



International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH AND POPULATION RESEARCH
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Cable : Cholera Dhaka

Memorandum

18 December 2003

To : Dr. Robert F. Breiman
Associate Director
Health Systems and Infectious Diseases Division

Dr. K. Zaman
Epidemiologist
Public Health Sciences Division

From: Professor AKM Nurul Anwar
Chairman
Ethical Review Committee (ERC)

Sub : Approval of research protocol # 2003-042

Thank you for your memo dated 17th December 2003 with the modified version of your research protocol # 2003-042 titled "Defining incidence of IS in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine". The modified version of the research protocol is hereby approved upon your satisfactory addressing of the issues raised by the ERC in its meeting held on 3rd December 2003.

You shall conduct the study in accordance with the ERC-approved protocol; and shall be responsible for protecting the rights and welfare of the subjects and compliance with the applicable provisions of ERC Guidelines.

You shall also submit report(s) as required under ERC Guidelines. Relevant excerpt of ERC Guidelines and '*Annual/Completion Report for Research Protocol involving Human Subjects*' are attached for your information and guidance.

Thank you and I wish you success in running the above-mentioned study.

cc: Acting Head
Public Health Sciences Division



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December 17, 2003

TO : Chairman, ERC

FROM: : Dr. R. F. Breiman
Dr. K. Zaman
PI, Rotavirus IS Study

SUBJECT : Revised protocol # 2003-042

Attached please find a revised version of the protocol entitled "Defining incidence of IS in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine". We have addressed all the comments raised by ERC in our protocol. Kindly find below our responses to those comments.

Responses to comments:

a) The age of the study participants

It has been made uniform (page 13 and 14).

b) Cost of hospitalization

Our study will bear all costs related to hospitalization of the patients. We have already established collaboration with Shishu hospital. Professor Shahid Karim, paediatric surgeon of the hospital is also co-investigator of the study. He will be responsible for taking care of referred children suspected having IS. This has been mentioned on page 14.

c) Bangla consent form

The Bangla consent form has been revised accordingly.

d) ERC face sheet

It has been corrected

The revised protocol may kindly be approved.

cc: Associate Director, PHSD

(FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator: Dr. R. F. Breiman and Dr. K. Zaman

Trainee Investigator (if any): _____

Application No. 2003-042

Supporting Agency (if Non-ICDDR,B) _____

Title of Study: Defining incidence of intussusception in
Bangladesh in preparation for a phase III
trial of a new rotavirus vaccine

Project Status: _____

☒ [X] New Study☐ [] Continuation with change☐ [] No change (do not fill out rest of the 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) Minor or persons under guardianship ☒ Yes ☐ No

5. Will Signed Consent Form be Required:

- (a) From subjects ☐ Yes ☒ No
 (b) From parents or guardian ☒ Yes ☐ No
 (if subjects are minor)

2. Does the Study Involve:

- (a) Physical risk to the subjects ☒ Yes ☐ No
 (b) Social risk ☐ 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

6. Will precautions be taken to protect anonymity of subjects ☒ Yes ☐ No

3. Does the Study Involve:

- (a) Use of records (hospital, medical, death or other) ☒ Yes ☐ No
 (b) Use of fetal tissue or abortus ☐ Yes ☒ No
 (c) Use of organs or body fluids ☒ Yes ☐ No

7. Check documents being submitted herewith to Committee:

- ____ Umbrella proposal - Initially submit an with 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*

4. Are Subjects Clearly Informed About:

- (a) Nature and purposes of the study ☒ Yes ☐ No
 (b) Procedures to be followed including alternatives used ☒ Yes ☐ No
 (c) Physical risk ☒ 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

* 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. Example 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 Committee for review

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

K. Zaman
Principal Investigator

Trainee

**ICDDR,B: Centre for Health & Population Research
FORM**

RRC APPLICATION

FOR OFFICE USE ONLY

RESEARCH PROTOCOL

Protocol No. 2003-042

RRC Approval: ☐ Yes / ☐ No Date:

ERC Approval: ☐ Yes / ☐ No Date:

AEEC Approval: ☐ Yes / ☐ No Date:

Project Title: Defining incidence of intussusception in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine

Theme: (Check all that apply)

- | | |
|---|--|
| ☐ Nutrition | ☐ Environmental Health |
| ☐ Emerging and Re-emerging Infectious Diseases | ☐ Health Services |
| ☐ Population Dynamics | X Child Health |
| ☐ Reproductive Health | X Clinical Case Management |
| ☐ Vaccine evaluation | ☐ Social and Behavioural Sciences |
| ☐ HIV/AIDS | |

Key words: Intussusception, vaccine, rotavirus, diarrhea, Bangladesh

Relevance of the protocol:

Rotavirus is the leading cause for diarrhea morbidity and mortality among children in developing countries. A safe and effective rotavirus vaccine is needed to reduce the enormous public health burden associated with rotavirus illness, especially in developing countries (at least 600,000 deaths worldwide annually). Earlier unanticipated adverse events experienced with a rhesus rotavirus vaccine (intussusception) led to the withdrawal of the vaccine from the market. GlaxoSmithKline Biologicals has developed a new rotavirus vaccine (RIX4414) based on the human rotavirus strain 89-12. Phase II trials, ongoing in Bangladesh, will likely be followed by phase III trials in Matlab. Baseline incidence rates of intussusception (IS) would be very useful in preparation for vaccine trials, and also for providing a context during analyses of data from vaccine clinical trials.

Programmes

- | | |
|---|---|
| X Child Health Programme | ☐ Health and Family Planning Systems Programme |
| ☐ Nutrition Programme | ☐ Population Programme |
| X Programme on Infectious Dis & Vaccine Science | ☐ Reproductive Health Programme |
| ☐ Poverty and Health Programme | ☐ HIV/AIDS Programme |

Principal Investigator: Dr. R. F. Breiman and Dr. K. Zaman

Division: HSID **Phone:** 9881761

Address: Infectious Disease Specialist

Email: breiman@icddr.org,

Co-Principal Investigator(s): Dr. Md. Yunus,

Co-Investigator(s): Dr. Hafizur Rahman Chowdhury, Dr. Tasnim Azim, Prof. Shahid Karim-(Shishu-Hospital, Dhaka)

Student Investigator/Intern:

Revised on: 15th April 200

Collaborating Institute(s): _____

Population: Inclusion of special groups (Check all that apply):

- | | | |
|--|--------------------------|------------------------|
| Gender | ☐ | Pregnant Women |
| X Male | ☐ | Fetuses |
| X Females | ☐ | Prisoners |
| Age | ☐ | Destitutes |
| X 0 – 5 years | ☐ | Service providers |
| ☐ 5 – 9 years | ☐ | Cognitively Impaired |
| ☐ 10 – 19 years | ☐ | CSW |
| ☐ 20 – 64 years | ☐ | Others (specify _____) |
| ☐ 65 + | ☐ | Animal |

Project / study Site (Check all the apply):

- | | |
|--|--|
| ☐ Dhaka Hospital | ☐ Mirsarai |
| X Matlab Hospital | ☐ Patya |
| X Matlab DSS area | ☐ Other areas in Bangladesh _____ |
| ☐ Matlab non-DSS area | ☐ Outside Bangladesh |
| ☐ Mirzapur | name of country: _____ |
| ☐ Dhaka Community | ☐ Multi centre trial |
| ☐ Chakaria | (Name other countries involved) |
| ☐ Abhoynagar | _____ |

Type of Study (Check all that apply):

- | | |
|---|---|
| ☐ Case Control study | ☐ Cross sectional survey |
| X Community based trial / intervention | X Longitud Stud (cohort or follow-up) |
| ☐ Program Project (Umbrella) | X Record Review |
| ☐ Secondary Data Analysis | ☐ Prophylactic trial |
| ☐ Clinical Trial (Hospital/Clinic) | ☐ Surveillance / monitoring |
| ☐ Family follow-up study | ☐ Others- vaccine evaluation |

Targeted Population (Check all that apply):

- | | |
|--|--------------------------------------|
| X No ethnic selection (Bangladeshi) | ☐ Expatriates |
| ☐ Bangalee | ☐ Immigrants |
| ☐ Tribal groups | ☐ Refugee |

Consent Process (Check all that apply):

- | | |
|-------------------------------|---|
| X Written | X Bengali language |
| ☐ Oral | ☐ English language |
| ☐ None | |

Proposed Sample size: Total sample size: About 11000 children <2 years ☐

Sub-group _____ ☐

_____ ☐

_____ ☐

_____ ☐

Determination of Risk: Does the Research Involve (Check all that apply):

- ☐ Human exposure to radioactive agents? ☐ Human exposure to infectious agents?
☐ Fetal tissue or abortus? ☐ Investigational new drug
☐ Investigational new device? ☐ Existing data available via public archives/source
(specify _____) X Pathological or diagnostic clinical specimen only
☐ Existing data available from Co-investigator ☐ Observation of public behaviour
☐ New treatment regime

Yes/No

- ☒ X ☐ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?
- ☐ X Does the research deal with sensitive aspects of the subject's behaviour; sexual behaviour, alcohol use or illegal conduct such as drug use?
- Could the information recorded about the individual if it became known outside of the research:
- ☐ X a. place the subject at risk of criminal or civil liability?
- ☐ X b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research (Check one):

- ☐ greater than minimal risk X no more than minimal risk
☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

Yes/No

- ☒ ☐ Is the proposal funded?

If yes, sponsor Name: NVPO and USAID_____

Yes/No

☐ X Is the proposal being submitted for funding ?

If yes, name of funding agency: (1) _____
(2) _____

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above?

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support (\$)

(Day, Month, Year - DD/MM/YY)

Beginning date: as soon as possible _____

End date: 2 years from date of starting

Cost Required for the Budget Period

a. **1st Year** **2nd Year** **3rd Year** **Other**
\$ 83,429 \$ 73,264 _____

b **Direct Cost : \$ 112,178 Total Cost : \$ 156,693**

Approval of the Project by the Division Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers. The protocol has been revised according to the reviewer's comments and is approved.

Robert F. Greenman
Name of the Associate Director

[Signature]
Signature

November 5, 2003
Date of Approval

Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil or admin. (applicable) penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

Signature of PI [Signature]

Date: November 5, 2003

Name of Contact Pers (if for the _____

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PROJECT SUMMARY: Describe in concise terms, the hypothesis, objectives, and the relevant background of the project. Describe concisely the experimental design and research methods for achieving the objectives. This description will serve as a succinct and precise and accurate description of the proposed research is required. This summary must be understandable and interpretable when removed from the main application. (TYPE TEXT WITHIN THE SPACE PROVIDED).

Principal Investigator R.F. Breiman and K. Zaman

Project Name : Defining incidence of IS in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine

Total Budget: US \$ 156,693
Ending Date 2 years from starting

Beginning Date: As soon as possible

A safe and effective vaccine is needed to reduce the substantial public health burden associated with rotavirus illness, especially in developing countries. About 40,000 children with rotavirus diarrhea are treated each year at the ICDDR,B hospitals. Globally there are an estimated 600,000 to 1 million deaths annually. Earlier unanticipated adverse events experienced with a rhesus rotavirus vaccine (intussusception) led the withdrawal of the vaccine from the market. GlaxoSmithKline Biologicals has developed a new rotavirus vaccine (RIX4414) based on the human rotavirus strain 89-12. Phase II trials, ongoing in Bangladesh, will likely be followed by phase III trials in Matlab. Baseline incidence rates of intussusception (IS) are needed to prepare for vaccine trials, and also for providing a context during analyses of data from vaccine clinical trials. In addition, establishing surveillance for IS will ensure that a system to detect and ensure effective treatment of IS is optimally functioning well before a phase III trial begins.

We will conduct retrospective and prospective studies to define baseline incidence rates for IS in Bangladesh. We will review existing data from hospitalization in Matlab at three ICDDR,B hospitals which service the Matlab area. Using the Brighton Case Definition for IS, we will estimate rates for probable IS.

Prospectively, we will establish surveillance for IS at the three ICDDR,B treatment centres serving Matlab, 4 District and sub-districts (upazilas) government hospitals, and 3 district-based private clinics serving people living in the Matlab area. Prospective surveillance will include systematic confirmation of IS (with ultrasound in Matlab and other procedures, if necessary, in Dhaka).

Infants and children diagnosed with IS will be transported to Dhaka Shishu Hospital for further evaluation and treatment. Surgeons and radiologists at Dhaka Shishu Hospital are experienced in diagnosis and management of IS. Children with symptoms consistent with IS in whom diagnostic tests are negative will be observed in hospital until symptoms improve or resolve. Children who do not improve or who worsen will be transported to Dhaka Shishu Hospital for further evaluation.

DESCRIPTION OF THE RESEARCH PROJECT

Hypothesis to be tested:

Concisely list in order, in the space provided, the hypothesis to be tested and the Specific Aims of the proposed study. Provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

There are cases of intussusception among children in rural Bangladesh

Specific Aims:

Describe the specific aims of the proposed study. State the specific parameters, biological functions/ rates/ processes that will be assessed by specific methods (TYPE WITHIN LIMITS).

1. Establish prospective surveillance for IS in a population-based surveillance area in Bangladesh.
2. Collect and review retrospective data from hospitalizations at three ICDDR,B hospitals serving a defined population (i.e. to provide population-based incidence rates) for cases meeting a clinical case definition for IS.
3. Enhance capacity for rapid detection of potential cases of IS, diagnostic confirmation, and non-surgical and surgical management of IS that would be in place during large scale field trials for efficacy of a new rotavirus vaccine.
4. To assess potential infectious causes of IS and mimics of IS.

Background of the Project including Preliminary Observations

Describe the relevant background of the proposed study. Discuss the previous related works on the subject by citing specific references. Describe logically how the present hypothesis is supported by the relevant background observations including any preliminary results that may be available. Critically analyze available knowledge in the field of the proposed study and discuss the questions and gaps in the knowledge that need to be fulfilled to achieve the proposed goals. Provide scientific validity of the hypothesis on the basis of background information. If there is no sufficient information on the subject, indicate the need to develop new knowledge. Also include the **significance and rationale** of the proposed work by specifically discussing how these accomplishments will bring benefit to human health in relation to biomedical, social, and environmental perspectives. **(DO NOT EXCEED 5 PAGES, USE CONTINUATION SHEETS).**

Rotaviruses, non-enveloped, double-stranded RNA viruses, infect both humans and animals and are distributed worldwide. In humans, rotavirus causes diarrhea of varying severity ranging from mild to severe. Deaths occur from rotavirus diarrhea when the diarrhea is sufficiently severe to cause dehydration. Most illnesses occur in infants, although adults and the elderly may also be affected. Rotavirus is the leading cause for diarrhea-related morbidity and mortality among children in developing countries. It is the most common cause of severe diarrhea leading to hospital treatment in every country where etiologies have been monitored, including both developed and developing countries. In developing countries, the number of deaths due to rotavirus is estimated to be between 600,000 and one million, almost all under age 2 years (Miller & McCann, 2000). Almost all children have been infected by the time they are 3 years of age, and previous infection protects children from subsequent illness. Re-infections are frequent, but subsequent illnesses tend to be less severe than the first infection. Thus, it is believed that if the first exposure to rotavirus occurs via an attenuated vaccine strain, subsequent infections with virulent wild-type rotaviruses will not cause the severe life-threatening diarrhea that now occur, even if they are caused by a different serotype of rotavirus than the vaccine strain. Vaccination with a safe and effective vaccine has the potential of averting the deaths of up to one million children per year, most of whom live in developing countries. In addition, such a vaccine will avert hospitalizations that occur in children in all parts of the world.

A licensed vaccine against rotavirus (RRV-TV), while effective was removed from use after it was found to be associated with IS. Newer generation vaccines are well along in development—one vaccine, a human derived vaccine, based on the G1 serotype, called RIX 4414 from GlaxoSmithKline has shown promise in clinical trials to date. Evaluation of this vaccine is proceeding first in developing countries (before evaluation in developed countries) where the benefits of vaccination (in terms of disease and mortality prevention) can be directly considered in the context of any risks identified. Phase II trials, ongoing in Bangladesh, will likely be followed by phase III trials at various sites within the country. Baseline incidence rates of IS would be very useful in preparation for vaccine trials, and also for providing a context during analyses of data from vaccine clinical trials. Having in place a system for rapid and effective management of IS for use during a large trial will help us to limit potential or perceived risks from IS associated with participation in the trial—this may be needed to assure protection of human subjects (during a large, phase III rotavirus vaccine trial).

Rotavirus is responsible for an estimated 600,000 deaths in children globally; 40% of all hospitalizations of children <5 years old are due to rotavirus in Bangladesh. Because

rotavirus is transmitted through interpersonal contact, improved water sanitation will not impact this disease—vaccination holds the key to reducing disease burden. Since most severe infections occur between the ages of 4 months and 2 years of age, vaccination should begin early in life, and immunization should be completed prior to 6 months. Hopes were high for dramatic global health impact when rhesus rotavirus vaccine, Rotashield, was licensed in the United States in 1998 and was granted a marketing authorization for Europe in 1999 but was withdrawn from the market in 1999 due to an increased risk of intussusception (IS) shortly after its administration (Anonymous, 1999; Murphy et al, 2001).

Intussusception is the invagination of one segment of the intestine into a distal segment of the intestine which results obstruction of the bowel. Most intussusceptions are ileocolic. In untreated condition this may lead to death. Symptoms consistent with intussusception are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C.

Epidemiologic evidence supports a causal relationship between intussusception and RRV-TV vaccine, although the exact mechanism is not known. It has been estimated that the population attributable risk of 1 per 10,000 (range 1 in 5,000 to 1 in 12,000) (Peter and Myers, 2002). The risk is greatest 3 to 7 days after the first vaccination dose (Kramarz et al, 2001). The incidence in developing countries appears to be lower than that industrialized countries but it is not clear whether this difference exists due to decreased case detection or differing cases definition (Kramarz et al, 2001).

While the risks were relatively low (attributable risk appears to be between 1 in 5,000 and 1 in 15,000 children immunized), the seriousness of the adverse events created an unacceptable balance between risk and benefits for use of the vaccine in the United States. While baseline rates of idiopathic IS in the US are estimated to be 50 cases per 100,000 children/year (1 per 2,000 children) (Chang et al, 2001), reliable rates from developing countries have been hard to come by.

Data on IS incidence is also limited in Asia. Both retrospective and prospective studies are being conducted in Asia-Pacific region to determine IS incidence rates. However, the results are yet to be published. Generally the rates varied between 50-100 cases per 100,000 infants.

While it is hoped that the GSK vaccine will not be associated with IS, the possibility cannot be ruled out, since the physiologic basis of the association with Rotashield has not yet been defined. Thus, as we approach a phase III trial, we need to: a) be prepared to identify potential cases of IS so that we can ensure optimal management and reduce the potential for untoward outcomes associated with participation in the trial, b) define baseline rates of disease—expected rates are useful for sample size calculations and for communication about the trial to the general public and parents who need to understand the risks and the potential for coincidental IS occurring during a trial, and c) have a context for interpreting attributable risk should there be any association of vaccination with IS.

The aim of this independent IS surveillance study is to estimate the background incidence of IS among children < 2 years in the population where the vaccine study will take place.

Rationale

Rotavirus disease is the most common cause of diarrhea and dehydration in young children in both developed and developing country. This global health burden prompted the development of vaccines against rotavirus. One vaccine, Rotashield®, a tetravalent rhesus human reassortant RV vaccine (RRV-TV), was licensed by Wyeth-Lederle in the United States of America (USA) in 1998 and was granted a marketing authorization for Europe in 1999 but was withdrawn from the market in 1999 due to an increased risk of intussusception (IS) shortly after its administration. GSK Biologicals' candidate rotavirus vaccine is a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. Phase II trials, ongoing in Bangladesh, will likely be followed by phase III trials in the country. Baseline incidence rates of IS would be very useful in preparation for vaccine trials, and also for providing a context during analyses of data from vaccine clinical trials.

Research Design and Methods

Describe in detail the methods and procedures that will be used to accomplish the objectives and specific aims of the project. Discuss the alternative methods that are available and justify the use of the method proposed in the study. Justify the scientific validity of the methodological approach (biomedical, social, or environmental) as an investigation tool to achieve the specific aims. Discuss the limitations and difficulties of the proposed procedures and sufficiently justify the use of them. Discuss the ethical issues related to biomedical and social research for employing special procedures, such as invasive procedures in sick children, use of isotopes or any other hazardous materials, or social questionnaires relating to individual privacy. Point out safety procedures to be observed for protection of individuals during any situations or materials that may be injurious to human health. The methodology section should be sufficiently descriptive to allow the reviewers to make valid and unambiguous assessment of the project. **(DO NOT EXCEED TEN PAGES, USE CONTINUATION SHEETS).**

Experimental design and methods

2.1 STUDY AREA

The study will be conducted in rural Bangladesh at Matlab, where the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) has been maintaining a field research project since 1963. Matlab is a low-lying riverine area which lies 45 km south east of Dhaka, the capital of Bangladesh. The principal occupations in the Matlab area are farming and fishing. Since 1966 a Health and Demographic Surveillance System (HDSS), which consists of regular cross-sectional censuses and longitudinal registration of vital events, has been maintained in the area (ICDDR,B, 1978). A central treatment facility, staffed by physicians and paramedics provides free therapy for 12,000-15,000 diarrhea patients a year. A Maternal, Child Health & Family Planning Program (MCH-FP) has been in operation for half of the population of the HDSS area (current population of HDSS is about 220,000) since 1978 and intensive research has been conducted in this population (Bhatia et al., 1980). The other half serves as a comparison area where regular government health care facilities are available. Each community health research worker (CHRW) in the intervention area covers a population of about 1800. She visits each household monthly and is responsible for recording of vital events, collecting health information about diarrhea, acute respiratory infections and breast feeding, immunization to children, referral of severely sick children and mothers etc. CHRW also provide service to mothers and children twice in a month through fixed site clinic located in her house. Each CRHW in the comparison area covers a population three times larger than a CHW in the intervention area. They are mainly responsible for recording of demographic events. The prospective study will be conducted in the whole HDSS area. Table 1 shows the population in the HDSS area in 2001.

In addition to treatment for diarrhoea patients, all < 5 children from the MCH-FP intervention area are also treated for other illnesses. Attached to Matlab hospital there are two Community Treatment Centres at Nayergaon and Kalirbazar to facilitate quick and easy accessibility of life threatening diarrheal diseases. These centres treats about 1,000-1500 diarrhea cases in a year.

Table 1: Matlab HDSS Population, 2001

Study Populations	Intervention Area
Total number	219,752
Crude birth rate (1)	26.8
Total number of births	5,880
Total children < 2 years	10,773
Total < 5 children	26,095
Total fertility rate (2)	3.3
Infant mortality rate (3)	43.7
Child mortality rate (0-4 years)	65.0

(1) Per 1,000 population

(2) Per woman

(3) Per 1,000 live births

Retrospective surveillance: We will review medical records for the years 2001 and 2002 at the three ICDDR,B treatment centres serving a population of 10,773 children <2 years old in Matlab, a rural area 55 km southeast of Dhaka. Medical records will be reviewed to identify patients who meet a clinical case definition of IS, put forward by the "Brighton Collaboration" (Brighton Collaboration-intussusception definition and guidelines).

The Brighton Collaboration case definitions (Annex II) enable an assignment of probable or possible IS based on clinical criteria (i.e. without surgical or radiographic findings). Since, radiographic or surgical confirmation will not be systematically available for the retrospective survey, we will rely on the Brighton case definitions to assign cases of probable and possible IS.

Based on the current definitions, a probable case will be defined as ≥ 2 of the following criteria (referred to by Brighton as "major criteria"):

- Evidence of intestinal obstruction
 - bile-stained vomiting and either abdominal distention/abnormal or absent bowel sounds
 - OR
 - plain abdominal radiograph showing dilated bowel loops and fluid levels);
- features of intestinal invagination with any of the following:
 - abdominal mass,

- rectal mass,
- rectal prolapse,
- visible intussusceptum or soft tissue mass on plain film
- evidence of intestinal vascular compromise or venous congestion
 - rectal bleeding or red currant jelly stool or blood on rectal examination.

A possible case of IS will be based on the presence of ≥ 4 "minor criteria":

- predisposing factors (age < 1 year and male gender)
- abdominal pain
- vomiting
- lethargy
- pallor
- hypovolumic shock
- plain radiograph of abdomen showing non-specific abnormalities

Pending further discussion with experts, a probable case may also be considered if there is presence of one major criteria (excluding rectal bleeding) and ≥ 3 minor criteria.

Prospective surveillance: We will establish prospective surveillance for IS among children living within Matlab HDSS area, half of which is a likely site for a phase III trial of a rotavirus vaccine. This will be established at the three ICDDR,B treatment centres serving Matlab, 4 District and sub-districts (upazilas) government hospitals, and 3 district-based private clinics serving people living in the Matlab area. As part of their routine monthly visit Community Health Research workers (CHRW) will visit homes and ask whether children < 2 years of age have experienced symptoms consistent with IS (based on above Brighton criteria). They will ask about abdominal pain and distention, abdominal mass, bile stained vomiting and passage of red current jelly or blood. Children with any of these symptoms will be referred to ICDDR,B Matlab hospital for further assessment by physician. These are included in Brighton criteria. But CHRW will not ask all questions of the Brighton criteria. Ultrasonogram will be done for all these cases. CHRWs will also remind and encourage parents to bring their children to ICDDR,B Matlab hospital should their child develop relevant symptoms. We will train staff to recognize possible IS and to refer, when indicated, to the hospital where we will provide and train medical officers on diagnosis and management. Ultrasound equipment will be provided to the hospital and hospital staff will be trained on ultrasonographic technique, in particular recognition of IS. A child with suspected intussusception will be referred to Dhaka Shishu hospital (Children's hospital) rapidly. Epidemiologic information and diagnostic specimens (to determine etiology when possible) will be obtained from all suspected cases of IS. A detailed history of feeding practices, immunization history, illness history will be obtained from subjects. One study physician will visit 4 district and 3 private clinics every 2 weeks to collect information about any cases of IS from children of Matlab HDSS area.

Cost of hospitalization

Our study will bear all costs related to hospitalization of the patients. We have already established collaboration with Shishu hospital. Professor Shahid Karim, paediatric surgeon of the hospital is also coninvestigator of the study. He will be responsible for taking care of referred children suspected having IS.

Training of the ultrasonographer

The physician responsible for ultrasonogram will be trained in Dhaka. We have already established collaboration with Sir Salimullah Medical college for training on ultrasonogram. The sonologist in the medical collage already trained some of our staffs in other studies (e.g. determination of size of the foetus, size of thyroid etc.). The duration of the training will be of two months. The sonologist from the medical college will provide hands on training also at Matlab and make follow-up. Photos of ultrasound will be sent to sonologist in Dhaka for review when necessary. Medical officers will return to Dhaka for one day every two months to refresh training by assisting in ultrasound examination under the direction of the expert sonologist(who will be responsible for initial training as well).

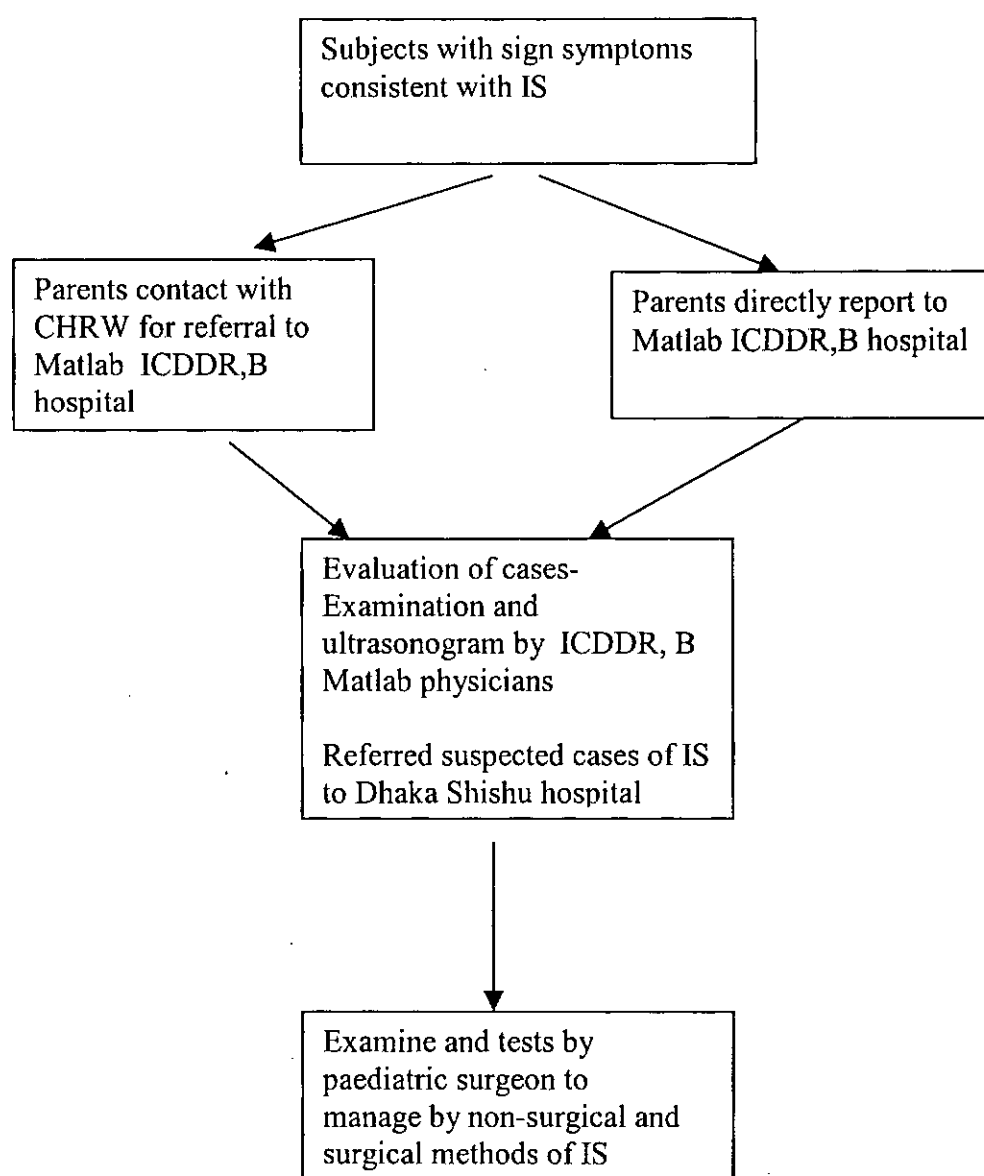
Sample size estimates: The birth cohort in the Matlab intervention area is 5880 and the number of <2 children is 10,773. If the rate of IS is 50 per 100,000 children <2 years of age, then we will expect to identify about 6 cases per year. Of course, these numbers would be proportionately higher or lower depending upon actual rates.

The following tests will be done in possible or probable cases of IS:

- Frozen stool samples or rectal swab and throat swab specimens by RT-PCR to determine the presence of RV, enteroviruses and adenoviruses. Stool samples will be tested for the presence of enteric pathogens (parasites and bacteria such as *Shigella spp.*, *Vibrio cholerae 01 and 0139*, *Salmonella spp.*) by standard techniques (WHO, 1987). Detection of Enterotogenic *E. Coli* will be done as described previously (Qadri et al, 2000). Tests for RT PCR and culture of organisms will be done at the ICDDR,B laboratory.
- This will be tested for the presence of enteric pathogens such as Salmonella, Shigella, Cholera, Enterotoxigenic *E. coli*.
- Acute and convalescent blood will be tested to detect an acute antibody response to RV and if possible to any pathogen identified by stool and/or throat swab tests or by histopathologic evaluation of tissue.
- If applicable, surgical specimens should be divided into 3 aliquots to be processed for routine fixation, for electron microscopy (fixation in 4% paraformaldehyde and 1% glutaraldehyde), and for frozen sectioning for detection of virus antigens by immunofluorescence. Routinely fixed specimens should be examined for histopathologic evidence of acute inflammation and presence of virus inclusions or other diagnostic signs. Additional testing including referral of tissue blocks for outside review and/or tests using immunohistochemistry, in situ hybridization, or PCR will be arranged.

Annex- 1 provides instruction on the evaluation of intussusception. Each case of suspected or confirmed intussusception will be reviewed by an Independent Data Monitoring Committee (IDMC).

Flow chart showing what happens to a child who presents with symptoms of IS



Facilities Available

Describe the availability of physical facilities at the place where the study will be carried out. For clinical and laboratory-based studies, indicate the provision of hospital and other types of patient's care facilities and adequate laboratory support. Point out the laboratory facilities and major equipments that will be required for the study. For field studies, describe the field area including its size, population, and means of communications. **(TYPE WITHIN THE PROVIDED SPACE).**

The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) has large multi-disciplinary international and national scientific research staff. Existing field,

hospital, laboratory and office facilities will be used for this study. ICDDR,B scientists have conducted a variety of vaccine studies including rotavirus.

Field site

The study will be conducted at rural Matlab. ICDDR,B has been maintaining a field research centre at Matlab for about forty years. Due to the presence of ongoing health and demographic surveillance system (HDSS), clinic and laboratory facilities, effective referral systems and well-established infrastructure at Matlab, it offers an excellent research facilities for this study. The HDSS is a regularly updated information system on about 220,000 population at Matlab.

Shishu hospital (Children's hospital)

Shishu hospital is the largest pediatric hospital in Bangladesh. The hospital has the experience and capacity for diagnosis, non-surgical and surgical management of intussusception, and a pediatric surgeon at this hospital is a co-investigator on the protocol to assume responsibility for the care of children suspected of having IS.

Laboratory facilities

Existing laboratory facilities in ICDDR,B will be used.

Data Analysis

Describe plans for data analysis. Indicate whether data will be analyzed by the investigators themselves or by other professionals. Specify what statistical softwares packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to monitor further progress of the study. **(TYPE WITHIN THE PROVIDED SPACE).**

Incidence rates of IS will be calculated based on the Brighton case definitions. Age, sex seasonality of IS cases will be determined. Relationship with feeding patterns and infectious agents will be explored.

Ethical Assurance for Protection of Human Rights

Describe in the space provided the justifications for conducting this research in human subjects. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how subject's rights are protected and if there is any benefit or risk to each subject of the study.

A child with suspected intussusception will be referred to a local hospital in Dhaka (Children's hospital, Shishu Hospital). The hospital has the experience and capacity for diagnosis, non-surgical and surgical management of intussusception, and a pediatric surgeon at this hospital is a co-investigator on the protocol to assume responsibility for the care of children suspected of having IS. During the study course, the parents/guardians will be instructed to contact the investigator and his staff immediately should the subject manifest any signs or symptoms they perceive as serious. No subjects will be deprived of existing care facilities.

Confidentiality of collected information will be maintained by keeping all data forms private and locked at the ICDDR,B Matlab office with access limited to those working in the study. Study subjects will only be identified by study numbers.

Use of Animals

Describe in the space provided the type and species of animal that will be used in the study. Justify with reasons the use of particular animal species in the experiment and the compliance of the animal ethical guidelines for conducting the proposed procedures.

No animal will be used in this study.

Literature Cited

Identify all cited references to published literature in the text by number in parentheses. List all cited references sequentially as they appear in the text. For unpublished references, provide complete information in the text and do not include them in the list of Literature Cited. There is no page limit for this section, however exercise judgment in assessing the "standard" length.

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Miller MA, McCann L. Policy analysis of the use of hepatitis B, *Haemophilus influenzae* type B, Streptococcus pneumonia-conjugate and rotavirus vaccines in National immunization schedule. Health Economics 2000; 9: 19-35.

Murphy TV, Gargiullo PM, Massoudi MS et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001; 344: 564-72

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Qadri F, Das SK, Faruque ASG, Fuchs GJ, Albert MJ, Sack RB, Svennerholm AM. Prevalence of toxin types and colonization factors in Enterotoxigenic *Escherichia coli* isolated during a 2-year period from diarrheal patients in Bangladesh. J Clin Microbiol 2000; 38: 27-31.

Ward R et al. Antibody to rotavirus on protection of adults challenged with a human rotavirus. J Infect Dis 1989; 159: 79-88.

World Health Organization. 1987. Programme for control of diarrhoeal disease (CDD/93.3 Rev 1), p. 9-20. In Manual for laboratory investigation of acute enteric infections. World Health Organization, Geneva, Switzerland.

Dissemination and Use of Findings

Describe explicitly the plans for disseminating the accomplished results. Describe what type of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Mention if the project is linked to the Government of Bangladesh through a training programme.

The findings from this study will be published in internal publications and peer reviewed journals, and disseminated in national and international conferences.

Collaborative Arrangements

Describe briefly if this study involves any scientific, administrative, fiscal, or programmatic arrangements with other national or international organizations or individuals. Indicate the nature and extent of collaboration and include a letter of agreement between the applicant or his/her organization and the collaborating organization. (DO NOT EXCEED ONE PAGE)

Intussusception Surveillance in Bangladesh

Personnel	Pay Level	Unit Cost	No. of Staff	% Effort	Monthly Rate	Year 1	Year 2
Robert Breiman	D1	no charge	1	10%	n/a	\$0	\$0
Dr. K Zaman	NO-D		1	10%	1,744	2,093	2,197
Dr. Hafizur Rahman	NO-C			10%	1,415	1,698	1,783
M. Yunus	P-5		1	1%	10,680	1,282	1,346
Dr. Tasnim Azim	NOD		1	2%	1,550	372	391
Emily Gurley			1	5%	-	-	-
Comm Health Res Workers	GS-2		87	5%	170	3,874	9,318
Medical Officer-retrospective review			1	25%	750	2,250	-
Medical Officer-Matlab-prospective surveillance			1	100%	726	8,712	9,148
Hospital Doctors			2	100%	254	3,559	6,102
Attendant			1	100%	201	1,407	2,412
Data Entry Technician	GS-3		1	50%	263	1,578	1,657
Capital Expenditures							
Ultrasound machine		12000	1			12,000	
UPS		100	1			100	
Ultrasound supplies						1,000	1,000
Computers/printers/UPS		1250	1			1,250	
Supplies--field office/health centres							
Supplies--specimen collection						1,000	1,000
office						1,000	1,000
communication/rent/utilities						500	500
Non-Stock Drugs (therapy)						3,000	3,000
Miscellaneous						500	500
Interdepartmental costs							
Shipping (Bangladesh--to--CDC)						1,500	1,500
Printing						500	500
Photocopying						500	500
Travel to site/transport specimens						2,000	2,000
Local transportation costs						3,000	3,000
Hospitalization costs		1000	3			8,000	8,000
Field worker training/retraining							
Medical officer training/retraining in ultrasound techniques						500	500
						1,000	1,000
Direct Cost						69,175	58,353
Direct Cost--ICDDR,B only excluding capital costs and CDC costs						54,825	57,353
Indirect cost--ICDDR,B only (at 26%)						14,254	14,912
Total						83,429	73,264

S. Haq
05-Nov-2003

Budget Justifications

The total duration of the proposed study will be of 24 months.

Investigators: The amount budgeted for the investigators reflects a reasonable estimate of the minimum time required to implement the study. Drs. R.F. Breiman and K. Zaman, will be responsible for overall implementation of the study. Dr. Md Yunus will provide guidance and supervise the study. Dr. Hafizur Rahman and other medical officer will be responsible for examining suspected cases of IS and take necessary action for referral. Dr. Tasnim Azim will be responsible for the lab part.

Supplies

Equipment includes purchase of ultrasound machine at Matlab hospital for purposes of diagnosing intussusception. Travel includes Dhaka to Matlab (multiple trips) and local travel by staff and community health workers. The shipping line item is to cover costs associated with shipping tissue and specimens to CDC for special diagnostic tests to determine etiologies of intussusception. Shipments from Bangladesh are expensive (avg \$ 1000-1500 per shipment via World Courier) to ensure appropriate conditions.

Follow-up of intussusception cases

The investigator will be asked to inform the parents/guardians of the signs and symptoms of intussusception. Parents/guardians/caretakers of study subjects will be asked to contact the investigator if they notice any signs or symptoms indicative of intussusception.

Symptoms consistent with intussusception are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. The investigator and his staff will take appropriate actions to treat the condition.

The following procedures will be followed by the investigator for work-up of the intussusception cases.

1. Case ascertainment

The diagnosis of intussusception would be done as defined by Brighton Collaboration definition.

2. Data collection for intussusception cases

The investigator will document all available information regarding any intussusception cases occurring during the study.

To allow for a complete assessment of the intussusception cases, information on the subject's feeding practices, immunization history, as well as any other information thought necessary for assessment taken.

Serum, throat and stool specimen collection from intussusception cases

Idiopathic intussusception is thought to be related to lymphoid hyperplasia in the intestinal sub-mucosa and/or mesenteric adenitis resulting from infections. Infectious agents most clearly linked to intussusception are enteroviruses and respiratory adenoviruses. Human rotaviruses also may cause intussusception, although epidemiologic data suggest this must be very unusual. In theory, any agent able to replicate in the small intestine could provoke this condition.

We will use a central laboratory to perform RT-PCR on throat swabs and stool samples for enteroviruses and adenoviruses and on stool samples alone for rotaviruses. The physician treating a case of intussusception should submit stool samples to the hospital microbiology laboratory for culture of enteric pathogens including *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*. If culture results suggest presence of enteropathogenic *E. coli*, representative colonies should be retained for further evaluation. The samples to be collected and their handling are described below.

If possible a stool specimen should be collected just prior to or immediately after the air or contrast enema as well as samples 24 hours and 48 hours after the reduction. The hospital microbiology laboratory should divide each stool specimen into an aliquot for its own testing and two additional aliquots of at least 2 grams each to be frozen at -20°C to -70°C . The frozen stool samples will be used for RT-PCR and other studies, such as virus culture, antigen detection by immunoassay, or electron microscopy for virus-like particles. Accordingly, a complete set of stool specimens (collected just prior to or immediately after the air or contrast enema, 24 hours and 48 hours after the reduction)

will be comprised of 3 specimens submitted for bacterial culture. In the event that feces are unobtainable at any of the requested sampling times, 3 separate rectal swab specimens should be collected. One swab specimen should be submitted for bacterial culture and the other 2 swabs should be placed each in a separate tube of 2 ml of sterile virus transport media and frozen at -20°C to -70°C .

A throat swab should be collected as soon as possible after intussusception is diagnosed. The throat swab should be placed in 2 ml of sterile virus transport media and frozen at -20°C to -70°C .

In case of surgical reduction, a surgical specimen of any enlarged mesenteric lymph should be obtained. If bowel or the appendix is resected, these specimens also should be included in the evaluation. If possible, resected tissue should be divided into 3 aliquots to be processed for routine fixation, for electron microscopy (fixation in 4% paraformaldehyde and 1% glutaraldehyde), and for frozen sectioning for detection of rotavirus antigens by immunofluorescence. Routinely fixed specimens will be examined at CDC for histopathologic evidence of acute inflammation and presence of virus inclusions or other diagnostic signs. Additional testing including referral of tissue blocks for outside review and/or tests using immunohistochemistry, in situ hybridization, or PCR will be arranged with CDC and possibly other collaborators.

Acute and convalescent blood (at least 2 ml of each) should be collected and stored at -20°C for serologic testing. Testing will be arranged to detect an acute antibody response to any pathogen identified by stool and/or throat swab tests or by histopathologic evaluation of tissue.

Brighton Collaboration
Case definition for the diagnosis of acute intussusception in infants and young children

Intussusception is the invagination of one segment of intestine into segment of distal intestine
Level 1 of Diagnostic certainty Surgical criteria The demonstration of invagination of the intestine at surgery and/or Radiologic criteria The demonstration of invagination of the intestine by either air or liquid contrast enema OR The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be reduced by hydrostatic enema on postreduction ultrasound and/or Autopsy criteria The demonstration of invagination of the intestine
Level 2 of Diagnostic certainty <u>Clinical criteria</u> Two major criteria or One major criterion and three minor criteria
Level 3 of Diagnostic certainty <u>Clinical criteria</u> Four or more minor criteria
Any Level of Diagnostic certainty <u>In the absence of surgical criteria with</u> the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (e.g. volvulus and congenital pyloric stenosis)

**Major or Minor criteria used in the case definition for the diagnosis of
intussusception**

Major criteria

1. Evidence of intestinal obstruction

- I. History of bile-stained vomiting
and either
- II. Examination findings of acute abdominal distension and abnormal or
absent bowel sound
or
- II. Plain abdominal radiograph showing fluid levels AND dilated bowel
loops

2. Features of intestinal invagination

One or more of the following:

- I. abdominal mass
- II. rectal mass
- III. intestinal prolapse
- IV. plain abdominal radiograph showing a visible intussusception or soft
tissue mass
- V. abdominal ultrasound showing a visible intussusception or soft tissue
mass
- VI. abdominal CT scan showing a visible intussusception or soft tissue
mass

2. Evidence of intestinal vascular compromise or venous congestion

- I. Passage of blood per rectum
or
- II. Passage of a stool containing "red current jelly" material
or
- III. Blood detected on rectal examination

Minor criteria

- Predisposing factors: age < 1 year and male sex
- Abdominal pain
- Vomiting
- Lethargy
- Pallor
- Hypovolemic shock
- Plain radiograph showing an abnormal but non-specific gas pattern

**International Centre for Diarrhoeal Disease Research,
Bangladesh****Voluntary Consent Form**

Title of the Research Project: Defining incidence of intussusception in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine

Principal Investigator: Dr. R.F. Breiman and Dr. K. Zaman

ICDDR,B has established surveillance for intussusception (IS) at Matlab to determine number of IS cases among children <5 years of age. Intussusception is the invagination of one segment of the intestine into a distal segment of the intestine which results obstruction of the bowel. The reason we are concerned about intussusception is that a study of a rotavirus vaccine to prevent an important cause of diarrhoea caused some cases of IS in children in the USA. A new vaccine has been developed for this type of diarrhoea and this vaccine will soon be evaluated in Matlab. Before that vaccine can be evaluated, we are making sure that occurrences of this serious problem can be diagnosed and treated, and also that we understand how frequently this problem occurs among infants and children at Matlab.

Symptoms of intussusception are abdominal pain and distention, abdominal mass, bile stained vomiting and passage of red current jelly or blood. Your child has developed one of these symptoms and your doctor would like to determine its cause. Your child will be referred to Matlab and will be examined by a physician. Ultrasonogram will be done at Matlab to help determine the cause of your child's illness, including the possibility of IS.

We are requesting you to allow your child to take part in a study about IS. We would like to know more about your child's illness. Participating in this study will involve collection of stool specimen and 3 ml of blood (about half tea-spoonful) during acute phase of illness and also 3 ml during convalescent after 3 weeks. We will ask you some questions which may provide useful information about the illness and its cause. In addition, to learn more about IS as part of the study we may transport your child to Dhaka (Children's hospital, Shishu Hospital). A paediatric surgeon there will examine your child and determine whether other interventions are needed.

Your child's participation is completely voluntary. Refusal to take part or continue with the study will involve no penalty or loss of benefits or attention to which your child are otherwise entitled. Also you may withdraw your child from the study at any time without any penalty or change in the routine care your child receives. You may wish to receive a signed copy of this form. Your child's participation in the study will be treated as confidential.

If you have any questions, please contact:

Name of investigator: Dr. Hafizur Rahman Chowdhury

Address of investigator: Matlab Health Research Centre, ICDDR,B

Informed Consent Signature Form

The study has been clearly explained to me and I have read and understood the information provided. I agree that my child be enrolled in the study. I understand that I have the right to decline the entry of my child into the study and that I have the right to withdraw my child from it at any time for any reasons, without consequence to his/her present or future health care and attention which my child from his/her healthcare provider. I have been made aware of my right to access and request correction of my child's personal data.

I, _____,
(subject's parent or legal guardian's first name and family name)

hereby freely give my consent for my child/ward to take part in this study.

Participant's Name:

(First Name, Family Name)

Participant's signature (where applicable): _____

Parent/Guardian's name:

(First Name, Family Name)

Parent/Guardian's signature: _____

Relationship to participant: _____

Participant's main address: _____

Participant's phone number: _____

Date: _____

Time: _____

(DD-MM-YY)

Witness: _____

Statement by Doctor, Nurse or Project Assistant who conducted the informed consent discussion:
I have carefully explained the nature, demands and foreseeable risks and benefits of the study to the person named above and witnessed the completion of the written consent form.

Name: _____

Signature: _____

Designation: _____

Date: _____

Time: _____

(DD-MM-YY)

International Centre for Diarrhoeal Disease Research, Bangladesh

শ্বেচ্ছামূলক সম্মতিপত্র

Title of the Research Project: Defining incidence of intussusception in Bangladesh in preparation for phase III trial of a new rotavirus vaccine

Principal Investigator: Dr. R. F. Breiman and Dr. K. Zaman

আইসিডিডিআর,বি পাঁচ বছরের কম বয়সী শিশুদের মধ্যে অল্পে প্রতিবন্ধকতার সংখ্যা নিরূপণ করতে মতলবে একটি অল্পে প্রতিবন্ধকতা সার্ভিলেন্স শুরু করেছে। অল্পে প্রতিবন্ধকতা বা intussusception হলো এমন একটি অবস্থা যেখানে অল্পের একটি অংশ তার নিম্নবর্তী অপর একটি অংশে প্রবেশের মাধ্যমে অল্পে প্রতিবন্ধকতা সৃষ্টি করে। আমরা যে কারণে অল্পে প্রতিবন্ধকতা সম্বন্ধে জানতে চাই তা হলো- ডায়রিয়া রোগের একটি গুরুত্বপূর্ণ কারণ রোটাবাইরাস প্রতিরোধকারী টিকা আমেরিকায় পরিচালিত একটি গবেষণায় কয়েকটি শিশুর অল্পে প্রতিবন্ধকতা সৃষ্টি হওয়া। এ ধরনের ডায়রিয়া রোগের বিরুদ্ধে বর্তমানে নতুন একটি টিকা তৈরী হয়েছে এবং মতলবে যার মূল্যায়ন শীঘ্রই শুরু হবে। এই টিকার মূল্যায়নের পূর্বে আমরা তাই এই গুরুত্বপূর্ণ সমস্যার সঠিক নির্ণয় এবং তার চিকিৎসা নিশ্চিত করতে চাই এবং বুঝতে চাই মতলবে শিশুদের মধ্যে কিরকমভাবে এই সমস্যার সৃষ্টি হয়।

অল্পে প্রতিবন্ধকতার লক্ষণগুলো হলো পেটে ব্যথা ও পেট ফুলে যাওয়া, পেটে ঢাকা, পিষ্টযুক্ত বমিএবং লাশ বর্নের জেলীর মতো তরল বা রক্তের নিঃসরণ। আপনার শিশুর এই লক্ষণগুলোর মধ্যে অন্তত:পক্ষে একটি আছে, যার কারণ আপনার চিকিৎসক নির্ণয় করতে ইচ্ছুক। আপনার শিশুকে মতলবে প্রেরণ করা হবে যেখানে একজন চিকিৎসক তাকে পরীক্ষা করবেন। মতলবে আপনার শিশুর রোগের কারণ এবং অল্পে প্রতিবন্ধকতার সম্ভাব্যতা নিরূপণের জন্য আলট্রাসোনোগ্রাম করা হবে।

আমরা আপনার শিশুকে অল্পে প্রতিবন্ধকতার একটি গবেষণায় অংশগ্রহণের জন্য আপনাকে অনুরোধ করছি। আমরা আপনার শিশুর অসুস্থতার ব্যাপারে আরও জানতে ইচ্ছুক। এই গবেষণায় অংশগ্রহণের মাধ্যমে আপনার শিশুর পায়খানার নমুনা, রোগের প্রারম্ভিক পর্যায়ে ৩ মি:লি: রক্ত (প্রায় আধা চা চামচ) এবং ৩ সপ্তাহ পরে আরো ৩ মি:লি: রক্তের নমুনা সংগ্রহ করা হবে। আমরা আপনাকে কিছু প্রশ্ন করবো যা কিনা এই অসুস্থতা এবং এর কারণ সম্পর্কে প্রয়োজনীয় তথ্য দিতে পারে। সেই সাথে, আরও তথ্য জানতে আপনার শিশুকে ঢাকায় (শিশু হাসপাতাল) প্রেরণ করতে পারি। সেখানে একজন শিশু শল্য চিকিৎসক আপনার শিশুকে পরীক্ষা করবেন এবং সিদ্ধান্ত নেবেন তার আর কোন চিকিৎসার প্রয়োজনীয়তা আছে কি না।

আপনার শিশুর অংশগ্রহণ সম্পূর্ণ শ্বেচ্ছামূলক। এই গবেষণায় অসম্মতি বা জড়িত থাকার ফলে আপনার কোন ক্ষতিপূরণ দিতে হবে না বা চিকিৎসার কোনরূপ ব্যাঘাত ঘটবেনা যেটা আপনার শিশু এমনিতেই পেত। কোন ক্ষতিপূরণ বা নির্ধারিত সেবা/ চিকিৎসার কোন ব্যাঘাত ছাড়াই আপনি আপনার শিশুকে যে কোন সময় গবেষণা থেকে প্রত্যাহারও করে নিতে পারেন। আপনি ইচ্ছা করলেই এই ফর্মের একটা সই করা কপি নিতে পারেন। এই গবেষণায় আপনার শিশুর অংশগ্রহণ গোপন রাখা হবে।

আপনার যদি কোন প্রশ্ন থাকে, অনুগ্রহপূর্বক যোগাযোগ করুন:

গবেষকের নাম: ডা: মো: হাফিজুর রহমান চৌধুরী

গবেষকের ঠিকানা: মতলব স্বাস্থ্য গবেষণা কেন্দ্র, আইসিডিডিআর,বি

সম্মতিপত্র স্বাক্ষর ফর্ম

এই গবেষণা আমাকে পরিস্কারভাবে ব্যাখ্যা করা হয়েছে এবং যে সব তথ্য দেয়া হয়েছে তা আমি পড়েছি/ বুঝতে পেরেছি। এই গবেষণায় আমি আমার শিশুর অংশগ্রহণে রাজি আছি। আমি বুঝতে পেরেছি যে আমার শিশুকে তার বর্তমান এবং

ভবিষ্যৎ স্বাস্থ্যসেবা এবং যত্ন যা সে তার সেবা প্রদানকারীর কাছে থেকে পাচ্ছে তার কোনরূপ ব্যাঘাত ছাড়াই এই গবেষণায় অংশগ্রহণ থেকে বিরত রাখার বা গবেষণা থেকে যে কোন সময় যে কোন কারণে প্রত্যাহার করার অধিকার আমার আছে। আমার শিশুর ব্যক্তিগত তথ্য দেখা এবং সংশোধনের অধিকার সম্পর্কে আমাকে সচেতন করা হয়েছে।

আমি _____

অংশগ্রহণকারীর পিতামাতা বা বৈধ অভিভাবকের প্রথম নাম এবং পারিবারিক নাম

এই গবেষণায় আমি আমার শিশু/পোষ্যকে অংশগ্রহণের জন্য স্বেচ্ছায় সম্মতি দিলাম।

অংশগ্রহণকারীর নাম _____

প্রথম নাম

পারিবারিক নাম

অংশগ্রহণকারীর স্বাক্ষর (যেখানে প্রযোজ্য) _____

পিতামাতা বা অভিভাবকের নাম _____

প্রথম নাম

পারিবারিক নাম

পিতামাতা বা অভিভাবকের স্বাক্ষর _____

অংশগ্রহণকারীর সাথে সম্পর্ক _____

অংশগ্রহণকারীর প্রধান ঠিকানা _____

অংশগ্রহণকারীর টেলিফোন নং _____

তারিখ _____

দিন

মাস

বছর

সময়

সাক্ষী _____

ডাক্তার, নার্স অথবা গবেষণা সহকারীর বিবৃতি যিনি সম্মতিপত্র আলোচনা করেছেন

উপরোল্লিখিত নামের ব্যক্তির কাছে আমি গবেষণার বিষয়বস্তু, এর প্রয়োজনীয়তা, ঝুঁকি ও উপকারিতা ব্যাখ্যা করেছি এবং লিখিত সম্মতিপত্র সম্পন্ন হতে দেখেছি।

নাম _____

স্বাক্ষর _____

পদবী _____

তারিখ _____

দিন

মাস

বছর

সময়

Reviewer ①

EVALUATION FORM

Title: Defining incidence of IS in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine

Summary of Referee's Opinions:

Rank Score

	High	Medium	Low
Quality of project	X		
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		

CONCLUSIONS

I support the project proposal

a) without qualification	X
b) with qualification	
c) on technical grounds	
d) on level of financial support	

I do not support the project proposal

Name of Referee:

Signature:.....Joseph Bresee, MD

Date: 23 October 2003.....

Position: Medical Officer IV

Institution: Centers for Disease Control and Prevention, Atlanta, GA 30333, USA

Detailed Comments : (Please use additional page if necessary.)

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 they are justified.

(Use additional pages if necessary)

Title: Defining incidence of IS in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine

This is well-designed, appropriate study to address critical needs – both to define the epidemiology and rates of intussusception in a developing country setting, and to develop a surveillance for IS that is sensitive and responsive enough for use in a clinical trial of rotavirus vaccine. The authors have addressed the major issues regarding surveillance for IS in a rural area in a thoughtful and thorough way. I have very few comments, listed below.

Specific comments:

When the CHRWs visit the homes to ask about symptoms of IS, will they use a standard questionnaire, and will it include questions about each of the Brighton criteria? Will any child who has any of the Brighton minor criteria be referred for evaluation, and will all of these children receive the lab work up described in the protocol, or is that only for children with confirmed cases of IS?

Is there a specific plan for training the ultrasonographers for this study? Will they be trained in Dhaka. What QA/QC activities will be integrated into this study? For instance, could photos or movies of the ultrasounds performed in Matlab and found to be negative for IS, be reviewed by ultrasonographers in Dhaka, to ensure that no cases are being missed?

The rates used for expected sample size are based on US rates. Are there any data from Bangladesh of other countries in the region that might be used to estimate expected numbers of cases?

Page 14 - In the first bullet under tests to be done – The testing of patients with symptoms related to IS is interesting, but it is not entirely clear how this will advance the goals set out in the proposal. Can the investigators add a fourth objective – to assess for potential infectious causes of IS and of mimics of IS? Are the methods for PCR for these agents well developed at ICDDR,B or will these samples be sent to other institutions? Can the investigators reference the methods to be used? Also, presumably no throat swabs will be tested for rotaviruses? What tests will be performed for the pathogenic bacteria listed here?

Page 14 - Second bullet – what tests will be done to detect anti-rotavirus antibodies? Which lab will do these tests?

EVALUATION FORM

Title: **Defining the incidence of IS in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine**

Summary of Referee's Opinions:

Rank Score

	High	Medium	Low
Quality of project	X		
Adequacy of project design	X		
Suitability of methodology	X		
Feasibility within time period		X	
Appropriateness of budget na			
Potential value of field of knowledge	X		

CONCLUSIONS

I support the project proposal

a) without qualification (See comments)	X
b) with qualification	
c) on technical grounds	
d) on level of financial support	

I do not support the project proposal

Name of Referee: Trudy V. Murphy, M.D.

Signature:.....

.Date: 10-06-03

Position: Medical Epidemiologist

Institution: National Immunization Program, CDC

Reviewer: T.V. Murphy

October 4, 2003

ICDDR,B:Centre for Health and Population Research

Project Title: Defining incidence of IS in Bangladesh in preparation for phase III trial of a new rotavirus vaccine.

General Comments:

Establishing the baseline rate of intussusception will be critical to assess the safety of any new rotavirus vaccine undergoing Phase III trials in a developing country population. The ICDDR,B's Centre for Health and Population Research is an ideal setting to determine the baseline rates of intussusception. Intussusception is a rare disease; the major limitation will be the relatively small size of the total population of infants and very small number of cases of intussusception that can be expected (page 14). The investigators should provide discussion about the usefulness of data that can be accumulated during the two years of study.

The protocol employs the definition of intussusception developed by the Brighton Collaboration, which currently are being validated. Overall, this investigation takes advantage of a unique trial center to determine information critical to the Phase III evaluation of new rotavirus vaccine.

It was not clear to this reviewer how the results might or might not differ between the ICDDR,B's Centre intervention group and the control population because of potential ascertainment bias. This reviewer also found no comment about identifying cases of intussusception that might not find their way to a health care center, for example, an infant who dies without hospitalization. The investigators may wish to discuss their plan to evaluate the completeness of their case ascertainment. This information will be critical if the same populations are to be used in the design of a Phase III trial.

Specific comments are listed below. They reflect this reviewer's lack of familiarity with the Centre. Please note also that no financial information was attached, and thus, no comment is appropriate.

Specific Comments:

1. page 7: Aim2: Are all cases of IS hospitalized? Is there an evaluation of the completeness component of the project that might be an additional AIM?
2. page 8: The size of Phase III safety trials when evaluating rare adverse events are much larger than the size of Phase III efficacy trials for a vaccine to prevent a common disease. The protocol could include a discussion about how the IS incidence data will be used under the circumstances of a Phase III trial. This discussion will be most critical when planning the Phase III trial but may also be a "cross-check" to be sure that the results from this project will sufficiently support the phase III trial.

3. page 9, para 4 and 5. The investigators allude to the rates of IS for the RRV-TV vaccine. Please note that the more common the IS events are after RRV-TV, the smaller the size necessary for future safety trials to demonstrate equivalent or greater safety.
4. page 11-12. The protocol setting (and thus the design) is not entirely clear to this reviewer. Page 12, para 1 indicates that retrospective review of records for intussusception will take place at *three* treatment centers. Which are the Centres? Are they the main pediatric hospital, and the two community treatment facilities (Nayergaon and Kalirbazar)? Will these three treatment centers include IS that occurs among children who receive care in the control non-intervention centers?
5. Will infant cases of intussusception be determined to arise among the persons in the intervention versus non intervention (control) communities? There may be an advantage to know the incidence of intussusception in both groups to assure that there is not bias resulting from the extensive contact in the intervention group.
6. Will infants who die before or without hospitalization be assessed for possible intussusception? If not, what assumptions are necessary to assure that changes in these cases over time will be accounted for?
7. What measures will be taken to train the ultrasonographer in the diagnosis of intussusception? This is a skill that requires experience, according to those who do it.
8. page 14. Is there interest in determining if parasitic diseases are co-factors in the symptom complex that will define intussusception? For example, whip worm is associated with rectal prolapse, also one of the minor criteria in the Brighton Collaboration definition of intussusception.
9. The investigators may have a study tool for determining characteristics of the patients with intussusception that is not included in the protocol. If so, this reviewer suggests that the investigators consider obtaining information about breast feeding and/or eating solid foods during the period immediately preceding onset of the intussusception.
10. OPV is thought by a minority of investigators to be associated with rare cases of intussusception. OPV at birth could have a protective effect against future intussusception. Information about past or concurrent OPV may be useful to collect.

Response to Reviewer 1**CHRWs visits:**

During their routine monthly visits, CHRWs will ask whether any children <5 years of age in the family have symptoms suggestive of IS. They will ask about abdominal pain and distention, abdominal mass, bile stained vomiting and passage of red current jelly or blood. Children with any of these symptoms will be referred to ICDDR,B Matlab hospital for further assessment by physician. These are included in Brighton criteria. But CHRW will not ask all questions of the Brighton criteria. Ultrasonogram will be done for all these cases. Children with suspected IS will be referred to Dhaka Shishu hospital and necessary lab tests will be done. This has been mentioned on page 13-14.

Training of the ultrasonographer

The physician responsible for ultrasonogram will be trained in Dhaka. We have already established collaboration with Sir Salimullah Medical college for training on ultrasonogram. The sonologist in the medical collage already trained some of our staffs in other studies (e.g. determination of size of the foetus, size of thyroid etc.). The duration of the training will be of two months. The sonologist from the medical college will provide hands on training also at Matlab and make follow-up. Photos of ultrasound will be sent to sonologist in Dhaka for review when necessary. It has been mentioned on page 14.

IS rates:

Data on IS incidence is also limited in Asia. Both retrospective and prospective studies are being conducted in Asia-Pacific region to determine IS incidence rates. However, the results are yet to be published. Generally the rates varied between 50-100 cases per 100,000 infants. With conservative estimate of IS incidence rate 50 per 100,000 children aged < 2 years of age at Matlab, we expect to identify about 6 cases in one year of surveillance.

Page 14 first bullet:

A fourth objective is added. Stool samples will be tested for the presence of enteric pathogens (parasites and bacteria such as *Shigella spp.*, *Vibrio cholerae* 01 and 0139, *Salmonella spp.*) by standard techniques (WHO, 1987). Detection of Enterotogenic *E. Coli* will be done as described previously (Qadri et al, 2000). Tests for RT PCR and culture of organisms will be done at the ICDDR,B laboratory.

Page 14 Second bullet:

IgA ELISA and neutralizing antibody tests will be done. This will be done in Dhaka ICDDR,B laboratory.

Response to reviewer 2

1. Page 7: Aim 2:

Since ICDDR,B has been maintaining a Health and Demographic Surveillance System (HDSS) area in a defined population, we expect all cases of IS in under 5 years of age from the intervention area will be hospitalized in any of the ICDDR,B treatment centre. However, children from the comparison area are admitted if they have any complaints of diarrhoea.

2. Page 8:

As mentioned in the protocol the results of the study would be useful in preparation of PIII vaccine trials and also provide a context during analyses of data. The study would enhance our capacity for rapid detection of potential cases of IS, diagnostic confirmation, and non-surgical and surgical management of IS that would be in place during large scale field trials for efficacy of a new rotavirus vaccine.

3. Page 9, Para 4 and 5:

Our aims are not to compare rates of IS with RRV-TV vaccine.

4. Page 11-12:

These three treatment centres are ICDDR,B Matlab and two community treatment centres (Nayergaon and Kalirbazar) run by ICDDR,B. These have been mentioned in response #1 above.

5. Cases of IS:

We planned to conduct pIII trial only in the intervention area of HDSS.

6. Infants who die:

As part of the HDSS causes of all deaths are ascertained through verbal autopsy which includes open-ended questions. The responses to open-ended questions will be screened by the research team to look for criteria consistent with Brighton case definition of IS.

7. Training of the ultrasonographers

The physician responsible for ultrasonogram will be trained in Dhaka. We have already established collaboration with Sir Salimullah Medical college for training on ultrasonogram. The sonologist in the medical collage already trained some of our staffs in other studies (e.g. determination of size of the foetus, size of thyroid etc.). The duration of the training will be of two months. The sonologist from the medical college will provide hands on training also at Matlab and make follow-up.

8. Page 14:

We will test for parasitic infections also.

9. Determining characteristics of the patients

A detailed history of feeding practices, immunization history, illness history will be obtained from subjects.

10. OPV:

As part of the Maternal Child Health programme all informations regarding administration of OPV are being collected and recorded routinely for all children in the intervention area. No OPV is given at birth.

Biography of the Investigators

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

1. **Name:** Robert F. Breiman, M.D.

2. **Present position:** Associate Director, ICDDR, B and Head, Health Systems and Infectious Diseases Division (HSID)

3. **Educational background:**

Institution and Location of Study	Degree	Year	Field
University of Arizona	B.A.	1975	Political Science
University of Arizona	M.D.	1979	Medicine
UCLA Affiliated Hospitals	Residency	1979-1982	Internal Medicine
UCLA Affiliated Hospitals	Chief Resident	1982-1983	Internal Medicine
UCLA	FELLOWSHIP	1984-1987	INFECTIOUS DISEASES
CDC	Fellowship	1987-1989	EIS Program

4. **List of ongoing research protocols**
(start and end dates; and percentage of time)

4.1. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time
2000-023	10/00	12/02	15%
2002-012	9/02	5/03	20%

4.2. As Co-Principal Investigator

Protocol Number	Starting date	End date	Percentage of time
2001-021	1/02	9/04	5%
2001-029	1/01	6/03	5%

4.3. As Co-Investigator

Protocol Number	Starting date	End date	Percentage of time
2001-14	5/02	10/02	10%

2002-10	4/02	7/02	2%
2002-28	10/01	9/03	10%
2002-022	10/02	9/03	5%
2003-030	9/03	9/05	10%

5. Publications

Types of publications	Numbers
a) Original scientific papers in peer-review journals	90
b) Peer reviewed articles and book chapters	9
c) Papers in conference proceedings	>50
d) Letters, editorials, annotations, and abstracts in peer-reviewed journals	10
e) Working papers	
f) Monographs/books	6

6. Five recent publications including publications relevant to the present research protocol

1) Feikin DR, Elie CM, Goetz MB, Lennox JL, Carlone GM, Romero-Steiner S, Holder PF, O'Brien WA, Whitney CG, Butler JC, **Breiman RF**. Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or 23-valent polysaccharide vaccine among HIV-infected adults. *Vaccine*. 2001;20:545-53.

2) **Breiman RF**, Keller DW, Phelan MA, Sniadack DH, Stephens DS, Rimland D, Farley MM, Schuchat A, Reingold AL Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med*. 2000;160:2633-8.

3) Rahman M, Rahman K, Siddique AK, Shoma S, Kamal AHM, Ali KS, Nisalak A, **Breiman RF**. First outbreak of dengue hemorrhagic fever, Bangladesh. *Emerg Infect Dis J* 2002;8:738-40.

4) Metlay JP, Hofmann J, Cetron MS, Fine MJ, Farley MM, Whitney C, **Breiman RF**. Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2000;30:520-528.

5) Nuorti JP, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS, **Breiman RF**. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;342:681-689.

CURRICULUM VITAE

Md. Khalequzzaman MBBS, MPH, PhD

1. (I) Name : K. Zaman

(ii) Designation : Scientist and Epidemiologist

(iii) Address : Child Health Unit, Public Health
Sciences Division, ICDDR,B,Dhaka,
Bangladesh, Tel: 8811751-60 ext. 2246, Fax: 880 2 8826050
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2. Academic background:

Degree	University	Field	Year
PhD	Johns Hopkins University USA	International Health	1999
MPH	Johns Hopkins University USA	International Health	1992
MBBS	Rajshahi University Bangladesh	Medicine, Paediatrics	1978

3. Field of speciality: Epidemiology, Infectious diseases, International Health, Paediatrics

4. (a) Research experience: Experienced in the design, implementation, and analysis of data from clinical and community-based epidemiological studies for 24 years

(b) Other experience: Patient care: Clinical care of the patients with diarrhoeal and respiratory diseases

Teaching: Served as a faculty member in different courses on 'Epidemiological methods in Public Health' organized by the ICDDR,B

Teaching Assistant: Department of International Health, Johns Hopkins University, USA

Administration: Overall supervision and management of ICDDR,B Matlab Diarrhea Treatment Centre

5. PUBLICATIONS

1. Zaman K, Sack DA, Chakraborty JC, Yunus M, Baqui AH, Black RE. Children's fluid intake during diarrhea: a comparison of questionnaire responses with data from observations. *Acta Paediatrica* 2002; 91: 376-382.

2. **Zaman K**, Yunus M, Rahman A, Chowdhury HR, Sack DA. Efficacy of a packaged rice ORS among children with cholera and cholera like illness. **Acta Paediatrica** 2001; 90: 505-510.
3. **Zaman K**. Children's fluid intake during diarrhea: a comparison of questionnaire responses with data from observations. Doctor of Philosophy dissertation. **Johns Hopkins University School of Hygiene and Public Health**, Baltimore, Maryland, USA, 1999.
4. **Zaman K**, Baqui AH, Yunus M, Sack RB, Bateman OM, Chowdhury HR, Black RE. Acute respiratory infections in children: a community based longitudinal study in rural Bangladesh. **J Trop Pediatrics** 1997;43:133-137.
5. **Zaman K**, Baqui AH, Yunus M, Sack RB, Chowdhury HR, Black RE. Malnutrition, cell-mediated immune deficiency and acute upper respiratory infections in rural Bangladeshi children. **Acta Paediatrica** 1997; 86: 923-927.
6. **Zaman K**, Zeitlyn S, Chakraborty J, Francisco A de, Yunus M. Acute lower respiratory infections in rural Bangladeshi children: patterns of treatment and identification of barriers. **Southeast Asian J Trop Med Pub Hlth** 1997;28:99-106.
7. **Zaman K**, Baqui AH, Yunus M, Sack RB, Bateman OM, Chowdhury HR, Black RE. Association between nutritional status, cell-mediated immune status and acute lower respiratory infections in Bangladeshi children. **Eur J Clin Nutr** 1996; 50: 309-314.
8. **Zaman K**, Yunus M, Baqui AH, Hossain KMB. Surveillance of Shigellosis in rural Bangladesh : A 10 year review. **J Pak Med Asso** 1991; 41: 75 - 78.
9. **Zaman K**, Yunus M, Hossain KMB. Changing pattern of bio and serotypes of *Vibrio cholerae* 01 in rural Bangladesh. **J Pak Med Asso** 1987; 37: 57.
10. **Zaman K**, Baqui AH, Yunus M. Hypokalaemia and urinary anomalies in children with diarrhoea in rural Bangladesh. **J Pak Med Asso** 1986; 36: 20 - 21.
11. **Zaman K**, Islam MR, Baqui AH, Yunus M. Hypokalaemia in children with diarrhoea in rural Bangladesh. **Indian J Med Res** 1985; 81: 169 - 174.
12. **Zaman K**, Islam MR, Baqui AH, Yunus M. Nutritional status and electrolyte anomalies in children with diarrhoea in rural Bangladesh. **Nutr Rep Int** 1984; 30: 865 - 871.
13. **Zaman K**, Yunus M, Baqui AH. 100 years of cholera. **The Pulse** 1984; 53: 11 - 12.
14. **Zaman K**, Yunus M, Baqui AH, Hossain KMB, Khan MU. Cotrimoxazole resistant *Shigella dysenteriae* type 1 outbreak in a family in rural Bangladesh. **Lancet** 1983; ii: 796 - 797.
15. Henning B, Stewart K, **Zaman K**, Alam AN, Brown KH, Black RE. Lack of therapeutic effect of Vitamin A for non-cholera, watery diarrhoea in Bangladeshi children. **Eur J Clin Nutr** 1992; 46 : 437- 443.
16. The cholera working group, ICDDR,B: Albert MJ, Ansaruzzaman M, Bardhan PK, Faruque ASG, Islam MS, Mahalanabis D, Sack RB, Salam MA, Siddique AK, Yunus M, **Zaman K** (in

- alphabetical order). A large epidemic of cholera like disease in Bangladesh caused by *Vibrio cholerae* non 01. **Lancet** 1993;342:387-390.
17. Baqui Abdullah H, Yunus M, **Zaman K**. Community-operated treatment centres prevented many cholera deaths. **J Diar Dis Res** 1984; 2: 92 - 98.
 18. Faruque ASG, Eusof A, Rahman ASMM, **Zaman K**. Study of makeshift hospital during cholera outbreak. **Bang Med Res Coun Bull** 1984; 10: 45 - 52.
 19. Faruque ASG, Rahman ASMM, **Zaman K**. Young childhood diarrhoea management by mothers and village practitioners in rural Bangladesh. **Trop Geo Med** 1985; 37: 223 - 226.
 20. Faruque ASG, Rahman ASMM, **Zaman K**. Young childhood diarrhoeal morbidity patterns in rural Bangladesh. **Bang Med J** 1985; 14: 66 - 69.
 21. Baqui Abdullah H, **Zaman K**, Yunus M, Mitra AK, Hossain KMB, Banu H. Epidemiological and clinical characteristics of Shigellosis in rural Bangladesh. **J Diar Dis Res** 1988; 6: 21 - 28.
 22. Baqui AH, Yunus M, **Zaman K**, Mitra AK, Hossain KMB. Surveillance of patients attending a rural diarrhoea treatment centre in Bangladesh. **Trop Geo Med** 1991; 43: 17 - 22.
 23. Fauveau V, Yunus M, **Zaman K**, Chakraborty J, Sarder AM. Diarrhoea mortality in rural Bangladeshi children. **J Trop Pediatr** 1991; 37: 31 - 36.
 24. Chowdhury HR, Fauveau V, Yunus M, **Zaman K**, Briend A. Is acute watery diarrhoea an important cause of morbidity and mortality among rural Bangladeshi children. **Trans R Soc Trop Med Hyg** 1991; 85: 128 - 130.
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 26. Chowdhury HR, Yunus M, Khan EH, **Zaman K**, Rahman R. Pivmecillinam resistant Shigella infections in rural Bangladesh. **Trop Doctor** 1995; 25:141-142.
 27. Islam MS, Hasan MK, Miah MA, Yunus M, **Zaman K**, Sack RB, Albert MJ. Isolation of *Vibrio cholerae* 0139 synonym Bengal from the aquatic environment in Bangladesh: Implications for disease transmission. **Appl & Env Microbiol** 1994; 60: 1684-1686.
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 29. Yunus M, Aziz KMA, **Zaman K**. Message for parents: Diarrhoea. **Child Health Dialogue** 4th Quarter, 1996, 5:5.
 30. Chowdhury HR, Yunus M, **Zaman K**, Rahman A, Faruque SM, Lescano AG, Sack RB. The efficacy of bismuth subsalicylate in treatment of acute diarrhoea and the prevention of persistent diarrhoea. **Acta Paediatrica** 2001; 90: 605-610.

31. Longini IM, Yunus M, **Zaman K**, Siddique AK, Sack RB, Nizam A. Epidemic and endemic cholera trends over thirty-three years in Bangladesh. **J Infect Dis** 2002; 186: 246-251.
32. Baqui AH, **Zaman K**, Persson LA, Arifeen SE, Yunus M, Begum N, Black RE. Effect of weekly supplementation with iron and/or zinc or a micronutrient mix on diarrhoea and acute lower respiratory infection-associated morbidity in Bangladeshi infants. **J Nutr** (in press).
33. Albert MJ, Qadri F, Wahed MA, Ahmed T, Rahman ASMH, Ahmed F, Baqui AH, **Zaman K**, Clemens JD, Black RE. Vitamin A and zinc supplementation amplifies vibriocidal antibody response to oral cholera vaccine in children. **J Infect Dis** 2003;187:909-913.
34. Black MM, Baqui AH, **Zaman K**, Persson LA, Arifeen SE, Le K, McNary SW, Begum M, Black RE. Iron and zinc supplementation promote motor development and exploratory behavior among Bangladeshi infants. **Submitted for publication.**
35. Raqib R, Sarkar P, **Zaman K**, Persson LA, Arifeen SE, Yunus M, Anderson J, Black RE, Baqui AH. A randomized controlled trial to assess the effect of weekly supplementation with iron, zinc or both iron and zinc or a micronutrient mix on immune response in Bangladeshi infants. **Submitted for publication.**

Annex VIII**Laboratory Procedure**

Samples	Time period	Methods
	Acute	
Stool	3 aliquots 2 gm each 1 aliquot for culture in ICDDR,B for pathogens such as <i>E coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>V. cholerae</i> . Colonies of Enterotoxigenic <i>E coli</i> should be saved for further evaluation. 1 aliquot for rotavirus EIA. If EIA is positive then perform rotavirus isolation . Rotavirus isolates will be sent to CDC for sequence analysis. 1 aliquot saved for future testing.	To be frozen at -20 C to -70 C
If no stool available	3 Rectal swab should be collected. 1 swab for culture in ICDDR,B for pathogens such as <i>E coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>V. cholerae</i> . Colonies of Enterotoxigenic <i>E coli</i> should be saved for further evaluation. 1 swab for rotavirus EIA. If EIA is positive then perform rotavirus isolation . Rotavirus isolates will be sent to CDC for sequence analysis. 1 swab saved for future testing.	To be frozen at -20 C to -70 C
Blood	3 ml for testing of IgA antibodies against rotavirus at ICDDR,B and adenovirus antibodies at CDC. 3 ml Convalescent (after 3 weeks) for testing of IgA antibodies against rotavirus at ICDDR,B and adenovirus antibodies at CDC.	Stored at -20 C

Samples	Time period	Methods
	Acute	
Throat swab	Tested for presence of adenoviruses at CDC.	To be placed in 2 ml sterile virus transport media. To be frozen at -20 C to -70 C
Surgical reduction	Enlarged mesenteric lymph nodes If bowel or appendix is resected - these samples should be collected If possible, resected tissue be divided into 3 aliquots.	To be processed for routine fixation, for electron microscopy (fixation in 4% paraformaldehyde and 1% glutaraldehyde), and for frozen sectioning for detection of virus antigens by immunofluorescence. Routinely fixed specimens should be examined for histopathologic evidence of acute inflammation and presence of virus inclusions or other diagnostic signs. All these tests will be done in CDC

Defining incidence of intussusception in Bangladesh in preparation for a phase III trial of a new rotavirus vaccine

Abstract summary for ERC

1. This project involves surveillance to define incidence rates for intussusception in Bangladesh. Intussusception (telescoping of the bowel) can result in intestinal obstruction, necrosis (bowel tissue destruction), and death unless special radiologic procedures or surgery are performed. Administration of a licensed rotavirus vaccine (Rotashield—Wyeth Lederle) in the United States resulted in intussusception in approximately one per 15,000 doses, resulting in its removal from the market. New generation rotavirus vaccines which will hopefully be effective and safe—free of intussusception—are in late stage development. The objective of this project is to establish systematic approaches for diagnosis and rapid management of intussusception and to define baseline incidence rates before a new generation rotavirus vaccine is evaluated for clinical efficacy in Bangladesh.

The focus of the study will be children <5 years old with clinical signs and symptoms consistent with intussusception, since this group would be most affected by rotavirus immunization (either directly or indirectly via herd effect).

2. Children who meet the case definition for intussusception (i.e. have clinical signs and symptoms consistent with intussusception) will have stool, acute- and convalescent-phase sera, and a throat swab collected which will be evaluated to identify possible inciting factors for intussusception. The risks associated with collecting these specimens are minimal. If the child requires surgery resulting in resection of bowel tissue or mesenteric lymph nodes, samples of this material will be stored for evaluation of factors associated with intussusception. This involves no additional risk to the patient.

3. Blood will be collected in minimal amounts (no more than 3 mL for acute-phase and for convalescent-phase collections) according to sterile technique to minimize blood loss and risk of infection.

4. Personal identifiers will be kept in a locked cabinet and will be available only to principal investigators and others on the research team who need the information in order to follow-up for convalescent-phase serum collection.

5. Informed consent will be obtained from parents (since the participants will be <5 years of age). No information will be withheld from parents. No study associated procedures are involved that would lead to need for treatment or compensation.

6. Information about the child and the child's illness will take place in the hospital setting while the child is being evaluated for possible intussusception. Interview will last less than 10 minutes.

7. No specific benefits will accrue to the study participants. The benefits to society may be large in that they will allow for thorough evaluation of a vaccine with potential substantial life-saving effect. Risks for participation in this project are minimal.

8. Medical records for children who require transfer to Shishu Hospital in Dhaka will be reviewed. If surgery is required and tissue is resected, a sample of this material will be stored for later histopathological evaluation.