ttachment 1.
FACE SHEET)

Date ~~28~~ 2/5/91

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator DRS BILQIS A HOQUE / D. MAHALANABIS Trainee Investigator (if any) x

Application No. 91-003 Supporting Agency (if Non-ICDDR,B)

Title of Study Environment & Shigella Dysentery

Project status:
(✓) 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 — (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.

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

Mahalanabis. Bilqis Hoque

Principal Investigator

Trainee

91-003
2/5/91

1) Title : ENVIRONMENT AND SHIGELLA DYSENTARY

2) Principal Investigators : Drs. Bilqis Amin Hoque & D. Mahalanabis

3) Starting Date : May, 1991

4) Completion Date : April,1993

5) Total Direct Cost : US$ 88,300

6) Scientific Programme Head: : Dr. D. Mahalanabis.

7) Signature of the Scientific Programme Head: D Mahalanabis.

Summary

Shigellosis is a major public health problem with high morbidity and mortality and as the bacteria are developing resistance to available antimicrobials the role of affordable water-sanitation interventions need to be investigated. Few studies have adequately defined the environmental risk factors which are amenable to affordable intervention. This study proposes to determine well defined environmental risk factors and prioritize them in order to develop a widely replicable preventive intervention guideline. Case-control method will be adopted. Cases will be 1 year to 10 years children those who come to the Dhaka ICDDR,B treatment centre with history of bloody diarrhoea and subsequently proven to have Shigella species in stool culture. There will be age strata and sex matched 2 controls for each case; Control 1: a child who has come to the Centre with history of non-bloody diarrhoea and, Control 2: a child randomly selected from the same neighbourhood of case but do not have diarrhoea. Effects of age will be controlled by matching the cases and controls by two strata, 1-4yrs and >4-10yrs. More than 700 cases and 700 controls of each type will be studied. The main prognistic and risk factors of interest will be (i) water availability and its use, (ii) sanitation practices (iii) kitchen hygiene practices and (iv) personal hygiene practices. Intervening variables, such as nutritional status, socio-economic and demographic factors, will be given due consideration. Although questionnaire interviews will be done observational indicators will be recorded. Data analysis will be done as suggested for case-control method giving due consideration to effects of confounding and intervening variables.

I. Background:

I.A. Statement of the Problem:

A.1. In Bangladesh fatality rate due to shigellosis even under institutional treatment, are among the highest in diarrhoeal diseases (1). An epidemiological analysis showed that the number of diarrhoea cases visiting the CRL/ICDDR,B facilities in Dhaka increased about ten-fold from 1969 to 1981 and the death rate was 10 times higher than for treated cholera case. (2). Oral-rehydration therapy (ORT) is not effective in reducing mortality from dysentary (3), which is mainly caused by members of the bacterial genus shigella. Antibiotic treatment is becoming difficult due to increasing bacterial resistance to it (2,4). Shigellosis preventive strategies through appropriate water-sanitation, personal hygiene and environmental health improvements seem appropriate and promising and therefore we propose to investigate relevant risk factors which are amenable to widely replicable interventions.

I.B.Background of the situation

I.B.I. Shigella dysentary in Bangladesh

1.1.Among the patients attending the ICDDR,B Dhaka hospital between 1979 and 1980 Shigella bacteria was the second most common isolate in over 2 years of age (5). The distribution of shigella species isolated during the 14-year period showed that the proportion of S. flexneri was the highest (63.5%), of S. dysenteriae (25.5%) was the second highest and that of S. boydii was the lowest (5.2%). (2). Of all the sh. dysenteriae, more than 90% were sh. dysenteriae type 1. Shigellosis in the developing countries is most commonly caused by S. flexneri and S. sonnei (6). Sh. dysenteriae is more commonly associated with poor hygiene, less developed

areas and certain custodial institutions.

1.2 The age distribution showed that 20.6% of all Shigellae cases occurred in children under 1 year old and 43.9% occurred in 1-4 year old children (2). Shigellae was also high in 5-9 years children (2,5). The proportion of cases among male children was significantly higher than female children (2). And Khan (1) reported that four out of 100 persons with shigellosis are infected but asymptomatic. Seasonality of shigellosis showed highest peaks around April-May (2,5).

1.B.2.Environmental Intervention Studies in Bangladesh

2.1. A few environmental intervention studies have been undertaken and various water supply-sanitation factors were found to be associated with reduction in diarrhoea incidence (7,8) and with reduction in dysentary (8). But most of these studies (7,8) were done through extensive efforts and at a high cost, a condition which is questioned for wide replicability. None of the community based intervention studies were designed to study the effects of the components on Shigella dysentary and were lacking in adequate sample size or method.

2.2 A water-sanitation intervention study of rural Teknaf, Bangladesh, found that households who owned their handpumps (having it located at a distance of <25meters) had the lowest Shigella isolation rate (8). But another concerted effort with high water-sanitation and hygiene education components failed to show impact on shigellosis in rural Mirzapur where the overall diarrhoea rate was reduced by 25% over the 3 years of study period (8). It was felt that this could be due to inadequate sample size for cases with shigellosis.

2.3 A water-sanitation education intervention in urban slums (9) and an experimental study on handwashing by soap (1) have shown impact on

diarrhoea incidence rates and Shigella incidence rates respectively. But none of these studies has defined handwashing technique or documented adequate guideline for such intervention at a wider scale. Preliminary analysis of data from an on-going study on handwashing suggested that existing practices of washing hands with soap or ash or water do not make statistically significant difference in bacterial contamination (10); therefore technique may be important.

I.B.3. Water and sanitation intervention studies abroad

3.1 Countries other than Bangladesh, also found that shigella infection was related to poor water supply, poor excreta disposal facilities, high fly counts, and to poor housing in general (11). In rural Maadurai the differential incidence of shigella disease was found in the proportion of 2:3:1 among the children in household using well water, treated water delivered through taps on streets and treated water from a reservoir delivered within household (12).

3.2 The transmission of shigellosis to a large extent depends on the contamination of clothes, hands, and household surfaces; the bacteria are transferred from those surfaces to mouth (13). Survival of shigellae in water depends upon factors such as the concentration of other bacteria, nutrients and oxygen and on the temperature. The contamination of food with shigellae is probably an important route of transmission in many communities (14).

I.B.4 Water-Sanitation Facilities in Dhaka

4.1 Dhaka city has gone through extensive development over the years as it moved from a provincial capital to a country capital and its impact on health is yet to be evaluated. In some reports 93% of the 4

million people of Dhaka is shown within the authorized water supply area (15). The existing sewarage system collects and treats only about 40% of the total wastewater production, the rest being discharged directly to the nearby drains and other open-water sources. Leakage, broken sewer and by-pass line alongwith storm water often worsen the hygienic condition (16).

4.2 Bangladesh is a developing country with severe resource constraint. As the shigella pattern is showing increasing trend with evergrowing antibiotic resistence of species of shigellae, it is important that affordable guidelines are suggested for health benefits to match with development plans. We propose to study the environmental risk factors of shigella dysentary which are amenable to widely replicable and immediately feasible interventions.

Objectives

1. To study the existing/practiced environmental risk factors and their hierarchy for shigella dysentery among children of 1-10 yeasrs age group in Dhaka city; the study will also allow evaluation of risk factors for all diarrhoeas reporting to the treatment centre.
2. To develop guidelines for widely replicable interventions which are particularly effective against shigella dysentery but might also control other types of diarrhoea.

Specific Objectives

1. To study the association between environmental variables and shigella dysentery and between environmental variables and non-shigella diarrhoea, disintegrating environmental variables into components which exist at local household levels.

2. To detect the environmental factors which are more strongly associated with shigellosis by measuring the magnitudes of relative risk of the factors for shigellosis and for non-shigella diarrhoea.

3. To prioritize the identified risk factors and draw guidelines for readily replicable and presently feasible shigella interventions.

IV. Justification

The proposed study to identify environmental risk factors of shigella dysentary in Dhaka metropolitan area is important for following reasons:-

1. Dhaka, the capital of the country, has developed and grown fast in the past decade but health problems from shigella dysentary has significantly increased.

2. Most of the water-sanitation interventions which significantly reduced diarrhoea were designed to assess their impact on diarrhoea incidence in rural areas. Neither the size of observed sample of shigellae patients was enough nor the conditions or intervention costs in rural areas are similar to the conditions in Dhaka or in other big cities to draw replicable intervention guidelines for shigella prevention.

3. To understand the relationship of environment and shigellosis, a study would need large number of identified shigella cases. Stool culture is done for in-patients of ICDDR,B Treatment Centre, Dhaka and therefore, an adequate number of cases can be obtained for the study at little cost to the proposed protocol. The major cost of the research would be for data collection on environmental factors only.

4. Case-control method of epidemiology has been scarcely used for

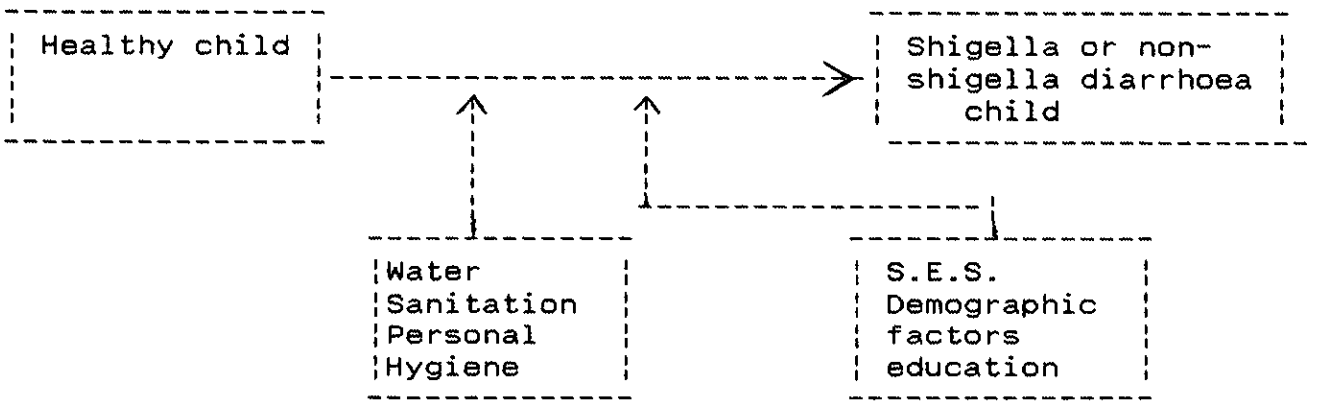
shigella study but it is recommended for evaluation of risk factors for such rare disease as it allows a more rapid evaluation and cost is low. Since Shigella accounts for about 10% of diarrhoea "rare disease assumption" is valid for calculating relative risk.

5. Reported environmental risk factors or intervention guidelines for shigellosis are mostly not detailed enough to identify the potential and intervention specific key issues at local household level as the studies were not adequately designed to understand the existing practices and the constraints for interventions likely to be useful by majority people.

V.Methodology

A.Hypothesis

Since shigellosis and non-shigella diarrhoea are feaco-orally transmitted diseases, the null hypothesis is that all environmental components existing at household levels are equally related to a healthy child becoming a shigella or non-shigella diarrhoea patient.



B. Research Questions:

1. Is dysentary due to shigellosis more common in contaminated

environment?

2. Does some indicators of environmental health factors associated with shigellosis vary from those associated with non-dysentary diarrhoea?
3. Is it possible to prioritize the environmental health risk practices in order to develop guidelines for widely replicable immediate interventions ?

C. Study method and Sampling technique

A case-control method will be adopted with one case and 2 sets of sex and age strata (1-4 years and >4 years) matched controls.

C.1. Definition of cases:

Case: All 1 year to 10 years old children admitted to Dhaka ICDDR,B treatment Centre with history of bloody diarrhoea and subsequently proven to have shigella species in stool culture over a period of 3 days.

C. 2. Definition of controls:

Control 1: 1 year to 10-years old children those who are admitted to the Centre with history of non-bloody diarrhoea of same sex and age group; they will be recruited concurrently from among those admitted after the Shigella cases. From the registrar next eligible watery diarrhoea case, in the age strata of 1-4yr or >4-10 yr and of same sex, will be recruited .

Control 2: 1 year to 10 years old children selected from the same neighbourhood of case and who did not have history of diarrhoea or dysentary in last 2 months. As one comes out of the house of the case onto the street a pencil will be tossed and then one will walk in the direction pointed by the sharp end of the pencil and start looking for a control

from the 10th house onwards until a similar control is found; the control should be for the same age stratum and same sex.

Cases will be all patients registered in the treatment centre with proven shigellosis. However, a register of minimum information on all attending with bloody diarrhoea will be maintained.

D. Validity of Control

Control set 1; will control for referral bias. Since watery diarrhoea is also likely to be related to water and sanitation, this will tend to underestimate the impact of improved water and sanitation facilities. Therefore, this first set of controls will offer a conservative estimate of benefit with risk of showing no difference. However, at micro level water use practices, water storage, kitchen/environmental hygiene practices are still likely to differ substantially and may offer meaningful information.

Control set 2; will apply to the community as a whole and enable to control a range of potentially confounding variables which might otherwise be difficult to quantify (18). It will be necessary to assume if the child would become a case if he/she gets dysentary. This will be ascertained by a set of questions e.g. knowledge of ICDDR,B or any other clinic, if the child gets bloody diarrhoea he/she will be taken to it. Effects of mis-classification will be controlled based on results from stool culture (asymptotic case) and taking additional samples as needed.

Sample size

About 72% of the people do not use latrines and considering the limiting condition of sanitation and scarcity of reliable data we have used this information in our sample size calculation (17). Assuming 72% of controls exposed to contaminated environment we would need about 700 cases to determine an odds ratio of 1.5 at

90% power and 5% significance level. We selected the odds ratio of 1.5 as a local water-sanitation intervention study has found similar value. About 15 months of data collection will provide us with the required samplesize. We included less than 10 year old children as shigella has been found to be high upto 9 years of age and consequently saves time/cost.

E. Data Collection:

The main prognistic and risk factors of interest are:

a) Water - amount and quality of water used, distance and crowding factors of water source, type of water sources, drainage, leakage and environmental condition around the water source, availability of water and specific qualities of water such as enteric bacterial count (using Hygicult) and NH_3.

b) Sanitation: type and use of latrines by age, disposal of feces, crowding at latrine site, solid waste disposal practices, kitchen hygiene practices, personal hygiene practices and enteric bacterial count ~~eount~~ of hands.

c) Feeding practices and home-management of children:- type of feeding, storage of food and water, knowledge on spread of diarrhoea and know about ICDDR,B.

d) Nutritional status, weight for height, weight for age of children.

e) Socio-economic and demographic:- floor space, type of roof, number of rooms, number of beds, type of fuel used for cooking, owns TV or radio or fan, family size, mother's education, father's education, occupation and number of under 5years children and combined income of parents.

f) The data collected by two methods will be matched during preliminary data management and discrepancies will be reinvestigated immediately. Although data will be collected by the health assistants, the supervisor will randomly recheck 20% of the data. One of P.Is (Dr. Hoque) will also spot check about 5% of data.

Qualitative and quantitative data on indicators of the above-mentioned factors will be collected as shown in Appendix I. Observational and interview, both methods of data collection will be adopted. Stool cultures of cases and control-1 (watery diarrhoea) will be done by the hospital (as a routine) to study asymptomatic infection in healthy controls, their stools will be collected and cultured by the project.

F. Data analysis

All data management and analysis will be done on a microcomputer. Comparison of different variables will be made on cases and controls by bivariate methods. The effect of potential confounders will be tested by stratifying by each confounder at a time and summary odd ratio calculated (Mantel-Haenszel). However, matched analysis will be performed between cases and Control set 2 (neighbourhood controls).

Variables found significant confoundors in this priliminary analysis will be ~~examined for trend analysis and~~ finally entered into a logistic regression model to determine the odds of shigella infection in relation to environmental factors.

It is expected that control 1 will control for bias in hospital attendance, nutrition state (malnourished child is more likely to be admitted) and SES. Control 2 will provide additional definition of

progriostic indicators (water, sanitation, personal hygiene and kitchen hygiene practices, socio-economic status, education).

G. Plan of action

Different actions will be undertaken as shown in Figure 2. About 3 months will be required to do the preparatory activities, including procurement of materials, training of staff, pre-testing of data collection and set-up of data entry/management method. Data will be collected for about 15 months but if the required number of samples cannot be collected within the period it will be extended. Data processing, analysis and final report writing will require about 3 months.

It is expected that the project will be completed within a period of 2 years.

Budget in U.S.Currency

	Year I	Year II
1. Personnel :		
Dr. Bilqis A.Hoque (30%)	6000	6000
Mr. N.Rahman (30%)	1700	1500
Laboratory technician (100%)	2000	1500
4 Community Health Assistants (100%	14400	10000
Daily wagers/trainee	5000	3000
Data entry technician/manager/progr	2000	2000
Consultant	0	3000
Sub-total	31100	27000
2. Travel		
Local Travel	3000	2000
sub-total	3000	2000
3. Equip. & Supplies:		
Glassware	1200	500
Lab. Reagents & Equipments	4000	1000
Office Supplies/communication	1000	2000
Print/Publications	2000	1000
Stool culture	5000	3000
sub-total	13200	7500
4. Data Processing		
Disks/tape/computer accessories	1500	1000
Miscellaneous	1000	1000
sub-total	2500	2000

88300

Figure 1. Project Adminstration Plan (May 1991 to April 1993)-

Activities	Quarters 1	2	3	4	5	6	7	8
1.New Recruitments	x..	...	...	...	...	...	...	...
2.Procurement of equipments	xx.	...	...	...	...	...	...	...
3.Tranining and pre-testings	.xx	...	...	...	...	...	...	...
4.Data collection	...	xxx	xxx	xxx	xxx	xxx		...
5. Data entry and management	...	.xx	xxx	xxx	xxx	xxx	xxx	x..
6. Data processing and analysis	...	...	...	xxx	xxx	xxx	xxx	xxx
7. Progress Report to the donar (no results)	...	...	...	..x	...	...	...	...
8. Draft Final report to the donar	...	...	...	...	...	...	...	xx

Questionnaire Part I (*=observation)

Identification and determination of socio-economic level

Interviewer: ___ Questionnaire No: _____

Date of interview: _____

Type of sample _____

CID (census No): _____

Sex _____ Date of birth _____ Age (m)_____

Address:

Mother's schooling: _____ Father's schooling: ___

Occupation of father:Primary_____ Secondary _____

Occupation of mother:Primary_____ Secondary _____

Family size_____ Number of <5 years children_____
(eating from same pot) (eating from same pot)

Number of male children_____ Birth order of sample _____

Marrital status of mother _____

*Roof: tin (1) Bricks (2) other (3)

*Wall: Bricks (1) Bamboo (2) Tin (3)

*Floor space area _____

*House: sharing (1)_____ Number of rooms _____

Possession of watch / radio / wooden bed /torchlight/T.V.

*Electricity_____ *Number of electric fans _____

*Kitchen: sharing _____ *Type of cooker _____ Gas. yes/No

Use bed-net _____ Number of person/bed net _____

Questionnaire Part II: Environmental factors (*=observation)

1.Water use variables:

Main source of water by activities:

	Source	* Distance from kitchen	Number of Users
Drinking water:	____	_____	_____
Cooking:	____	_____	_____
Washing food:	____	_____	_____
Bathing:	____	_____	_____

(Piped connection (1) Yard tap (2) Street tap (3) Tubewell (4) Pond (5) Ditches (6) Canal/River (7) Dug well (8))

Protection around used water sources:

*Apron around tap/tubewell_____ absent (1) cracked (2) broken (3) ok (4)

*Drainage around tap/tubewell_____

*Leakage in pipe line _____

*Possible contaminantion of surface water source:yes/no_____

*Functional condition of tubewell_____

Service hours of tap_____

Any treatment of drinking water _____

*Condition of drinking water storage container: covered/open _____
shape _____
size _____

Frequency of drinking water collection _____

Amount of water stored for personal use _____

*Water quality:

Enteric bacterial count $\frac{NN - N}{3}$

Drinking water

Secondary source

Questionaire Part 3: Sanitation Variables
(Filled in hospital and compared during field visit).

*Latrines used:

	Females	Males	<5years
No fixed place	_____	_____	_____
Fixed place	_____	_____	_____
Open latrine on low land	_____	_____	_____
Open latrine on surface water	_____	_____	_____
Sanitary latrines	_____	_____	_____

Total number of people using the latrine: _____

*Condition of the latrine: Clean (1) Dirty (2)

smell: yes/ no

flies: yes/ no

Latrine facilities for night:

no / for children / for all

Handwashing methods following defecation: Agent used_____

Both hands/left hand_____

*Handwashing arrangements in/near latrine: water stored _____

Agent stored_____

3.Hygiene and household/child management practices:

*Any animal in the same compound yes / no

*Cleanliness of courtyard:

rubbish yes / no

children faeces yes / no

animal faeces yes / no

*Disposal of domestic waste:_____

(Bury in a fixed place (1), Dispose in fixed place (2), Throw in a hole (4) No fixed place (5)).

Feeding:

fully breastfed / partially breastfed / non breastfed

Store the main food/feed freshly cooked food

Food in last 3 days: breakfast/lunch/dinner

Wash hands before feeding: Both hands/single hand

Wash with soap/ash/mud/others/water

Wash hands before eating: Both hands/single hand

Wash with soap/ash/mud/others/water

Enteric bacterial counts:

Left Hand _____ Right Hand_____

*Immunization _____

*Measle vaccine

Vitamin A _____

Weight_____ Height_____ Arm Cir_____

Any birth complications_____

Duration of pregnancy _____

Any diarrhoea in last 1 month_____ Type _____ Treatment____

Heard about ICDDR,B _____ Approx. distance _____

Heard about any other health facilities _____ Approx. distance____

Would you take your child to a health clinic if she/had bloody dysentaery_____

when _____

Given any ORS _____

How was ORS prepared and fed _____

Stool culture (control 2) _____

Questionaire 3 :Patient History

Cases or control from hospital:

CID_____

Type of treatment before hospitalization_____

Symptoms before hospitalization: Stool_____

Fever

Vomiting

Abdominal pain

Duration of diarrhoea prior to hospitalization _____

Symptoms:

Culture _____

Sensitivity _____

Total duration of diarrhoea _____

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Response to Referees

We have carefully considered the comments of the reviewers and revised the protocol to incorporate their suggestions as many as possible. The main revised points are as follows:

Referre-1

A. General overview; objectives, specific objectives, justification, and questionnaire sections have been sharpened, rephrased or elaborated to reflect the purpose, need and expected outcome of the study.

B.1 Some specific comments - The hypothesis has been rearranged as suggested.

B.2 The sample size was calculated based on reported sanitation facilities, as it was the known limiting factor.

B.3 The neighbourhood controls will be visited after 4 weeks to ascertain disease status in the post 4 weeks. We prefer to agree with Referee-2 in this point (This issue is contradicting to the referee 2) and retain to our definitions since bloody diarrhoea is relatively rare. To reduce misclassification bias we will consider the recent history and any exclusions are not warranted.

B.4 Questionnaire has been elaborated. It may be more elaborated or refined during the pre-testing process.

B.5 We expect to categorize certain factors like water quantity per capita (about which we already have extensive experience from Mirzapur handpump project) and hand contamination (bacterial concentration per hand about which we have experience from recently conducted WHO supported project).

B.6 The timing has been increased to 6 months for final analysis and report writing.

B.7 The measures of quality control to be taken during the study are now added under "Data Collection" section.

Referee 2

1. We plan to do separate analysis i.e. between case and control 1 & between case and control 2.

2. We agree to the suggestion of matching by sex and single year of age. It is now stated in the "sample size" section that in order to get the required number of samples we should include children below 10 years of age. Shigella dysentery have been reported to be high upto 9 years of age (2,5).

3. We have calculated the sample size based on our experience from a water-sanitation intervention study, which showed a relative risk of about 1.4. (The text is now corrected as 72% of the people do not use latrines).

4. Yes, we plan to do structural observation of some variables and for all cases and controls. Day long observation has ethical as well as logistic limitations. Besides, we believe that presence of an observer may affect certain behaviours.

Reference 3

1. ICDDR,B hospital receives patients from every zone of the city of Dhaka. The socioeconomic background is generally low to some representation from middle class.

2. Among the benefits associated with case-control study is we can

obtain a much larger number of cases of sh. dysentary and that should outweigh the limitations mentioned although the inherited methodologic ones still remains. But a study on a rare disease, here bloody dysentary, by prospective community based method would be prohibitively expensive and time consuming.

3. Our hypothesis is to refute if it is only a matter of chance that one of them got dysentery.

Ref: 1

Environment and Shigella Dysentery

General overview

The project is generally well presented although, as detailed below, I believe some areas require further clarification and specification. The focus on Shigella dysentery is quite original and, as indicated by the authors, an important focus in the Bangladeshi situation. The adoption of a case-control methodology is appropriate for the aims of the study and sensible given the epidemiological pattern of Shigella dysentery. One major concern I have is how the information gained from the risk factor study will be used afterwards. This obviously has implications for the case-control study itself and since this is not clearly delineated it is hard to fully assess the adequacy of the study. The study's objectives (section II) state that "appropriate guidelines for prevention of Shigella dysentery" will be developed. The study design chosen, however, could permit some investigation of environmental risk factors for all diarrhoeas reporting to the treatment centre. Comparison of cases with healthy neighbourhood controls, for example, is likely to show up risk factors that apply to many types of diarrhoea and not just to Shigella dysentery. This is to be expected since many of the transmission modes of Shigella dysentery are shared by other diarrhoea-causing pathogens. Therefore, as the authors acknowledge, some factors which distinguish children at greater risk of Shigella dysentery may be rather subtle - techniques of handwashing for example. The need for rather detailed study of risk factors is not reflected in the proposed questionnaire, however. Perhaps the authors wish to identify interventions which are particularly effective against Shigella dysentery but might also have an impact on other diarrhoea types. If this is the case then this should be stated more clearly. In general then, the stated objectives which reflect the utilisation of the results are not adequately addressed in the protocol. Rectifying this would help tighten up the risk factor study, including improvement of the questionnaire.

Some specific comments

1 - The figure drawn in section V part A raises some points. Firstly the model is not clearly stated and indeed the figure implies that a healthy child "acts on" intervening variables. Secondly the assumption that " .... Shigella dysentery is more likely to occur ....." is not backed up by evidence. Indeed, this is the basis for the hypothesis testing involved in this study. It would be more correct to state a null hypothesis ("no more likely ...") and to try and refute this. The model categorises diarrhoea into 2 types - watery diarrhoea and dysentery - this is oversimplified, and causes confusion throughout the protocol when referring to Control group 1. By the description given, it would seem that diarrhoea is categorised as Shigella dysentery and non-Shigella dysentery (i.e. the complement of Shigella dysentery).

2 - The sample size calculations should be presented for a number of risk factors and not just one. An alternative approach would be to take a given sample size (that is feasible within resources and time available) and determine the minimum relative risks detectable for various levels of exposure to a risk factor. The computer package Epi Info is useful for doing such calculations rapidly.

3 - If a neighbourhood control becomes a case soon after inclusion as a control (e.g. within 1-2 months) will they still be included as a control? Allowance for a diarrhoea-free period before enrolment has been made, it might be advisable to consider something similar for afterwards. This is likely to lead to the post-exclusion of some controls but that is manageable.

4 - Data collection. More details should be presented on the collection of

certain risk factor information - some of the factors noted are notoriously difficult to measure and they should be either defined adequately or not included ("bad data are worse than no data"). One such example is water quantity. For feeding modes it is important to know the feeding practices before the episode of diarrhoea as these are often changed as a consequence of the illness. Similar problems apply to nutritional status.

5 - Data analysis - What are the reasons for not doing a matched analysis with Control group 1. Agreed, the results will probably be very similar to a stratified analysis but the methodology implies that they will be matched in a similar way to the second control group with the exception of the variable 'neighbourhood'. The use of the term "trend analysis" in the context it is set seems inappropriate. Trends are not confined to confounders and are appropriate in the study of categorical factors with >2 categories where there is some logical ordering of the categories and some 'dose-response' might be expected - e.g. water quantity per capita grouped into 4 categories.

6 - Timing. I suspect that 3 months for data processing, analysis and final report writing is not sufficient, especially if the PI spends only 30% of time on this project.

7 - As mentioned earlier, the questionnaire needs improvement both in terms of its content and organisation. Questions should reflect the objectives of the study and should not include material peripheral to these objectives - quality vs quantity. There is no mention of quality control measures to be taken during the study.

8 - I find it hard to comment on the adequacy of the budget as I have little idea of costs in Dhaka these days. No justification of the budget items is provided.

Project Title: Environment and Shigella Dysentary

Principal Investigator(s): xxx, xxx, xxx, xxx, xxx

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project			
Adequacy of Project Design		X	
Suitability of Methodology		X	
Feasibility within time period	X		
Appropriateness of budget	X		
Potential value of field of knowledge	X		
	X		

Conclusions

I support the application:

a. without qualification /___/

b. with qualification

- on technical grounds /X/
- on level of financial support /___/

I do not support the application /___/

This is an interesting project which adequately uses the case-control methodology to examine risk factors for shigellosis. In that respect, it is original and relevant to diarrhoeal diseases control.

While supporting the project, I have some qualifications on methodological grounds. These include:

1. I think the second (neighbourhood) control group is fully justified. I am not so sure, however, about how much the first control group will add to the study. It is justified by the author in terms of controlling referral bias and the confounding effect of malnutrition. These, however, may be controlled by asking where the control child would be taken if it presented bloody diarrhoea (as the author proposes to do) and by multivariate analysis (in the case of malnutrition). The disadvantage of the first (diarrhoea) control group is that it would only allow the identification of risk factors which are associated with dysentery but not with acute watery diarrhoea; these findings may be difficult to interpret. Even if the two control groups are kept, I suggest that two separate analyses are performed.

2. Excluding children with recent diarrhoea from the neighbourhood controls is open to discussion. Firstly, one has to establish a time period for this exclusion, probably not more than two weeks due to faulty recall. Even then, since diarrhoea is recurrent, this exclusion may not be effective. In any case, since cases include children with bloody diarrhoea, which is relatively rare, I do not think that any exclusions are warranted. These issues have been recently discussed by L. Rodrigues and B. Kirkwood in the International Journal of Epidemiology.

3. The two age strata (<4 and 4-10 years) are too wide. I suggest that the matching be done by sex and single year of age. Such type of matching has been used in several other case-control studies and did not result in a great increase in field workers' time. Also, the author has not justified why the study is not restricted to children under five years.

4. The required sample size seems rather large. The author has used the information that 72% of the cases have poor sanitation but the usual information in most sample size formulae is the proportion of controls - and not cases - exposed (which should be smaller than 72% if the hypothesis is true). I have recalculated the sample size allowing for this and it seems that 580 children are required. Allowing for attrition, this would mean that a total of 700-750 cases and another 700-750 controls are needed. This is still a large sample size for case-control studies, and I believe this is due to the author's intention of detecting relatively small increases in the relative risk (eg 1.5, whereas most case-control studies aim at detecting a relative risk of 2 or greater). Since, from a Public Health point of view, one is really interested in the major risk factors, the author should

weigh the pros and cons (particularly in terms of budget) of having such a large study.

5. I strongly suggest that structured observations of several hours' duration be performed on a subsample of the cases and controls. These should aim at documenting a number of common hygiene practices, rather than asking about them. The proposed data collection forms do include some observations but these tend to be rather static (facilities, cleanliness, etc) rather than actual hygiene behaviours.

Ref. 3

Environment and Shigella Dysentery

Referee's Opinions: Please see the following table to the various aspects of the proposal by checking the te boxes. Your detailed comments are sought on a attached page.

	Rank Score		
	High	Medium	Low
f Project		✓	
of Project Design		✓	
ty of Methodology		✓	
ity within time period		✓	
ateness of budget			
l value of field of knowledge		✓	

ONS

t the application:

a) without qualification ☐

b) with qualification

- on technical grounds ☑
- on level of financial support ☐

t support the application ☐

Referee: SHAFIQUR RAHMAN Signature: ...
Date: 28.2.91
on: Coordinator, Medical College Hospital, Model clinic
ution: Ministry of Health & Family welfare

Detailed Comments

Please briefly provide your opinions of this proposal, giving special attention to the originality and feasibility of the project, its potential for providing new knowledge and the justification of financial support sought; include suggestions for modifications (scientific or financial) where you feel thay are justified.

(Use additional pages if necessary)

Title: Environment and Shigella dysentry

PI:

Reviewer: Dr. Shafiqur Rahman

1. I think that the patients with dysentry/diarrhoea admitted in ICDDR,B Hospital are not representative of Greater Dhaka or Dhaka city in socio-economic status and dewelling conditions. A large majority of these patients either get treatment from private sources or are admitted in other Hospitals. People of middle class or lower middle class in most cases are likely to use private treatment or will use Hospitals nearby; while people from slums of distant places will use Hospitals near to them or use some other forms of treatment. Thus, this study is not likely to have a representative sample of enviornmental conditions of Dhaka city for the patients admitted in ICDDR,B Hospitals. The study findings thus can not be generalised. Studies referred in background statement gives some indications on effect of environmental conditions in causation of dysentry. How this study will improve upon those findings.

2. It is likely that the environmental factors including sanitary conditions for contrle cases or the dysentry cases will be same. It is only a matter of chance that one of them got dysentry. I am not sure that the approaches in the study will be able to asses spefic environmental factors causing dysentry. How this can be improved.

3. The study may be approved after improvement in the protocol on the basis of the comments.

S. Rahman 2/3/91

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র, বাংলাদেশ,

সম্মতিপত্র

বাংলাদেশে অবস্থিত আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র ডায়রিয়া জাতীয় রোগ, কলেরা ও রক্ত আমাশয়, নিয়ন্ত্রণ লক্ষ্যে বিভিন্ন ধরনের গবেষণা করে থাকে। দেশ ও বিদেশের কয়েকটি গবেষণা থেকে জানা গেছে পরিবেশের সাথে এগুলোর সম্পর্ক আছে এবং এই পরিবেশের উন্নতির মাধ্যমে রোগ নিয়ন্ত্রণ সম্ভব।

পরিবেশ একটি বিরাট ব্যাপার। আমরা এই গবেষণার মাধ্যমে পরিবেশের কয়েকটি দিক, পানি, স্যানিটেশন এবং পরিবেশ-জ্ঞান/ব্যবহার সংযুক্ত কিছু বিষয় নিয়ে রোগের সাথে এগুলির সম্পর্ক দেখতে চাচ্ছি। বাংলাদেশে হাজার হাজার বাচ্চা মারা যায় এই ধরনের রোগে। আমরা আপনাকে অনুরোধ করছি পরিবেশের এই সকল আচরণগত দিকগুলি নির্ণয়ে সাহায্য করতে। আমরা আচরণগত দিকগুলি জানতে পারলে ভবিষ্যতে এগুলিকে ব্যক্তিগত পর্যায়ে এবং সরকারী পর্যায়ে উন্নতি করার চেষ্টা নেয়া যাবে। আমাদের গবেষণার থেকে যা পাব তা-ও আপনাদের সবক্ষেত্রে অবশ্যই গোপন হবে।

আমরা পানির ব্যবহার, পায়খানার ব্যবহার, আপনাদের পরিবেশ ও সাধারণ অভ্যাসের উপর কিছু প্রশ্ন করব। আপনি উত্তর না দিলেও আগের মতই সুবিধাদি পাবেন।

উপরের প্রস্তাবে রাজি থাকলে অনুগ্রহ করে এখানে সহি বা টিপ-সহি দেন।

গবেষক,

উত্তরদাতার সহি