Library

Attachment 1.
FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date ~~Jan 26/94~~ Aug. 9/94

Principal Investigator A. DE FRANCISCO

Application No. 94-014

Title of Study PERSISTENCE OF TETHNUS ANTIBODY IN WOMEN IMMUNIZED WITH DIFFERENT IMMUNIZATION SCHEDULES...

Trainee Investigator (if any) _____

Supporting Agency (if Non-ICDDR,B) _____

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

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

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

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

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

Principal Investigator

ENTERED 2 1 JUN 1994

Trainee

APPLICATION FOR PROJECT GRANT

1.	Principal investigator	:	Dr. A. De Francisco
2.	Co- Principal Investigator	:	Mr. J. Chakraborty Dr. J. Albert Prof. R.B. Sack
3.	Title of project	:	Persistence of Tetanus Toxoid antibody in women immunized with different immunization schedules in rural Bangladesh
4.	Starting date	:	As soon as possible
5.	Date of completion	:	After nine months
6.	Funding source	:	
7.	Total budget requested	:	US$33038.
8.	Head of programme	:	

Ilmaaziz

Dr. K.M.A. Aziz
Acting Head
Community Health Division

August 1994

INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASES RESEARCH, BANGLADESH
MATERNAL AND CHILD HEALTH AND FAMILY PLANNING PROGRAMME

PERSISTENCE OF TETANUS TOXOID ANTIBODY IN WOMEN IMMUNIZED WITH DIFFERENT IMMUNIZATION SCHEDULES IN RURAL BANGLADESH

PROPOSAL FOR A STUDY IN MATLAB

Dr. A. DE FRANCISCO,
Matlab MCH-FP Project Director

Mr. J. CHAKRABORTY,
Manager, MCH-FP Programme

Dr. J. ALBERT,
Scientist, Laboratory Sciences Division

Prof. RB. SACK,
Associate Director, Community Health
and Laboratory Sciences Divisions

ABSTRACT

Tetanus Toxoid (TT) vaccination either during pregnancy or during female reproductive life is undoubtedly an important intervention. TT immunisation, through antibodies passed from the mother to the offspring in utero, protects the neonatal against tetanus mortality. It also protects the mother against tetanus and creates an important contact with the health services. Current recommendations are that at least three TT doses are required to protect mothers and newborns and that five doses protect them for life. However, available information from a demographic study from Matlab indicates that the protection of one or two TT doses may be higher than previously thought.

In Matlab, we know that with a very high vaccination coverage (98% of women in reproductive age at present) neonatal tetanus is practically eradicated. However, numbers of TT doses given to women in the programme range from 0 to 12. We do not know, at present, what the protection of each dose, or if three doses may protect for more than five years or not. This can be addressed with a cross-sectional survey by evaluating antibody levels of women vaccinated with different total TT doses by the Programme. The rational for this is that if less than five TT doses may protect for life, the savings in time and resources for the EPI Programme in Bangladesh would be enormous.

Further, it is not known if vaccination during infancy may affect the number of doses required during reproductive life. One may like to think that if a female infant received three doses of DPT (which has Tetanus Toxoid on it), when reaching reproductive age she will not require a further five doses for complete immunization. It is not known if DPT vaccination during infancy will prime T cells during infancy and therefore, lead to a better response to TT during adulthood. We propose to address this issue by including in this cross-sectional survey women who participated in the 1974 cholera vaccine trial (which used TT as a placebo), we can see current antibody levels of women who were vaccinated during reproductive life with various total doses who had received 0, 1 or 2 TT doses during 1974 when they were infants.

INTRODUCTION

In developing countries, where a great proportion of deliveries occur outside the reach of the health services and the characteristics of these deliveries are generally unhygienic, Maternity Care Programmes rely heavily on Tetanus Toxoid (TT) immunization for the control of neonatal tetanus. Considerable efforts are placed on immunising either pregnant women or all women of reproductive age.

Vaccination of pregnant women with TT reduces the incidence of neonatal tetanus.**(1-5)** The transfer of antibodies to the fetus after maternal immunization with aluminum-adjuvant-adsorbed TT has been well described.**(6)** Fetal antibody titres rise progressively from the fourth month of pregnancy reaching concentrations at birth equal or higher than the mother's titres.**(6,7)** A fall in maternal serum antibody concentrations after primary and booster vaccinations over time are well described.**(10)** Protection against infection by C. tetani is assumed to be directly proportional to the anti-toxin level in serum and has been described as 0.01 unit/ml.**(1,6,7)**

Even though contradictory reports have been published regarding the duration of clinical protection that follows one or more TT doses,**(1,8,9)** the World Health Organisation recommends the application of five doses of TT during reproductive life; two doses should be given during the first pregnancy as widely apart as possible but with the last one applied a maximum of four weeks before delivery.**(1,3,6,7,11)** Two doses are claimed to protect the infants of 80% of women for the following three years. After that period, however, a maternal booster is required in order to protect the next newborn and/or the mother.**(1)** A third TT dose will protect mother and newborns for up to five years,**(1,6)** and a fourth dose, for up to 10 years.**(6)** Five TT doses are reported to give protection for life in 99 percent of the cases.**(12)**

These calculations have arisen from studies carried out in American Soldiers.**(6)** However, these recommendations have been questioned and it has even been postulated that protective levels of antitoxin may last up to 20 years.**(13,14)** Even though TT is a safe and relatively cheap vaccine,**(11)** and although secondary reactions are uncommon,**(15)** serious questioning on issues of over-immunization have been raised in developed countries.**(8,9)** Unnecessary doses would affect the EPI system by competing with availability of other EPI routine vaccines as well as with health worker's time to deliver them.

As EPI programmes around the world increase their DPT coverage**(17)**, infants are becoming increasingly exposed to the

Tetanus Toxoid component of the DPT. It is not known if the early contact with the Tetanus Toxoid component of the DPT can prime the immunological system and have an effect on the response to TT vaccination later in life. In other words, it is not known if a woman who received three DPT doses during infancy will respond better to a TT dose given during reproductive age than a woman who did not receive three DPT doses during infancy. The former may be possible, as it is known that higher antibody levels are induced after the second TT shot than after the first one.**(6,7)**

In order to address which number of TT doses may be required for achieving adequate protection for the newborns, a cross-sectional survey of women whose immunization history is well documented in a rural area of Bangladesh is proposed. The findings of this study may influence the immunisation policies with TT in developing countries.

OBJECTIVES

Main objectives

1- To evaluate the antibody levels achieved by each TT dose in a highly vaccinated population of women of reproductive age in rural Bangladesh.

2- To evaluate if fewer doses than those recommended currently may be acceptable to reach appropriate, sustained antibody levels.

Secondary objectives

1- To evaluate the influence of infant immunisation with Tetanus Toxoid on the TT vaccination response during adulthood.

2- To review the role of other priming doses on TT immunization schedules.

MATERIALS AND METHODS

Study population

The Matlab MCH-FP Programme provides health services and conducts epidemiological and operational research in a population of approximately 16,000 women in reproductive age and their children under five years. Tetanus Toxoid has been given to pregnant women in the area since 1978 and to all women of reproductive age since 1985 following Government recommendations. The Programme has kept information on dates of immunisations administered for almost two decades. Recent studies showed that immunisations with TT are almost entirely given by ICDDR,B in this area. Currently, the coverage of eligible women with TT immunisation is about 98%. Community Health Workers of the Programme gave an average of 4,500 TT doses at home during 1993. There are still between 1 and 4 neonatal tetanus deaths in the area reported by the Demographical Surveillance System in the area every year.

Tetanus Toxoid and the cholera vaccine trial of 1974

A double blind, randomised, placebo controlled cholera toxoid vaccine trial was carried out in Matlab in 1974 to estimate cholera vaccine efficacy.**(19,20)** The placebo used was 0.5 ml of aluminum phosphate tetanus-diphtheria toxoid.**(21)** The randomisation was done at the individual level. One intramuscular dose of aluminum phosphate-absorbed Td toxoid was given to 13,220 individuals of all ages, and two doses, with 42 days between them were given to 33,175 individuals. Subsequent analysis showed marked reductions in neonatal mortality after immunisation with TT,**(21)** and this effect seemed to be long lasting.**(22)** The findings of the latter study imply that women who received two TT doses may have a long lasting protection against neonatal tetanus mortality, and those with only one TT dose may also experience lower early neonatal mortality.

A total of **163 women** who took part in the 1974 cholera vaccine trial as children (0-4 years of age) have been detected. They received either 0 TT (n=79), 1 TT (n=25) or 2 TT (n=59) doses during the 1974 cholera vaccine trial, and received one dose recently. These women are now living in Matlab and would potentially be available for this study. The Record Keeping System (RKS) keeps data on dates of immunisation and on their location.

STUDY DESIGN

A cross-sectional survey will be conducted in order to evaluate the antibody levels of women in reproductive age who have been vaccinated with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 TT doses in their lives. Women will be chosen from vaccination records of the Record Keeping System of the MCH-FP Programme by selecting them depending on the vaccination experience (i.e., total TT doses given). They will be selected from the computer data files through identification numbers to cover the whole of the MCH-FP area in order to avoid clustering. However, all of them will have received the last vaccination dose at least one year before the study.

Women detected through this system will be approached by a senior health assistant and will be requested to participate. All women included in the study will have received a TT dose longer than one year before the study, since we want to compare decay of protective antibody levels in the various groups. A blood sample will be taken by finger stick, labelled appropriately and placed in a microtainer. Samples will be sent to Matlab, centrifuged on the same day and frozen at -20^{0} C until all samples have been collected. All women taking part in the study **will be bled by finger stick only once.**

1974 cohort

All women who participated in the 1974 vaccine trial who are currently present in the Matlab MCH-FP area will be requested to participate. Mother's '1974' vaccination status and their subsequent vaccination experience with TT will be subsequently extracted from existing data files. Information on their antibody levels will be subsequently evaluated in the light of their number of vaccines received during reproductive age as well as the number of vaccines received during infancy in 1974.

Sample size

The minimum protective antibody level is widely acknowledged. Protection is assumed to be directly proportional to the anti-toxin level in serum and has been described as 0.01 unit/ml.**(1,6,7)** Data of mean titres of serum tetanus antitoxin after two TT doses shows that about 70% of adults have a high antibody titre nine months after two doses but about 30% have lost the titres.**(7,23)**

The study design allows to evaluate antibody levels only on women who have had their last dose longer than one year before. Preliminary information from data files of doses given since 1981 indicate that by 1992, about 2000 women have received no doses, 1000 have received one dose, 1000 have received 2 doses, 800 three doses, 500 four doses, 300 five doses and 500 more than five doses. The records indicate that there are mothers who have received up to 12 TT doses.

In the present study, we intend to select the following groups of women to be recruited depending on the number of doses received:

DOSES RECEIVED DURING HER LIFE*	NUMBER OF WOMEN TO BE SELECTED
1	100
2	100
3	100
4-7	100
8+	100
	500

* **Includes doses received during infancy.**

1974 cohort

The following table shows the women who participated in the 1974 study and who are currently living in the MCH-FP area by their vaccination experience:

Number of doses received up to 1993*	Number of TT doses received in 1974			TOTAL
	0	1	2	
1	2	2	3	7
2	40	13	35	88
3	31	5	17	53
4+	6	5	4	15
TOTAL	79	25	59	163

* at least one TT was given in 1993.

The sample size is calculated based on the proportions of vaccinated women who have protective levels of antibodies by their vaccination status in infancy. A comparison between 0 TT and 2 TT doses received in 1974 will be performed. We will assume that 60% of women of the group 0 TT in 1974 will still be protected after two and three doses before 1993. In order to detect an increase to 85% of protection in the group which received 2 TT doses during infancy, with a power of 80% and an alpha error of 5%, we require about 57 women in each group.

All 163 women who participated in the 1974 study will be requested to participate and are included in the 500 women who will be recruited.

RELEVANCE OF THE STUDY

Demographical information emerging from Matlab seems to indicate that fewer TT doses than those which are actually being given protect against neonatal mortality (i.e. neonatal tetanus)(22). The MCH-FP Programme, and the National EPI Programme, is giving high priority to increase coverage of TT vaccination. Neonatal tetanus deaths are scanty in the MCH-FP intervention area, but we actually do not know if we are 'over-vaccinating' our population. Extrapolated to the Government services, a recommendation to vaccinate with less doses than the ones required today would release stress on vaccination programmes all over Bangladesh.

The study intends to evaluate the TT antibody levels achieved through the total number of doses given to women in reproductive age. It will also address the issue of possible effects of infant vaccination on vaccination schedules for adults. If infant vaccination has a beneficial effect on tetanus toxoid immunological responses during reproductive life, vaccination programmes operating with a high DPT coverage may have to review the current recommendations for TT doses. This may lead to a reduction of actual doses required by women in reproductive age.

This is a unique opportunity to address that issue as Matlab if probably the only place in the developing world where accurate records of vaccination profiles exist for the last 20 years.

ETHICAL CONSIDERATIONS

All women will have the study explained to them by the CHW. Women who have received TT vaccination in the past have the purpose of the injection explained when they receive their TT dose. We consider it ethical to evaluate the antibody levels resulting from TT vaccination. This may, in turn, reduce the number of doses of vaccines recommended to women of reproductive age. Women detected to have been vaccinated with two doses and who don't have appropriate antibody levels will be revaccinated.

We envisage no problems in the collection and handling of blood samples by finger stick.

ANALYSIS

Estimated proportions of women with protective antibody levels in the various groups will be tested by X^2 and Mantel-Haenzel tests. We will attempt to compare mean values of antibody levels, and t tests will be used to test significance.

A comparison of the current proportions of protected women who were vaccinated with either 0, 1 or 2 TT doses in 1974 will be drawn taking into account the number of subsequent doses received.

LABORATORY METHODS

Blood will be collected by finger stick into a microtainer and transported on the same day to the Laboratory in Matlab. The samples will be centrifuged and frozen.

The sera will be stored at - 20°C until tested. The serum tetanus antibody titre will be determined by an ELISA described by Sedgwick *et al.* **(24)** Microtitre plates will be coated with tetanus toxoid antigen. The antigen will be treated with varying dilutions of human serum. The antigen-antibody reaction will be detected by reacting with anti-human species immunoglobulin conjugated to horseradish peroxidase enzyme and its substrate.

The ELISA will have a pooled serum as an internal control and a standard tetanus immunoglobulin (World Health Organisation or Cutter Laboratories, Berkeley, California, USA) for calculation of antibody levels as international units (IU) per millilitre of serum. Using the standard tetanus immunoglobulin,

"ELISA area" will be calculated. The "ELISA area" will be plotted against IU per ml of antitoxin as a log-log plot. This curve will be used to extrapolate the "ELISA area" of test samples to find out the antitoxin content (IU per ml).

STUDY DURATION

It is required to select women to be included in the study from the computer data files, including those who participated in the 1974 study. It is envisaged that all blood samples will be collected within a period of six months. The total duration of the study, including sample processing, analysis and report writing will last a total of nine months.

REFERENCES

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A3

INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH
MATERNAL AND CHILD HEALTH AND FAMILY PLANNING PROGRAMME
PERSISTANCE OF TETANUS TOXOID ANTIBODY IN WOMEN IMMUNIZED WITH DIFFERENT IMMUNIZATION SCHDULES

DETAILED BUDGET

US DOLLARS

3100 LOCAL SALARIES

DESIGNATION	LEVEL	POSITIONS	MAN-MONTHS	RATE/MONTH	TOTAL
Manager H.S.	NOC	1	1	1200	1200
Techn Lab Dhaka	NOA	1	6	650	3900
Research Assis.	GS4	1	6	280	1680
SHA	GS4	1	6	280	1680
Techn. Lab Matlab	GS3	1	6	300	1800
CHW	CHW	10	3	90	2700
3200 INTERNATIONAL STAFF					
MCH-FP Physician	P5	1	1	7060	7060
				TOTAL STAFF	20020

3700 SUPPLIES AND DRUGS

CODE	ITEM	
3708	Lab. supplies	4000
	TOTAL SUPPLIES	4000

4800 INTERDEPARTMENTAL SERVICES

4802	Transport Dhaka	100
4803	Transport Matlab	100
4804	Water transport Matlab	1000
	TOTAL INTERDEPT	1200

TOTAL DIRECT COSTS	25220
overheads (31%)	7818
TOTAL PROJECT COST	33038

7/8/94

PERSISTENCE OF TETANUS TOXOID ANTIBODY IN WOMEN IMMUNIZED WITH DIFFERENT IMMUNIZATION SCHEDULES IN RURAL BANGLADESH

C O N S E N T F O R M

You have been vaccinated by the Community Health Worker of the Maternal and Child Health and Family Planning Programme with Tetanus Toxoid vaccine to prevent neonatal tetanus. Neonatal tetanus is a serious disease which affects some infants soon after delivery. Fortunately, the vaccine given to you by the Community Health Worker should protect you and your subsequent babies against this disease. The Community Health Workers have been requested to help the Programme find out how many doses of Tetanus Toxoid vaccine are necessary to fully protect you against that disease.

In order to achieve this, the Programme wants to see what is your level of protection after the doses which you have been given. For this, a senior health assistant from the programme will require to take a small sample of blood from your finger and place it in a small container. You will feel some pain in the place of the puncture but this will cease soon after. This sample of blood will be taken to the laboratory and examined to see what you protection level is against that disease. You will be informed of the result of your protection level. If we see that your protection is low against the disease, we will instruct the Community Health Worker to re-vaccinate you.

I agree to participate in this study to find out the protection I have now against neonatal tetanus.

_____ _____

Mother's left thumbprint or signature Date (DD/MM/YY)

_____ _____

Mother's name Witness' name

_____

Mother's CID

Ext. Reviews (1)

CONFIDENTIAL

18 November, 1993

R. Bradley Sack, M.D., Sc.D
Associate Director and Head
Community Health and Laboratory
Sciences Divisions

Dear Brad:

Infant DPT immunization and adult response to TT

Thank you for your letter of 14 November requesting my review of the protocol addressing the above issue. While I of course appreciate being asked for my views, I am not an expert in this subject. I would suggest that you send this protocol to the Expanded Programme on Immunization, WHO/Geneva, asking for their comments. The individual most knowledgeable in this area is Dr Artur Galazka of the EPI staff.

I will offer a few comments myself, but these are impressions based on memory and must not be considered authoritative. I believe that the effect of DPT immunization in infancy on responses to TT immunization later in life is in fact well enough documented to provide the basis for the policy being recommended by the EPI. The 'five dose' schedule referred to in the protocol encompasses the doses given in infancy, with the proviso that the three doses given before 12 months of age only be counted as two, given the less than optimal intervals between them. So it might well be that the questions to be addressed by the study would need to be a bit more specific in order to add significantly to our knowledge in this area. I also have the impression that the ELIZA test being proposed may not be adequate, at least not without a direct comparison to the neutralization test. But here I am getting far out of my depth!

I note that the budget proposed for this study is some US$ 55,000. This seems high to me, especially if a result of major public health significance is not expected. I note among other things $2,500 for the principal investigator to travel to London and $3,000 for a computer. There is also an overhead charge of $13,000 (31%). Most of the cost, understandably, is in staff time ($28,600). The 3 man-months time needed from 20 CHW's seems reasonable, as does the cost. But there seems to be a rather large component of time (some 3.5 man-years) required of other supporting staff. I guess if I were called upon to fund this study out of my own programme resources I would find it too expensive.

I do hope that you will also ask EPI for their comments. Perhaps you would also care to share this letter with them so they could correct any errors I have made.

With best personal regards,

Yours sincerely,

cc: - Dr de Francisco

WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

EXT. REVIEW (2)

Téléphone Central/Exchange: 791.21.11
Direct: 791

4415

In reply please refer to :
Prière de rappeler la référence:

I8/372/2 ICD

Dr R. Bradley Sack
Associate Director and Head
Community Health and
Laboratory Sciences Divisions
International Center for
Diarrhoeal Disease Research
GPO Box 128
Dhaka - 1000
Bangladesh

1 December 1993

CONFIDENTIAL

Dear Dr Sack,

Thank you for your letter of 15 November concerning the study proposal on: "The effect of DPT vaccination during infancy on tetanus toxoid protection during adulthood of women in reproductive age".

First of all, I would like to say that the study determined by the above mentioned title would be of great value in better understanding the postvaccinal immunity. There are insufficient data on the duration of tetanus immunity following three primary doses of DPT vaccine given early in infancy. Early observation of Scheibel from Denmark suggested long-lasting immunity following two doses of DT vaccine reinforced with a third dose. However, other studies (Collier et al. 1979) suggested the possibility of an insufficient response to booster dose given 15 years after primary series. The booster response may vary individually and a pronounced dispersion of antibody levels can be expected with time following a primary series. The current knowledge on these issues and a guidelines for reduced number of tetanus toxoid doses for women who were immunized in the past are reviewed in the attached EPI document WHO/EPI/GEN/93.13, published within the series The Immunological Basis for Immunization.

Having said so, I have to mention that the content of the study proposal does not correspond with the promising title. If I understand properly the study design, 163 women who took part in the 1974 cholera vaccine trial will participate in the study. They received 0, 1, or 2 doses of aluminium phosphate-adsorbed Td toxoid at the age 0 to 4 years. This is clearly not the same as the routine early immunization with DPT vaccine given in the first 5 months of life.

Furthermore, it would be rather difficult to assess the role of the primary series of Td vaccine in women who received 3, 4 or more doses of tetanus toxoid in their reproductive age.

Finally, the study will deal with the level of tetanus antibody tested in vitro and not with protection against tetanus. The term "protective level" of antibodies is often misused when it is assumed that the level of 0.01 IU/ml as determined by in vitro technique (HA, ELISA, or RIA) is equivalent to the same level of antitoxin determined by the neutralization method.

In conclusion, I would suggest to accept the study protocol under the changed title: "Persistence of tetanus antibody in women immunized with different immunization schedules in their infancy and adulthood". Such a study can provide some useful information on the impact of the number of Td/TT doses on the persisting tetanus antibody.

A study, designed specially to assess the duration of tetanus antibody levels following three early doses of DPT vaccine and the capacity to answer to booster doses administered following various intervals is still needed.

I hope my remarks will be of some help. We are usually not accepting an honorarium for reviewing a study proposal. Please use it for immunization fund in Dhaka.

Best regards.

ANSWER TO THE EXTERNAL REVIEWERS

THE EFFECT OF DPT VACCINATION DURING INFANCY ON TETANUS TOXOID PROTECTION DURING ADULTHOOD OF WOMEN IN REPRODUCTIVE AGE

I-

The first reviewer acknowledges that the protocol should be sent to the EPI Unit in WHO, Geneva. He raises questions on the budget, stating that US 55,000 is too high for this study.

The budget has been revised accordingly.

II-

The WHO reviewer raises questions about the title: **THE EFFECT OF DPT VACCINATION DURING INFANCY ON TETANUS TOXOID PROTECTION DURING ADULTHOOD OF WOMEN IN REPRODUCTIVE AGE.** That title intended to show the potential main finding of the study.

I have changed the title to: **PERSISTENCE OF TETANUS ANTIBODY IN WOMEN IMMUNIZED WITH DIFFERENT IMMUNIZATION SCHEDULES IN RURAL BANGLADESH.** The new title is more in line with the objectives of the protocol.

The reviewer accepts that the protocol can provide useful information on the impact of the number of Td/TT doses on the persisting tetanus antibody and recommends further studies. I agree with this statement and would add that the only place with this a unique long term recording system in which such vital information for EPI Programmes can be studied is Matlab.

A. de Francisco