6)B. Village practitioners.).

Whatever the mechanism of resistance ,if home treatment of bloody diarrhoea with nalidixic acid is to be started, one has to make sure that (1)full course treatments are taken and (2) development of resistant strains is carefully followed.

(6)Current management of dysentery in the Matlab MCH-FP area.

A. ICDDR'B

In the community the CHW refer all cases of bloody diarrhoea to the ICDDR'B treatment centre (TC). ICDDR'B operates 1 TC in Matlab and 1 community based subcentre. All patients attending the TC are admitted and stools of patients residing in the DSS area are routinely cultured for Salmonella and Shigella. Microscopic examination for ova and parasites is not routinely done. Dysentery is treated with nalidixic acid and the treatment is adapted according to the microbiology result.
Management of dysentery in patients residing outside the DSS area is mainly based on clinical appreciation by the physician. Bloody-mucoid stool is currently being treated with nalidixic acid.

B. Village practitioners

One can not ignore the extensive system of village practitioners,qualified or unqualified, providing treatment for all types of diseases, including diarrhoea and dysentery (18,19). A survey currently being conducted in the Matlab MCH-FP area attempts to describe the health care choice and the treatment received for diarrhoea in under-five-children. Preliminary data show that most of the cases of bloody diarrhoea are treated by village practitioners with inappropriate doses of antibiotics.

The most frequently used drugs are ampicillin, metronidazole and furazolidone; prescribed under tablet form (average 2-3 tablets) or syrup (1 bottle). Though the CHW's refer all cases of dysentery the TC, only 5 out of 150 cases enrolled upto now have attended the ICDDR'B TC. This low referral rate is a strong argument supporting home treatment for dysentery.

3.Rationale.

The rationale for antibiotic treatment of dysentery in young children is to reduce associated mortality, to reduce morbidity and to reduce the adverse consequences of nutritional wasting.

B.SPECIFIC AIMS

1. To determine the incidence of different types of diarrhoea and the case-fatality rate for dysentery in under-five-children in the Matlab community.

2. To measure the impact of home treatment of dysentery with nalidixic acid on the case fatality rate for dysentery.

C.METHODS

Area: MCH-FP area Matlab.

Duration: 2 years

Diarrhoea surveillance: During each fortnightly visit the CHW will ask whether any child 3 to 59 months old has or had diarrhoea during the 14 days since her last visit. Types of diarrhoea will be recorded as (1)**dysentery** ,(2) **watery diarrhoea**, (3) **loose stool** and (4) **mucoid diarrhoea**. The following definitions will be used:

Type of diarrhoea	Frequency of stools in last 24h	Consistency	Blood	Mucus
Dysentery	> 1	loose or watery	seen	seen or not seen
Watery	> 3	watery	not seen	seen or not seen
Loose	> 3	loose	not seen	seen or not seen
Mucoid	whatever the mother identifies as "amasha"			

The duration of diarrhoea will be reported as the total number of days .A new attack will be defined when the child has at least 3 days of normal stool.

Case fatality rate: The ongoing "cause of death" reporting will reveal the number of deaths associated with dysentery in children 3 to 59 months old.

$$\text{case fatality rate (CFR)} = \frac{\text{no of deaths due to dysentery}}{\text{no of episodes of dysentery}}$$

Intervention: The Matlab MCH-FP area is devided into 4 blocks (see map , annex 1). The intervention will be proposed in 2 of the 4 blocks (block B & D) and will be part of the routine work of the CHW's. Each CHW will be provided with antibiotic tablets and will be asked to treat any child 3-59 months old with dysentery on the day of the visit and with a total duration of less then 14 days. Basic education on hygiene and sanitation will be given as well. It is expected that mothers will also seek treatment for their children at the house of the CHW ,between 2 visits, as soon as they know that antibiotics are provided.
The total number of treated episodes is estimated to be 2,000 for one year.

In the control area (block A & C) the children with dysentery will be referred to the TC (Matlab for block A and Nayergaon for block C). The mother will be given a referral sheet and a supportive referral system will be proposed.

In the TC the children will be admitted and stools will be examined for presence of E. histolytica and Shigella spp.. Treatment will be given according to sensitivity pattern of the isolated pathogen. Pathogen isolated, treatment given , days of hospitalisation and outcome will be recorded.

Treatment failure: In most cases of shigellosis due to organisms susceptible to the prescribed antibiotic an improvement in the patients condition would be expected within 48-72 hours (20-21). Treatment failure will be evaluated by the mother: she will be asked to take the child to the TC if there is still blood in the stool after 3 days of treatment.

Training: Training on diagnosis and management of dysentery will be given by a physician.

Quality control:
*1 senior field research officer (SFRO): He will be the supervisor of the programme. His task will be to attend the fortnightly subcentre meetings where field data will be compiled, to report to the houses of a randomly selected sample of children , and to carry out a 3 monthly cross sectional survey on prevalence of dysentery to assess the accuracy of the data collection.
*2 medical assistants in block B&D: They will guide the CHW's and check the field work. They will ensure that children who don't improve after 3 days are being referred to the TC and -through random-checking of households- that full course treatments are being taken .
*2 health assistants in block A&C: They will supervise the data

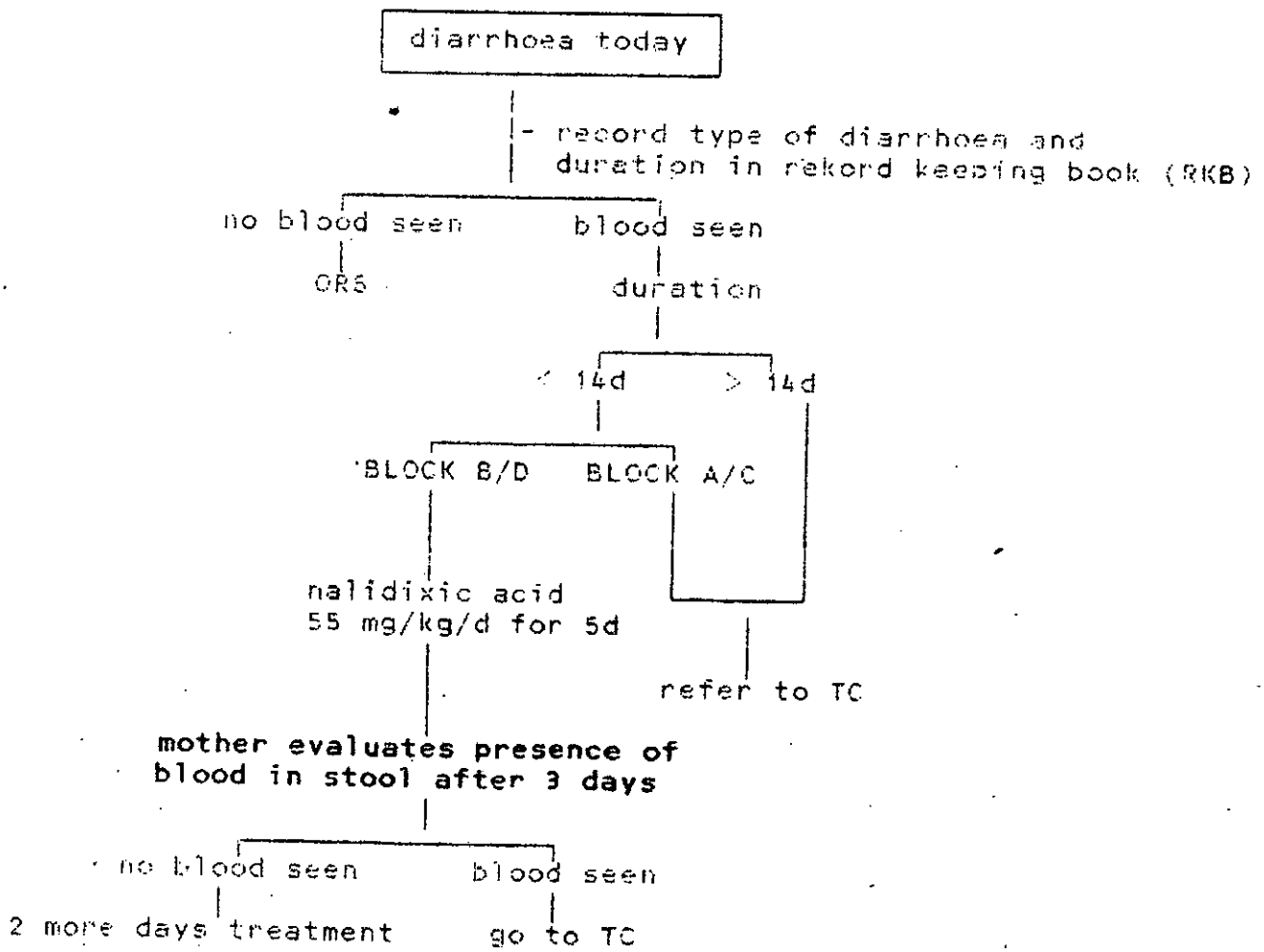
collection (duration and episodes of diarrhoea).
*1 physicians from the Matlab hospital will be responsible for training and medical supervision of CHW during subcentre meetings.

Treatment: Nalidixic acid 55mg/kg/day in 4 dd for 5 days. The first dose will be taken in the presence of the CHW. Resistant cases will be treated in the TC with pivmecillinam 50mg/kg/d in 4dd for 5 days.

Monitoring of resistance: (1) The Matlab laboratory is currently carrying out sensitivity tests for all stools positive for Shigella. This information will be compiled monthly and trends followed.
(2) Every 3 months a rectal swab (R/S) in buffered glycerol saline (BGS) will be collected from a random sample of 240 children with dysentery in the 4 blocks. Every 3 months each CHW will collect a R/S from the first 3 children encountered during her routine visits. The R/S will be sent to the Matlab TC for culture and sensitivity testing within 24h after collection.

Intervention algorithm:

I.IN THE COMMUNITY



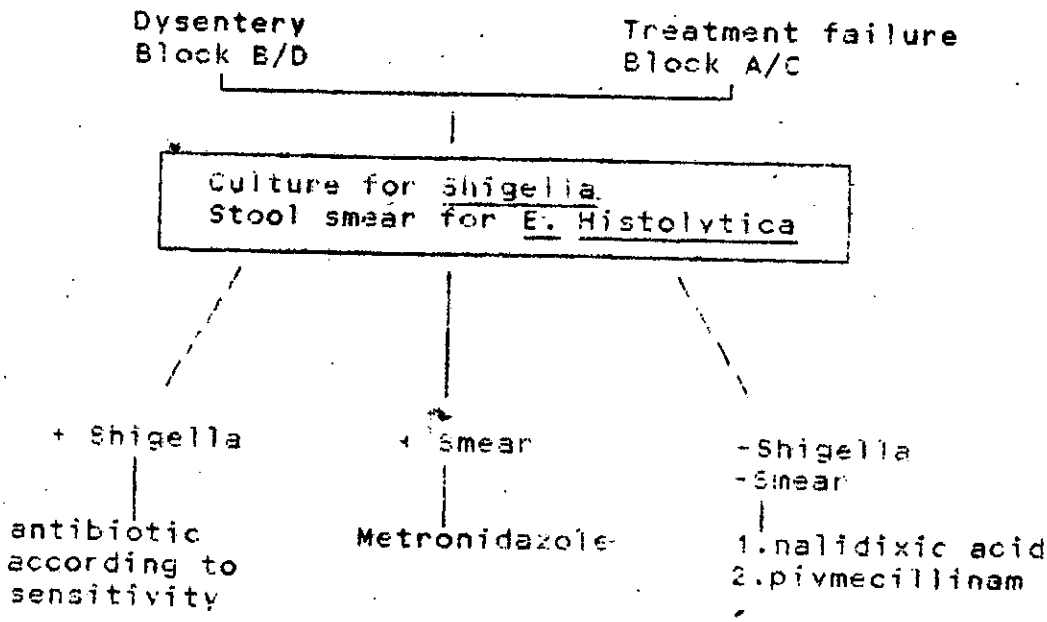
next visit, 2 weeks later

- record total no of days of diarrhoea after last visit
- record outcome (*)
- record total no of tablets remaining

(*)Outcome will be recorded as: -cured (**)
-referred to ICDDR'B
-referred to village doctor
-not cured but not referred

(**) cured means that the child has < 3 normal stools without blood in the last 24h.

2. IN THE TREATMENT CENTRE



Data analysis and evaluation of effectiveness of the intervention:

(1) Epidemiology of dysentery in under five children in the community will be described.

(2) Outcome of illness will be described in children treated with nalidixic acid. The main focus will be:
- duration of illness
- clinical failure and it's relation to sensitivity pattern of

isolated pathogen
- risk factors for fatal dysentery despite treatment. Risk factors to be evaluated are: nutritional status (monthly AC), absence of breastfeeding and repeated episodes of diarrhoea.

(3) The difference in case-fatality rate for dysentery between the treatment and the control area will be evaluated after 2 years.

Sample size: The sample size is based on an expected reduction in CFR for dysentery of 50% in the treatment area compared to the control area.

$$\text{The actual estimated CFR} = \frac{\text{No. of deaths due to dysentery in 1986 in children under five in MCH-FP}}{\text{No of children under five x attack rate f dysentery in 1 year}}$$

$$= \frac{78}{15{,}000 \times 0.3(*)} = \frac{17{,}3}{1000}$$

Based on this case fatality rate, the minimum sample size needed for evaluating a 50% reduction in CFR is 3663 (90% power and 5% significance). This number will be reached in 2 years time.

(*) attack rate based on data from Mirzapur handpump project.

D.SIGNIFICANCE

Programmes for control of diarrhoeal diseases focus almost entirely on the problem of watery diarrhoea and the use of ORT. None of those programmes have drawn much attention to dysentery, mainly due to shigellosis and the major cause of death in under-five-children in Bangladesh. Hoping for an effective vaccine for shigellosis to be developed, one can not await the beneficial effect of interventions like improvement of personal hygiene, nutritional education etc. in the long term, short term interventions are needed.
If antibiotic treatment shortens the course of illness and reduces severity of shigellosis in children admitted to the hospital (20,21); one can reasonably assume that early antibiotic treatment of children with bloody diarrhoea in the community will prevent deaths from dysentery due to shigellosis.

This study aims at first assessing the feasability of home treatment of dysentery by CHW and second at measuring the impact of such an intervention on mortality from dysentery.

REFERENCES.

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ABSTRACT SUMMARY

The study aims at evaluating whether the high mortality rate from dysentery in under-five children can be reduced by having CHW's treat dysentery at the homes. In 2 blocks of the Matlab MCH-FP area the CHW's will treat each child 3 to 59 months old with dysentery with antibiotics. In 2 other blocks children with dysentery will be referred to the treatment centre. The case-fatality rate between the 2 areas will be compared.

1. Mortality from dysentery is highest in chidren less than 5 years old.

2. There are no risks to individuals. Treatment of dysentery will only benefit to the child.

3. The risk for promoting resistance against antibiotics in the community will be limited by ensuring that a full course treatment is being taken. Resistance will be monitored through 3-monthly examination of 120 stoolsamples for culture and sensitivity.

4. To ensure confidentiality all children will be given a code number by which to identify them.

5. The study will be a part of the regular service activities provided in the MCH-FP area. Verbal informed consent will be obtained from parents of children with dysentery.

6. An interview of about 5 minutes will take place each time the CHW encounters a child with dysentery. Information will be collected on type and duration of diarrhoea.

7. Home treatment of dysentery should reduce morbidity and mortality from dysentery in under-five children.

8. "Cause of death" report forms will be used.
For monitoring of resistancy and for evaluating clinical failures rectal swabs will be taken.

SECTION III:BUDGET

DETAILED BUDGET FIRST YEAR

1.Personnel requirement (local):

Job	Level	No	Man mo	$/mo	$ Amount
SFRO	GS6	1	12	410	4,920
Medical assistant	GS4	2	24	220	5,280
Health assistant	GS3	1	6	170	1,020
Health assistant	GS3	2	24	170	4,080
				TOTAL:	**15,300**

2.Supplies and materials:

3701	Drugs and hospital supply	3,000
3704	Stationery and office supplies	300
	TOTAL:	**3,300**

3.Other costs:

4300	Printing and publication	500
4500	Service charges (boatman)	600
	TOTAL:	**1,100**

4.Interdepartmental services:

4802	Transport Dhaka-Matlab-Dhaka	2,000
4804	Water transport Matlab	2,000
4806	Xerox	200
4808	Microbiology tests (1100 x 11.80US$)	12,980
4815	Medical illustration	200
	TOTAL:	**17,380**

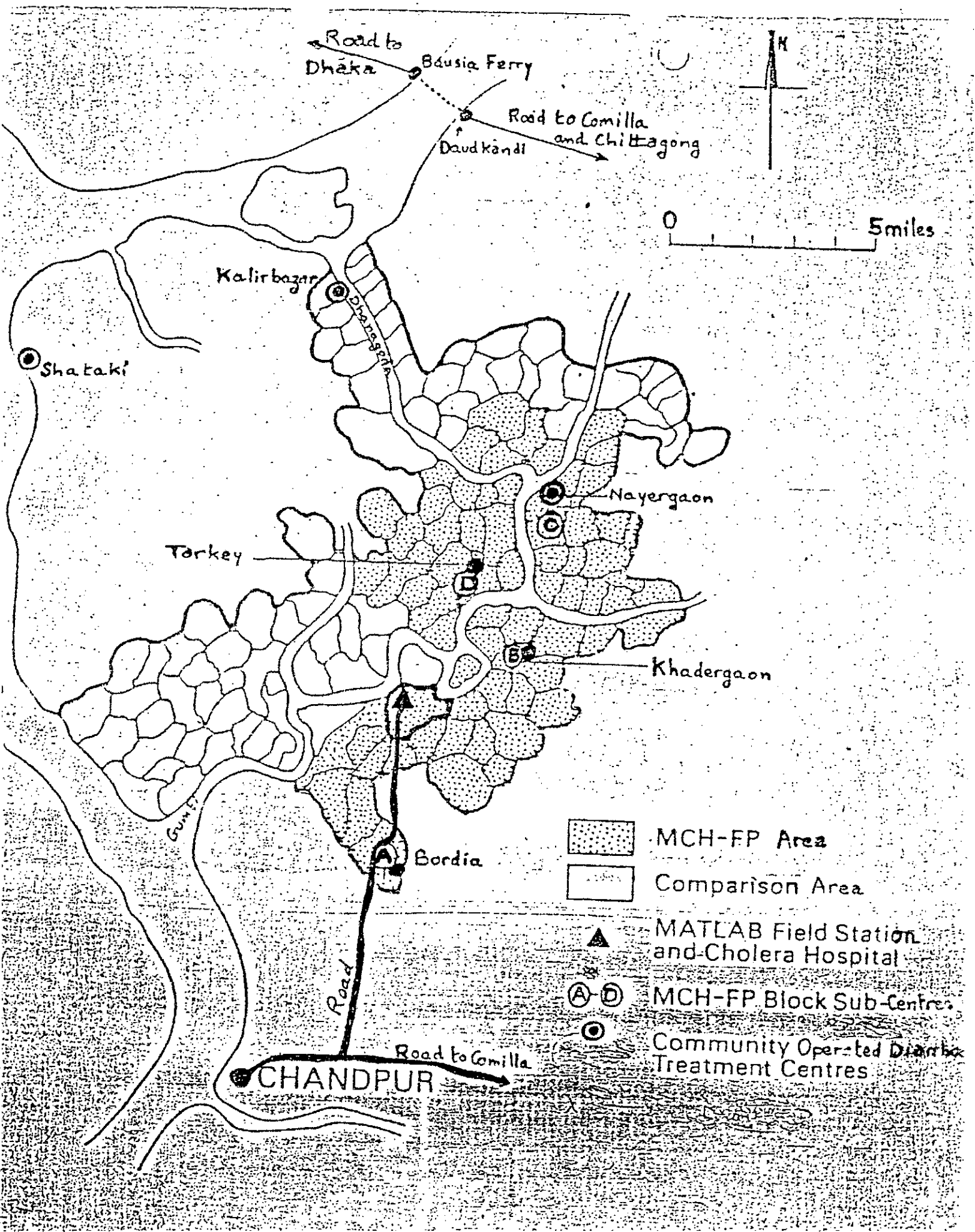
5. Capital expenses.

Personal computer		2,000
	TOTAL:	**2,000**

TOTAL for FIRST YEAR: **39,080**

DETAILED BUDGET SECOND YEAR

1.Personnel requirement (local):		15,300
2.International travel:		2,500
3.Supplies and materials:		3,300
4.Other costs:		1,100
5.Interdepartmental services:		17,380
	TOTAL:	39,580
		+15%
TOTAL for SECOND YEAR:		45,517
TOTAL for 2 YEARS:		**84,597**


Road to Dhaka
Bausia Ferry
Road to Comilla and Chittagong
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Dhanagora
Shataki
Nayergaon
Tarkey
Khadergaon
Gumti
Bordia
Road
Road to Comilla
CHANDPUR
MCH-FP Area
Comparison Area
MATLAB Field Station and Cholera Hospital
A-D MCH-FP Block Sub-Centres
Community Operated Diarrhoea Treatment Centres