

7/6/90
20/6/90

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. M.S. Akbar

Trainee Investigator (if any) _____

Application No. 90-011

Supporting Agency (if Non-ICDDR,B) _____

Title of Study The prevalence of Hepatitis B in Bangladesh - (P)

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).

Source of Population:

- (a) Ill subjects Yes No
- (b) Non-ill subjects Yes No
- (c) Minors or persons under guardianship Yes No

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

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

Are subjects clearly informed about:

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

5. Will signed consent form be required:

- (a) From subjects Yes No
- (b) From parent or guardian (if subjects are minors) Yes No

6. Will precautions be taken to protect anonymity of subjects

Yes No

7. Check documents being submitted herewith to Committee:

- Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
- Protocol (Required)
- Abstract Summary (Required)
- Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
- Informed consent form for subjects
- Informed consent form for parent or guardian
- Procedure for maintaining confidentiality
- Questionnaire or interview schedule

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:

1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

(PTO)

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

Dr. M.S. Akbar
Principal Investigator

Trainee

- 10-011 7.0.90/20701
1. Title : The prevalence of Hepatitis B in Bangladesh - A pilot study.
 2. Principal Investigator : Professor M.S. Akbar, Shishu Hospital, Dhaka
 3. Co-Investigators : Dr. A.K. Azad, ICDDR,B
Dr. A. Haque
Dr. A.N. Alam
 4. Consultant : Dr. Saul Tzipori
 5. Starting Date : As soon as approval is given
 6. Completion Date : Within 4-5 months
 7. Total Budget : US\$16,000 (AGCD/ABUS)
 8. Division : Laboratory Sciences Division
S. Tzipori
 9. Aims of the Programme:

a) General Aim:

To determine the prevalence of the infection in a selected population at risk in order to formulate appropriate vaccination strategies.

b) Specific Aims:

1. To determine the prevalence of infection in one hundred health workers.
2. To determine the prevalence in one hundred pair of mothers and their infants aged 2-5 months.
3. To determine the prevalence in one hundred pair of mothers and their children aged 3-5 years.

10 Significance:

This pilot study will enable the health authorities of Bangladesh to establish the true prevalence of Hepatitis B in the population, particularly those at risk (health workers) in order to formulate appropriate steps, should control by vaccination be feasible.

11. Ethical Clearance:

Three ml of blood will be drawn aseptically, using disposable syringes and needles, from:

- a) one hundred, 2-3 months old infants, and from their mothers;

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1990 one hundred children, 3-5 years old and from their mothers;

- c) Fifty health workers' aged between 18-45 years, and 50 aged between 45 and 60 years old.

Exclusion criteria for bleeding include:

- a) Clinical jaundice,
- b) Clinical anaemia,
- c) Very severe illness,
- d) Severe malnutrition.

A consent form outlining the purpose behind the study and the procedures involved, has been prepared for signature and a copy is attached (Appendix 1).

The blood will be drawn by a qualified individual and under the supervision of a physician.

12. Background Information:

Hepatitis B virus (HBV) belongs to the hepadnavirus family, and is found only in man and other primates. The hepatitis B virus uses a reverse transcriptase step in replicating itself which suggests that it may be related to retroviruses.

Like the human immunodeficiency virus (HIV) which causes AIDS, the hepatitis B virus is transmitted by sexual contact, by exposure to infected blood, by sharing of contaminated needles or syringes through intravenous drug use, and from mother to child during the birth process. Hepatitis B infects many more people than HIV, but it has received much less attention from the public health community and international donors. It is also transmitted much more easily than HIV: Saliva and other mucous discharges from a hepatitis B patient are infectious, and the virus can survive up to two hours outside the body, even when the fluid containing it has dried out. Open sores and shared personal items such as toothbrushes and razors have been shown to be possible routes of infection.

Scientists have not yet been able to grow HBV in cell culture, but they do know that it has three main sections: an outer envelope of fat, carbohydrate and the viral protein coat (HBsAg); an inner layer of core protein (HBcAg); and a DNA strand for viral replication.

The incubation period averages two to three months, but HBsAg - the marker used in blood tests to diagnose hepatitis B can be detected in the blood as early as four weeks after exposure to the virus. As is true with most viruses, there is no treatment for HBV, but usually the infected person's

immune system eliminates the virus from the body. HB antibodies in the blood indicate that an individual has been exposed to the virus or vaccinated for it.

Some infected persons, however, are not able to eliminate the virus and become chronic carriers, remaining infectious for life. Many appear healthy, while others have a persistent, chronic form of the disease. Chronic carriers are at high risk of cirrhosis and liver cancer.

The hepatitis B virus is especially prevalent in Asia, the Pacific Islands and sub-Saharan Africa. It is a threat even in isolated populations. According to the Centers for Disease Control in Atlanta most of the people in the world live in areas that are endemic for hepatitis B and therefore immunization of the populations in these places could reduce the carrier rate by 80% to 90%.

With either chronic form of the disease, the liver is prone to scarring and eventual development of malignant cells. As a consequence, chronic hepatitis B carriers account for most of the world's cases of hepatocellular carcinoma and cirrhosis.

Males are more likely than females to become carriers, and persons with immune deficiencies, such as people with AIDS, are at higher risk.

Prevalence

According to current estimates, there are some 300 million carriers of hepatitis B around the globe. In such endemic areas as Asia and Africa, the number of carriers in the general population may be as high as 20%. Other parts of the world, including Eastern Europe, Japan, the Middle East and the Soviet Union, report carrier rates from 2% to 10%. In contrast, the number of carriers in the West accounts for less than 1% of the population, but is rising rapidly.

Where carrier rates are low, as in Northern Europe, North America and Australia, only 10% of the population shows any evidence of ever having been infected with the virus. Those who are infected usually acquire the illness in early adolescence or adulthood through sexual contact, blood transfusions or high-risk practices. Intravenous drug users, homosexuals, hemodialysis patients and health care workers are at an unusually high risk of contracting hepatitis B.

Maternal transmission

In China and Southeast Asia, transmission of HBV from mother to child during labor and delivery may be responsible for 40% to 50% of chronic infections. The high rate of perinatal transmission is probably linked to the presence of

especially infectious hepatitis B e antigens (HBeAg) in the blood of Asian female carriers.

In much of Africa, mother-to-child transmission at birth is less of a problem than in Asia because chronically infected women tend not to produce as much HBeAg, perhaps due to genetic differences. Still, the majority of the population is infected by the time children are five years old through close contact with infected siblings or other chronic carriers. Open sores, over crowded living conditions, pre-mastication of children's food by mothers, and inoculations with unsterilized needles may all play a role in the spread of the disease. To a lesser degree, so may traditional medicine practices, such as ritualistic scarification and tattooing with unsterilized instruments.

National immunization programs

A hepatitis B vaccine derived from human plasma has been commercially available since 1982. A new vaccine derived from genetically engineered yeast is also available, and its use is now being urged by the World Health Organization.

The first country to institute a mass immunization program was Taiwan, which has one of the highest rates of chronic hepatitis B infection in the world. In 1984, the country began voluntary screening of all pregnant women, most of whom use the island's prenatal clinics, for evidence of the hepatitis B surface antigen (HBeAg) in their blood. Those who tested positive were retested for the highly infectious HBeAg.

There are 25 other countries engaged in or planning national hepatitis B programs. The People's Republic of China has made hepatitis B vaccination for children a national priority and expects to begin inoculating all newborns by 1995. Thailand currently is conducting several pilot projects in preparation for including the vaccine in its Expanded Programme on Immunization (EPI) schedule within the next two years. Other programs are underway in Hong Kong, Singapore and Indonesia.

Small-scale demonstration studies are planned for endemic areas of South America, such as the Amazon Basin. Work in sub-Saharan Africa is just beginning, with vaccination projects taking place in the Gambia and Senegal, and others being readied for Cameroon and Botswana.

Universal screening of pregnant women for chronic hepatitis B is in progress in Hawaii, some Canadian provinces, Italy, West Germany, New Zealand, Australia and Japan. Unfortunately, the costs for such screening range from US\$3.50 to \$21 per test, a figure prohibitively high for many countries.

In 1988, the World Health Organization advised countries to allocate scarce resources to national health programs like the one developed in Taiwan and based on the rate of chronically infected persons in the population, the number of infections attributable to perinatal transmission, and the death rate from liver disease. WHO recommends that for regions with carrier rates of more than 10%, hepatitis B immunization be made a major public health priority, and recommends vaccination of all newborns in areas with intermediate prevalence rates. It is easier and cheaper to inoculate every infant, rather than screen pregnant women for the disease.

When given in early infancy, the vaccine is known to reduce the likelihood of chronic infection and its devastating consequences by 70% to 90%. Ideally, the vaccine is given within one week of birth, followed by an injection one month later and a final dose two to six months later. Because the vaccine appears to be most effective when given intramuscularly, infants and children are routinely inoculated in the thigh; adults, in the arm. Immunization lasts for at least five years. Current guidelines recommend a booster dose three to five years after the initial series. Children at risk of perinatal transmission of hepatitis B can be further protected by administering a dose of HB immunoglobulin within 48 hours of birth, which decreases their chances of becoming chronic carriers by another 5% to 25%.

While hepatitis B is probably best controlled by immunization programs, these means of transmission could be decreased by improvements in education of health workers and the public.

The situation in Bangladesh is not clear. There have been several studies which were conducted by several investigators which point out to a procedure similar to other Asian countries. But a more systematic study is needed.

The request for Hepatitis B vaccination was proposed during the 4th Session of Bangladesh Belgian Joint Commission. The Belgian Government subsequently proposed a pilot project to assess the prevalence of the infection in Bangladesh before an immunization program can be initiated.

This protocol is the result of these deliberations which will hopefully provide the necessary information.

13. Methods:

Approximately one half of the 500 blood samples will be collected from each Centre; the Shishu Hospital and ICDDR,B.

Medical histories with age sex and location from each participant will be collected in conjunction with the specimens. After an incubation of the blood the serum will be separated, labeled and stored below -20°C until the end of the collection. The frozen sera will be shipped to Belgium for testing for Hepatitis B at the Belgian Institute of Tropical Medicine.

Once the testing is complete the results will be forwarded to Professor Akbar and his co-investigators for analysis. The prevalence of the infection in each category will be determined and the results will be forwarded to the Ministry of Health and Family Planning. Professor Akbar and his colleague may consider publication of the results in a scientific journal.

14. Budget

1. One physician has been assigned in each Centre for this task which is estimated to last 2-5 months. This should cost \$6,000.
2. Approximately \$5,000 will be required to cover costs of syringes, needles, blood-collection vessels, vials for serum storage, and other items.
3. Transport of specimens to Belgium, records keeping, and communication expenses should not exceed \$5,000.

Total budget requested is \$16,000.

CONSENT FORM

Your child is suffering from diarrhoeal illness. This disease usually leads to dehydration and there might be changes in the electrolyte balance in the body. To diagnose these changes of blood electrolyte and monitor the improvements, usual blood drawing is needed. At present, in different hospitals of Bangladesh, the incidence and character of hepatitis B infection amongst Bangladeshi population is being estimated by doing blood tests. This is a combined project of Govt. of Bangladesh and Govt. of Belgium. It has been noted in other countries that this disease can be transmitted from the mother to her child.

For this reason we need to draw an extra 3ml of blood from your child and you. There will be no health problem for you and your child by drawing such a small amount of blood. The information acquired from this study will help for future design of strategies needed to intervene into this disease in Bangladesh.

For helping Bangladeshi people, if you are agreeable to volunteer, please sign or put your thumb print below.

Even if you are not agreeable to volunteer, your child will receive all the available treatment facilities in our hospital.

Signature of the
Investigator

Signature of Witness

Signature

Date:

Date:

Name:

Thumb Impression:

Registration
No. of Patient:

Date:

স্মৃতিপত্র

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আপনার মিনু তালিকাভুক্ত হুগেছে। এ রোগের প্রাধিকারন। রোগীর মস্তিষ্ক জনস্বাস্থ্যতা এবং রোগে মনন ও
 সমুদায় পরিমার্জনের পরিবর্তন ঘটে। এই পরিবর্তন নির্ণয় করার জন্য এবং চিকিৎসার চলাচল নষ্ট করার
 জন্য প্রাথমিক রোগ পরীক্ষার প্রয়োজন। বর্তমান বাৎসরিকের বিভিন্ন রোগের রোগ পরীক্ষা করে
 এবং রোগের কারণ প্রকাশ এবং প্রকৃতির পরিপ্রেক্ষিত করা হলে। এটা বাৎসরিক পরীক্ষা করে
 থেকে বাৎসরিক মস্তিষ্ক সংশ্লিষ্ট হতে পারে। এ জন্য আপনার মিনু এবং আপনার মস্তিষ্ক থেকে
 বিভিন্ন রোগ (যাও) জাভা চামচ বা (৩ মি:মি:) রোগের প্রয়োজন। এতে আপনার এবং আপনার
 বাৎসরিক মস্তিষ্ক রোগ অনুবিধা হতে না। উল্লেখ্য এই মস্তিষ্ক বাৎসরিকের রোগের কারণে
 রোগ প্রতিরোধের পরিচালনা প্রণয়নে সহায়তা করবে।

বাৎসরিকের মানুষের হিতকরনে আপনি এই পরীক্ষায় রাজী থাকলে নিম্নে স্বাক্ষর বা টিপসই দিন।
 আপনি যদি এই পরীক্ষায় রাজী না-ও থাকেন, তা হলেও আপনার বাৎসরিক এই রোগের কারণে পরিচালনা
 অনেক সুচিকিৎসাদি পারে।

রোগের কারণে স্বাক্ষর
 তারিখ:

স্বাক্ষর
 তারিখ:

স্বাক্ষর
 টিপসই
 রোগের কারণে পরিচালনা নং:
 তারিখ:

Project title: The Prevalence of Hepatitis B
 Principal Investigator(s): Bangladesh
 Dr. M. S. Akbar

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	✓		
Quality of Project Design		✓	
Feasibility of Methodology		✓	
Completeness within time period	✓		
Appropriateness of Budget	✓		
Potential value to field of knowledge		✓	

CONCLUSIONS

Support the application:

- a) without qualification
- b) with qualification:
 - on technical grounds
 - on level of financial support

do not support the application

Name of Referee: Dilip Mahalanabis
 Position: Accounts Director, CSO
 Institution: I.C.D.A. Dhaka

Signature:
 Signature

26.5.90
 Date

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 they are justified.

(Use additional pages if necessary)

Under significance, the claim that "true prevalence of Hepatitis B in the population" will be established is not justified; this study will not give true prevalence.

Statistical analysis plans have not been provided. It will however provide important information.

2/4/91



BANGLADESH INSTITUTE OF HERBAL MEDICINE

A non-profit non-government organisation for research and development of Herbal Medicine, Food and Nutrition

May 28, 1990.

To
Dr. Saul Tzipori
Associate Director and Head,
Laboratory Sciences Division,
ICDDR, B
Mohakhali
Dhaka.

Sub : Prevalence Study on Hapatitis-B Virus

A study on the prevalence of Hapatitis B Virus infection among the population in the Country is important.

The present proposal for the study even though called 'pilot' would have added volue if samples were better defined.

- a) Blood of 2-3 months old infants 100
- b) Their mothers 100
- c) 3-5 years old children 100
- d) Their mothers 100
- e) Health workers between 18-45 50
- f) Health workers 45-60 years 50

500

As these subjects will be taken from the Shishu Hospital and ICDDR, B one may assume that they are patients of diarrheal diseases. Indeed the questionnaire says so but not the text of the protocol. In that case it would be the prevalence study of hapatitis-B in diarrheal patients.

The term, health workers also need to be defined. Doctors, nurses, ward boys, paramedics are all health workers. Not only the age or sex but also years of service, nature of duty, the community they live with history of their contact hepatatitis patients etc will also play a role. If so, is the sample size good enough to make the study any meaningful in any quantitative terms ?



BANGLADESH INSTITUTE OF HERBAL MEDICINE

A non-profit non-government organisation for research and development of Herbal Medicine, Food and Nutrition

How is it the whole proposal has not got a single reference to publications on studies done any where ?

While the PI is to be held responsible for the conduct of the study the Centre cannot be absolved of the responsibility of the outcome of the study.

Somebody in the office of the Director may like to examine the budget identifying itemised supplies and services.

In view of the fact this is a study of hospital patients and workers, it may not be taken as representing the situation in Bangladesh.

Such terms as clinical anemia, very serious illness, severe malnutrition are vague and should be described precisely.

[Handwritten Signature]

Subject title: The prevalence of Hepatitis B in Bangladesh - A pilot Study

Principal Investigator(s): Drs. M.S. Akbar, A.K. Azad, A. Haque, A.N. Alam

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		✓	
Quality of Project Design			✓
Feasibility of Methodology	✓		
Completion within time period	✓		
Appropriateness of Budget	?		
Original value to field of knowledge		✓	

CONCLUSIONS

Support the application:

- a) without qualification
- b) with qualification:
 - on technical grounds
 - on level of financial support

Do not support the application

Signature of Referee: Professor Kamaluddin Akbar
 Position: Research Director
 Institution: Bangladesh Institute of Hospital Medicine

K. Akbar
 Signature

26.5.90
 Date