Library

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date 6/12/83
15.1.84

Principal Investigator J Clemens

Application No. 84-002(P)

Title of Study Impact Evaluation of Measles Vaccination in Matlab, 1982-84

ICDDR,B Library
Trainee Investigator (if any)
Dacca—12

Supporting Agency (if Non-ICDDR,B)

Project status:
(✓) New Study (PILOT)
( ) Continuation with change
( ) No change (do not fill out rest of form)

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

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

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

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

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

5. Will signed consent form be required:
   (a) From subjects — Yes (No)
   (b) From parent or guardian (if subjects are minors) — Yes (No)

6. Will precautions be taken to protect anonymity of subjects — (Yes) No

7. Check documents being submitted herewith t Committee:

   ___ Umbrella proposal - Initially submit overview (all other requirements will be submitted with individual studies)
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ___ Statement given or read to subjects o 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 summar
   1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
   2. Examples of the type of specific questions to be asked in the sensitive areas.
   3. An indication as to when the questionnaire will be presented to the Cttee. for review.

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

John F Clemens MD
Principal Investigator

16 JAN 1984
Trainee

SECTION I - RESEARCH PROTOCOL (PILOT)

1. Title: Impact Evaluation of Measles Vaccination in Matlab, 1982-1984.

2. Principal Investigator: John D. Clemens

   Co-Investigators: Bonita F. Stanton, Nigar Shahid, M. Yunus, J. Chakraborty, Bogdan Wojtyniak

3. Starting Date: January 1, 1984

4. Completion Date: November 1, 1984

5. Cost (Approx.): $3,000

6. Scientific Program Head:

   This protocol has been approved by the _____

   Working Group:

   Signature of Scientific Program Head: W. B. S

   Date: 9/1/84

7. Abstract Summary:

Considerable uncertainty exists about the practical effectiveness of attenuated measles vaccine in reducing clinical measles in developing countries, and about the role of the vaccine in reducing the frequency of invasive diarrhoea as well as overall and diarrhoeal-related childhood mortality. To provide data addressing these issues, a measles vaccine program was initiated in March, 1982, in one-half of the Maternal-Child Health (MCH) intervention portion of the Matlab field study area. The remainder of the field study area was left unvaccinated. The present study will evaluate the effects of this program upon several outcomes from March 1982-April 1984. For each outcome, we will use a case-control strategy, comparing the rate of vaccination among "cases" with the outcome of interest vs. the rate in "controls" without the outcome. The odds ratio for each comparison closely approximates the relative risk of the outcome in vaccinees vs. non-vaccinees. Thus, (1-odds ratio), controlling for potentially confounding factors (e.g., age, gender, maternal education,

other childhood mortality in the family, and family size estimates the protective efficacy of the vaccine against the outcome. The effectiveness of the vaccine will be evaluated with respect to the following: Clinical measles (ascertained from ongoing measles surveillance); clinical dysentery requiring treatment (ascertained from patient rosters at Matlab Hospital); diarrhoea and measles-treated deaths (ascertained from DSS rosters); and deaths due to any cause (also ascertained from DSS rosters). In each case-control comparison, all children 9-60 months from the field study area with the outcome of interest will serve as cases; for each case one age and gender matched controls residing in the field study area will be selected randomly from the same birth cohort as the case. We will ensure that each control had not experienced any of the measles-related outcomes under study before the time of the outcome in the case. Information about antecedent measles vaccination will be obtained from record books of community health workers; information about other variables that might confound the relationship between the vaccine and the outcomes under study will be taken from census data.

These retrospective case-control analyses, which can be accomplished more efficiently than a cohort analysis of the vaccine and without loss of validity, will provide valuable information on the practical usefulness of the vaccine for developing countries.

8. Reviews:

a. Research Involving Human Subjects: _____

b. Research Review Committee: _____

c. Director: _____

Objectives:

To evaluate the impact of measles vaccination in areas A and C of the MCH-FP portion of Matlab field study area upon mortality (overall and cause-specific) and morbidity (severe dysentery and measles) in subjects aged 9 months - 5 years.

Background:

Measles is acknowledged to be an important cause of childhood morbidity and mortality in developing countries (1). Although an effective attenuated parenteral vaccine is available for measles (2), considerable controversy surrounds its use in developing countries. Critics of the vaccine argue that the high cost of the vaccine and the need for maintaining a cold-chain make the vaccine impractical for countries with limited resources (3). Questions have also arisen about the effectiveness of the vaccine under field conditions and about whether the prevention of measles does any more than delay by a short period of time the inevitable demise of severely malnourished and compromised children, who are the typical measles fatalities (4). Completely unknown is the impact of the vaccine upon serious diarrhoeal morbidity (5).

To address these uncertainties, ICDDR,B initiated a program of measles vaccination in certain blocks (A and C) of the MCH-FP portion of the Matlab field studies area. In this program, children aged 9 months - 5 years have been immunized with parenteral attenuated live measles vaccine since March, 1982. Vaccination rounds for the intervention areas have

been repeated at 3-month intervals so that a stable level of 80% coverage of potential recipients has been maintained. Concurrently, several types of surveillance have been maintained. Firstly, morbidity surveillance for measles cases has been carried out in Matlab since 1979. This surveillance is carried out by health assistants who visit each home in the MCH-FP and comparison areas on a monthly basis.During each such visit, historical inquiries are made about measles cases occurring during the past month; and specific signs, symptoms, and complications of measles are noted. Secondly, the Demographic Surveillance System (DSS) of Matlab has for many years maintained on accurate registration of deaths in the field study area and has tabulated cause-specific mortality on the basis of lay-reporting. Thirdly, Matlab Hospital maintains an ongoing registry of patients presenting for care of diarrhoea. Sufficient clinical details are available to classify diarrhoea by severity, and patients are identified by village location within the field studies area.

Methods:

General

Because this study will evaluate the efficacy of measles vaccine against rare outcomes (e.g., death, serious diarrhoea), the case-control design will be employed for the evaluations. In this design, "cases" with the outcome of interest will be compared with "controls",lacking the outcome, for histories of antecedent vaccination. The standard measure of association for such assessments is the odds ratio; (1-odds ratio), controlling for potentially confounding variables, estimates the vaccine's protective efficacy against the outcome. Separate case-control analyses

will be conducted for mortality, serious diarrhoeal morbidity, and measles.

Sampling Frame:

Subjects will be selected from the population living in the Matlab field study area between March 1, 1982 and April 1, 1984.

Eligibility:

To be eligible, both cases and controls must be aged between 9-59 months at the time of the outcome for the case and must have been born in Matlab field study area. No constraints will be placed upon the particular location of residence within the field study area.

Cases: Definition and Selection

1. Death analysis:

   For this analysis, cases will be all deaths among children aged 9-59 months who are otherwise eligible for the study. These deaths will be ascertained from DSS registers.

2. Dysentery morbidity analysis:

   For this analysis, cases will be all eligible children aged 9-59 months with dysentery (bloody diarrhoea) requiring care at Matlab Hospital. Identification of these cases will be accomplished through Hospital registers.

3. Measles Morbidity Analysis:

For this analysis, cases will be eligible children aged 9-59 months with measles identified through DSS surveillance. To qualify as a case of measles, a subject must have a history of rash, coryza, and fever. A subject will be excluded if the diagnosis of measles is made in the context of a family outbreak involving family members >10 years of age.

Controls: Definition and Selection:

The basic strategy for selecting controls in each of the three analyses will be similar. First, birth cohorts, arranged by month and year of birth, will be produced for all children who were aged 9-59 months at any time during the study interval (March 1, 1982 - April 1, 1984). Second, using simple, formally random selection, one control aged 9-59 months will be selected for each case. Third, it will be ascertained that each control a) (in all analyses) was alive at the time of the outcome event of the case (using DSS census lists); b) (in the measles morbidity analysis) did not have measles during the study interval (using DSS Surveillance lists); c) (in the diarrhoea analysis) had no inpatient or outpatient care and when for diarrhoea at Matlab Hospital using patient rosters). Potential controls fulfilling all of these criteria will be selected for analysis.

Ascertainment of Measles Vaccination:

After selection for the study, the measles vaccination history, including date of vaccination, will be ascertained for each subject

selected for the study. Histories will be obtained by consulting field books of the community health workers in the areas where subjects resided during the study interval.

Prevention and Control of Bias:

In a retrospective study of this type, several biases may occur. To safeguard against bias, several measures will be taken. First, the ascertainment of eligibility and the selection of cases and controls will be accomplished without knowledge of the study areas or of specific vaccination histories. Second, in the determination of vaccination histories, no information will be provided about the status of the subject as a case or control. Third, use of birth cohorts for subject selection will allow us to prevent migration biases that arise when subjects "immigrate" into a study population during the course of a study, and will permit us to estimate whether bias could have occurred as a result of subject migration out of the study area. Fourth, several sources of confounding will be controlled in the analysis. Potential confounding factors include gender, history of measles before the study interval, geographic patterns of utilization of Matlab Hospital (for the dysentery analysis), family SES, maternal education, family size, and childhood mortality before the death of the case (for the death analysis). Information about these variables will be obtained through the existing DSS data bank on all Matlab families, as well as from the specific surveillance for measles that has been implemented since 1979.

Analyses

1. Sample Size:

a. Death Analysis:

Based on earlier work in Bangladesh (6), we estimate that 50% of deaths in the following categories will be related to measles, and will hence be potentially preventable by vaccination: dysentery, diarrhoea, dropsy, respiratory, and measles. Based on cause-specific mortality rates from Matlab (7), we expect that there will be about 600 deaths in these 5 categories. With this sample and with an equal number of controls, we shall be able to detect 80% efficacy of the vaccine against measles-related deaths in these categories with .8 power. We will also evaluate the impact of the vaccine upon all deaths using the ~ 1000 available deaths as cases and with equal numbers of controls.

b. Dysentery Analyses:

Based on surveillance data from Dhaka (8) and Matlab (9), we expect 500 cases of dysentery among eligible children during the study interval. With an equal number of controls, we will able to detect with .8 power a one-third overall reduction of dysentery by the vaccine. If 42% of serious dysentery cases were related to measles, such a reduction would correspond to 80% vaccine efficacy.

c. Measles Analysis:

Preliminary inspection of DSS measles surveillance data indicates that approximately 500 eligible measles cases will be available for analysis. Selecting one control for each case, this sample will permit us to detect protective efficacy rates of ≥40% with .8 power, and of ≥50% with .95 power.

It should be noted that the total anticipated sample size for all three analyses is 4000 subjects. It can readily be appreciated that this approach is considerably more efficient, as well as more powerful, then performing a simple cohort study comparing the outcomes of the ~5000 subjects who have been vaccinated to date and a suitable unvaccinated control group.

2. Estimation of Vaccine Efficacy:

As noted earlier, the expression (1-odds ratio) for each 2 x 2 outcome vs. vaccination analysis estimates vaccine protective efficacy. To adjust for the potential confounding effects of gender, SES, maternal education, access to care, and the other variables already mentioned, multiple logistic regression will be used. With multiple logistic regression, the regression coefficient for the vaccination variable equals the ln (odds ratio) relating the outcome to vaccination. By placing potential confounding variables in the model, the coefficient (β) for vaccination is adjusted for the confounding effect of these

variables. An estimate of protective efficacy that "adjusts" for these variables is thereby obtained by taking the expression (1-antiln β).

3. Analytic Strategy: Pragmatic Considerations:

It is possible that the above analyses will require more funding then is possible with a pilot protocol. The work will therefore be performed in stages, analyzing mortality and measles morbidity first. If it becomes clear that more resources are required, a full protocol will be submitted.

REFERENCES

1. Walsh, J. Selective primary breath care: Strategies for control of diseases in the developing world. IV Measles. Rev. Inf. Dis. 1983. 5:330-340.

2. Anon. Rationalizing measles vaccinations. 1981. Lancet, 2:236-237.

3. McBean, A.M., Foster, S.O., Heuman, K.L., Gateff, C. Evaluation of mass measles immunization campaign in Yaovade, Cameroun. Trans. Roy. Soc. Trop. Med. 1976, 70-206-212.

4. The Kasongo Project Team. Influence of measles vaccination on survival patterns of 7-35 month-old children in Kasongo, Zaire. Lancet, 1981, 1:764-767.

5. Feachem, R., Koblinsky, M. Interventions for the control of diarrhoel diseases among young children: Measles immunization. Bull WHO. 1983, 61:641-652.

6. Koster, F., Curlin , G., Aziz, K., Haque, A. Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. Bull WHO. 1981, 59:901-908.

7. Zimicki, S. Unpublished data.

8. Stoll, B., Glass, R., Huq, M., Khan, M., Holt J., Banu, H. Surveillance of patients attending a diarrhoeal disease hospital in Bangladesh. Br. Med. J. 1982, 285:1185-1188.

9. Zimicki, S., Yunus, M., Chakraborty, J., D'Souza, S. A field trial of home-prepared oral rehydration solution in rural Bangladesh. Submitted for publication.

A. DETAILED BUDGET

1. PERSONNEL SERCICES

Name	Position	% of effort	Annual Salary	Project Requirement Taka	Dollar
Dr. J. Clemens	P. Investigator	30%	-	-	-
Dr. B. Stanton	C. Investigator	10%	-	-	-
Dr. N. Shahid	C. Investigator	10%	-	-	-
Mr. J. Chakrabarty	C. Investigator	10%	-	-	-
Dr. M. Yunus	C. Investigator	10%	-	-	-
Dr. B. Wojtynyak	C. Investigator	10%	-	-	-
To be named	Coding Assistant	50%	Tk. 46,000	23,000.00	-
To be named	Health Assistant	20%	$ 2,951	-	590.0
			Sub-total:	23,000.00	590.0

2. SUPPLIES AND MATERIALS - Office supplies and xeroxing - - 150.0

3. EQUIPMENT - None

4. PATIENT HOSPITALIZATION - None

5. OUTPATIENT CARE - None

6. ICDDR,B TRANSPORT - None

7-8. TRAVEL AND TRANSPORT OF PERSON AND THING - None

9. RENT AND COMMUNICATION - None

10. PRINTING OF DATA FORMS - 250.0

11. OTHER CONTRACTUAL SERVICES:

Computer Data Entry and Editing	3,634.00	-
Computer Programming	15,000.00	
Computer Time (40 hours @ Tk. 200/hour)	8,000.00	-
Sub-total:	26,634.00	-

12. CONSTRUCTION, RENOVATION & ALTERATIONS - None

B. BUDGET SUMMARY

		Taka	Dollar
1.	Personnel Services -	23,000.00	590.00
2.	Supplies and Materials -	-	150.00
3.	Equipment -	-	-
4.	Patient Hospitalization -	-	-
5.	Outpatient Care -	-	-
6.	ICDDR,B Transport -	-	-
7 & 8.	Travel & Transport of Persons & Things -	-	-
9.	Rent and Communication -	-	-
10.	Printing of Data Form -	-	250.00
11.	Other Contractual Services -	26,634.00	-
12.	Construction, Renovation & Alteration -	-	-
	Total:	49,634.00	990.00

Grand Total: US$ 2,999.47

U.S.$ 1.00=Tk. 24.70

ABSTRACT SUMMRY

1. The study population will consist of children aged 9 months - 6 years who have been eligible for the routine measles vaccination program in Matlab between March 1982 and April 1984. This study is entirely retrospective, using routine data acquired by DSS and Matlab Hospital, and hence requires no direct interview.

2. No risks will be involved.

3. No risks will involved.

4. All records will be kept in a locked file cabinet and subjects will be identified by code number only.

5. No consent will be required, since only information that has been obtained in the course of the routine activities of the Matlab field study area will be used.

6. No interview will be required.

7. There are no risks. Benefits include new information about the usefulness of measles vaccination and its applicability to developing countries.

8. This research will require the use of DSS census records, as well as Matlab Hospital medical records.