Attachment 1. 96 Date 17/8/82

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. G.H. Rabbani
Application No. 82-034
Title of Study Nutritional impact of periodic deworming of young children in Bangladesh.

Trainee Investigator (if any) _____
Supporting Agency (if Non-ICDDR,B) _____
Project status:
(X) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects — Yes (No)
   (b) Non-ill subjects — (Yes) No
   (c) Minors or persons under guardianship — (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects — Yes (No)
   (b) Social Risks — Yes (No)
   (c) Psychological risks to subjects — Yes (No)
   (d) Discomfort to subjects — Yes (No)
   (e) Invasion of privacy — Yes (No)
   (f) Disclosure of information damaging to subject or others — Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) — Yes (No)
   (b) Use of fetal tissue or abortus — Yes (No)
   (c) Use of organs or body fluids — Yes (No)
4. Are subjects clearly informed about:
   (a) Nature and purposes of study — (Yes) No
   (b) Procedures to be followed including alternatives used — (Yes) No
   (c) Physical risks — (Yes) No
   (d) Sensitive questions — (Yes) No
   (e) Benefits to be derived — (Yes) No
   (f) Right to refuse to participate or to withdraw from study — (Yes) No
   (g) Confidential handling of data — (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — (Yes) No
5. Will signed consent form be required:
   (a) From subjects — Yes No
   (b) From parent or guardian (if subjects are minors) — (Yes) No
6. Will precautions be taken to protect anonymity of subjects — (Yes) No
7. Check documents being submitted herewith to Committee:
   - NA Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   - X Protocol (Required)
   - X Abstract Summary (Required)
   - X 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)
   - X Informed consent form for subjects
   - X Informed consent form for parent or guardian
   - X Procedure for maintaining confidentiality
   - ___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

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

G. H. Rabbani
Principal Investigator

Trainee

82-034
26/8/82

SECTION I - RESEARCH PROTOCOL

TITLE: NUTRITIONAL IMPACT OF PERIODIC DEWORMING OF YOUNG CHILDRENS IN BANGLADESH.

PRINCIPAL INVESTIGATOR: Dr G H Rabbani

CO-INVESTIGATORS: Dr M M Rahaman, Dr Asma Khanam,
Dr Ralph Muller, Helmithologist (School of Hygiene, University of London).
B. Kirkwood (School of Hygiene, University of London).
Dr A H Baqui, (Matlab)
Mr Emdad (Matlab)

STARTING DATE: June 1982

COMPLETION DATE: July 1983

TOTAL DIRECT COST: US $ 6,822 (Bangladesh Taka 150,084)
ICDDR,B Staff Comitment US $ 4,000.00
Pfizer Res. Grant US $ 1800 (Tk. 40,000.00)

SCIENTIFIC PROGRAM HEAD: This protocol has been approved by the Nutrition Working Group.

SCIENTIFIC PROGRAM HEAD: M H Rahaman

DATE: 16/8/82

ABSTRACT:

A prospective follow-up field study to measure the nutritional impact of periodic deworming of preschool children in rural Bangladesh is planned. In a village (Matlab VTS area) 300 children infected with Ascaris and Hookworm will be periodically and selectively dewormed 6 times a year and a comparable group of 300 children will be followed as controls without deworming. After one year of nutritional follow-up the childrens will be compared in relation to their growth changes. Interrelationship between worm-load and egg excretion will be studied. This study is expected to provide important data to understand the complex host-parasite relationship and would be helpful for developing mass therapy procedure as a national helth programs.

a Research involving human subjects: _____

b Research Review Committee: _____

c BMRC: _____

d Director: _____

e Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION:

A.1. OBJECTIVES:

To assess the nutritional impact of periodic deworming of young children in Bangladesh in relation to Ascaris and Hookworm infection.

A.2. BACKGROUND:

The Problem:

Ascariasis is a world wide problem, more than one quarter of World's Population in the developing areas are infected with one or more species of intestinal parasites, notably Ascaris and Hookworm (WHO, JOICEF 1980). The interaction between the human host and the parasite is a complex one and involves a multiplicity of confounding factors. However, it is generally agreed that massive helminthic infections produce an adverse effects on the status of nutrition. It is however not clear to what extent different grades of infection contribute to malnutrition in the community. Field studies should therefore be carried out to assess the effects of various parasites at varying levels of wormload upon status of nutrition. It is not known whether parasite control by mass treatment improves community nutrition.

The prevalence rate of Ascaris infection varies widely depending upon the socio cultural condition of the population studied and the surrounding environmental condition. In Bangladesh, uncontrolled observations indicate that the prevalence rate of Ascaris infection in hospitalized adult population is about 60% and that for Hookworm 80% (Rabbani and Gilman 1979, CRL Pub.No. 30). Data collected at the Matlab Field Station of ICDDR,B indicate an infection rate for Ascaris of 85%,Hookworm 44% and Trichuris 36% (Hossain et al 1981). It is presumed that with concentration technique the infection rate in children may be much higher. The above report also showed that the prevalence of Ascaris (65%), Hookworm (52%) and Trichuris (36%) was gratest among children 5-14 years age. Prevalence data on helminthic infection in Bangladesh has been given in the following table:

Prevalence of Ascaris and Hookworm infection in Bangladesh:

Source	Area	Hookworm	Ascaris
Kuntz, 1960	Around Dacca City	48%	66%
Begum NN, 1975	N. A.	51%	24%
N. Zaman et al, 1967	Mymensingh	50%	41%
Muazzam et al 1961	Rural Area	57% (all helminths)	
Huq N et al, 1974	Urban Dacca	15%	55%
Mackay et al,	Sylhet Tea State	9%	48%
Aftabuddin, 1973	Mymensingh	32% (combined infection)	
Muttalib, 1975	Dacca University students	7%	39%
Hossain et al, 1981	Matlab Surveillance area, ICDDR,B	44%	85%

Complete reference at the end.

Effects of Ascaris infection on hosts nutrition (clinical studies):

Ascaris infection affects the physiology of the host in several ways, the most important of which is the effects on nutrition. There is abundant clinical evidence to suggest that Ascaris may affect the host's nutrition in the several ways:

a by competing with it for nutrients (Venkatachalam 1953),

b by causing malabsorption of fat and carbohydrate (Tripathy et al, 1971),

c by inhibiting digestive enzymes (Collier 1941, Thompson et al, 1952),

d by inducing negative nitrogen balance (Platt et al, 1965, Jelliffe 1953, Bulatao-Jayme et al, 1966, Tripathy et al, 1971, Venkatachalam et al, 1953, Brown et al, 1980),

e by interfering with vitamin absorption and utilization (Sadun et al, 1950, Rodger et al, 1969, Jelliffe 1968, Singh 1968, Venkatachalam, 1966, Rocival et al, 1978, Sivakumar et al, 1975, Mahalanabis, 1979, Blumenthal et al, 1970),

f by ingesting host's food in the intestine (Woodraf 1967, Li et al),

g by directly damaging intestinal wall (Tripathy, Jelliffe 1953), and

h by Toxic action on the smooth muscle of the intestine (Raba 1967, Guardiaola 1964).

A critical analysis of these studies would clearly indicate that presence of Ascarids in the intestine is most likely to lead to intestinal malabsorption and malnutrition. Indeed a good number of clinical studies have demonstrated this fact and indicated that therapeutic removal of ascarids from previously infected individuals resulted in increased food utilization and subsequent improvement in the status of nutrition. (Brown et al, 1980, Lagmdoye 1972). On the basis of these grounds the treatment of individual patient, particularly those with heavy infection remains naturally justified.

Hookworm infection:

The relationship between the Hookworm infection and iron deficiency anemia is well established. Earlier studies indicated that Hookworm infection could cause mal- absorption (Boycott et al), low vitamin utilization (Foster 1932, 1935) and decrease in nitrogen absroption (Darke et al, 1959). The blood loss produced by the worms was found to range from about 2 ml/day in lightly infested subjects to about 100 ml/ day in subject with heavy infestation. Studies in Japan showed that lower serum iron level and decreased work ability has been associated with Hookworm anemia (Masuya 1980). Similar observation has been reported in sugar cane cutters and lattex trapers in Indonesia. In Bangladesh, where the Hookworm infection is highly endemic and the population in general has low iron reserve, the deletarious effects of the infection can easily be conceived.

Trichuriasis:

Trichuris infection occurs through the fecal contamination of foods. The adult worm resides in the caecum or lower ileum where it attaches itself to the mucosa. In general, trichuriasis has been considered a relatively harmless parasite producing symptoms only when present in large numbers. However, several workers have reported iron deficiency anemia in children with heavy trichuris infection (Jung et al 1951, Larysee et al 1968). This has been attributed to blood loss from the gut, though it is much less compared to Hookworm infection. Larysee et al found that the mean daily fecal blood loss ranged from 0.8 to 8.6 ml in heavily infected children.

Community Studies:

At the community level, studies were undertaken to assess the nutritional impact of mass treatment in several countries, however the results obtained were conflicting. Field studies done so far are only few, some of them failed to show the expected improvement in nutrition after mass chemotherapy.

To our knowledge only few longitudinal studies were conducted in the recent past to examine the relationship between Ascariasis and malnutrition in children. Results of these studies are conflicting and have to be interpretated with great caution.

Gupta et al (1977) studied the effect of periodic deworming on the nutritional status of Indian preschool children in two villages, one of which served as control. The results showed that the nutritional status remained unaltered in the controls but improved strikingly in treated children 8 to 12 months after therapy. These results may be inconclusive because (a) the number of subjects studied is too small (154) to demonstrate the nutritional impact and in addition, (b) food supplementation was given to some of the children by a food aid program (UNICEF) which has directly influenced the outcome on nutrition. Moreover no information was taken on the magnitude of weight changes and intensity of infection which is an important parasite factor on nutrition. No other parameters except weight for age was taken to measure the changes in nutrition.

Willet et al, (1979) studied Tanzanian preschool children who were randomly assigned to a levamisole or placebo treatment which was given at 3 months interval. The authors reported that in children infected with Ascaris, the rate of weight gain was 21% greater in treated than in untreated children. However, the sample size was small and the difference was only marginally significant. They have used levamisole which is a broad spectrum antihelminthic and probably has taken care of many other parasites too.

Freij et al, (1979) studied Ethiopian children with Ascariasis and reported that antihelminthic treatment did not produce any evidence of improved intestinal morphology and absorption of nutritional elements. Therapy had no impact on anthropometric measurements in an additional study group of children. The major difficiency of the study is the smallness of the sample size (only 13 and 84 in two trials). The intensity of infection was very mild which might have influenced the nutritional outcome.

Shah et al, (1975) studied the effect of periodic deworming on the nutritional status of 320 Indian preschool children in a study and control village in Bombay. The authors reported that the impact of periodic deworming on the nutritional status of the children could not be proved significant. This observation is not convincing because the children were followed up only for 3 months, the placebo treatment contained folic acid and iron, wormload was not determined and nutritional status was measured by direct weight changes only.

Stephenson et al, (1980) performed a similar study in 375 Kenyan preschool children and reported that after deworming, previously infected children showed a better weight gain than the controls. Skinfold thickness

also showed significant improvement after treatment. The authors conclude that Ascaris infection adversely affects the nutritional status and therefore periodic deworming is highly recommended. However, the study design was not precise since the authors selected the initially negative children as their own controls and removed those children from the final analysis who later contracted the infection.

Greenberg et at, (1981) treated 185 Bangladeshi Ascaris infected children with a single dose of piperazine and followed them nutritionally for 7 months. No difference was found between the treated and non treated group. A single dose of treatment was given and the cure rate was 31-53%. This indicates partial removal of worms, one would not expect significant improvement in nutrition from this kind of therapy. Children with heavy infection are most likely to benefit from such treatment, however the number of such children were too small in the study.

Results of these studies were summerised in the following table:

Nutritional Impact of Deworming

Authors	Place/Time	Effect on Nutrition	Study design
Gupta et al	India (1977)	+	-
Stephenson et al	Kenya (1980)	+	±
Freij et al	Ethiopia (1979)	-	-
Shah et al	India (1975)	-	-
Willet et al	Tanzania (1979)	+	-
Greenberg et al	Bangladesh (1981)	-	±

COMMENT:

All these studies must be considered inconclusive because they examined very limited population and because most of the experimental design lacked precision.

A comprehensive review of available literature on parasitic infection and malnutrition was done by the recent seminar ''On parasite control in the prevention of malnutrition'', jointly organized by WHO, UNICEF, Japanese organization for International Cooperation in Family Planning (JOICEF) and Japan Association of Parasite Control (JAPC) 1980. After careful review of the current knowledge the committee agreed:

''THAT THE RELATIONSHIP BETWEEN INFECTION BY THE SOIL-TRANSMITTED HELMINTHS AND NUTRITION DEFINITELY EXISTS, BUT THE EXTENT OF ITS CONTRIBUTION TO THE GENERAL PROBLEM OF MALNUTRITION IS NOT WELL UNDERSTOOD. SPECIALLY PRECISE INFORMATION IS LACKING ABOUT THE EFFECT THAT PARASITE CONTROL THROUGH PERIODIC DEWORMING WOULD HAVE ON THE STATE OF NUTRITION''.

'' ... THEREFORE THE ASSEMBLED RECOMMEND THAT A WELL DESIGNED EPIDEMIOLOGICAL STUDY OF THE EFFECT OF PERIODIC DEWORMING ON NUTRITION BE CONDUCTED ... ''.

And this is what has been planned in the present protocol.

A.3. RATIONALE:

Parasitic infestations are thought to be a very common health problem in developing countries. Much has been talked about this problem but little has been done. Still we do not definitely know to what extent each individual helminth can impair growth in a developing child. However many programs have been launched on the assumption that deworming would improve nutrition. At this point it is essential to answer the question that to what extent a parasite control program, through periodic deworming would have on the status of nutrition. This information are crucial for the formulation of a national health policy.

B. SPECIFIC AIMS:

1. The primary aim of this study is to determine if there is any significant improvement in nutrition after repeated deworming of the helminth infected children.

2. However, the data obtained during the course of the study will also be available for answering the following secondary questions.

   (a) determination of prevalence and incidence of ascaris and Hookworm infections in children 2-3 years age.

   (b) correlation of fecal egg excretion with the number of worms expelled and weight of the worms (biomass) and

   (c) identification of species(Ancylostoma and Necator) of Hookworm.

C. METHODS AND PROCEDURES (REVISED):

C.1. Study village: The study will be conducted in the Matlab field surveillance area of ICDDR,B. This field unit has an excellent organizational set up to conduct field surveys, particularly those requiring frequent home visit. Matlab hospital will provide all clinical facilities and will act as a centre for patients referal. The demographic surveillance system at Matlab keeps an updated record of all vital events from which an accurate base line data including the age of the child can be determined. A recent survey indicates that the area has high infection rates of intestinal parasites, 70% of children below 4 years has ascaris, 36% hookworm and 33% trichuris, only 22% were helminth free (Hossain et al 1981).

C.2. Study population and patient selection: In this study a cohort of 600 children, aged 2-3 years will be selected and followed over a period of 12 months. Both male and female child who has infection with either Ascaris alone or with Ascaris and Hookworm will be included. All children will be initially screened by stool examinations to identify the helminth infected children. Written informed consent will be obtained from the legal guardians of the children before inclusion into the study. Children infected with Giardia lamblia or E. histolytica will be excluded. The criteria for selection will include the following:

Selection criteria (600 children)

(a) age between 24-36 months

(b) male or female

(c) either positive for Ascaris only or positive for both Ascaris and Hookworm.

After stool examination 300 children with only ascaris infection and another 300 with ascaris and hookworm infection will be selected. Children with only ascaris will be treated with Piperazine and those with ascaris and hookworm will be given treatment with Pyrantel Palmoate.

After selection, the patient will be assigned into one of the two groups. in the following order:

A. children with ascaris only (n=300) → Piperazine (150), Placebo (150)

B. children with Ascaris and Hookworm (n=300) → Pyrantel (150), Placebo (150)

Light, Moderate, Heavy

Children in each groups will be further subdivided into three subgroups

on the basis of intensity of infection. Intensity of infection will be defined as light, moderate and heavy depending on the number of helminth eggs present per gram of feces.

This type of the study design outlined above will allow to examine the specific impact on the host due to ascaris alone and also in combination with hookworm. The use of placebo treatment will assure optimum patients compliance since every child included into the study will get treatment. The cases and control children will occur in the same village. This will tend to distribute the impact of intercurrent variables equally on all subjects and thereby minimize bias.

C.3. Followup procedures:

C.3.1. Preparatory phase: collection of base line data: At the begining of the study, initial three months period will be required for:

a background preparation,

b collection of base line data,

c training of staffs for stool microscopy,

d nutritional anthropometry

e general socio-economic data, and

f randomization of children into groups.

C.3.2. Treatment procedures: After the completion of preparatory phase administration of deworming drugs and placebo will take place at 2 monthly intervals. On the first week of the month, 600 children will be treated, during the second week stool will be re-examined and over the third and fourth week anthropometric measurements will be taken.

Preparatory phase	1st visit (0 month)	2nd visit (2 month)
(3 months) - base line data - anthrop. - stool screening - staff training	Rx 1 - stool exam. - worm counting	Rx 2 stool exam. - anthrop.

3rd visit (4 month)	4th visit (6 month)	5th visit (8 month)
Rx 3 - stool exam. - anthrop.	Rx 4 - stool exam. - anthrop.	Rx 5 - stool exam. - anthrop.

6th visit (10 month)	7th visit (12 month)
Rx 6 - stool exam. - anthrop.	No Rx - stool exam. - anthrop.

C.3.3. Mass therapy: After the initial deworming subsequent treatments will cover study children (300) irrespective of their infection status. This design will allow optimal situation for a mass therapy program to be evaluated. However, since all children will have their stool examined at each time, some idea about the reinfection rate can be obtained (ref. discussion with V. Reddy, June 1982).

C.4. Administration of drugs in the field:

Selective chemotherapy will be given for ascaris and hookworm infections using piperazine and pyrantel preparation respectively (these drugs are described later). The field workers will carry these drugs during their home visit and the children will be directly supervised by the field workers at the time of administration. Drugs or placebo will not be left to the mothers for subsequent administration. All drugs and placebo will be prescribed in the form of flavoured liquid preparation to be given by mouth. Pyrantel will be administered in a single dose while piperazine will be given for 2 consecutive days. Administration of the drugs to 600 children will be completed within one week's time and will be repeated in the corresponding week at each 2 months intervals (Appendix IV).

C.4.1. Piperazine for Ascaris infection: Piperazine will be used for selective deworming of ascaris infection. Piperazine preparation are particularly effective against ascaris lumbricoides infection, cure rate reaches almost 100% against this cosmopolitan nematode (Goodman et al 1975). It is not effective against hookworm infection. Official preparation such as piperazine citrate, USP or Piperazine phosphate, N.F. will be used in this study. It should be noted that citrate or phosphate radicals do not make any difference in their antihelmintic activity. There is no need of cathertics and no prior fasting is necessary. The dose recommended is 75 mg/kg for children given orally for 2 consecutive days in liquid form. Piperazine will selectively remove the Ascaris worms, this is expected to demonstrate specific impact due to individual parasite. The drug is well tolerated and has infrequent side effects such as dizziness or CNS symptoms. Liquid placebo formulation will be prepared with identical physical characteristics, but without piperazine.

C.4.2. Pyrantel Palmoate for Hookworm, Ascaris and Trichuris infection: The emergence in the last few years of safe, effective broad spectrum antihelmathic has revolutionised the treatment of intestinal nematode. Of these agents pyrantel palmoate has been widely accepted as the first drug of choice for the treatment of Ascaris and Hookworm infection in which it has 76% - 98% cure rate. (Current Therapy 1980, p 402, Current Med Diag and Treat 1981, p 878). Pyrantel has the advantage of single dose treatment given orally at a dose of 10 mg/kg body weight (maximum 1.0 gm) and has infrequent side effects of nausea, headache, vomiting, dizziness and occassional diarrhoea (Med letter 1974). Alternative drugs are Mebendazole which is an effective broad spectrum antihelminthic but the treatment needs multiple dosage for several days, this may be difficult for a mass therapy procedures. Pyrantel palmoate will be administered as a liquid

preparation in a single dose. Placebo preparation will have indistinguishable physical characteristics as the pyrantel preparation but will not contain the active ingradient.

C.5. Control of confounding variables:

C.5.1. External factors: During the course of the study certain external factors may affect some of the children of treatment and control groups and this may possibly influence their nutrition. These factors include intercurrent infections such as pneumonia, diarrhoea, meningitis, measles etc. Clinical history of these illness will be recorded for each children in a prescribed form (appendix II) by the field workers during their fortnightly visit to each family. During the analysis of the records, attempts will be made to examine their impacts on nutrition.

C.5.2. Socio economic factors: Socio economic condition of the family may also affect the nutrition of the children. General socio-economic data will be collected and compared during analysis (see appendix VIII).

C.5.3. Dietary history (Appendix III): Dietary history will be obtained from the family during the home visit by the field staffs. Information about diet will be obtained from the responsible members of the family by 12 hours recall method.

C.5.4. Blinding design of the study: The study will be made single blind, the placebo code will be known only to the principal investigator. Neither the patient nor the field staffs will have the knowledge of the coded placebo. Most of the data will be recorded by the field staffs, employed as salaried personnels, they are most likely to represent a team of non-interested persons so far as the objectives of the study are concerned. Since anthropometric measurements and stool examination are all objective data, there is little scope for subjective bias.

C.6. Treatment and benefit of the subject:

Childrens who are heavily infected and having symptomatic disease such as vomiting of worms or intestinal obstruction due to the presence of Ascarids will be given appropriate form of therapy. If required hospitalized care will be provided. In addition, general health care facilities will be provided to the members of the family or the study children free of cost. All control children will be dewormed at the end of the study.

C.7. Assessment of nutritional status:

Anthropometric measurements will be taken from all children in order to assess and classify the status of nutrition at the begining of the study. These measurements will include: age, height, weight, mid-arm circumference

cranial circumference and triceps skinfold thickness. Measurements will be repeated at 2 months interval for a period of 12 months and recording will be made at the field by trained field staffs. Several nutrition surveys have already been completed in Matlab, reliable methods and equipments are now available at the Matlab centre (see Appendix I).

C.8. Method of stool examination:

KATO thick smear technique: (WHO 67, KATO 68): For egg excretion studies, Kato thick smear technique will be used to count number of eggs present per gram of stool. Kato technique is a very simple but efficient method for ova counting and had been extensively used for schistosomiasis surveys in Japan and African countries. In this technique, an estimated amount of faeces (50-70 mg) is placed on a glass slide and covered with a glycerin soaked cellophane paper cut into the size of a cover slip and examined under the low power microscope. The count in the whole field can be expressed as number of eggs per gram of faeces (Appendix V,VI).

At the ICDDR,B pathology laboratory, I have standardised this technique using commercially available test kits OVO-FEC (Bohringer Lab, Riode Janeiro). The method gave satisfactory and reproducible results with Hookworm, Ascaris and Trichuris ova. In the fields stool will be collected in pre-marked containers and examined the same day.

C.9. Egg excretion, worm-load studies:

The quantitative relationship between the egg excretion and worm-load will be determined by estimating the number of eggs excreted per gm. of faeces and counting the number of Ascaris worms expelled after treatment. The weight of expelled worms will also be taken to determine the biomass of the worms. This part of the study will be done in a sub sample of 50 children with varying degrees of infection. These children will be admitted in the Matlab treatment centre and will be treated for worms. The worms expelled will be collected into a bucket and seived for counting and weighing. Children will be released from the hospital after 2 days.

This part of the study will be directly supervised by the principal investigator.

C.10. Determination of Hookworm species:

Two species of hookworm are generally prevalent in most tropical countries. These are Ancylostoma duodenale and Necater Americana. Data on the relative prevalence of these two species are not available from Bangladesh. Identification of hookworm species is important because ancylostoma species suck more blood from the hosts' intestine due to its mode of

attachment than the Necator species.The dose of the anthelmintics also depend to some extent on the type of the species being treated. The species are differentiated on the basis of morphological structure of the buccal apparatus of the adult worms.

In this study, hookworms expelled from the children after deworming will be collected and preserved in formalin for subsequent species identification. This work will be done in collaboration with Dr Ralph Muller of commonwealth Institute of Parasitology in London.

C.11. Data Analysis:

Data will be recorded on prescribed forms and analysis will be carried out using IBM system 34 computer at the ICDDR,B computer centre. Data will be analysed according to the following format:

(a) Comparison of nutrition parameters such as height/age, weight/age and weight/height will be made between the control and treatment groups by applying appropriate statistical tests outlined in the following section. Secondly nutritional indicators such as arm circumference, cranial circumference and skin fold thickness will also be compared (appendix VII).

(b) Comparability of the treatment and control group will be examined by simple frequency distribution of intensity of infection, socio economic variables, dietary habits and other confounding factors.

(c) Correlation and regression analysis of data on egg excretion, worm-load and worm-mass.

(d) Determination of point prevalence and incidence rate of ascaris and hookworm infection in 2-3 years old children.

(e) Distribution of ancylostoma and necater species of Hookworm in this population.

C.12. Steps of Analysis:

For all ages and sexes combined:

C.12.1. General comparison: Perform a general comparison of nutritional indicators in case and control groups. Apply chi-square test to see if the comparison reveals any difference (Table 1).

C.12.2. Comparison of anthropometry: Perform a comparison of the prevalence of malnutrition in case and control groups at different rounds of anthropometry. Apply at each round the chi-square test to detect the statistical significance of the difference if any. Apply also a suitable statistical procedure to see if the intervention reduces progressively the prevalence of malnutrition in the study group (Table 2-3).

D. Significance:

(See Rationale).

E. Facilities required:

Office space	: Present office space will be used.
Laboratory space	: Existing laboratory space will be utilized.
Hospital source	: Matlab Hospital will be used.
Animal resources	: None.
Logistic support	: Data processing at the ICDDR,B Computer centre will be done.
Major equipment	: None.
Others	: None.
Transport	: Transport will be needed to move between the field and the Laboratory.

F. Collaborating Arrangement: None.

ABSTRACT Summary

Field studies to determine the nutritional effect of deworming of preschool children in rural Bangladesh

1. This study will be conducted in 600 children aged 2-3 years in the Matlab field area. 300 children in the village will be periodically treated with pyrantel palmonate and Piperazine 6 times a year while the other 300 will serve as control. Age, height, weight and other anthropometric measurements will be taken and followed up for 12 months period. Stool will be examined for Hookworm and Ascaris ova 6 times a year. In 50 selected children worms will be counted after expulsion in the faeces. Ascaris and /or hookworm infected children will be the subjects of this study.

2. Children will be treated with pyrantel palmoate or Piperazine which are safe drugs and has little undersirable side effects. The study involves no risk as to the psychological, social, legal or other aspects of the subject. The fundamental procedure is to collect stool samples and give treatment for the parasites.

3. Ascaris and hookworm infected children under the study surveillance will be closely supervised by the field workers. Medical attention will be provided if there is any need.

4. Data collected will be computerized and confidentiality will be maintained. All data will be abreaviated and will be published without reference to the subjects name and identity.

5. Informed written consent will be obtained from the parents/legal guardian the children at the time of admitting into the study.

6. No personal interview except relevant history of illness will be taken.

7. The direct benefit to the subject will be the cost free treatment of Hookworm and Ascaris infection. The long term social benefit may be formulation and implementation of national parasite control program in the country.

8. No retrospective hospital records will be used. No biological specimens except stool will be taken from the subjects.

SECTION - III

BUDGET

PERSONNEL SERVICES:

Personnel services	Position	% effort	Annual salary (Taka)	Project requirement (Taka)
Dr. G. H. Rabbani	Principal Investigator	20%	6,700.00	14,000.00
Dr. M. M. Rahaman	Co-Investigator	-	-	-
Dr. M. U. Khan	Co-Investigator	-	-	-
Dr. Asma Khanan	Co-Investigator	5%	-	4,000.00
Mr. M. K. Chowdhury	Statistician	5%	-	4,000.00
Field supervisor (Matlab)		20%	-	10,000.00
Dr. R. Muller (Helminthologist, London)			No cost involved	
Dr. B. Kirkwood (Statistitian, London)			No cost involved	
			Sub Total:	Tk. 32,000.00 ($ 1454.00) (@ $ = Tk. 22.00)

Field staffs:

Microscopist (one)	Tk. 1000.00/month	Tk. 18000.00
Field worker (one male)	Tk. 750.00/month	Tk. 13500.00
Field worker (one female)	Tk. 750.00/month	Tk. 13500.00
Field Asstt. (one)	Tk. 750.00/month	Tk. 13500.00
Boatman (one)	Tk. 500.00/month	Tk. 9000.00
	Sub Total:	Tk. 67,500.00 (US $ = 3068)

SUPPLIES:

Microscope (one)	Supplied by Pfizer
Microscope slides (1000 pc)	Tk. 1000.00
Laboratory Reagents/Supplies	Tk. 2000.00
Pyrantel palmoate (1200 Doses)	Provided by Pfizer
Country boat for Matlab	Tk. 5000.00
Plastic stool cups (2000 pcs, reusable)	Tk. 2000.00
Printing and publication	Tk. 2000.00
Weighting Balance/Measuring Board (Existing) Skinfold calipers	Tk. 3000.00

Sub Total: Tk. 2000.00 (US $ 1000.00)

EQUIPMENTS: None

PATIENT HOSPITALIZATION:

50 pts X 2 day X Tk. 160 = Tk. 16000.00 (US $ 800.00)

OUTPATIENT CARE: None

TRANSPORT: None

TRAVEL AND TRANSPORTATION OF PERSONS: Country boat will be used for for field visits in Matlab.

TRANSPORTATION OF THINGS: None

IMPORT: None

RENT, COMMUNICATION & UTILITIES: None

PRINTING AND REPRODUCTION: Tk. 2000.00 (US $ 100.00)

CONTRACTUAL SERVICES:

Computer time = $ 400.00

D. BUDGET SUMMARY

Category:	US $
1. Personnel services	4,522.00
2. Supplies	1,000.00
3. Equipments	Nil
4. Patients Hospitalization	800.00
5. Out patient care	Nil
6. Transport	Nil
7. Travel of persons	Nil
8. Transport of Things	Nil
9. Rent/Communication	Nil
10. Printing/Reproduction	100.00
11. Contractual services	400.00

Grand Total: $ 6,822.00

(Staff comitment $ 4,522.00 + Operational cost $ 2300.0

(Pfizer grant US $ 1,800.00)

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Appendix - I

Deworming study - Anthropometric Determinations

VTS _____ Name _____ Date of birth _____

Routine - Anthropometrics

Month														
Day of Month														
Weight (kg)														
Length (cm)														
Arm circumference (cm)														
Skinfold thickness (mm) 1														
2														
3														
mean														
Anthropometrist														

Appendix - II

Deworming study

Name: _____ Age: _____ Sex: _____ Case No. _____

Complaint Date	Date	Date	Date	Date	Date
Diarrhoea					
Loose					
Liquid					
Watery					
Blood					
Mucus					
Vomiting					
Dehydration					
Fever					
Temp.					
Nasal disch.					
Cough					
Skin rash					
Ear pus					
Anorexia					
Measles					

Treatment: Physician /___/ Quack /___/ Homopath /___/

CRL Hospital /___/ Others /___/

Deworming drugs from other sources: _____

Appendix - III

DIETARY HOSTORY

Name: _____ Age: _____ Sex: _____ Case No. _____

Drug code: _____ Date of visit: _____ Location: _____

No.s of meals cooked per day: _____ Breast milk: _____

Snacks consumed per day: _____

	Food item		Estimated amount
1. Breakfast:	Rice (panta)	/___/	_____
	Bread	/___/	_____
	Muri	/___/	_____
	Chira	/___/	_____
	Milk	/___/	_____
	Banana	/___/	_____
	Curry	/___/	_____
	Egg	/___/	_____
2. Lunch:	Rice	/___/	_____
	Veg. curry	/___/	_____
	Bread	/___/	_____
	Dal	/___/	_____
	Fish	/___/	_____
	Meat	/___/	_____
	Gur	/___/	_____
	Other specify		_____
3. Supper:	Rice	/___/	_____
	Veg. curry	/___/	_____
	Bread	/___/	_____
	Dal	/___/	_____
	Fish	/___/	_____
	Meat	/___/	_____
	Milk	/___/	_____
	Others (specify)		_____

Appendix - IV

TIME SCHEDULE FOR FIELD WORKERS

(No.s Field staffs = 3, Supervisor = 1)

1st week of the month: (Drug administration):

One worker will treat 33 children in one day

3 workers will treat 100 children/day

3 workers will treat 600 children in 6 days.

2nd week of the month: (Stool examination):

One microscopist will examine 50 stools/day
(one Kato test takes 6-10 min)

For 300 stool specimens (treated case only) = 6 days.

3rd week of the month: (anthropometry):

3 workers will cover 50 (approx) children per day

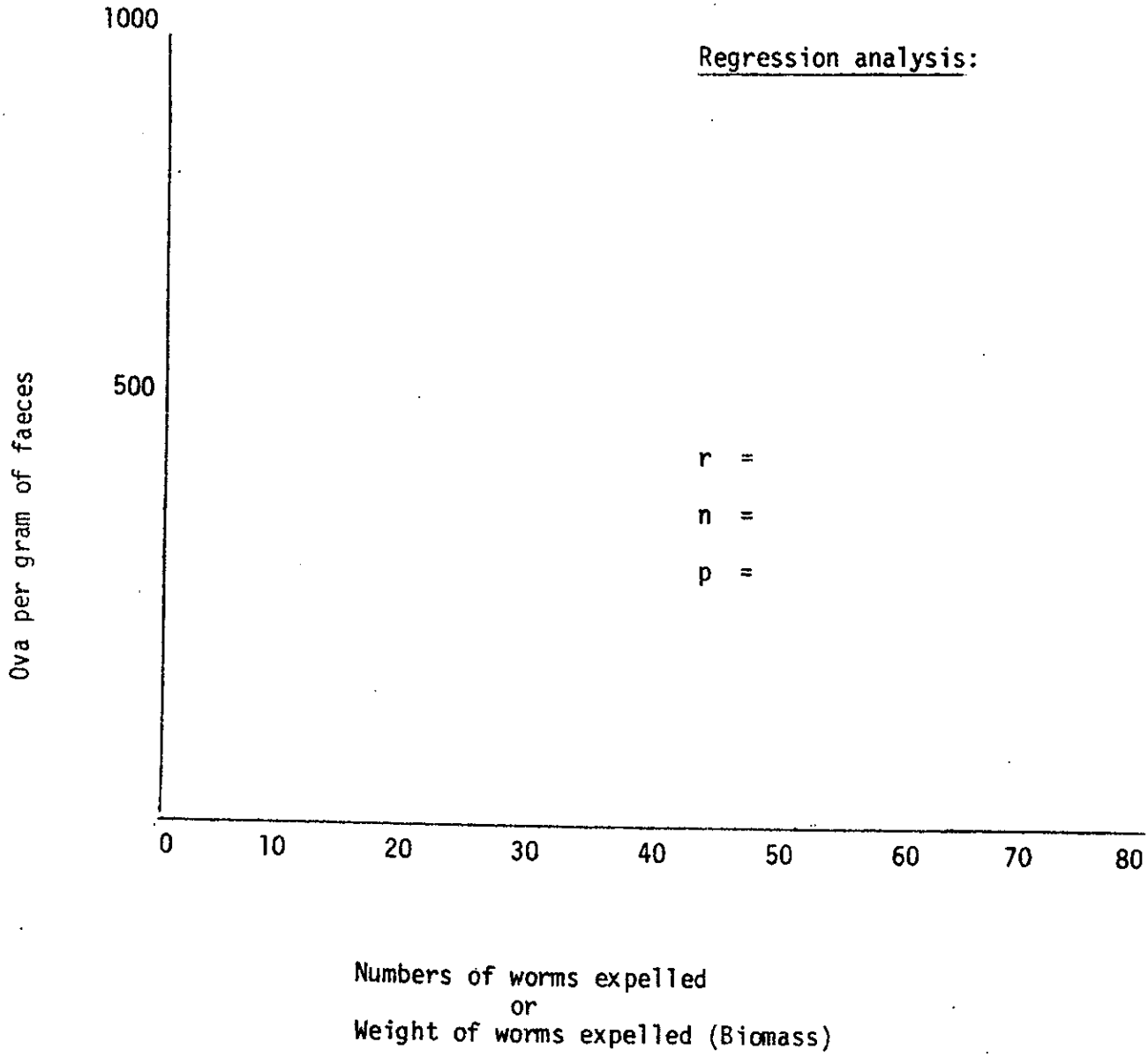
600 children will be covered = 12 days.

4th week of the month:

During the 4th week and in between they will record the clinical data by home visit. The work of the Field staff will be checked by the supervisor twice weekly.

Appendix - V

Figure: Relationship of ova count to number of worms expelled after therapy



Appendix - VI

Stool examination for parasites, visits 1-5

Parasites	Visit 1 control treated	Visit 2 control treated	Visit 3 control treated	Visit 4 control treated	Visit 5 control treated
Ascaris ova					
Light					
Moderate					
Heavy					
Hookworm ova					
Light					
Moderate					
Heavy					
Trichuris:					

Appendix - VII

Anthropometric measurement
(Study and control sample)

Parameter	Group (n)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
			Mean ± SD			
Weight (kg)	Control					
	Study					
Wt/Age (%)	Control					
	Study					
Height (cm)						
Ht/Age (%)						
Arm circumf (cm)						
Arm cirf/Age (%)						
Skin fold (mm)						
Skin fold/Age (%)						

Appendix - VIII

Deworming study

Socio-econonic data

Name: _____ Age: _____ Sex: _____ Case No.: _____

Tot. Nos. of individuals in the family: _____

Level of education: Father /___/ Illiterate /___/ Prim. school /___/

Mother /___/ Illiterate /___/ Primary school /___/

Monthly income of Head of Family: _____

Occupation: Farmer /___/
Labour /___/
Business /___/
Others /___/

Defecation Habits: Open field /___/
Privy /___/
Bush /___/

Water source:
Tube well /___/
Pond /___/
Well /___/
River /___/

Type of Housing: _____

Table - 1

DISTRIBUTION OF NUTRITIONAL INDICATORS BY WORM LOAD FOR CASE-CONTROL GROUPS

Worm load		wt/age				ht/age				wt/ht			
		-2 SD[a]	-2 SD -1 SD	-1 SD Median	X^2 (P)	- 2 SD	-2 SD -1 SD	- 1 SD Median	X^2 (P)	-2SD	-2 SD -1SD	-1SD Median	X^2 (P)
Severe	Case												
	Control												
Moderate	Case												
	Control												
Low	Case												
	Control												
Total	Case												
	Control												

a Classes refer to NCHS Standard.

Table - 2

PREVALENCE OF MALNUTRITION IN CASE AND CONTROL GROUPS AT DIFFERENT ROUNDS

Nutritional indicator	Round	Proportion* Malnourished		X^2	P	Trend Co-efficient (t, P value)
		Case	Contr.			
Wt./age	1					
	2					
	3					
	4					
Ht./age	1					
	2					
	3					
	4					
Wt./age	1					
	2					
	3					
	4					

* Malnutrition is defined as the proportion of children in the population falling below the median - 2 SD by comparison with the reference population.

Table - 3

CENTILE DISTRIBUTION OF NUTRITION INDICATORS

Worm load		wt/age										ht/age										wt/age									
		10	20	30	40	50	60	70	80	90	+	10	20	30	40	50	60	70	80	90	+	10	20	30	40	50	60	70	80	90	+
Severe	Case																														
	Contr.																														
Moderate	Case																														
	Contr.																														
Mild	Case																														
	Contr.																														

+ Upper bound of centile class.

Deworming study (Matlab)

Consent Form

I understand that International Centre for Diarrhoeal Disease Research, Bangladesh is carrying out a community research to determine the nutritional effect of periodic treatment of Ascaris and Hookworm infection of children. I also understand that my child has been found infected with intestinal worms (ascaris and/or hookworm) and may be included into the study if I wish. The child will have his/her height, weight, and body measurements taken at regular intervals of 2 months for one year. Stool samples will be collected and examined for intestinal owrms 6 times a year. The child will unpredictably receive treatment with one of the following drugs. Piperazine (2 doses), or Pyrantel (1 dose). The child may also get treatment with identical preperation as the drugs, but without the active ingradients (Placebo), this will not cure the worms. Each child will be treated for worms 6 times a year at 2 months intervals. All worms, however will be effectively treated using drug afterwards. At the end of the study all infected children will be dewormed. Expelled worms will be collected. Treatment of diarrhoeal illness and general medical care will be provided free of cost to the study subjects.

I also understand that I always preserve the right to have my child join in the study or withdraw from the study at any time.

I agree that my child be included into the study.

Signature of Investigator:

Signature/Left Thumb impression of patient's Guardian

Date:

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র
মহাখালী, ঢাকা।

(দৈহিক পুষ্টির উপর কৃমি চিকিৎসার প্রভাব)

সম্মতি পত্র

আমি অবগত হইয়াছি যে আমার সন্তানের (ছেলে বা মেয়ে) পেট কৃমি (কিড়ে) দ্বারা আক্রান্ত হইয়াছে (নম্বা অথবা বক্রু কৃমি)। এই গবেষণা প্রকল্পে অংশ গ্রহণ করিলে আমার সন্তানের পায়খানা পরীক্ষা করা হইবে। এবং প্রয়োজন মোতাবেক বৎসরে ছয় বার কৃমি নিষ্কাশনের ঔষধ দেওয়া হইবে। যদি আমার সন্তান কনট্রোল গ্রুপে পড়ে তবে তাহাকে বৎসরে ছয় বার এমন ধরণের ঔষধ দেয়া হইবে, কৃমির উপর যাহার কোন ক্রিয়া নাই (PLACEBO)। তবে বছরের শেষে সকলকেই ঔষধের দ্বারা ক্রিয়মুক্ত করা হইবে। এক বৎসর পর গবেষণা শেষ হইলে সকলকেই ঔষধের দ্বারা কৃমিমুক্ত করা হইবে। সন্তানের দৈহিক উচ্চতা, ওজন ও শরীরের বিভিন্ন অংশের পরিমাপ বৎসরে ছয় বার লওয়া হইবে। সন্তানের অন্য কোন প্রকার অসুস্থতা দেখা দিলে তাহারও বিনা খরচে চিকিৎসাদি করা হইবে। আপনার সন্তানের গবেষণায় অংশগ্রহণ করা বা না করা সম্পূর্ণ আপনার ইচ্ছার উপর নির্ভর করে।

ইচ্ছা করলে যে কোন সময় গবেষণা থেকে আপনার সন্তানকে প্রত্যাহার করে নিতে পারেন।

আমার সন্তানকে এই গবেষণায় অংশগ্রহণ করার জন্য আমি স্বেচ্ছায় ও সুস্থভাবে মত দিলাম।

সন্তানের নাম----------

পিতার নাম/স্বাক্ষর----------

তারিখ----------

গবেষকের স্বাক্ষর

London School of Hygiene and Tropical Medicine

Keppel Street (Gower Street) London WC1E 7HT

Telephone 01-636 8636
Telegrams Hygower London WC1

Department of Medical Statistics and Epidemiology

W. Brass MA
Professor of Medical Demography
and Departmental Head
M. J. R. Healy MA
Professor of Medical Statistics
G. A. Rose DM FRCP FFCM [redacted]
Professor of Epidemiology

Dr G H Rabbani
ICDDR B
GPO Box 128
Dacca 2
Bangladesh

21 July 1982

Dear Rabbani

Thank you for your letter. I would be pleased to collaborate on the antisecretory drug trial and look forward to seeing the results. I agree that, as the volume of data is small, it may not be necessary to computerise them. It will depend on just how much analysis is needed and how many variables you are investigating.

I have now read your deworming study protocol and I have several comments/queries.

1. The study will demonstrate whether deworming children every 3 months for one year has a beneficial effect on their nutritional status during that year. Are you planning further follow-up visits to assess whether there is any long term benefit? Also further studies will be needed to determine the optimum interval between dewormings and the age-groups to be included in a control programme.

2. I am not entirely clear about the study design and in particular the allocation to the 3 treatment groups (pages 10,11). Is the criterion for entry, infection with ascaris (with/without hookworm or trichuris) with random allocation to one of the 3 treatment groups. Alternatively, is the criterion, infection with ascaris and/or hookworm and/or trichuris with random allocation (i) to piperazine or placebo for children with only ascaris and (ii) to pyrantel or placebo for children with hookworm and/or trichuris. But what about children with mixed infections of ascaris with hookworm/trichuris - are these allocated to any of the 3 groups or only to pyrantel or placebo?

3. Pyrantel is described on page 18 and will be administered as a liquid preparation. No description is given of piperazine and the placebo - will these also be liquid preparations?

4. It is not clear whether at visits 2-5 only positive children are treated (see page 11) or whether all children are treated (see page 18). The former would allow some assessment of reinfection rates over different periods.

5. Children aged 2-3 years do not have the highest rate of growth velocity (page 9). It was considered better to concentrate initially on demonstrating the effect in a narrow age-group and to expand to other ages later.

6. It is easier to take socioeconomic variables into account during the analysis rather than to try and match them at the start of the study (page 13). Random allocation to the treatment groups should avoid any bias.

7. I would like to check that families found to have a progressive improvement or deterioration in their daily food ration will be studied for the entire year and only excluded from the analysis (page 14).

8. How is intensity of infection as distinct from number of eggs and number of worms defined (page 16)?

9. I would recommend that to minimise error for the Kato examinations the actual number of eggs counted is recorded and that the multiplication to convert these to eggs per gram is carried out during the analysis.

10. The analysis in Table 1 is perfectly valid but it would be more sensitive to compare mean wt/age, ht/age and wt/ht between the three treatment groups.

11. The trend test proposed in Table 2 and page 20 is not valid since the proportions in each round are not independent as they are based on the same children. The analysis should take this into account and link the results from each child. The examination of improvement during intervention should be based on a comparison of the number of children improved in each group.

12. Are you sure that the sample size of 178 recommended by WHO is for the whole study and not for the number of children in each group?

I look forward to receiving your reply. Also can you please give me some details on dates for the fieldwork and when the data are expected for analysis.

Very best wishes

Yours sincerely

Betty

BETTY KIRKWOOD
Tropical Epidemiology Unit

WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

Téléphone Central/Exchange: 91 21 11
Direct: 91 34 98

In reply please refer to :
Prière de rappeler la référence: (PDP) N4/445/7

Dr G. H. Rabbani
International Centre for Diarrhoeal
Disease Research (ICDDR,B)
GPO Box 128
Dacca - 2
Bangladesh

28 July 1982

Dear Dr Rabbani,

Thank you for sending me the protocol of your studies on "Nutritional Impact of Periodic Deworming of Preschool Children in Bangladesh". My comments are as follows:

(1) The title: "deworming" is not a precise term (e.g. the group treated with piperazine will be only Ascaris and Enterobius free).

(2) The number of children examined seems to be too small; in the optimal case you will have only 33 children in each specific group (light, moderate or heavy infection, each divided into three placebo, piperazine or pyrantel groups).

(3) The aims of the studies as described on page 8 may not be fully realized: you are going to examine the nutritional status only in children aged two and three years - not in the community as a whole; the reinfection rate may be difficult to evaluate if the children are treated every three months; the correlation of the number of eggs excreted and the number of worms present could not be calculated without additional stool examinations after each therapeutic intervention as the number of worms present may not be the same as the number of worms expelled. You may add to the aims of the studies "to determine both the prevalence and the intensity of intestinal parasitic infections" ....

(4) A faecal examination one week after treatment is missing from the procedure, and this is essential for evaluation of the efficacy of treatment.

.../2.

(5) It would be better to have two month rather than three-month intervals between each treatment, otherwise you may have a number of infections with pre-adult Ascaris which are difficult to identify by microscopical stool examination but which may influence the nutritional status.

(6) The differentiation between Necator and Ancylostoma is not mentioned but it is essential for proper evaluation of the results; the effect of each species on the host nutrition differs quantitatively.

(7) A single inspection of the stool after treament, as described, may not identify all the Ascaris worms expelled (some may be evacuated later), and it may be too primitive a technique to detect all the hookworms evacuated (for this purpose repeated simple sedimentation of several stool evacuations is needed).

(8) If 70 mg samples of faecal material are used, the number of eggs per gram is expressed only in the multiplication of 15 (one egg found in a 70 mg sample is about 15 eggs per gram, two eggs are 30 etc.); therefore the categories 1 to 100, 101 to 1000 in appendix III are not precise. "Below 100" would mean between 15 e.p.g. (1x15) and 90 e.p.g. (6x15), 105 e.p.g. (7x15) to 990 (66x15) but not 101-1000 etc. I would suggest you record the absolute number of eggs per gram and formulate the categories (light, moderate and heavy) later on. An Ascaris infection of less that 2000 e.p.g. is usually a light one. According to Croll et al. (1982), in Iran, each Ascaris female produces 2000 eggs per gram of faecal material if the worm burden is over 10, and up to 8000 e.p.g. when the burden is below 4. The same comment is true for hookworms.

Please do not hesitate to contact me if you have any questions or problems in relation to your studies on the effect of intestinal parasitic infections on nutrition.

Yours sincerely,

Dr Z. S. Pawlowski
Medical Officer
Parasitic Diseases Programme