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(FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date 1/3/95

Dr. G. Fuchs, Massee Bateman MD

Principal Investigator

Trainee Investigator (if any)

Application No. 95-013

Supporting Agency (if Non-ICDDR,B)

Title of Study Surveillance of HIV-1 ropositivity in Bangladeshi Children with sistent Diarrhoea and Malnutrition

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 NA
   (b) Procedures to be followed including alternatives used — Yes No NA
   (c) Physical risks — Yes No NA
   (d) Sensitive questions — Yes No NA
   (e) Benefits to be derived — Yes No NA
   (f) Right to refuse to participate or to withdraw from study — Yes No NA
   (g) Confidential handling of data — Yes No NA
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — Yes No NA
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.

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

Principal Investigator

Trainee

15 JUN 1998

1. PROJECT TITLE

Surveillance Of HIV-1 Seropositivity In Bangladesh Children With Persistent Diarrhea And Malnutrition.

2. INSTITUTIONS INVOLVED IN PROJECT

i. International Centre for Diarrhoeal Disease Research, Bangladesh.
Dr. George Fuchs, Massee Bateman, MD

ii. Geographic Medicine, University of Alabama-Birmingham (USA).
Dr. Sten Vermund

3. OBJECTIVES

i. To determine the prevalence of HIV seropositivity in Bangladeshi children with persistent diarrhea and malnutrition.

ii. To initiate a surveillance system of children admitted to the ICDDR,B treatment centre with persistent diarrhea and malnutrition. The information from this surveillance would indicate if, and when, HIV infection in this group of patients might represent a confounding variable in ICDDR,B persistent diarrhea/malnutrition protocols.

4. RATIONALE

i. Children with persistent diarrhea and malnutrition have up to a forty fold increase in prevalence of HIV infection compared to the general population in regions endemic for HIV infection.

ii. The presence of HIV infection in children with persistent diarrhea and malnutrition would affect the results and interpretation of epidemiological and intervention studies of persistent diarrhea and malnutrition at the ICDDR,B.

5. BACKGROUND INFORMATION

The acquired immunodeficiency syndrome (AIDS) has become a global pandemic with more than 400,000 cases officially reported from 162 countries.[1] The WHO estimates that 9 to 11 million people are infected with human immunodeficiency virus (HIV). Of these infected individuals, approximately 3 million are women of reproductive age and 500,000 are infants and children.[2] In the United States, the rate of new AIDS diagnoses is increasing more rapidly among women than among men.[3] As heterosexual transmission of HIV is the primary mode of transmission in adults the number of infected women and consequently their children is increasing. According to World Health Organization (WHO) estimates, by 1991 approximately 180,000 AIDS cases were in children 0-4 years in sub-Saharan

Africa.[4] Worldwide, estimates indicate that 3 million or more women and 2.7 million children will die in the HIV pandemic over the next ten years alone.[2]

Malnutrition is a near-universal component of pediatric AIDS, particularly in the latter stages of illness, and has a major role in the morbidity and mortality of the disease.[5,6] Malnutrition is such an integral feature of AIDS that the causes of debilitation and ultimately death due to opportunistic infections are often difficult to distinguish from those of primary protein energy malnutrition (PEM).[7] In the Central African Republic, Lesbordes et al observed that of 175 children with severe PEM, 12% were HIV antibody positive compared to a background prevalence of 5.6% in the symptom-free adult population.[6] In Burkina Faso, 14% of children less than 48 months of age hospitalized with severe PEM were HIV seropositive compared to an estimated background prevalence among the general adult population of 1%.[5] HIV infection, therefore, is significantly more prevalent in children with severe malnutrition compared to the general population in regions where infection is endemic.

Existing data for the prevalence of HIV seropositivity in children presenting with persistent diarrhea is very limited, and we have been able to identify only a single study from our search of the literature. Twenty three of 59 (39%) Tanzanian children with persistent diarrhea were HIV seropositive, most of whom were also malnourished.[8] This substantially exceeded ($\approx$40 fold increase) the background seropositivity rate of approximately 1% of Dar es Salaam children in this age group.

The combination of PEM and persistent diarrhea in children is a common presenting feature of pediatric HIV infection. More than 75% of children presenting with AIDS to a hospital in Chiang Mai Thailand from 1989 to 1992 had "failure to thrive" and just over half presented with persistent diarrhea (**Table 1**).[9] Only 3 (4%) of the 82 of the children had a normal nutritional status at presentation as measured by the Gomez classification (weight-for-age) (**Table 2**). Two-thirds of all children had Grade II or III malnutrition. Children with vertically acquired HIV infection often manifest with AIDS at an early age, and most will die before age one year (**Table 3**).

It can be concluded that both PEM and persistent diarrhea are associated with HIV infection in children. It is probable that the combination of PEM and persistent diarrhea in young children is more strongly associated with HIV infection than either condition alone, even in countries such as Bangladesh where the background prevalence among the general population might be relatively low. We believe that characterization of the prevalence of HIV seropositivity among this population of Bangladeshi children has implications for many of the research protocols implemented at the ICDDR,B. In particular, the critical relevance of this information to the several current and planned persistent diarrhea protocols is readily apparent. We therefore propose to establish a surveillance system for HIV seropositivity of children admitted to the ICDDR,B treatment centre with persistent diarrhea and malnutrition.

6. METHODS

6.1 Study Design

All children admitted to the treatment centre with a diagnosis of persistent diarrhea and malnutrition will be enrolled into the survey. Based on past history of the centre, we expect approximately 400-500 children will be admitted with this diagnosis. *Testing of children for HIV antibody will be unlinked and anonymous, and will be performed "off-site" at the University of Alabama-Birmingham.*

6.2 Inclusion Criteria

i. Age 2 years or younger.

ii. Diarrhea lasting for 14 or more days within the previous 3 weeks, with average number of stools greater than 3 per day.

iii. Weight-for-height less than 90% (grade I PEM, Waterlow classification).

6.3 HIV Serology

200 μl of serum from each subject will spotted on filter paper in two aliquots. No additional blood will be taken from subjects for this study. Instead, sera remaining after testing for serum electrolytes or other clinical testing that would otherwise be discarded will be used. The initial 100 μl will be placed on filter paper for HIV antibody screening.[10] Specimens will be marked with an age group of each child (0-5.99 mo, 6-11.99 mo, 12-17.99 mo, 18-24 mo), degree of PEM (weight, length), and disease category (presence or absence of pneumonia, thrush, fever, any enteric pathogen identified on stool culture). The second 100 μl serum specimen from each subject will be individually spotted on the same card as the pooled specimen for additional testing only if a pooled specimen tests seropositive.

The filter paper serum specimens will be tested for HIV-1 antibody by enzyme-linked immunosorbent assay (ELISA) at the University of Alabama-Birmingham. Seropositive pooled specimens by ELISA will be confirmed by Western Blot analysis since seropositivity in infants less than 18 months of age might represent transferred maternal antibody rather than infant antibody and infection. In the event of a pooled specimens confirmed positive by Western blot, infection of the infant will be established and HIV typing done on the individual spots by polymerase chain reaction analysis.

TABLE 1

CLINICAL FEATURES AT INITIAL PRESENTATION OF PEDIATRIC AIDS IN NORTHERN THAILAND*

Clinical Finding	Number of children[1]	%
Secondary infection (pneumonia, enteric infection, thrush, etc.)	75 (82)	91
Failure to thrive	62 (82)	76
Chronic diarrhea	42 (82)	51
Chronic fever	36 (81)	44
Lymphadenopathy	43 (81)	53
Lymphoid interstitial pneumonitis (LIP)	18 (82)	22

*Reference #9.

TABLE 2

NUTRITIONAL STATUS AT PRESENTATION OF 82 THAI CHILDREN WITH AIDS*

CRITERIA	%	(N)
Gomez Classification		
Normal (>90%)	4%	(3)
Grade I PEM (75-90%)	30%	(25)
Grade II PEM (60-74%)	48%	(39)
Grade III PEM (<60%)	18%	(15)
Z-score**		
> -2.00	35%	(29)
≤ -2.00	65%	(53)
≤ -3.00	27%	(22)
≤ -4.00	10%	(8)

*Reference #9; **Weight for age.

TABLE 3

CHARACTERISTICS OF CHILDREN WITH VERTICALLY TRANSMITTED HIV INFECTION

Characteristic		Northern Thailand[1] (n=82)	Italy[2] (n=132)	Houston[3] (n=161)
Age at first symptoms	Mean	3 mo	4 mo	
	Range	1-15	1-55	
Age at diagnosis	Mean	6 mo		
	Range	1-26		
Age at death	Mean	7 mo	10 mo	23 mo
	Range	2-26	2-40	4-72

[1]Reference #9.
[2]Reference # .
[3]Reference #3.

References

1. Quinn TC, Ruff A, Halsey N. Pediatric acquired immunodeficiency syndrome: special considerations for developing nations. Pediatr Infect Dis J 11:558-68, 1992.

2. Chin J. Current and future dimensions of the HIV epidemic. Lancet 336:221-4, 1990.

3. Kline MW and Shearer WT. Infect Dis Clin N Am 6:1-17, 1992.

4. Chin J, Sato PA, Mann JM. Projections of HIV infections and AIDS cases to the year 2000. Bull WHO 1990;68:1-11.

5. Prazuck T, Tall F, Nacro B, et al. HIV infection and severe malnutrition: a clinical and epidemiological study in Burkina Faso. AIDS 1993;7:103-8.

6. Lesbordes JL, Chassignol S, Ray E, et al. Malnutrition and HIV infection in children in the Central African Republic. Lancet 1986;2:337-8.

7. Hughes WT, Price RA, Sisko F, Havron WS, Kafatos AG, Schonland M, and Smythe PM. Protein-calorie malnutrition: a host determinant for *Pneumocystis carinii* infection. Am J Dis Child 128:44-52, 1974.

8. Cegielski JP, Msengi AE, Dukes CS, et al. Intestinal parasites and HIV infection in Tanzanian children with chronic diarrhea. AIDS 1993;7:213-21.

9. Virat Sirisanthana, Personal Communication.

10. Nyambi P, Fransen K, De Beenhouwer K, Chomba EN, Temmermen M, Ndinya-achola JO, Piot P, van der Groen G. Detection of human immunodeficiency virus type 1 (HIV-1) in heel prick blood on filter paper from children born to HIV-1 seropositive mothers. J Clin Microbiol 1994;32:2858-60.

Title: Surveillance of HIV-1 Seropositivity in Bangladeshi children with persistent diarrhoea and Malnutrition

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		✓	
Suitability of Methodology	✓		
Feasibility within time period	✓		
~~Appropriateness of budget~~	-	-	-
Potential value of field of knowledge	✓		

CONCLUSIONS

I support the application:

a) without qualification ☑

b) with qualification

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

I do not support the application ☐

Name of Referee: Chris Beyrer Signature: [signature]

Position: Research Associate Date: May 1, 1994

Institution: Johns Hopkins University S. Hygiene + Public Health

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: Surveillance of HIV-1 Seropositivity in Bangladeshi children with pers. Diarrh & Malnutr

PI:

Reviewer: Chris Begg MD MPH.

1) General: Active surveillance for HIV in this population makes sense, and choosing a pediatric clinic population where infected children might attend is sound.

2) Pediatric HIV cases often "lag" adult by several years, so if few cases are found, this does not rule out a problem.

3) 1 yr is short for a surveillance; it may make sense to extend, or do 2-3 times per year.

4) PEM and diarrhea are not truly "risk factors" as much as potential markers in this population. They are associated with HIV in most settings, but the text is somewhat unclear on this point.

over ⇒

5) It might help to know the size of the population (catchment) from which these children will be drawn.

6) This surveillance will hopefully "catch" the infants/children who do worst with PEDS HIV. The reason the Chiang Mai ages of death are so low is that maternal/pediatric screening is not done, so the children who presented in the early epidemic phase were those who progressed first. These are typically children infected in fetal life, not during Labor + delivery or lactation. The method here will bias older children, but this is probably not so much an issue in Bangladesh today.

Title:

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	X		
Adequacy of Project Design		X	
Suitability of Methodology		X	
Feasibility within time period			
Appropriateness of budget	-	-	-
Potential value of field of knowledge	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 [ ]

Name of Referee: D. W. Mulder Signature: .....

Date: 25.4.95

Position: Senior Lecturer

Institution: London School of Hygiene and Tropical Medicine

Project Title
"Surveillance and Prevalence of HIV-1 Seropositivity In Bangladeshi Children with Persistent Diarrhoea and Malnutrition"

Investigators
Dr G Fuchs, Dr M Bateman, Dr S Vermund

General comments
Little is known about the current magnitude of the HIV problem in Bangladesh. Diarrhoea and malnutrition are common manifestations of HIV-associated disease and, as rightly indicated by the investigators, HIV would thus be an important confounder for studies of diarrhoea and malnutrition. From a science perspective the proposed project is, therefore, of considerable interest and importance. Moreover, the project would provide a unique opportunity to monitor the trend in the HIV problem among a segment of the population of Dhaka.

By international (NCHS) standards the majority of Bangladeshi children aged 5 years or less are stunted or underweight. Many children with persistent diarrhoea will, moreover, present with a low weight for height as a result of the diarrhoea. In view of these standard, definition and confounding problems it may be better to initially include in the surveillance system 3 categories of children, namely those with persistent diarrhoea alone, those with malnutrition alone and those with a combination of diarrhoea and malnutrition, rather than the proposed one category diarrhoea and malnutrition. This would allow to define in due course a surveillance definition which is mort appropriate under the working conditions of the Centre.

Tuberculosis is presumably an important course of malnutrition in Bangladeshi children. One could argue that it would be important to rule out tuberculosis among children who satisfy the surveillance definition.

Specific comments
Project title and objective i: the HIV surveillance system will automatically result in prevalence estimates. 'Prevalence' in the title and objective i are superfluous therefore.

objective ii: surveillance systems are by definition longitudinal; the issue of initially using more than one disease category has been discussed above; "if, and when,": perhaps better is to say: "the extent to which".

Rationale i: It is not true that children with persistent diarrhoea have an increase in prevalence of HIV infection, but children with HIV have a risk of developing diarrhoea or malnutrition which is manifold the risk in those HIV-negative. The population attributable risk of HIV for diarrhoea or malnutrition depends on the prevalence of HIV.

Rationale ii: The presence of HIV infection will affect the

results of various studies.

Background information
The figures quoted in the first paragraph are out of date. More than a million AIDS cases had been notified to WHO by the end of 1994. The current estimate of the cumulative number of HIV infections is 18 mln. WHO estimates that by the year 2000 38 mln people will be infected, 15 mln of these in Asia alone.

page 2, paragraph 4: As mentioned above, there are important problems related to the definition of malnutrition: in a Matlab study of children aged 5 years or less showed the following results (NCHS standard):

weight for age	< -2 SD	70%
height for age	< -2 SD	70%
weight for height	< -2 SD	20%

Study design
If the total expected case load of children who satisfy the surveillannce definition is only 400 per year, one would probably wish to continue to monitor all children for at least a number of years.
Do admissions also include 12hr treatment?
Inclusion criteria: see earlier comments

HIV serology
Thhe investigators propose to collect blood using filter paper blots and to use pooled sera for the first HIV screen. The use of blot eluates for HIV serology has been well established and the method has the great advantage that relatively little material is required and that handling of the blots is very convenient. The disadvantage is that little material is available for PCR, and I would recommend that, during the initial period, microtainers be used.

Pooling of sera is recommended when the prevalence of HIV infection is low and large numbers of samples have to be tested. Pooling may result in some loss of sensitivity and in higher error rates. As numbers are small, I would not be in favour of pooling. Microtainers (or blots) can be marked with the age-group and disease-category of the participant, as this is the only information which is required for the analysis, and by doing so anonymity will be guaranteed.

The proposal seems to suggest that by using Western Blot techniques it may be possible to distinguish between maternal antibodies and infection in the child. This is not the case and it would be cheaper to use a second, independent EIA, and western blot only if the two EIA results are discordant or weakly concordant. PCR is then used to confirm infection in children aged 18 months or less.

SURVEILLANCE OF HIV IN CHILDREN WITH PERSISTENT DIARRHEA-RESPONSE TO REVIEWERS

Reviewer #1 (Dr. Beyer)

The first two reviewer comments are agreeing with the merits of the study.

3. We agree with the reviewer that we should plan to continue the surveillance beyond a one year period. The protocol has therefore been revised.

4. The reviewer is correct that PEM and diarrhea are potential markers and are not risk factors for HIV infection. The proposal has been accordingly revised.

5. The reviewer asks that additional information be obtained regarding the population of origin of our surveillance subjects. We therefore plan to obtain this information from the ongoing hospital surveillance study.

6. The reviewer provides some descriptive information about the epidemiology of pediatric HIV infection that does not directly relate to the proposal.

Reviewer #2 (Dr. Mulder)

1. The reviewer suggests that, instead of the single group of children with PEM and persistent diarrhea (PD), three groups of children (PEM alone, PD alone, and PEM + PD) be studies. From review of available information, the combination of PEM + PD is probably more specific for HIV infection than either condition alone, at least in those areas such as Bangladesh where the background prevalence of PEM is so high. We are not opposed to screening the additional children. However, because the prevalence of PEM is so high among the young children admitted to the ICDDR,B Treatment Centre (82% mild to severe PEM by weight-for-height criteria), we would agree with the reviewer's suggestion on the second page of his review that it would be desirable to screen all children ≤ 2 yrs of age admitted to the Treatment Centre so that more definitive information is obtained.

2. While tuberculosis (T.B.) is associated with PEM and is probably an important cause, it is not a *common* cause of PEM in children, i.e. only a small proportion of the children with PEM are found to also have T.B. Current practice in the Treatment Centre is to evaluate all children with PEM for T.B. when clinically indicated.

3. The title of the proposal has been changed as suggested.

4. The phrase in the objectives has been corrected.

5. The relationship of PEM and PD to HIV has been re-stated.

6. Based on the reviewer's suggestion, we will not pool the specimens. We will also plan to mark specimens with age group and disease category information which will not compromise the anonymity of the subjects.

7. The proposal does not suggest or indicate that Western Blot will distinguish between maternal antibody and infection of the child. The reviewer has misread the proposal. The decision to use Western Blot, which is the best method for confirmation, is based on the availability and preference of the collaborating laboratory at University of Alabama-Birmingham. PCR will then be used to confirm infection in the child as well as to serotype the HIV organism.