International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH AND POPULATION RESEARCH
Mail : ICDDR,B, GPO Box 128, Dhaka-1000, Bangladesh
Phone : (880-2) 8826318 / 8810117, PABX: 8811751-60
Fax : 880-2-8823116, 8826050, 8811568, 8811686, Cable: Cholera Dhaka
Email: analam@icddrb.org or ted@icddrb.org or brsaha@icddrb.org

CSD 2000

Memorandum

2 May 2002

To : Dr.Kuntral Kumar Saha
Public Health Sciences Division

Dr. Shahadat Hossain
Clinical Sciences Division

From: Professor Mahmudur Rahman
Chairman, Ethical Review Committee (ERC)

Sub : **Permission for using data of the protocol # 92-026**

This has reference to your memo of 15th April 2002 requesting the approval of the Ethical Review Committee for using the secondary data of the protocol # 92-026 entitled "Healthcare use pattern of the slum residents in Dhaka, Bangladesh" for the protocol # 2000-017 entitled "Modelling the impact and incremental cost-effectiveness of introducing vaccines against hepatitis B..... Bangladesh and Peru". Since there appears to be no ethical consideration, the ERC doesn't have any objection in using the data of the above mentioned protocol.

Thank you.

Copy: Associate Director
Public Health Sciences Division

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Email: analam@icddrb.org or ted@icddrb.org or brsaha@icddrb.org

Memorandum

DRAFT

2 May 2002

To : Dr.Kuntral Kumar Saha
Public Health Sciences Division

Dr. Shahadat Hossain
Clinical Sciences Division

To
ERC chairman
For your review and approval, please.
Thank you.
1/5/2002

From: Professor Mahmudur Rahman
Chairman, Ethical Review Committee (ERC)

Sub : **Permission for using data of the protocol # 92-026**

This has reference to your memo of 15th April 2002 requesting the approval of the Ethical Review Committee for using the secondary data of the protocol # 92-026 entitled "Healthcare use pattern of the slum residents in Dhaka, Bangladesh" for the protocol # 2000-017 entitled "Modelling the impact and incremental cost-effectiveness of introducing vaccines against hepatitis B..... Bangladesh and Peru". Since there appears to be no ethical consideration, the ERC doesn't have any objection in using the data of the above mentioned protocol.

Thank you.

Copy: Associate Director
Public Health Sciences Division

d) We see that there was a mention that a sample of children will be re-interviewed. This was a typographical error. This should have been 'mothers' and not 'children'. We regret the confusion caused by this typo.

e) We explored the feasibility of transporting the specimens to Dhaka *Shishu* Hospital within 24 hours and confirmed that it is feasible. All specimens will be collected from the villages before midday and transported to Sylhet town by mid-afternoon. We intend to have most of the specimens transported to Dhaka from Sylhet by overnight courier service, reaching the Shishu Hospital by the following morning, i.e., within 24 hours of collection. We do not think it is feasible to set up a field laboratory mainly because of our concern that we will not be able to maintain the quality of laboratory work in a field laboratory. Field offices will be set up to manage field operations but there are no plans to establish laboratory facilities there.

f) These are important points and we fully appreciate the concerns of the committee. We considered these issues carefully during the design of the project. There are two related issues in this context: (1) whether GoB health workers and CHWs can appropriately give antibiotics, and (2) whether they can give injections correctly and safely. Regarding the competence of CHWs in prescribing antibiotics, we believe that the committee is aware that the government health workers who are comparable to CHWs currently treat acute lower respiratory infection (ALRI) cases with antibiotic (cotrimoxazole). They use a clinical algorithm to diagnose ALRI. The success of community-based ALRI case management strategy by health workers is widely known. The proposed CHWs will have educational qualifications and skills comparable to government health workers. The competence of health workers in giving injection should not be a concern. In Bangladesh, government health workers give almost 4 million DPT first dose injections every year. The health workers currently give these immunizations to infants of six weeks of age, slightly older than the newborns targeted in the proposed project. We proposed that the health workers would diagnose serious infections in the neonates using a clinical algorithm and refer them to the Thana Health Centre. They will treat the cases with appropriate antibiotics only if the refer fails. If these babies are not taken to the referral facility and if the health worker is not allowed to give the appropriate injections, then most of these babies are likely to die. The families may even seek care from local village practitioners and quacks who actually may also give injectable antibiotics without the training and supervision we propose to give to the project CHWs. In that sense we hope to rationalize the use of antibiotics through this intervention. This strategy of treating serious neonatal infection by health workers using injectable antibiotic was successfully tested in India with 62% reduction in neonatal mortality. Obviously, the competence of health workers will depend on the quality of training and support provided to them. We will provide adequate attention to these aspects of the project and as stated in item one above we will have effective quality assurance procedures in place.

g) Currently, it is recommended by the WHO that empirical management of serious bacterial infections in young infants up to age 2 months include use of benzylpenicillin or ampicillin plus an aminoglycoside such as gentamicin administered parenterally.[1,2] The standard recommendation is to treat neonatal sepsis cases with appropriate antibiotics for 10-14 days. The American Academy of Pediatrics approves use of penicillin G procaine at 50,000 units/kg daily for

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Cable : Cholera Dhaka

April 15, 2002

To : Chairman, ERC

From : Kuntal Kumar Saha
Shahadat Hossain

Subject : Use of secondary data.

Since these appear to be no Ethical considerations, ERC doesn't have any objection in using data for above purpose.
16/4/02

Dear Mr. Chairman,

We are the Principal Investigators of the project entitled "Modelling the impact and incremental cost-effectiveness of introducing vaccines against hepatitis B, *Haemophilus influenzae* type b and rotavirus into routine infant immunization programmes in Bangladesh and Peru (Protocol # 2000-017). As a part of this study, we would like to use secondary data of the study "Healthcare Use Pattern in the Slum Population of Dhaka City" conducted in 1993-94.

A proposal on the data use and analysis plan was sent for RRC approval. It is to be noted here that no identifier will be used for this analysis and that there will be no deviation from the original RRC approved protocol of the study.

A copy of the proposal has been attached herewith this letter for your approval. We will highly appreciate your cooperation in this regard.

Thank you.

cc: Dr. Peter Kim Streatfield, Acting Associate Director, PHSD
Dr. Abbas Bhuiya, Acting Head, HEU, PHSD
Dr. Ishtiaq Bashir
Mr. Nazmul Sohel

Project

The impact and incremental cost-effectiveness of introducing vaccines against hepatitis b (HBV), *Haemophilus influenzae* type-b (Hib) and rotavirus (RV) into routine infant immunisation programmes in Bangladesh and Peru.

Title of sub-component of project:

What are the costs borne by patients and their families due to vaccine-preventable disease in Bangladesh?

Background:

We are involved in a UK Department for International Development funded project that will model the impact and incremental cost-effectiveness of introducing three new vaccines into routine infant immunisation programmes or extending coverage of the existing EPI in Bangladesh and Peru. Optimising the use of vaccines will increase the potential for economic development of the poorest groups by reducing their out-of-pocket costs of obtaining treatment. Frequently, families must sell assets, such as farm animals, at a loss, or take out loans at high interest rates to pay for care. Therefore, as part of this study, we would like to assess the costs borne by patients and their families of treating vaccine preventable diseases, and subsequently, the 'saved' treatment costs due to introducing new or under-utilised vaccines. To date, there have been few published estimates of the costs borne by the community of measles, pertussis, HBV, Hib and RV.

Names of investigators:

London School of Hygiene & Tropical Medicine: Vivian Valdmanis, Elisabetta Pegurri, Julia Fox-Rushby, Damian Walker

ICDDR,B, Bangladesh: Kuntal K. Saha, Shahadat Hossain, Nazmul Sohel

Aims and objectives:

We propose to use the health-care seeking behaviour study entitled "Healthcare Use Pattern in the Slum Population of Dhaka City" conducted in 1993-94 by the Health Systems Research Team of ICDDR,B's Health Economics Programme at the Public Health Sciences Division to estimate, from the perspective of patients and their families, the direct and indirect (productivity losses) costs associated with vaccine-preventable diseases. Briefly, this study aimed at describing both health-care use and spending in Dhaka City. Data were collected fortnightly via a six-month longitudinal survey. The types of information sought included episodes of illness, including acute or chronic illness, as well as health care seeking behaviour, and the direct costs borne by the community, defined as all out-of-pocket expenditures from users, non-users and their families, whether home-care or delivered by a provider. These costs not only include items such as drugs and diagnostic tests, but also official and 'unofficial' fees, transport costs, and food for the patients and attendants at all types of facilities.

The overall aim of our study, from the perspective of patients and their families, is to estimate the direct and indirect (productivity losses) costs associated with measles, pertussis, HBV, Hib and RV in Dhaka, Bangladesh.

More specifically, the objectives of this study are:

1. To document the health-care options individuals perceive to be available for the diseases and /or associated symptoms we are focussing on, and the reasons and constraints operating when choices are made about which health-care option to use;
2. To determine and investigate variables that contribute to the choice and extent of utilisation by type of health-care provider;
3. To describe the pattern of direct household expenditure on health-care;
4. To study indirect costs on health-care;
5. To explain variation in costs.

Methods:

We propose to use the existing database to identify all cases of measles, pertussis, HBV, Hib and RV and / or associated symptoms. In the absence of direct diagnoses, we will develop a list of proxy measures based on the patients' symptoms to estimate the prevalence of diseases in question, e.g. diarrhoea, cirrhosis, jaundice, liver cancer, meningitis and pneumonia.

During their field trip to Bangladesh, we plan to meet with investigators from LSHTM to review the data items as well as glean the required data on symptoms, diagnoses, costs and factors that may explain variation in costs. We also plan to conduct a multivariate analysis on the data items to ensure that there are no discrepancies or obvious measurement errors in the data set. We will also decide on dummy tables as to how the data should be prepared and presented for the Working Paper Series. In particular, analyses will include the following: burden of disease/cost analysis in order to measure the magnitude of the problem; sensitivity analysis in order to gauge the range of results given different proxy measures; analysis of matched pairs to test statistical significance of various socio-economic status variables on disease burden and costs.

Projected outputs:

1. Estimates of the costs borne by patients and their families due to vaccine-preventable disease;
2. Reports to the Working Paper Series;
3. Compilation of results in a refereed journal.

Provisional timeline:

1-17 April: literature search
19-24: fieldtrip to Bangladesh
25 April-14June: data analysis
15 June-14 July: prepare report (including a first draft, comments and final draft)
15 July-31 August: prepare journal article for submission

Dr. M.A. Salam

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Memorandum

Date: 6 November 2001-11-06

To: Prof DA Sack
Chairman, RRC

Through: Dr. M.A. Salam
Head and Acting Associate Director, CSD

From: Dr. S.M. Akramuzzaman

Subject: Handing over the responsibility of the Principal Investigator

I was one the Principal Investigators of the project entitled "Modeling the impact and incremental cost-effectiveness of introducing vaccines against hepatitis B, *Haemophillius influenza* type B and rotavirus into routine infant immunization programmes in Bangladesh and Peru (Protocol # 2000-017). You are aware that I have taken up a job with the MRC, UK and I am leaving the Centre tomorrow. I would like to hand over the responsibility of the Principal Investigator to Dr. Shahadat Hossain. I would be grateful if I am allowed to continue working on the project as a co-investigator.

Thank you.

cc. Dr Kuntal K. Shaha, PHSD
Dr Shahadat Hossain, CSD

Attachment I

Date: July 19, 2000

(FACE SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator: DISHA ALI , SM AKRAMUZZAN

Trainee Investigator (if any): .....

Application No. 2000-017

Supporting Agency (if Non-ICDDR,B) .....

Title of Study: Modelling the impact and incremental cost-effectiveness of introducing vaccine against hepatitis B, Hib and RV into routine infant immunisation program in Bangladesh & Peru

Project Status: .....

[X] New Study

[ ] Continuation with change

[ ] No change (do not fill out rest of the form)

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

1. Source of Population:
   (a) Ill subjects — (Yes) No
   (b) Non-ill subjects — Yes No
   (c) Minor or persons under guardianship — (Yes) No

2. Does the Study Involve:
   (a) Physical risk to the subjects — Yes (No)
   (b) Social risk — Yes (No)
   (c) Psychological risks to subjects — Yes (No)
   (d) Discomfort to subjects — Yes (No)
   (e) Invasion of privacy — Yes (No)
   (f) Disclosure of information damaging to subject or others — Yes (No)

3. Does the Study Involve:
   (a) Use of records (hospital, medical, death or other) — (Yes) No
   (b) Use of fetal tissue or abortus — Yes (No)
   (c) Use of organs or body fluids — Yes (No)

4. Are Subjects Clearly Informed About:
   (a) Nature and purposes of the study — (Yes) No
   (b) Procedures to be followed including alternatives used — Yes No NA
   (c) Physical risk — Yes No NA
   (d) Sensitive questions — Yes No NA
   (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 NA

5. Will Signed Consent Form be Required:
   (a) From subjects — (Yes) No
   (b) From parents or guardian (if subjects are minor) — (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 with overview (all other requirements will be submitted with individual studies
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw) (Required
   ✓ Informed consent form for subjects
   ✓ Informed consent form for parent or guardian
   ___ Procedure for maintaining confidentiality
   ___ Questionnaire or interview schedule*

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

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

Disha Ali 19.7.2000

Akram 19-7-2000

Principal Investigator

Trainee

ABSTRACT SUMMARY FOR E.R.C

This study has been designed to estimate the cost and find out the incremental cost-effectiveness of introducing Hepatitis B, *Haemophileous influenzae* and Rota Virus vaccines in Expanded Programme on Immunization (EPI) in Bangladesh. Standard EPI guideline will be used to collect the cost data. Information about cost incurred by the patient or the households will be collected from patients admitted at different hospitals of Bangladesh. A combination of prospective and retrospective data collection techniques will be used to identify, measure and value direct medical costs of treating disease. Where records are inadequate or not available, administration of a simple questionnaire to carers will complement and complete data collection. Direct non-medical costs of treatment include: transportation to, and from, health care facilities; household costs to accommodate the needs of the affected person; and social services. The indirect costs include cost of time allocated by the caregivers to the patients. These costs will be ascertained by interviewing a sample of caregivers. The data on costs of the EPI will provide estimates of the total, average, marginal and incremental cost of each vaccine, and combination of vaccines in each setting. This will be compared with the data on costs of illness to estimate the net cost of introduction of these vaccines. The incremental cost-effectiveness of introducing each vaccine will be assessed for Bangladesh.

1. Adults who provide care to the patients especially children will be interviewed to find out the time spent providing care. In-case of adult patients, patients will also be interviewed to find out the loss of earning due to illness and cost of treatment borne by the family for the particular disease.

2. There is no risk involved to the patient or the interviewee in this study.

3. Not applicable.

4. No person other than the investigators of the project will have the access to the data generated in the proposed study.

5. Informed consent will be obtained from the respondent.

6. An interview will be taken to find out about the cost, which will not take more than 15-20 minutes.

7. If it is found that incorporating these vaccines in EPI is cost-effective then many additional lives will be saved through the existing EPI programme.

8. Patients record will be required to find out the correct diagnosis, how long one has been suffering from the disease, and the treatment provided to calculate the direct treatment cost.

সম্মতি পত্র

আমরা আই , সি , ডি , ডি , আর , বি (ঢাকা) থেকে এসেছি । অসুস্থ অবস্থায় চিকিৎসা এবং অন্যান্য খাতে একজন ব্যক্তি বা একটি পরিবারের কত খরচ হয় , এ বিষয়ে আমরা গবেষনা করছি । এ উদ্দেশ্যে আমরা আপনাকে এই স্বাস্থ্যকেন্দ্রে আসা যাওয়া বাবদ; বাড়ীতে এবং হাসপাতালে চিকিৎসাবাবদ কত খরচ করেছেন , এ বিষয়ে কিছু প্রশ্ন করবো। পুরো জিজ্ঞাসাবাদ করতে আমরা আপনার ১৫ - ২০ মিনিট সময় নেব। আপনি যে সব তথ্য দেবেন , সেসব বিষয়ে সম্পূর্ন গোপনীয়তা পালন করা হবে।

এই গবেষনায় অংশগ্রহন করার কারনে আপনার কোনরকম ক্ষতির সম্ভাবনা নাই । আপনার পূর্ণ স্বাধীনতা আছে এই গবেষনায় অংশগ্রহন না করার কিংবা যে কোন প্রশ্নের উত্তর দেওয়া থেকে বিরত থাকা।

এই গবেষনালব্দ ফল আমাদের সম্প্রসারিত টিকা দান কর্মসূচীতে বিশেষ ভূমিকা রাখবে বলে আমরা আশা করি। আপনার সহযোগীতা আমাদেরকে এই গবেষনায় বিশেষ সহযোগীতা করবে।

সাক্ষাৎকার গ্রহনকারী সই

তারিখ---------

উত্তরদাতার সই / টিপ সই

Check List

After completing the protocol, please check that the following selected items have been included.

1. Face Sheet Included
2. Approval of the Division Director on Face Sheet ☑
3. Certification and Signature of PI on Face Sheet, #9 and #10 ☑
4. Table on Contents ☑
5. Project Summary ☑
6. Literature Cited ☑
7. Biography of Investigators ☑
8. Ethical Assurance ☑
9. Consent Forms ☑
10. Detailed Budget ☑

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

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

RESEARCH PROTOCOL

FOR OFFICE USE ONLY

Protocol No: Date received:

RRCApproval: Yes/ No Date:

ERC Approval: Yes/No Date:

Project Title: **Modelling the impact and incremental cost-effectiveness of introducing vaccines against hepatitis B, *Haemophilus influenzae* type b and rotavirus into routine infant immumnisation programmes in Bangladesh and Peru**

Theme and key words: **Cost-effectiveness of vaccine preventable disease. Cost-effectiveness, Markov models, hepatitis B, *Haemophilus influenzae* type b, rotavirus, vaccine, developing countries**

Principal Investigator: **Dr. Disha Ali & Dr. S.M. Akramuzzaman** **Division: PHSD & CSD** **Phone:** 2218/2328

Address: **PHSD, ICDDR,B**
CSD, ICDDR,B

Email: **disha@icddrb.org**
azaman@icddrb.org

Co-Principal Investigator(s):

Co-Investigator(s):
Dr. Felicity Cutts
Dr. Fox-Rushby
Dr. Sanderson Colin
Dr. Mahmud Khan
Mr. Damian Walker
Dr. M. Miller

Student Investigator/Intern:

Collaborating Institute(s):
London School of Hygiene & Tropical Medicine
Tulane University, School of Public Health, New Orleans, USA
Instituto de Investigacion Nutricional, Lima, Peru
National Inst of Health, Bethesda, USA

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

Gender
- ☒ Male
- ☒ Females

Age
- ☒ 0 – 5 years
- ☒ 5 – 9 years
- ☒ 10 – 19 years
- ☒ 20 +
- ☐ > 65

☐ Pregnant Women
☐ Fetuses
☐ Prisoners
☐ Destitutes
☐ Service providers
☐ Cognitively Impaired
☐ CSW
☐ Others (specify _____)

Project / study Site (*Check all the apply*):

- ☒ Dhaka Hospital
- ☒ Matlab Hospital
- ☒ Matlab DSS area _____
- ☐ Matlab non-DSS area
- ☐ Mirzapur _____
- ☒ Dhaka Community
- ☐ Chakaria
- ☐ Abhoynagar _____
- ☐ Mirsarai
- ☐ Patyia
- ☐ Other areas in Bangladesh not yet decided
- ☐ Outside Bangladesh
  name of country:
- ☐ Multi centre trial
  (Name other countries involved)

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

Type of Study *(Check all that apply)*:

- ☐ Case Control study
- ☐ Community based trial / intervention
- ☐ Program Project (Umbrella)
- ☐ Secondary Data Analysis
- ☐ Clinical Trial (Hospital/Clinic)
- ☐ Family follow-up study
- ☐ Cross sectional survey
- ☐ Longitudinal Study (cohort or follow-up)
- ☐ Record Review
- ☐ Prophylactic trial
- ☐ Surveillance / monitoring
- ☐ Others Survey of care givers

Targeted Population *(Check all that apply)*:

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

Consent Process *(Check all that apply)*:

- ☒ Written
- ☐ Oral
- ☐ None
- ☐ Bengali language
- ☐ English language

We will stratify institutes by providers (Gov & NGO). Random sampling of the fixed facilities and outreach within each stratum (approximately 5 institutions).

Proposed Sample size: Total sample size: ☐

Sub-group _____ ☐ _____ ☐

_____ ☐ _____ ☐

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

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

Yes/No

☐ ☒ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

☐ ☒ **Does the research deal with sensitive aspects of the subject's behavior; sexual behavior, alcohol use or illegal conduct such as drug use?**

Could the information recorded about the individual if it became known outside of the research:

☐ ☒ a. place the subject at risk of criminal or civil liability?

☐ ☒ b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research *(Check one)*:

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

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

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

Yes/No

☑ ☐ Is the proposal funded?

If yes, sponsor Name: DFID

Is the proposal being submitted for funding ?

☐ ☐ If yes, name of funding agency: _____

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

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

Dates of Proposed Period of Support	**Cost Required for the Budget Period ($)**
(Day, Month, Year - DD/MM/YY)	*a. Ist Year* *2nd Year* *3rd Year* *Other years*
Beginning date September 2000	$ 8,800 $ 52,764 $ 7,504 _____
End date August, 2003	*b. Direct Cost :* $ 85,252 *Total Cost :* $ 92,280

Approval of the Project by the Division Director of the Applicant

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

ABBAS BHUIYA
Name of the Division Director

Signature

July 16, 2000
Date of Approval

Certification by the Principal Investigator

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

Signature of PI: Disha Akram

Date: July 17, 2000

Name of Contact Person (if applicable)

_____

Table of Contents

☐ Check here if appendix is included

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

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

Principal Investigator: Dr. Disha Ali & Dr. S.M. Akramuzzaman

Project Name: Modelling the impact and incremental cost-effectiveness ... in Bangladesh and Peru

Total Budget: $ 92.280.00 Beginning Date: 1.9.00 (tentative) Ending Date: 30.8.2003

A decision-analytic framework will be used to assess the incremental cost-effectiveness of introducing vaccines against Hepatitis B (HBV), *Haemophilus influenzae* type b (Hib), and rotavirus (RV). Fieldwork will be conducted in Bangladesh and Peru in order to evaluate the incremental net costs from a societal perspective of introducing infant vaccination against additional vaccines.

Standard EPI/WHO costing guidelines will be used to determine the costs of each country's EPI, and we will estimate the incremental costs of introducing HBV, Hib and RV vaccines at various coverage levels, through different distribution mechanisms and with given equity-driven policies. A standardised human capital, incidence based cost-of-illness approach will be developed to estimate the direct (medical and non-medical) and indirect costs of the diseases.

Markov models will estimate the disease burden in terms of the number of deaths and disability-adjusted life years (DALYs) due to HBV, Hib and RV. Transition probabilities will be estimated by reviewing published and unpublished studies and epidemiological data from each country. The impact of each vaccine will be modelled in terms of the number of deaths and DALYs averted. Incremental net costs of introducing each vaccine will be estimated, these being the incremental costs of introducing the vaccines, minus the costs of averted disease and productivity losses due to disease. The estimated impact of each vaccine will be combined with the net incremental cost to obtain estimates of cost-effectiveness. Sensitivity analyses will assess the robustness of the results to changes in economic and epidemiological data. This study will provide guidance to policy-makers in Bangladesh, Peru and the international community as to whether these vaccines should be introduced. We will explore a method for evaluating the generalisability of the cost-effectiveness of each vaccine to different settings.

KEY PERSONNEL (List names of all investigators including PI and their respective specialties)

Name	Professional Discipline/ Specialty	Role in the Project
1. **Dr. Disha Ali**	**Public Health & Health Economics**	**Principal Investigator**
2. **Dr. S.M. Akramuzzaman**	**Epidemiology & Medicine**	**Principal Investigator**
3. **Dr. Felicity Cutts**	**Epidemiology & International Health**	**Co-investigator**
4. **Dr. Fox-Rushby**	**Health Economist**	**Co-investigator**
5. **Dr. Sanderson Colin**	**Health Service Researcher**	**Co-investigator**
6. **Dr. Mahmud Khan**	**Health Economist**	**Co-investigator**
7. **Mr. Damian Walker**	**Health Economist**	**Co-investigator**
8. **Dr. M. Miller**	**Modelling Specialist**	**Co-investigator**

DESCRIPTION OF THE RESEARCH PROJECT

Hypothesis to be tested:

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

To model the impact and incremental cost-effectiveness of introducing additional infant vaccines against HBV, Hib and RV in Bangladesh and Peru.

Specific Aims:

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

Cost analysis

From a societal (government, donors, patients and their families) perspective, in each country:

- Estimate the cost of the EPI, and investigate service delivery factors affecting the cost;
- Estimate the incremental costs of introducing HBV, Hib and RV vaccines;
- Estimate the marginal costs of introducing vaccination against HBV, Hib and RV at different levels of coverage, and to different priority groups;
- Estimate the direct (medical and non-medical) and indirect (productivity losses) costs associated with HBV, Hib and RV diseases.
- Estimate the incremental net costs of introducing HBV, Hib and RV vaccines into the EPI of Bangladesh and Peru, where incremental net costs are equal to the incremental costs of introducing vaccines into the EPI, minus the direct costs of averted disease, and productivity losses due to disease.

Markov modelling

- Review Markov models of HBV, Hib and RV transmission developed by CVI, CDC Atlanta and others;
- Develop revised Markov models of HBV, Hib and RV transmission in Bangladesh and Peru;
- Model the burden of disease in terms of DALYs lost due to HBV, Hib and RV in Bangladesh and Peru;
- Model the impact in terms of DALYs averted due to introducing HBV, Hib and RV vaccines into the EPI of Bangladesh and Peru.

Economic evaluation

- Estimate the incremental cost-effectiveness of introducing HBV, Hib and RV vaccines into the EPI of Bangladesh and Peru;
- Explore the relationship between the marginal costs of expanding coverage and expected impact at different coverage levels;
- Discuss the generalisability of the results to other countries.

Background of the Project including Preliminary Observations

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

Vaccines are one of the most cost-effective health interventions available (World Bank, 1993). The Children's Vaccine Initiative (CVI) estimates that up to 12 million lives could be saved by new global vaccination efforts leading to the introduction of additional vaccines in national immunisation programmes (NIPs). Delegates to the World Health Assembly in 1992 recommended that all countries should integrate HBV vaccine into their NIPs by 1997 (Cutts and Olive, 1998), and Hib vaccine was recommended for introduction into the global EPI in 1998 (WHO, 1998). One RV vaccine has been licensed for use in the USA and a variety of other RV vaccines are in phase II-III trials. This study will provide estimates of the costs, impact and cost-effectiveness of introducing new vaccines against HBV, Hib and RV in countries and regions representing different levels of development and health services infrastructure.

Bangladesh is currently considering introducing HBV vaccination and is planning a demonstration project of the use of Hib vaccine. Peru introduced HBV vaccination in jungle (high-risk) areas several years ago, and, more recently, Hib vaccination in the poorest districts. A rhesus reassortant tetravalent RV (RR-TV) vaccine was licensed in the USA in 1998, but its use was suspended in July 1999 while reports of intussusseption that may be related to the vaccine are investigated (MMWR, 1999). Other RV vaccines are under development in the USA and China, including a live attenuated human RV vaccine which gave 89% efficacy against RV diarrhoea in a recent trial in the US (Bernstein *et al.*, 1999). Thus, while RV vaccines have not yet been recommended for introduction into the EPI, there are a number of vaccine candidates in advanced stages of clinical trials. Peru has valuable experience with RV vaccine trials (Lanata, 1996). Prior use of vaccines in a trial setting is one of the factors that encourages countries to adopt additional vaccines (Brooks *et al.*, 1999). In this study, we will undertake (i) *ex-ante* studies prior to implementation; and (ii) *ex-post* studies after programme implementation. Factors that affect the marginal costs of vaccine introduction will be explored. This study will also provide important information regarding the efficiency of equity-driven policies such as those initiated in Peru which target remote areas and the poor.

HBV epidemiology Hepatitis B is a major public health problem even though safe and effective vaccines have been available for nearly 20 years. WHO estimates that hepatitis B infection results in more than one million deaths every year world-wide (Kane *et al.*, 1993). The major burden of disease due to HBV is chronic liver disease, including primary liver cancer. This arises in persons who are chronic carriers of the virus, 25% of whom will die as a result of their infection (Dusheiko, 1997). The younger the age at infection, the greater the likelihood of being a carrier as measured by HBV surface antigen (HBsAg) prevalence (Edmunds *et al.*, 1993; Edmunds *et al.*, 1996). Endemicity of HBV is measured in terms of the proportion of adults who are carriers of the virus. In Peru the carrier rate in most of the population is 1-2%, although in the Amazon basin this rises to 5-10% (Fay, 1990). In Bangladesh recent unpublished data shows an adult carrier rate of 4-5% (Salmon, CDC Atlanta, personal

communication). Child-to-child transmission under the age of ten years is probably the major determinant of this endemicity. In addition, a proportion of carriers is infected perinatally.

HBV vaccine Hepatitis B vaccine is estimated to be as cost-effective as measles vaccine in highly endemic countries (≥8% prevalence of carriage of HBsAg) (Kane *et al.*, 1993). Vaccination has an immediate effect on individual protection by reducing the pool of infectious children, and also long term effects by reducing the number of women of child bearing age who are infectious. The high effectiveness of the vaccine has been demonstrated by reductions in the carrier rate from over 8% to under 2% in immunised cohorts of children in the Gambia, Singapore, Hong Kong, Taiwan, Alaska, Thailand, Indonesia, South Korea and American Samoa (Van Damme *et al.*, 1997). In Taiwan, 10 years after implementation of a mass vaccination programme, a fall in the annual incidence of hepatocellular carcinoma in children aged 10-14 years has already been documented (Van Damme *et al.*, 1997). HBV vaccination has been part of the EPI of Peru for infants since 1995, but only in jungle areas. Peru uses a multi-dose recombinant vaccine produced by Bago, Cuba. HBV vaccine does not form part of the EPI of Bangladesh.

Economic evaluations of HBV vaccination programmes in developing countries Most economic evaluations on the addition of HBV vaccine to routine vaccination programmes have been conducted in industrialised countries of low endemicity (Jefferson and Demicheli, 1994). The few published studies in countries of high endemicity include those in Venezuela (Barboza *et al.*, 1991), The Gambia (Hall *et al.*, 1993), China (Zhuang and Xu, 1993; Liu *et al.*, 1995) and India (Aggarwal and Naik, 1994). Some of these studies failed to take account of the costs of treating disease. Such data are rare in developing countries. Further studies are indicated to support decision-making in high endemic countries (Beutels, 1998).

Jefferson and Demicheli (1994) conducted a systematic review on the efficiency of introducing HBV vaccine to routine vaccination programmes. Their main findings were:

- Large variability in the main parameters of the efficiency equation (disease incidence, costing methods, use of marginal theory, discounting and study timespan, sensitivity analysis and reporting methods);
- Inconsistencies in definition and study design;
- Scarce decision-making impact (perhaps due to uncertain or unclear methodology).

They concluded that few studies reach valid conclusions and thus future decisions may be based on biased evidence and scarce resources committed to untested programmes. Therefore they recommended the standardisation of study methods and definition of a common set of procedures. In light of their findings, our project will help to develop such a standardised approach to estimating the incremental cost-effectiveness of introducing HBV and other vaccines. They also stated that "Few studies costed administrative and material costs of the introduction of vaccination procedures and most of these were based on estimates". The data we collect from Peru will therefore be very important in order to fill the gap of this missing data. Another observation was the small number of developing country studies. As the authors noted, there is an "inverse geographical relationship between the bulk of Hepatitis B pathology and the number of studies on the economics of its vaccination".

Hib epidemiology Hib primarily causes meningitis and pneumonia with peak incidence in the first year of life. The infection is transmitted from other children who harbour the bacterium in their nasopharynx. Some 10% of children under two years of age are infected. While Hib is accepted as a major cause of meningitis and otitis media in industrialised countries, and in addition of pneumonia in Africa and Latin America, the burden of disease is disputed in Asia (Levine *et al.*, 1993). Surveillance projects are ongoing to assess this in Asia, under the auspices of the International Clinical Epidemiology Network (INCLEN), WHO and the International Vaccine Institute (IVI).

Hib vaccine Hib vaccine has virtually eliminated invasive Hib disease from much of the industrialised world (Steinhoff, 1997). In addition to direct protection of the individual, vaccination has a major "herd immunity" effect because it reduces nasopharyngeal colonisation in children. Hib vaccine had an efficacy of over 90% in the Gambia (Mulholland *et al.*, 1997) where it also significantly reduced the incidence of radiologically-defined pneumonia by 21% (95% CI, 4.6-34.9%). This suggested that about 20% of episodes of pneumonia in young Gambian children were due to Hib. If this is similar in other developing countries, the introduction of Hib vaccines could substantially reduce childhood mortality due to pneumonia as well as meningitis. Peru began Hib vaccination in September 1998; the vaccine is given through the public sector to the poorest districts. It is estimated that this strategy will provide 40% coverage among children.

Economic evaluations of Hib vaccination programmes in developing countries Economic analyses of Hib vaccination programmes have been undertaken in Chile (Levine *et al.*, 1993; Lagos *et al.*, 1998) and South Africa (Hussey *et al.*, 1995). However, these countries are classified as middle-income economies. The CVI estimated that for Asia, the annual net cost of a regional Hib vaccination programme would be almost $300 million. Most cost savings would occur in high income countries, while mortality savings would occur in low income countries (Miller, 1998). There are no published data on the efficiency of introducing Hib vaccines into low-income nations such as Bangladesh and the regional estimates conducted for CVI need confirmation by careful studies at the national level.

RV epidemiology RV is the commonest cause of severe watery diarrhoeal disease in infants and young children, causing an estimated 870,000 deaths per year, mostly in developing countries (Bresee *et al.*, 1999). This represents 25% of diarrhoeal-deaths and 6% of all deaths in children under five years of age (Jacobson, 1999). In Bangladesh, RV is estimated to cause between 15-27,000 deaths per year, equivalent to 1 RV death per 111 to 203 children under five (Unicomb *et al.*, 1997). RV was isolated from about 20% of diarrhoea specimens from children hospitalised for diarrhoea in Argentina, Bolivia and Brazil (Jacobson, 1999). In Peru, it is estimated that by five-years of age, one child in 1.3 will have an episode of RV diarrhoea, one in 45 will be hospitalised, and between one in 500 to 1000 children will die from the disease (Lanata, personal communication).

RV vaccine RR-TV protected 49-83% of recipients against all forms of RV disease, and 70-95% against severe forms in one Finnish and three US trials. This vaccine also protected 48% of infants against all RV disease and 88% against severe disease in Venezuela (Perez-Schael, 1997). Peru conducted some of the early trials with a lower dose of RR-TV (Lanata, 1996), and Dr Lanata and colleagues have recently completed a re-analysis of their data to estimate efficacy in preventing severe disease. A number of immunogenicity trials were initiated in 1998 under the auspices of WHO, including a study in Bangladesh (Roger Glass, CDC personal communication), and Ghana (funded by DFID). These trials have been interrupted pending investigation of suspected adverse events in the USA. Meanwhile, a number of other vaccines are under development and evaluation (Jacobson, 1999). Some may need fewer than three doses hence reducing vaccine costs (Bernstein *et al.*, 1999).

Economic evaluations of RV vaccination programmes in developing countries To date, there are no published studies pertaining to the cost-effectiveness of a RV vaccination programme in developing countries. Nonetheless, in Argentina, a recent study estimated that in 1991 RV led to roughly 84,500 outpatient visits and 21,000 hospitalisations, each averaging four days, with associated direct medical costs of US $27.7 million (Gomez *et al.*, 1998). In Peru, the mean direct costs to hospitalise a child with diarrhoea in 1994 were
estimated as $40-50, while each outpatient visit for diarrhoea cost an estimated $7-16 (Lanata, unpublished data from Proyecto 2000). Further economic analyses will enable an empirical measurement of the effects on economic productivity and the number of DALYs averted of a vaccine which has little effect on disease incidence but reduces disease severity.

Research Design and Methods

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

Review of secondary data on disease epidemiology, the impact, cost and cost-effectiveness of HBV, Hib and RV vaccines will be done. Sources of data will include:

- Established bibliographic databases;
- Appropriate resources referenced in primary articles;
- Web pages of major donors in the field;
- Epidemiologists known to be conducting studies on the burden of disease from HBV, Hib and RV in developing countries, e.g. Dr Mark Steinhoff who runs Hib surveillance networks in Asia through INCLEN, and Dr Roger Glass at CDC who is co-ordinating RV trials world-wide (both are technical advisors to the Bill and Melinda Gates Children's Vaccine Programme (CVP), of which Dr Cutts is a council member);
- Experts from UNICEF, New York and the BASICS programme in Washington as these organisations have been closely involved with programme implementation for 10-20 years, and staff at the Cochrane Collaboration;
- Other professionals in the field, in particular WHO, the CVP, IVI and the Global Alliance for Vaccines and Immunization (GAVI).

During the first five months of the literature review will take place. In addition, reviews of secondary data, including unpublished reports, will take place in Bangladesh and Peru during the preparatory trips in order to identify local studies. After this, additional data will be collected on an *ad hoc* basis, e.g. attendance at conferences.

Systematic reviews on the impact of HBV, Hib and RV vaccines will be used. Protocols for HBV and Hib exist (Boxall *et al.*, 2000a; Boxall *et al.*, 2000b; Hussey *et al.*, 2000) and will be completed by the end of 2001. Because RV vaccine is currently being investigated in relation to adverse events, a systematic review will not be performed, but the available vaccine trial data to ascertain the likely range of protection from new vaccines will be used. Review of data on HBV, Hib and RV disease epidemiology in order to identify critical parameters (i.e. the transition probabilities) for the models, and the cost and cost-effectiveness of HBV, Hib and RV vaccination programmes will be done. Established guidelines for such reviews published by the Cochrane Collaboration will be followed. The objective of these reviews is two-fold: firstly to identify existing data; and secondly, to identify the gaps in and reliability of existing data.

Identifying potential sources of bias and uncertainty is important. For example, inaccurate vaccination coverage data, the misclassification of disease epidemiology and inaccurate sources of cost information could substantially change the findings of our research, and hence our recommendations for policy-makers. A systematic search for, and critically review all literature will be obtained in order to ascertain the validity of the methods and findings.

Cost of EPI Information on the costs needed to equip facilities adequately to (a) sustain coverage or (b) increase coverage of DTP (and, by implication, of HBV, Hib or RV if introduced), will be sought at national level and during visits to health facilities.

Standard EPI costing guidelines will be used (WHO, 1979; Brenzel, 1990). Information on prices of equipment, supplies, salaries and wages of health workers, among other types of data, will be collected from existing records of donor agencies, government and NGOs. Surveys will be conducted to determine the types and quantities of personnel and equipment used at different sites.

The incremental costs of introducing each additional vaccine into the EPI of each country will be estimated. Because these vaccines are given at routine EPI visit for DTP/polio, no extra health service contacts with children are needed. The additional costs are likely to include the cost of: the vaccines (including international freight) (Schreuder *et al.*, 1997); their storage at, and distribution to, different levels of the health services; additional cold chain requirements for storage; costs of injection equipment (except for RV); time spent on vaccine administration and patient education; new vaccination records; social mobilisation to increase coverage; health worker training, both at start-up and during any changes in vaccine formulation (Lanaverde *et al.*, 1999); and dealing with any side effects associated with the new vaccines. There may also be substantial costs in developing surveillance of these infections to monitor programme impact (Lanaverde *et al.*, 1999). These resources will be estimated in conjunction with EPI programme managers, other relevant staff and NGOs. The estimates from Bangladesh, and observations of resources used in facilities that provide HBV or Hib in Peru, will be combined with local unit costs to calculate incremental costs.

The calculation of marginal costs requires an understanding of how costs change with the number of people vaccinated. Marginal costs will be estimated from two positions. The first will examine the relationship between total costs (separately, and in combination for fixed, semi-fixed and variable costs) and the number of people vaccinated in each facility. Secondly, interviews will be held with health providers at each facility focusing on the resources required for vaccinating different numbers of people within their catchment area.

Cost of illness: A human capital, incidence-based cost-of-illness approach will be used to estimate the direct and indirect costs incurred (and thereby potential economic gains) due to HBV, Hib and RV (Paul and Mauskopf, 1991). The direct costs of a disease are defined as the costs of medical care. An ingredients approach to costing will be used to measure the quantities of resources consumed during treatment.

Assessment of direct costs of illness. This will involve the following steps:

- Estimate the incidence of, and morbidity from, each disease in Bangladesh and Peru. In addition to reviewing the literature, all potential sources of data will be reviewed in-country. These will include published and unpublished community-based and health facility-based studies (particularly common for RV diarrhoea); notifications of diarrhoea; special surveillance projects; morality surveys; and, for HBV, serological data from blood banks, antenatal clinics, or special studies. Where adequate local epidemiological data are not available, we will examine the use of estimates from nearby countries of similar demographic, climatic and economic structures.
- Document the course of treatment for each level of severity of the disease. In particular, the following will be recorded: the number of hospital days (by type of department); the time of health care personnel with different levels of training (doctors, nurses, health aides); the use of diagnostic equipment; the quantity of pharmaceuticals and supplies consumed; and other facility-based costs (e.g., type of bed, food and laundry);
- Estimate the unit costs of resources for treatment for each level of severity of the disease;

- Estimate the total costs of treatment for each level of severity of the disease;
- Classify costs as variable (drugs and supplies), semi-fixed (labour) or fixed (facilities and equipment) because some resources can be used to treat other diseases. Following the introduction of additional vaccines, variable costs will be avoided in the short term.

Surveys of health facilities and patients Costs for acute watery diarrhoea, meningitis and pneumonia irrespective of aetiology will be estimated, and secondary data will be used to determine to what extent the aetiological agent affects treatment costs. Because of seasonal variations in disease incidence, particularly for RV, the facilities selected will be visited 3-4 times each year, depending on local disease patterns. To estimate costs of RV and Hib, paediatric inpatients aged less than 2 years (Hib) or 5 years (RV) and outpatients (RV) will be studied. For HBV, costs of acute illness (jaundice) in children and adults will be estimated at inpatient and outpatient facilities, and costs of chronic illness (cirrhosis/liver cancer) in adults will be studied to the extent possible. It is likely that adults with liver cancer will be seen primarily at tertiary care facilities (e.g. the cancer centre in Lima), hence these facilities in the capital cities will be included.

A combination of prospective and retrospective data collection techniques will be used to identify, measure and value direct medical costs of treating disease. A detailed retrospective analysis of medical records will be used to document the process of treatment for each condition. Where records are inadequate or not available, observation of patients and the administration of a simple questionnaire to carers will complement and complete data collection.

Sampling of health facilities: As one of the objectives of the study is to compare and contrast the results between Bangladesh and Peru in order to facilitate discussions pertaining to the generalisability of the findings, methods used in each country should be comparable. Hence, in Bangladesh, certain Administrative Divisions will be selected, to represent different population densities, degree of urbanisation, ethnic mix, and level of risk for HBV. Institution will be stratified by provider institutions by provider (i.e. government or non-government organisations). Fixed facilities and outreach sited will be selected randomly within each stratum, visiting approximately 5 institutions (one major vaccination centre, two other fixed facilities and two outreach sites) in each Division. The details of selection of Divisions and facilities will be finalised during the initial workshop that involves investigators from both countries.

Direct non-medical costs of treatment include: transportation to, and from, health care facilities; household costs to accommodate the needs of the affected person; and social services. This "out-of-pocket" expenditure often represents a considerable proportion of the economic costs of disease. These costs will be ascertained by interviewing a sample of caregivers.

Assessment of indirect costs Indirect costs are borne by patients through morbidity and premature mortality, by caregivers during the period that they spend taking the patient to health facilities, and whilst at home caring for the patient. The indirect costs of disease relate to the loss of income-earning capacity of caregivers during the period that they spend taking patients to health facilities and while caring for patients. There are also productivity losses due to the disability and premature mortality of infected individuals. Traditionally, the 'human capital' approach has been adopted to estimate such costs (an evaluation which equates the value of a human life with the individual's lifetime earning capacity).

In order to measure the time required to care for a sick child, a short questionnaire will be administered to a sample of caregivers to gauge the period of time spent away from productive activities. If possible, families of persons with chronic liver disease or cancer will be interviewed to estimate indirect costs.

From a societal perspective, costs also include care for patients who are not taken to health services. It

is beyond the scope of this study to measure these costs directly, but we will estimate the proportion of cases of each disease which are seen by the formal health sector and the costs of treatment obtained outside the formal health sector from:

- The literature;
- Unpublished information from relevant programmes at WHO (in particular the programme for Control of Diarrhoeal Diseases, and the Global Programme on Vaccines which is supporting Hib surveillance studies);
- Local studies of health-care seeking behaviour (e.g. the series of Working Papers on health-care seeking in Bangladesh conducted by the Health Systems Research Team of ICDDR,B's Health Economics Programme at the Public Health sciences Division);
- Discussions with relevant bodies at the Ministry of Health (e.g. units working with traditional medicine);
- Visiting pharmacies and interviewing pharmacists;
- Discussions with NGOs working in the field.

Modelling the impact of vaccination : Markov models will be explored to investigate how costs and savings may vary according to the characteristics of persons who use preventive and/or curative care, and to estimate the number of disability-adjusted life years averted by introduction of additional vaccines (Miller, 1998). The different attributes of individuals and groups affect the chance of acquiring or transmitting a disease, of seeking care at different places once they suffer an illness, and of using available preventive services. Markov models provide a framework in which individuals interact according to specified stochastic distributions. The solution procedure is by means of repeated simulations from which a measure of the average behaviour, and the variability about the average, can be obtained.

The Markov models will be constructed through collaboration within the team and with those involved with policies. This will ensure that policy-makers can understand what the models are aiming to do, and should facilitate the development of user-friendly models which will ultimately be used to guide future policy decisions. Critical parameters (i.e. the transition probabilities) will be collected by reviewing published and unpublished studies to identify the probabilities of developing HBV, Hib and RV, of having illness of varying severity, of recovery or death, and how these vary in different populations.

The data on costs of the EPI will provide estimates of the total, average, marginal and incremental cost of each vaccine, and combination of vaccines in each setting. This will be compared with the data on costs of illness to estimate the net cost of introduction of these vaccines. Next we will assess the incremental cost-effectiveness of introducing each vaccine separately, and in all possible combinations, compared to the status quo in Bangladesh and Peru. Table 1 shows the different implementation scenarios available to policy-makers. It is likely that there will be economies of scope and scale, such that the introduction of several vaccines at the same time will be cheaper (e.g. because training will be done for all vaccines at once; public information and communications activities will be synchronised etc). A decision-tree will explore these different options, however it is likely that there will be cases of dominance (i.e. effectiveness higher and costs lower) and extended dominance (i.e. the incremental cost-effectiveness ratio for a given alternative is higher than that of the next, more effective, alternative), in which case the actual number of options will be reduced.

Table 1: Vaccination options

Option
HBV
Hib
RV
HBV, Hib
HBV, RV
Hib, RV
HBV, Hib, RV

Because uncertainty is pervasive in economic evaluation, it has been proposed to use probabilistic sensitivity analysis that is based on a large number of Monte Carlo simulations. This technique examines the effect on the results of an evaluation when the underlying variables are allowed to vary simultaneously across a plausible range according to predefined distributions. The technique provides "confidence intervals" around point estimates of cost-effectiveness (Briggs *et al.*, 1994). For primary data collected during the project, the confidence intervals around point estimates will be derived following standard statistical procedures.

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

Time Line of the study:

FIRST PROJECT YEAR 2000 - 2001	**D** *S*	**A** *O*	**T** *N*	**E** *D*	**S** *J*	**:** *F*	**M** *M*	**o** *A*	**n** *M*	**t** *J*	**h** *J*	*A*
Review of eco & epi literature, development of data collection tools & draft Markov models	■	■	■									
Preparatory trip to Bangladesh (economist) and collection of unpublished data				■	■							
International workshop						■						
Data collection in Bangladesh & Peru							■	■	■	■	■	■
Interim analysis of data from Bangladesh & Peru									■	■	■	■

SECOND PROJECT YEAR 2001 – 2002	**D** *S*	**A** *O*	**T** *N*	**E** *D*	**S** *J*	**:** *F*	**M** *M*	**o** *A*	**n** *M*	**t** *J*	**h** *J*	*A*
Data collection in Bangladesh and Peru	■	■	■	■	■	■						
Interim analysis of data from Bangladesh	■	■										
Present the draft result of cost analysis to expert make changes according to feedback			■	■	■	■						
Final cost analysis from field-sites							■	■	■	■	■	■
Revision and completion of Markov Model							■	■	■	■	■	■
							■	■	■	■	■	■

THIRD PROJECT YEAR 2002 - 2003	**D** *S*	**A** *O*	**T** *N*	**E** *D*	**S** *J*	**:** *F*	**M** *M*	**o** *A*	**n** *M*	**t** *J*	**h** *J*	*A*
Combination of cost and impact data	■	■	■	■	■							
International workshop											■	
Writing-up of papers and dissemination						■	■	■	■	■	■	■

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

Facilities Available

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

ICDDR,B office space will be required.

Data Analysis

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

Data management and analysis All cost data will be collected on standard forms. The data from these forms, and patient data will be entered in EpiInfo. All patient data will be kept confidential. Basic descriptive analysis will be conducted within EpiInfo, but regression analysis will use STATA. We will use DATA 3.0, decision analysis software, (TreeAge Software, Inc., Williamstown, Massachusetts) to calculate costs and outcomes, and to perform sensitivity analysis.

Ethical Assurance for Protection of Human Rights

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

The study proposal will be submitted to the Ethical Review Committee of ICDDR, B for approval. No invasive techniques will be used in the study. Data collected from medical records and from interviewing caregivers will be kept anonymous and confidential. Informed consent will be obtained for all interviews.

Details on the procedure for maintaining confidentiality:

1. During training of the interviewers, emphasis will be given on the aspects of confidentiality in handling information and records.

2. Collected data will be kept under lock and key and will only be available to the investigators or under strict supervision.

3. Computer files containing the data will also be maintained in a secure place for access only to the researchers.

Use of Animals

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

No animal will be used in the study.

Literature Cited

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

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Additional references:

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Dissemination and Use of Findings

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

Strategy for dissemination of findings: Workshops will be held in Bangladesh and Peru to communicate the results to local decision-makers. A workshop will be held at LSHTM at the end of the study, inviting participants from WHO, UNICEF, CVP, IVI and GAVI. In this workshop, the generalisability of results to other settings will by discussed, by examining the links between clinical and economic outcomes, and also reasons for variation in country-specific costs, as well as other potential reasons for cost-effectiveness to vary. A literature review of the causes of variation in cost-effectiveness ratios will form the basis to examine other country differences. In the workshop, a series of practical recommendations will be formulated for circulation to national and international decision-makers. Final results will be published in peer-reviewed medical, public health and health economics journals, and newsletters such as the *Health Economics Exchange*. At the final workshop, we will discuss the need for a generic protocol to evaluate the cost-effectiveness of these vaccines, and should such a protocol be considered useful, identify a collaborative process to develop the protocol.

Collaborative Arrangements

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

Dr Cutts has extensive experience in running immunisation programmes in Africa and Asia and has conducted research on vaccines over the last 15 years, including a 6-year collaboration with Dr Akramuzzamman from ICDDR,B on measles and measles vaccine. Related projects include: RV surveillance and phase II trial of RV vaccine in Ghana; the cost-effectiveness of vaccination against pneumococcal disease and influenza in the UK.

Dr Fox-Rushby's principal area of research is the efficiency of health. She has worked on standardised approaches to the measurement of costs in international trials (e.g. economic evaluation of antenatal care (ANC) in Cuba, South Africa and Thailand.

Dr Sanderson was trained in Operational Research at Imperial College, and did research on System Dynamics modelling in industry. He teaches mathematical and simulation modelling at LSHTM. Recently he has published a multi-state life-table-based Markov model for estimating incidence from prevalence in benign prostatic hyperplasia.

Dr Mahmud Khan has extensive experience in costing vaccination programmes, and is participating in the study of the cost-effectiveness of measles vaccination in Bangladesh with Dr Akramuzzamman.

Dr Penny has experience as co-investigator and principal investigator in phase II and III vaccine efficacy studies (cholera and RV). She is currently principle investigator of a dose ranging study of a Hib vaccine in Peru (funded by Merck, Sharp and Dohme).

Dr Lanata has extensive experience in diarrhoeal and respiratory diseases, has been in charge of large vaccine field trials in poor areas of Peru, and is on several international committees monitoring research on RV, cholera, pneumococcal and Hib vaccines. Currently he is a co-investigator in a phase II trial of an improved Hib vaccine in Lima, Peru, and has done preliminary work assessing whether RV vaccine should be introduced in Peru.

Dr Miller has been developing a methodology to perform economic evaluations of vaccine preventable diseases integrating epidemiological and economic data to provide guidance to policy-makers on financing, and prioritisation of vaccination options.

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

Biography of the Investigators: Attached as appendix

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

Name	Position	Date of Birth

Academic Qualifications (Begin with baccalaureate or other initial professional education)

Institution and Location	Degree	Year	Field of Study

Research and Professional Experience			

Concluding with the present position, list, in chronological order, previous positions held, experience, and honours. Indicate current membership on any professional societies or public committees. List, in, chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. **(DO NOT EXCEED TWO PAGES, USE CONTINUATION SHEETS).**

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

APPENDIX 1

International Centre for Diarrhoeal Disease Research, Bangladesh
Voluntary Consent Form

Title of the Research Project: Modelling the impact and incremental cost-effectiveness .... inBangladesh and Peru

Principal Investigator: Dr. Disha Ali and Dr. S.M. Akramuzzaman

Before recruiting into the study, the study subject must be informed about the objectives, procedures, and potential benefits and risks involved in the study. Details of all procedures must be provided including their risks, utility, duration, frequencies, and severity. All questions of the subject must be answered to his/ her satisfaction, indicating that the participation is purely voluntary. For children, consents must be obtained from their parents or legal guardians. The subject must indicate his/ her acceptance of participation by signing or thumb printing on this form.

I have come from ICDDR,B, Dhaka. We are conducting a study on health care expenditure and for this purpose we would like to ask you some questions on transportation to and from health care facilities; household costs for treatment; time spent for caring the patient. For each interview we will take about 15-20 minutes. All the information collected will be kept confidential.

There is no risk for you to participate in this study. We are requesting you to take part in the study. You have option to accept or refuse participation in the study.

Your participation will help us to plan better immunisation programme in future.

If you agree, you may sign or give your thumb impression on this form.

Signature of theInterviewer:_____

Date:_____

Signature/Thumb impression of Interviewee_____

Date:_____

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

Detailed Budget for New Proposal

Project title: Modelling the impact and incremental cost-effectiveness ... in Bangladesh and Peru							
Name of the PI: .Dr. Disha Ali and Dr. S.M. Akramuzzaman							
Sl. #	Account description	Salary/m	% effort	1st yr	2nd yr	3rd yr	Total
1	Dr Disha Ali (#5470-0)*	690	50	4554	4968	5382	14904
2	Dr S.M. Akramuzaman (#3159-1)	1104	20		1160	1220	1160
3	Data Entry Technician	277	100		3490	1832	3490
4	Field Res Asstt. - 6	231	6x100		15246	0	15246
5	Budget Officer	500			6000	3000	6000
	Sub-total			**4554**	**30864**	**11434**	**46852**
International Travel (Ticket cost, Per Diem etc.)				5000	nil	5000	10000
	Sub-total			**5000**	**nil**	**5000**	**10000**
Local Travel & Per Diem				0	20000	0	
	Sub-total			**0**	**20000**	**0**	**20000**
Supplies and Materials							
1	Office stationeries			300	500	200	1000
	Sub-total:			**300**	**500**	**200**	**1000**
Other contractual services							
1	Tel/Fax/Post/Courier			200	500	200	900
2	Photocopying			300	900	300	1500
3	Dissemination Workshop			0	0	2000	2000
	Sub-total			**500**	**1400**	**2750**	**4400**
Capital Equipment							
Computer, Printer and accessories				3000	0		
	Sub-total			**3000**	**0**	**0**	**3000**
15% Overhead over personnel							**7028**
Total Cost				**8800**	**52764**	**7504**	**92280**

* 50% effort in 3rd year

Total Direct Cost: $85,252
15% Overhead over personnel: $ 7,028
Total Project Cost: $ 92,280

Principal Investigator: Last, first, middle: Ali Disha & Akramuzzaman S.M.

Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item. Justify use of man power, major equipment, and laboratory services.

Capital equipment

A Dell Optiplex GX1 computer will be required by the health economist for data entry and data analysis. A printer is also required for the same purpose.

Salaries

A full-time health economist is required to: perform a detailed literature review of the published and unpublished literature pertaining to the economics and epidemiology of HBV, Hib and RV disease; develop data collection tools; review existing Markov models of HBV, Hib and RV; develop new Markov models for Bangladesh; preliminary data analysis; perform final analysis of cost data and combine with epidemiological data generated by the models; facilitate a workshop during which results will be discussed with the members of the team; and finally to prepare documents for publication.

Dr Disha Ali and Dr Akramuzzamman will supervise the project. Dr. Ali will be paid fulltime for second year and 50% for third year and Dr. Zaman will be paid 20% for first and Second year. Six field staff (for 12 months FTE) will be hired during the second year to collect data in selected sites of six divisions.

Respective institutions will contribute the salaries of the Co-Investigators.

Other Charges

First international travel is for detail planning of the study through a workshop. Second international visit is for write-up and dissemination in a workshop. Local workshops have been budgeted for dissemination of the study findings at national level.

Ethical Assurance:

This proposal has been submitted to the Ethics Committee of the London School and Hygiene and Tropical Medicine, and the Ethics committee of each collaborating research centre.

CURRICULUM VITAE

Name: SYED MOHD AKRAMUZZAMAN

EDUCATION

1999: Postgraduate Diploma of the London School of Hygiene and Tropical Medicine by research in Infectious & Tropical Diseases, UK.

1998: Ph.D. in Epidemiology, London School of Hygiene and Tropical Medicine, University of London, UK.

1992: M.Sc. in Public Health in Developing Countries. London School of Hygiene and Tropical Medicine, University of London, UK.

1982: M.B.B.S. Rajshahi Medical College, Rajshahi University, Rajshahi, Bangladesh.

DISSERTATION AND THESIS

MSc dissertation: Epidemic measles in rural Bangladesh: The need for intensification of measles vaccine coverage and an effective vaccine. Dissertation submitted for MSc. London School of Hygiene and Tropical Medicine, University of London, 1992.

PhD thesis: A cohort study of the effect of measles on childhood morbidity in urban Bangladesh. Thesis submitted for PhD. London School of Hygiene and Tropical Medicine, University of London, 1998.

EMPLOYMENT

1982 -1983: Medical Intern, Rajshahi Medical College Hospital, Rajshahi, Bangladesh.

1983 – 1985: Resident Medical Officer, Dhaka Shishu (Children) Hospital, Shalmoli, Dhaka, Bangladesh.

1985 – 1993: Medical Officer, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh.

2000: Present position: Senior Medical Officer, ICDDR,B: Centre for Health and Population Research, Dhaka, Bangladesh.

RECENT PUBLICATIONS

Roy SK, Islam A, Molla A, Akramuzzaman SM, Jahan F, Fuchs G. Impact of single megadose of vitamin A at delivery on breastmilk of mothers and morbidity of their infants. Eur J Clin Nutr 1997;51:302-7.

Roy SK, Tomkins AM, Akramuzzaman SM, Behrens RH, Haider R, Mahalanabis D, Fuchs G. Randomized controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. Arch Dis Child 1997;77:196-200.

Roy SK, Tomkins AM, Akramuzzaman SM, Haider R, Behrens RH, Fuchs G. Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi Children. Acta Paediatr 1998;87:1235-9.

Akramuzzaman SM A cohort study of the effect of measles on childhood morbidity in urban Bangladesh. Thesis submitted for PhD. London School of Hygiene and Tropical Medicine, University of London, 1998.

Roy SK, Tomkins AM, Haider R, Behrens RH, Akramuzzaman SM, Mahalanabis D; Fuchs GJ. Impact of zinc suplementation on subsequent growth and morbidity in Bangladeshi children with acute diarrhoea. Eur J Clin Nutr 1999;53:529-34.

Mitra AK, Akramuzzaman SM, Fuchs GJ, Rahman MM, Mahalanabis D. Long-term oral supplementation with iron is not harmful for young children in a poor community of Bangladesh. J Nutr 1999;127:1451-5.

Rahman MM, Akramuzzaman SM, Mitra AK, Fuchs GJ, Mahalanabis D. Long-term supplementation with iron does not enhance growth in malnourished children. J Nutr 1999;129:1319-22.

Akramuzzaman SM, Cutts FT, Wheeler JG, Hossain MJ. Increased childhood morbidity after measles is short-term in urban Bangladesh. Am J Epidemiol 2000;151:723-735.

Curriculum Vitae
Dr. Disha Ali, MBBS, MPH

EDUCATION

University of Alabama at Birmingham
School of Public Health, Alabama, USA **1999**

Masters in Public Health in Epidemiology (MPH).

University of Chittagong **1991**
Chittagong Medical College, Chittagong, Bangladesh

Bachelor of Medicine and Surgery (MBBS).

PROFESSIONAL EXPERIENCES

ICDDR, B, **Aug-97 to present**
Centre for Health and Population, Dhaka, Bangladesh
Health Economics Program, Public Health Sciences Division

Research Investigator. Involved in economic evaluation (cost-effective studies) of different health interventions in the area of reproductive health, child health and nutrition. Specific responsibilities includes, identification of areas in need of research, writing proposals, supervising ongoing researches, data management and analysis of data, report writing, preparing seminar documents, presenting research findings, representing the program in various workshops and seminars. Presently involved in cost analysis of emergency obstetrics care (EOC) in a rural population.

BRAC **Jul-95 to Jul-97**
Dhaka, Bangladesh
Health and Population Division

Medical Officer. STD/ RTI Pilot Project

ICDDR, B **Apr-93 to Oct-94**
Centre for Health and Population, Dhaka, Bangladesh
Clinical Sciences Division

Research Fellow. Nutritional Project.

TECHNICAL PAPERS/ PUBLICATION

- Chowdhury SA, Ziauddin M, Ali D. "Breaking the Silence - Rural Women's Perception of Vaginal Discharge." BRAC. Presented at Annual Scientific Conference VI (ASCON VI), ICDDR,B, Dhaka, Bangladesh, March 1997.
- Khan MM, Ali D, Mamun AA, Ferdousi Z. "Estimating the Optimal Number of Comprehensive EOC Facilities for Bangladesh." Presented at interdivisional scientific forum, ICDDR,B, Dhaka, Bangladesh, September 1997 (under finalization)
- Chowdhury SA, Ziauddin M, Ali D. "Rural Community Based RTI/STD Management and Control Program Using Syndromic Approach: A preliminary Assessment of BRAC's Pilot Initiative." Presented at workshop -Implementing Women's Health Program in the Community, Centre for Developmental Management (CDM), BRAC, Dhaka, Bangladesh, December 13-15, 1997
- Khan MM, Hawkes S, Ali D. "Economic Evaluation of MCH-FP Clinic Based Syphilis Screening in Rural Bangladesh, Presented at Annual Scientific Conference VII (ASCON VII), ICDDR,B, Dhaka, Feb 1998 (under finalization).
- Ali D, Khan MM. "Evaluating the Alternative Strategies for Hepatitis B Vaccination in Bangladesh- an Economic Analysis." Poster presented at Annual Scientific Conference VII (ASCON VII), ICDDR,B, Dhaka, Feb 1998 (under finalization) .
- Ali D, Khan MM. "Economics of breast feeding". Presented at Breast Feed Week Conference. ICDDR,B, July, 1998.

CV of Disha Ali

RESPONSE TO POINTS AND QUESTIONS

a) *Care will be required to ensure that potential sources of bias and uncertainty are rigorously documented – page 10 in the paragraph about the literature review & page 13 in the paragraph about data management and analysis*

We recognise the importance of noting potential sources of bias and uncertainty for our project. For example, inaccurate vaccination coverage data, the misclassification of disease epidemiology and inaccurate sources of cost information could substantially change the findings of our research, and hence our recommendations for policy-makers. In their review of economic models of HBV vaccination, Jefferson and Demicheli (1994) noted that there was "a closed loop of frequently quoted studies. As some of these revealed methodological inconsistencies, these are perpetuated and magnified by the expanding number of studies". Hence, we will systematically search for, and critically review all literature obtained in order to ascertain the validity of the methods and findings.

Because uncertainty is pervasive in economic evaluation, we propose to use probabilistic sensitivity analysis that is based on a large number of Monte Carlo simulations. This technique examines the effect on the results of an evaluation when the underlying variables are allowed to vary simultaneously across a plausible range according to predefined distributions. The technique provides "confidence intervals" around point estimates of cost-effectiveness (Briggs *et al.*, 1994). For primary data collected during the project, the confidence intervals around point estimates will be derived following standard statistical procedures. For data on vaccine efficacy, we will consult the Cochrane database for results of meta-analysis, and if necessary, update such analyses in consultation with LSHTM statisticians. Published and unpublished data without confidence intervals, and consultations with international experts, will provide additional data, where distributions will be assumed (e.g. rectangular and triangular). These assumptions will be documented and subjected to sensitivity analysis as well.

b) *Should the study include rotavirus vaccination, as the vaccine is currently being investigated in relation to adverse events? – page 5 under point 2(i)*

We believe that a cost-effectiveness analysis of a hypothetical rotavirus vaccine would still provide useful guidance to policy-makers and industry. With support from the Gates Children's Vaccine Programme, efforts to identify new vaccine candidates are being actively pursued, and the investigators in this project (F. Cutts, C. Lanata) are in close contact with international policy-makers and vaccine trialists. Therefore an incremental cost-effectiveness analysis would be possible. Indeed, several papers have evaluated the cost-effectiveness of hypothetical vaccines that have stimulated discussion between industry and policy-makers, and helped promote the need for additional research and development funds in the area of immunology (AIDS - Cowley, 1993; schistosomiasis - Evans & Guyatt, 1997; malaria - Graves, 1998). Knowledge of the epidemiological and economic burden of rotavirus is in itself a useful contribution to national and international research. Therefore, in conclusion, we are keen to include rotavirus vaccination in our project.

c) *Please specify the number of providers who will be surveyed in Bangladesh – page 10*

As one of our objectives is to compare and contrast the results between Bangladesh and Peru in order to facilitate discussions pertaining to the generalisability of our findings, methods

used in each country should be comparable. Hence, in Bangladesh, we will select certain Administrative Divisions, to represent different population densities, degree of urbanisation, ethnic mix, and level of risk for HBV. We will stratify institutions by provider (i.e. government or non-government organisations). We will select a random sample of fixed facilities and outreach sites within each stratum, visiting approximately 5 institutions (one major vaccination centre, two other fixed facilities and two outreach sites) in each Division. The details of selection of Divisions and facilities will be finalised during our initial workshop that involves investigators from both countries.

d) Please provide justification for your decision not to estimate social opportunity costs as part of indirect costs – page 12

While on page 5 of our original proposal we had stated that an objective was to estimate the "*indirect (productivity losses) costs* associated with HBV, Hib and RV diseases", and later on page 11, "A human capital, incidence-based cost-of-illness approach will be used to estimate the direct and *indirect costs incurred (and thereby potential economic gains)* due to HBV, Hib and RV", we then failed to sufficiently delineate how we would proceed in the calculation of these costs. However, the identification, measurement and valuation of productivity losses is a contentious issue of economic evaluation. The indirect costs of disease relate to the loss of income-earning capacity of caregivers during the period that they spend taking patients to health facilities and while caring for patients. There are also productivity losses due to the disability and premature mortality of infected individuals. Traditionally, the 'human capital' approach has been adopted to estimate such costs (an evaluation which equates the value of a human life with the individual's lifetime earning capacity). However, the 'friction cost' method assumes that production losses will be confined to the period needed to replace a sick worker (Koopmanschap & Rutten, 1993). The length of this period and the resulting indirect costs depend on the labour market. In developing countries, and Bangladesh and Peru in particular, there exist large pools of unemployed individuals that can replace incapacitated staff.

In our original proposal, we dealt purely with indirect costs borne by caregivers, and proposed the administration of a sample of short questionnaires to caregivers in order to ascertain time spent away from productive activities. But this leaves the substantial component of indirect costs borne by society due the infected patients themselves. Due to the concerns outlined above, we will proceed according to current guidelines that suggest the following (Drummond *et al.*, 1997):

i. Report productivity changes separately so that the policy-maker can make a decision on whether or not to include them;
ii. Report the quantities (in days of work, or normal activity lost or gained) separately from prices (e.g. earnings) used to value the quantities
iii. Consider whether earnings adequately reflect the value of lost production at the margin and whether an approach based on the adjustments necessary to restore productivity (e.g. the friction approach) would be more valid.

e) Please provide further details as to how incremental cost-effectiveness will be assessed – page 13

We will assess the incremental cost-effectiveness of introducing each vaccine separately, and in all possible combinations, compared to the status quo in Bangladesh and Peru. Table 1

shows the different implementation scenarios available to policy-makers. It is likely that there will be economies of scope and scale, such that the introduction of several vaccines at the same time will be cheaper (e.g. because training will be done for all vaccines at once; public information and communications activities will be synchronised etc). A decision-tree will explore these different options, however it is likely that there will be cases of dominance (i.e. effectiveness higher and costs lower) and extended dominance (i.e. the incremental cost-effectiveness ratio for a given alternative is higher than that of the next, more effective, alternative), in which case the actual number of options will be reduced.

Table 1: Vaccination options

Option
HBV
Hib
RV
HBV, Hib
HBV, RV
Hib, RV
HBV, Hib, RV

Studies are ongoing to evaluate the potential for reduced numbers of doses of Hib vaccine, to reduce total costs, and conversely, to determine whether booster doses of Hepatitis B will be required. The results of these studies may suggest that the different vaccines could be administered following different schedules. This would obviously have implications for incremental costs, and we will assess the effect of introduction of vaccines under different potential schedules (numbers of doses and intervals between them).

f) Will the study produce a generalised model with standard inputs for both countries? – page 13

The model will be generalisable to countries where the important variables are the same (e.g. population structure; prevalences; vaccine distribution and take-up; cost, effectiveness, cost-output relationships, relationships between inputs, substitution rates between inputs and utilisation of treatment services) and the relationships involved are similar in form.

If our proposed models for Bangladesh and Peru are to be good, all the factors and relationships that are important in these countries should be included. Extension to a third such as Ghana, is then a matter of **recalibration** as long as the important factors are the same, and the relationships are of similar form. Recalibration does not involve reprogramming as long as the model's 'control panel' provides access to the various values and coefficients. Therefore, the main issue is one of data availability. Through our liaison with international agencies who are also involved in the assessment of costs of immunisation, in different forms, we will explore the potential for recalibration of our data in other countries in collaboration with other interested groups.

g) Please provide further information about the literature review, including time allowed, research methods and opportunity costs – pages 10

We will review secondary data on disease epidemiology, the impact, cost and cost-effectiveness of HBV, Hib and RV vaccines. We have identified the first five months of the project as the

main period during which the literature review will take place. In addition, reviews of secondary data, including unpublished reports, will take place in Bangladesh and Peru during the preparatory trips in order to identify local studies. After this, additional data will be collected on an *ad hoc* basis, e.g. attendance at conferences.

Systematic reviews on the impact of HBV, Hib and RV vaccines will be used. Protocols for HBV and Hib exist (Boxall *et al.*, 2000a; Boxall *et al.*, 2000b; Hussey *et al.*, 2000) and will be completed by the end of 2001. Because RV vaccine is currently being investigated in relation to adverse events, we will not perform a systematic review, but we will use the available vaccine trial data to ascertain the likely range of protection from new vaccines. We will review that data on HBV, Hib and RV disease epidemiology in order to identify critical parameters (i.e. the transition probabilities) for the models, and the cost and cost-effectiveness of HBV, Hib and RV vaccination programmes. We will follow established guidelines for such reviews published by the Cochrane Collaboration. Initially, we will develop review protocols that we will subject to peer review by the following Cochrane Groups and Fields: Acute Respiratory Infections Group; Infectious Diseases Group; Cochrane Vaccines Field; and Cochrane Economics Methods Group. The objective of these reviews is two-fold: firstly to identify existing data; and secondly, to identify the gaps in and reliability of existing data. We will, of course, have free access to various online databases and to the Internet. We have made estimates in our budget for photocopying and inter-library loans. As with all activities, there are associated opportunity costs to performing the literature review. However, we feel that an initial period of five months is sufficient for full-time work on the literature review, which will then be continued throughout the project.

In addition to the review process outlined in our proposal (page 10), we will also seek data from UNICEF, New York and the BASICS programme in Washington as these organisations have been closely involved with programme implementation for 10-20 years, and staff at the Cochrane Collaboration.

h) Please provide further discussion on the findings of Jefferson and Demichelli's systematic review on HBV vaccination – page 7

The main findings of Jefferson and Demichelli's review were:

- Large variability in the main parameters of the efficiency equation (disease incidence, costing methods, use of marginal theory, discounting and study timespan, sensitivity analysis and reporting methods);
- Inconsistencies in definition and study design;
- Scarce decision-making impact (perhaps due to uncertain or unclear methodology).

They concluded that few studies reach valid conclusions and thus future decisions may be based on biased evidence and scarce resources committed to untested programmes. Therefore they recommended the standardisation of study methods and definition of a common set of procedures. In light of their findings, our project will help to develop such a standardised approach to estimating the incremental cost-effectiveness of introducing HBV and other vaccines. They also stated that "Few studies costed administrative and material costs of the introduction of vaccination procedures and most of these were based on estimates". The data we collect from Peru will therefore be very important in order to fill the gap of this missing data. Another observation was the small number of developing country studies. As the authors noted, there is an "inverse geographical relationship between the bulk of Hepatitis B pathology and the number of studies on the economics of its vaccination". Therefore, our project will help redress this disequilibrium.

i) Please provide further details of the criteria that will be used to validate the models – page 13

The models will be validated in three ways:

i. Can the models mimic past behaviour? We will use the "best estimates" of critical parameters relating to disease epidemiology and compare them with primary data on disease incidence and mortality without vaccines against HBV, Hib and RV in Bangladesh and Peru. In Peru, we will compare the expected impact of vaccination against HBV and Hib with surveillance data in those areas of the country, which have introduced HBV and Hib vaccines.

ii. Do the cost-effectiveness models predict theoretically expected relationships between costs and effects? For example, "U-shaped" cost curves, of falling and then rising average costs, are hypothesised by economists as coverage rates increase. Does the model predict this type of relationship?

iii. Do different models give different results? We will use other published models to corroborate our findings (Edmunds *et al.* 1996a; Edmunds *et al.* 1996b; Anderson & May, 1991; McLean & Blumberg; Coen *et al.* 1998);

iv. Are the models acceptable for decision-making? It is important that the models are acceptable to national and international policy-makers. We will discuss the implications of the data with policy-makers in the participating countries, and with international agencies in particular WHO and the Gates CVP.

j) Please provide written confirmation of Government and ethical approval.

We had planned to obtain ethical clearance when the data collection instruments have been developed, in order for the ethics committees to approve them. We have planned to prepare data collection tools within 6-8 months of the start date. Therefore, we can guarantee that we will provide the necessary clearance before starting primary data collection. However, we will seek overall ethical clearance for the project and forward confirmation as soon as possible.

RD 578 Dr. F. Cutts London School of Hygiene & Tropical Medicine REVIEWER F.

Modelling the impact and cost-effectiveness of introducing vaccines against hepatitis B, Haemophilus influenzae type b and rotavirus into routine infant immunisation programmes in Bangladesh, Ghana and Peru

Many less developed countries have not introduced the above vaccines - HBV, Hib and RV. While the cost benefit of the other vaccines (DPT, Polio and Measles) have been widely promoted, the additional three have not. There are various reasons for this but a lack of good data on the economic and epidemiological burden of the three diseases contributes to the low level of popularity of these three vaccines.

The applicants seek to perform three levels of analysis.

1. A straight forward cost analysis describing the overall direct, incremental and marginal costs of the vaccines.
2. Mathematical modelling in which they will examine transmission dynamics of the three infections and establish information on the burden of the disease in disability adjusted life years lost.
3. They wish to perform an economic evaluation examining cost effectiveness of introducing HBV, Hib and RV vaccines into the EPI programmes of Bangladesh, Ghana and Peru.

The background information on the epidemiology of these three infections is well presented. I am not competent to comment on the mathematical models that have been produced and their critique of them.

The team have excellent credentials in their special areas of the epidemiology of infection, vaccine efficacy and effectiveness and health economics.

They aim to select two to three facilities in each health care strata in each country providing 20-30 facilities per country, the main purpose being to capture any variations in treatment practices or unit costs.

They describe the stratification according to age and discharge diagnoses but my concern is that the ability to be able to diagnose the 'discharge diagnosis' is very limited. None of these three countries uses high quality diagnostic tests to distinguish between liver cancer and liver cirrhosis and I am not certain that many will be able to diagnose acute HBV infection. Obviously meningitis, paediatric watery diarrhoea and pneumonia will be much more straight forward because there are careful clinical criteria, as used by the IMCI diagnostic indices. This seems to be an important part of the analysis and the proposal does not give any indication of the rigour with which these discharge diagnoses can be made.

The methods for cost analysis are quite straight forward as regards the incremental and marginal costs. These can easily be obtained through field surveys and discussions with officials in ministries of health.

The applicants propose to develop a human capital incidence based cost of illness approach to estimate the direct and indirect costs incurred due to introduction of HBV, Hib and RB vaccines. This will require detailed costing on the clinical, non medical and social costs of the disease. Again, this analysis seems to stand and fall on the rigour of the ability to diagnose their discharge categories, and even meningitis may be largely undiagnosed in primary and secondary health care.

Their final analysis moves on to producing a generic protocol for including cost data on the burden of disease and thereby enabling future researchers to promote a standardised format of reporting cost data.

This application has been carefully put together by experts in the field and it seeks to address an important subject, namely whether it will be cost effective to introduce new vaccines. While in no way seeking to decrease the importance of HBV vaccine, there are considerable differences in the epidemiology of liver cirrhosis and cancer between countries (indeed that is why they are not satisfied with extrapolating from the Gambian data where the diagnostic rigour is high), but the problem is that lack of rigour in diagnosis of adult disease makes if very difficult to perform the cost benefit analyses that they propose. They may have information on the reliability of diagnosis of these HBV preventable diseases and it would have been helpful if they had given them. Similarly Hib has had a major impact on the epidemiology of meningitis and other important infections such as middle ear disease in communities where morbidity is well defined, but

assessment on meningitis (often confused clinically with malaria in field studies) is very likely to be a problem in the three countries that they propose to study. Again, they may well have information which refutes this problem. They could provide this.

Assessment of the epidemiology of acute watery diarrhoea is always extremely difficult except in the presence of carefully performed intervention studies or investigations of specific incidents and prevalence of diarrhoeal disease. The applicants aim to use two types of studies (those prior to implementation and those after implementation). It is not clear from the proposal whether the applicants propose to use the data on vaccine trials or whether they intend to use epidemiological data that were routinely collected in Peru during the introduction of vaccines.

Overall, this is a very important project, to be performed by experts with excellent track records, but I cannot find in the proposal sufficient to enable me to be convinced that the epidemiology of the diseases that they seek to avoid by vaccines will be sufficiently clearly defined. It might be that the authors have this information. If the epidemiology can be really relied on then I would support this application, but at the present time I have problems because of the lack of information about rigour of diagnosis.

KD: Number (Project No.): KD 570

PI/Institution: Dr Felicity Cutts, LSHTM, London

Project Title: Modelling the impact and cost-effectiveness of introducing vaccines against hepatitis B, haemophilus influenzae type b and rotavirus into routine infant immunisation programmes in Bangladesh, Ghana and Peru

Part 2: Appraisal

(a) quality of approach

This is a very important area and the rationale for undertaking this study are well set out in this proposal. The authors have experience of undertaking studies like this in the developing world and are well placed to do the work. However, I believe that the development of the 'model' to which economic data are applied is vital to this study and the way this is to be done and definitions of terms in the proposal could be clarified.

Objectives

The cost analysis objectives are well defined. (page 5). However, in the last objective did the authors mean 'minus the costs of averted disease' and not 'averting disease'?

It is not specifically stated that there will be an incremental cost-effectiveness analysis; although objective 2 of the economic evaluation (page 6) states that the cost-effectiveness of introducing the 3 vaccines into the EPI of the 3 countries will be estimated. Would this involve an incremental analysis to compare cost-effectiveness of ***each added vaccine*** separately so that decision makers could have an option of deciding only to add one vaccine to EPI? The proposal is ambitious in attempting to include societal costs as well in an already quite complex study.

Background

The case for undertaking the study is well set out. It would be useful to have more detail about models of disease transmission, disease prevalence and disease outcomes which have been developed

by CVI in their economic modelling of vaccine-preventable disease, and how they have been used by decision makers to date. The authors state that economic field data have not been yet been applied - how then was the cost-effectiveness of introducing new vaccines estimated as stated in paragraph 1, page 7??

The epidemiology and vaccines for HBV, Hib and RV are well described in the background. The justification for the mathematical models to be used in this proposal are not very clear, and there is little discussion about model validity. To my understanding, models are developed for decision-making purposes and may not necessarily represent reality. However, the parameter ranges in any included model, for example on HBV natural history, would need to be appropriate for the country to which the model was being applied, and could be validated by comparison with appropriate cohort or clinical trial data. The terms "deterministic" and "Markhov" modelling are not well defined. Instead, shouldn't deterministic be compared with scholastic modelling? Markhov modelling describes the process. Thus, one can have deterministic Markhov models which are based on point estimates and not distributions. It is unclear what the point is of comparing deterministic and Markhov models in this proposal (page 7, first para, and also page 12) and whether this is correct? It is also unclear ***how*** comparisons would be undertaken, especially as there is sketchy reference to data upon which assumptions about model parameters would be based on. If good models on mortality and recovery have been developed for HBV and Hib already, surely the appropriate thing would be to ensure the assumptions in those models are relevant to the settings in the 3 countries respectively, before using them in the full analysis of cost-effectiveness.
Whereas it is clear how cost data will be collected, it is not clear how locally relevant parameter values for the diseases in the 3 countries will be decided from the data that are to be collected?

The methods for cost analysis are well described. The methods for modelling are rather confusing as stated above. Although early in the proposal it appeared that currently available models would be adapted, on page 12, second last para, it is stated that 'new mathematical descriptions of HBV, Hib and RV will be developed. There is no detail about how variations in seroprevalence within different groups by country or geographic area within country would be modelled, although this is referred to in the background.
Under 'methods for economic evaluation', it is unclear how the generic protocol will be used in this study and to which studies of 'burden of disease' and 'intervention trials', it will be applied.

(b) applicability of approach beyond the area where it is being undertaken
This area of work could have wide and important applicability beyond the 3 countries named in the proposal. However, I am concerned that a lot rests on the quality of the mathematical modelling, and

although a mathematical modeller is requested, only one years salary will be 'sought from other sources'. It is unclear exactly where, how and with whom this modeller will work and be supervised. I would expect there to be a need for a senior mathematical/'modelling' supervisor as well as close collaboration with the epidemiologists and economist over a longer period of time.

(c) likely contribution of the approach to elimination of poverty and other objectives set out in DFID's purpose statement

High contribution is possible by the nature of the area. If results are clearly set out so that decision makers are able to compare adoption of new vaccines into EPI with other options for expenditure on health care. In order for this to be done, results should be expressed in terms of incremental cost per DALY of introducing a new vaccine.

(d) potential for the approach to improve the capacity of groups in poorer countries to access, generate and apply new knowledge

This will depend on:

1) availability of sufficiently trained decision makers in the area of health-care who can make decisions across a number of areas about the relative cost-effectiveness of different healthcare interventions.
2) availability of similar analyses in other areas of healthcare. for comparison
3) Data collection will be undertaken by local data managers in each participating country and dissemination workshops held in each country. Involvement of members of the research team from each country will increase their experience in working on economic studies.

(e) ethical aspects

There is no mention of ethics approval being sought for data collection from patients. I would have thought that as these data will be entered onto a database, this should be done.

(f) value for money

This is quite an expensive study and yet funding is not sought for the mathematical modeller. More details of this should be included.

Part 3: Recommendation

I think the proposal needs revision, but could then be funded.

RD. Number (Project No.): RD 578 REVIEW 1Y1.

PI/Institution: LSHTM

Project Title: Modelling the impact and cost-effectiveness of introducing vaccines against hepatitis B (HBV), *Haemophilus influenza* type b (Hib) and rotavirus (RV) into routine infant immunisation programmes in Bangladesh, Ghana and Peru

Part 2: Appraisal

Principal knowledge function: generation of new knowledge, techniques or products

(a) Quality of approach

This study looks to be examining an important problem: vaccination is currently highly effective at low cost, there is likely to be significant burden caused by the three diseases chosen, but the costs and impact of vaccination on these diseases is not known. Peru has introduced HBV and Hib vaccination, and Bangladesh and Ghana are considering their introduction and likely to consider RV vaccination once this is licensed.

This proposed study of three diseases aims to collect data on their epidemiology; and use these data to model the impact of vaccination in Bangladesh, Ghana and Peru. For each disease, a deterministic model of transmission (based on differential equations) will be developed, and compared with a simpler stochastic model (based on Markov chains). The impacts of vaccination will be measured in Disability-Adjusted Life Years (DALYs) averted. These DALYs will be related to costs to indicate the cost-utility of the different vaccination options in the three countries. The results will be subjected to sensitivity analysis in each country. A method will be explored to evaluate the cost-utility of vaccines in different settings, and hence indicating what these might be in different countries.

There are questions over modelling, staffing, study design, implementation and dissemination.

Modelling: it would be helpful to know more about how the deterministic and stochastic models are to be compared. Presumably the deterministic model incorporates feedback (the impacts of herd immunity) and the stochastic model does

not. This means that each type of model may have advantages and disadvantages: the deterministic model may better where feedback dominates, and the stochastic model where variation dominates. Hence there may not be a best model in all circumstances. The proposal does not make this clear, nor how their performance will be evaluated in the absence of empirical results on how vaccination actually works.

Staffing: The study depends crucially on the development of deterministic and stochastic models. For this purpose, the research team will recruit a full-time mathematical modeller for two years. The team itself, however, appears to have no mathematical expertise. (It appears to rely on Dr Miller of the Children's Vaccination Initiative in WHO Geneva as a collaborator.) It would be better if the team included an expert who could closely supervise the modelling work, and be available throughout the four years of the study.

Study design: the proposed design of developing models is to first develop a deterministic model for each disease over the first two years, and then spend three months in the third year developing a stochastic model for each disease (allowing a month for each). Might it be better to begin with studying one disease, compare deterministic and stochastic models for that disease to gain understanding of their likely strengths and weaknesses? This sequence offers the opportunity, in developing models for the other diseases, that the researchers may know better what may be important and research may then be designed as a learning process.

Implementation and dissemination: The proposal states that it assumes that policy-makers are influenced by cost-effectiveness analyses and proposes the usual means of dissemination of findings through publication and a workshop. Might it be better to see the delivery of user-friendly models as the main output? And, if so, to begin the project by working with those involved with policies so that they can understand what the models are aiming to do, and also that they can indicate what they would find most useful. In this way models could be developed that address their questions, are easy for them to use and do their own sensitivity analysis.

(b) Applicability of approach beyond the area where it is being undertaken

The proposal states that a method will be explored to evaluate the cost-utility of vaccines in different settings, which will draw on a review of the literature. It would be helpful to know more about this work and when it will be done (this is not clear from the project plan).

(c) Likely contribution of the approach to elimination of poverty and other objectives set out in DFID's purpose statement

If this study were to lead to vaccination that reduced infectious diseases, then would contribute to the elimination of poverty.

(d) Potential for the approach to improve capacity of groups in poorer countries to access, generate and apply new knowledge

The proposal seems to assume that by developing models and subjecting these to sensitivity analysis, the research will generate robust findings and hence provide the

bases of vaccination policies. But the capacity of groups in poorer countries to access, generate and apply new knowledge this new knowledge would be more powerfully achieved by designing models that could be used by those responsible for policies in each country.

(e) Ethical aspects

This study does raise ethical aspects through sampling of patients. There seems no good reason for supposing that ethics approval would be refused.

(f) Value for money

This is good value for the importance of the subject of study and the work entailed.

Part 3: Recommendation

(ii) Support, subject to questions raised over staffing, study design, implementation and dissemination being satisfactorily answered.

KD. Number (Project No.) : [illegible]
PI/Institution : London School of Hygiene and Tropical Medicine
Project Title : Cost-effectiveness of introducing additional infant vaccines.

Part 2: Appraisal

Please identify the principle knowledge function(s) * addressed through this proposal, and - in relation to them - consider:

Generation of new knowledge, techniques or products;

(a) quality of approach (with particular reference to scientific analysis and proposed actions)

The study will examine the cost-effectiveness of introducing vaccines against hep. B (HBV), Haemophilus influenza type b (Hib) and rotavirus (RV) into routine childhood immunisation programmes. The research will be carried out in a number of ways.

1. Mathematical model of HBV and Hib will be modified to examine the effect of vaccination in the Gambia.
2. A new mathematical model of RV will be developed to examine the impact of vaccinations.
3. Cost data will be collected in Bangladesh, Ghana and Peru using standard WHO cost guidelines.
4. Cost together with estimates of incidence from the mathematical models will be combined to assess the cost-effectiveness of the interventions in terms of cost of DALYs gained.

The description of the costing methodology is well structured and comprehensive. The costs will include both direct health costs and indirect community costs. Indirect costs will be assessed using a questionnaire administered to caregivers to provide estimates of amount of time away from productive activities.

The investigators have considerable experience in undertaking economic evaluations in developing countries and evaluating vaccination programmes. The balance of skills appears to be appropriate for the proposed research.

The dynamic mathematical modelling proposed is an interesting way of examining the current and future impacts of vaccinations. These models involve specifying a small system (large systems become complex to solve) of

differential equations that model the progression of individuals from uninfected to infected groups and back again. Testing these models involve obtaining a small amount of critical data on group sizes and estimates of key parameters – rate of exchange of uninfected to infected group, recovery rates, birth and death rates.

The budget includes provision for a mathematician with costs similar to the health economist. This implies that this researcher will be expected to do some significant work in developing the model. It is slightly surprising that the proposal does not include a discussion of the collection of the critical parameters. If the project will largely make use of established models using data already collected then is large mathematical input really required. As it stands the proposal requires HPACORD to commit quite a large amount of money to the development of models with little real discussion of the type of work that will be required and difficulties that will be faced. This is in contrast to the economics work which is well specified with plenty of detail.

(b) applicability of approach beyond the area where it is being undertaken

The theoretical models are general and the use in three very different countries should show how much variation there is in the practical impact.

(c) likely contribution of the approach to elimination of poverty and other objectives set out in DFID's purpose statement -see attached

Vaccines can be a very cost-effective way of providing health care. If cost-effective, the impact of these programmes are likely to substantially benefit poorer groups.

(d) potential for the approach to improve capacity of groups in poorer countries to access, generate and apply new knowledge

It is not clear whether the data analysis will be conducted inside the focal developing countries which would be one way of developing capacity. The proposed workshop will be useful for dissemination.

(e) ethical aspects

- Treatment denied for some: No
- Intervention or interviews conducted with consent: Yes
- Permission sort from local community and administration: Yes
- Data protected: Yes

(f) value for money

Quite expensive. The description of the mathematical work to be done does not properly justify the budget. Value for money is, therefore, ambiguous.

Please note: Your comments may be fed back, unattributed, to the applicants unless you indicate that you do not wish this. Please use square brackets ([ ]) and/or the heading "confidential" to indicate any comments you do not want fed back.

Part 3: Recommendation

Please indicate whether, in your judgement, this application should be (i) supported, (ii) supported with modifications or (iii) rejected.

Possibly support if much more detail of the mathematical models and data required to motivate them is provided.

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* *Knowledge functions that can be supported through HP-ACORD include: Generation of new knowledge, techniques or products; Synthesis and refinement of existing knowledge, techniques or products; Dissemination and communication of refined knowledge, techniques or products for a specified purpose.*

HP-ACORD October 1997