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REVIEW BOARD ON THE USE OF HUMAN VOLUNTEERS Date 12.1.78
CRL

Principal Investigator Michael H. Merson Trainee investigator(if any) _____

Application No 78-004 Supporting Agency(if Non-CRL) _____

Title of study Pre-test of Cholera Vaccines for the 1978 Cholera Vaccine Field Trial

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

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

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 possibly 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
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 Board for review.

We agree to obtain approval of the Review Board on Use of Human Volunteers for any changes involving the rights and welfare of subjects before making such change.

Michael H. Merson
Principal Investigator

Trainee

Please return 2 copies of entire protocol to Chairman, Review Board on Use of Human

Rec'd 12/1/78
78-004

SECTION I - RESEARCH PROTOCOL

1. Title: Pre-test of Cholera Vaccines for the 1978 Cholera Vaccine Field Trial.

2. Principal Investigator: Michael H. Merson.

3. Starting Date: January 23, 1978.

4. Completion Date: April 1, 1978.

5. Total Direct Cost: $6,000.00 (incremental).

6. Abstract Summary:

Three new cholera vaccine products manufactured by Wellcome Foundation, London, will be field tested to confirm their safety and determine their immunogenicity in approximately 1030 Bangladeshis living in the CRL Vaccine Trial Surveillance (VTS) area. These vaccines are: (1) an aluminum-hydroxide adjuvanted, formalin-treated cholera toxoid; (2) an aluminum hydroxide adjuvanted cholera whole cell vaccine, and (3) a vaccine containing both the toxoid and whole cell vaccine. Tetanus toxoid will be administered as a placebo vaccine. All vaccinees will receive two 0.5 ml injections of one of the cholera vaccines or of tetanus toxoid at 6 week intervals. Physicians will examine each vaccinee on the day of inoculation, for 4 days following, and 14 days after each injection. Fingertip blood specimens will be obtained on the day of each inoculation and 2 weeks after for determination of vibriocidal and antitoxin responses to the vaccines. If the cholera vaccines are found to be safe, a large scale field trial will be conducted with the vaccines prior to the fall 1978 cholera season.

7. Reviews:

a) Research Involving Human Subjects: _____

b) Research Committee: _____

c) Director: _____

d) BMRC: _____

e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

BACKGROUND:

Since it will be approximately one month before the protocol for the 1978 cholera vaccine trial will be completed and submitted to the Review Board on use of Human Subjects and the Research Review Committee for consideration, this document has been prepared to present for approval proposed plans for pre-testing of the cholera vaccines that are to be used in the 1978 cholera vaccine field trial. The proposed starting date for this pre-test is January, 1978.

The 1978 vaccine trial will be a four cell trial and will include testing of three new vaccines prepared by Wellcome Foundation, London: an aluminum hydroxide adjuvanted, formalin-treated cholera toxoid (TOX), an aluminum hydroxide adjuvanted cholera whole cell vaccine (WCV) and a vaccine containing a mixture of the toxoid and whole cell vaccine (TOX-WCV). Tetanus toxoid will be given as a placebo. Previous field trials in Indonesia and India have demonstrated that aluminum adjuvanted cholera whole cell vaccines are highly efficacious. The only previous testing of a cholera toxoid was carried out at CRL in 1974. This glutaraldehyde treated toxoid offered limited protection for a short duration. No vaccine product containing a toxoid and whole cell antigens has been previously tested.

Preliminary testing in adult prison volunteers in the United States has shown the toxoid in dosages up to 800 ug per ml (400 ug per 0.5 ml dose), the whole cell vaccine, and the TOX-WCV to be safe (tables 1, 2). The vaccine products to be tested in the pre-test are from a new production lot. However they are composed of the same constituents as those used in the products previously tested in the United States. We are planning to test the toxoid

at dosages of 150, 300 and 600 ug per ml, the whole cell vaccine, and the TOX-WCV mixture at toxoid dosages of 150, 300 and 600 ug per ml in Bangladeshi adults and children to confirm the safety of the products in the local population. It is the primary purpose of the pre-trial to demonstrate the safety of the vaccine products. Serologic responses to the vaccines will also be determined.

METHODS

1. Location

The vaccine trial will be carried out in villages V23, H, V29 and V25, in the Matlab VTS area.

2. Vaccines

Eight vaccines will be given (table 3). These will consist of cholera toxoid at dosages of 150, 300 and 600 ug per ml, whole cell vaccine, TOX-WCV mixtures with toxoid dosages of 150, 300 and 600 ug per ml, and tetanus toxoid. Each injection will contain 0.5 ml of vaccine.

3. Vaccinees

We will attempt to vaccinate all adult, non-pregnant women, age 15 years and over and all children age 5-14 in villages V23 and H, and all children age 1-4 in villages V23, H, V29 and V25. We estimate that 54 adult women, 34 children age 5-14, and 41 children age 1-4 will receive each of the eight vaccines. In calculating these estimates it was assumed that 70% of the total eligible population would be vaccinated in each age group and that this population would be divided equally among the eight cells. Our plan is to start vaccinations in villages H and V23 and then proceed to V29 and V25 for completion of vaccinations in the 1-4 year old children. Assignments of vaccinees were made by a

member of the statistics branch in the Dacca census books after January 1 after the census for the involved villages had been updated through December 1, 1977.

4. Schedule

All vaccinees will receive 2 injections intramuscularly by jet gun at six weeks intervals. Prior to each injection and 2 weeks following a 200 ul fingerstick blood specimen will be obtained from each vaccinee and diluted in 1.8 ml of saline. To deliver the vaccines two teams each consisting of ten persons will be used. One will supervise, four will handle jet guns, two will bleed, two will be chasers and one will record. We anticipate that each team will be able to vaccinate fifty to seventy-five persons per day so that it will take seven to ten days to complete each of the two rounds of vaccinations. Doctor teams will examine each vaccinee on the day of each injection, for four days following, and 14 days after the injection. The approximate schedule for the vaccinations, bleedings and doctor examinations is shown in table 4.

5. Field Personnel

The ten members in each vaccine team will consist of FSAs (1), SFAs (1) and FAs (7) from the Matlab field staff. Dr. Merson and Dr. Black will accompany each of the vaccine teams. Four FAs will obtain second and fourth fingertip blood specimens. The doctor follow-up teams will consist of three physicians and three female FAs. One physician will be from the Matlab hospital staff and two will be assigned from the Dacca hospital staff.

6. Reaction Form

A reaction form has been prepared for use in the field (attached).

7. Serology Tests

All fingertip blood specimens will be examined in the immunology laboratory for vibriocidal and antitoxin titers using standard CRL procedures. It is anticipated that this work will be completed by the end of April so that results will be available prior to the main trial. A sample of blood specimens will also be tested in the rabbit skin test, adrenal cell assay and ELISA assay for determination of antitoxin levels, and in the ELISA assay for determination of anti-lipopolysaccharide antibodies.

8. Other Blood Tests

In purification of the toxoid an equine antitoxin immunosorbent column is used. Extensive testing has demonstrated that the toxoid elicits no sensitivity to horse serum in guinea pigs challenged with toxoid cutaneously or systemically and sera obtained from human volunteers before and after toxoid vaccination exhibited no increase in IgE or IgG antibodies to equine protein. Radioimmunassay studies have shown the horse protein content of the toxoid to be minimal (maximum concentration 2.8 nanograms/ml) and some or all of the activity measured may be non-specific. To maximally minimize the possibility of anaphylactic reactions occurring from the toxoid paired sera from 200 adult vaccinees obtained prior to the first and two weeks after the second injection will be analyzed for IgE titers to equine protein by the RAST test (performed by Pharmacia Laboratories Inc., Pescataway, New Jersey, USA) and for IgG titers to equine protein by radioiummunassay (done at Wellcome Laboratories, London).

9. Cholera Cases

Once the pre-trial has begun all cases of cholera in persons visiting from any of the four pre-test villages will be identified. A standard form will be used to describe clinical features of these cases.

10. Abstract Summary

Attached is an abstract summary prepared according to guidelines of the Review Board.

11. Investigators

The investigators in the trial include Dr. Michael H. Merson (principal investigator), Dr. Robert E. Black, Dr. Mizanur Rahaman, Mr. Maklasur Rahaman, Dr. Ansarrudin Ahmed, and Dr. David Sack.

12. Budget

The incremental cost for the pre-test will be approximately $6,000.00 A detailed budget will be included in the protocol for the main trial.

Table 1

Summary of Human Reaction* to Primary Immunization with Wellcome Toxoid and Vaccine

H-19 Study

Vaccine	Dose (per 0.5ml)	No. Volunteers	Tenderness	Pain	Induration	Oral Temperature >99.6***	Reaction at 14 days
Wellcome Toxoid PX 3898	100 ug	17	41%	-	6%	12%	-
	200 ug	17	71%	-	-	-	-
	400 ug	18	72%	-	11%	6%	-
Wellcome Toxoid PX389B + Wellcome Bivalent Vaccine**	100 ug	18	94%	-	-	28%	-
	200 ug	18	94%	-	-	22%	-
	400 ug	17	94%	-	-	24%	-
Wellcome Bivalent Vaccine	0.5 ml	16	100%	-	6%	44%	-
Wellcome Bivalent Vaccine Absorbed	0.5 ml	17	94%	-	12%	24%	-

* All reactions were observed within 48 hours and tended to subside after 24-48 hrs.
** Each dose contained 0.5 ml of Wellcome Bivalent Vaccine
*** Maximum temperature 101.4°F

Table 2

Summary of Human Reaction to Primary Immunization with Cholera Toxoids

Reactions	H-8 Study Wyeth 00101 12.5 ug PL[1]	H-9 Study Wyeth 11201 100 ug PA[2]	H-11 Study Wyeth 20101 100 ug PA[2]	H-12 Study Wellcome PX-389 100 ug AL[3]
Tenderness	68%	63%	32%	30%
Pain	16%	0%	0%	0%
Induration	74%	34%	26%	0%
Temp. $\geq$ 99.6°F	5%	6.8%	5%	20%
Reaction 14 days	21%	0%	0%	0%
No. Volunteers	19%	59%	19%	10%

[1]PL - plain toxoid

[2]PA - aluminum chloride + protamine sulfate + phosphate buffer

[3]AL - aluminum hydroxide

[4]Percent of volunteers with any side reactions

Table 3

Vaccines in Pre-Test

Cholera toxoid 150 ug/ml
Cholera toxoid 300 ug/ml
Cholera toxoid 600 ug/ml
Cholera whole cell vaccine
Cholera toxoid 150 ug/ml - whole cell vaccine
Cholera toxoid 300 ug/ml - whole cell vaccine
Cholera toxoid 600 ug/ml - whole cell vaccine
Tetanus toxoid

Table 4

Schedule for Pre-Test

First injection and first bleed	January 23 - January 30
Doctor examination	January 24 - February 4
Second bleed	February 6 - February 14
Second injection and third bleed	March 6 - March 14
Doctor examination	March 7 - March 18
Fourth bleed	March 20 - March 28
Main trial begins	May 1

VACCINE REACTION FORM

Name _____ Vaccine _____

VTS No. _____

Age _____ Sex _____

	Injection 1 Day					Injection 2 Day				
	0	1	2	3	4	0	1	2	3	4
DATE										
	LOCAL					LOCAL				
Pain										
Tenderness										
Redness										
Induration										
	GENERAL					GENERAL				
Temperature										
Urticaria										
Glandular Enlargement										
Activity										
Anaphylaxis										

SCORING CRITERIA

LOCAL REACTIONS

Pain: 0 - No pain
1+ - Dull ache with or without movement of limb
2+ - Pain only on movement of limb
3+ - Pain at rest with partial limitation of movement
4+ - Pain at rest with total limitation of movement.

Tenderness: 0 - No tenderness
1+ - Tenderness on firm pressure
2+ - Tenderness on light pressure
3+ - Tenderness on firm touch
4+ - Tenderness on light touch.

Redness: 0 - No redness
1+ - Redness only at injection site
2+ - Redness extending 2-5 cm
3+ - Redness extending 6-10 cm
4+ - Redness extending > 10 cm

Induration: 0 - No induration
1+ - Induration extending up to 2 cm
2+ - Induration extending 2-5 cm
3+ - Induration extending 5-10 cm
4+ - Induration extending > 10 cm

GENERAL REACTIONS

Temperature: Record oral temperature after 1 minute in all vaccinees age 5 and over.
Record rectal temperature after 1 minute in all children age 1-4.

Urticaria: 0 - absent
+ - mild
++ - severe

Glandular Enlargement: 0 - absent
+ - present

Activity: 0 - normal activity
1+ - interfered with work but not totally bedridden
2+ - totally bedridden - no work possible.

Anaphylaxis: 0 - absent
+ - present.

Abstract Summary

A field test will be conducted in approximately 1040 Bangladeshis living in the CRL Matlab VTS area to confirm the safety of three new cholera vaccines prepared by Wellcome Foundation, London. These vaccines are:

1. An aluminum hydroxide adjuvanted, formalin-treated cholera toxoid (TOX).
2. An aluminum hydroxide adjuvanted whole cell vaccine (WCV)
3. A vaccine containing a mixture of the toxoid and whole cell vaccine (WCV-TOX).

The toxoid and WCV-TOX mixture will be tested using vaccines with toxoid concentrations of 150 ug, 300 ug and 600 ug per ml. Previous safety testing of the toxoid and WCV-TOX products with toxoid concentrations up to 800 ug/ml have been found safe in adult male prison volunteers in the United States. Two 0.5 ml injections will be given at 6 week intervals of one of the cholera vaccine products or of a control vaccine (tetanus toxoid). Physical examinations will be given by physicians to each vaccinee on the day of each inoculation, four days following and two weeks after inoculation. Fingertip blood specimens will be collected prior to each injection and 2 weeks following for measurement of vibriocidal and antitoxin responses to the vaccines. If no serious side reactions are encountered, the three cholera vaccines will be tested for their efficacy in the entire Matlab population prior to the 1978 fall cholera season.

1. The subject population for this pre-test will include adult women and children age one or over. These are the populations at greatest risk of contracting cholera and would thus benefit most from an effective vaccine.

2. Previous safety testing has demonstrated the vaccine products to be safe. The likelihood of any serious reactions to the vaccines such as anaphylaxis is believed to be very minimal. The taking of fingertip blood is felt to have no associated risk.

3. To minimize potentially serious risks from the vaccines, emergency kits containing adrenalin will be carried by vaccine teams. Physicians will be in the field during the entire period of inoculations. Minor side reactions such as low grade fever or pain, induration, or erythema at the injection site will be treated symptomatically.

4. The vaccine received by each vaccinee will be recorded in the Dacca census volume. These volumes are available only to designated CRL personnel. Information as to which vaccine was received by each participant will be made available only with the permission of the senior investigator.

5. Informed consent will be obtained from each vaccinee. Dependent children (age 1-14) will be immunized only if accompanied by a parent or guardian. A statement (attached) will be read to each adult female and parent/guardian of children. Every effort will be made to insure that each adult female or parent/guardian understands the tenets of informed consent. A register will be kept of signatures or thumb-prints of those who give consent. Males over 14 who wish to be vaccinated will be allowed to give consent for themselves and will receive vaccine.

6. No interview will take place.

7. Cholera is endemic in Matlab Thana and in other areas in Bangladesh and no adequate measures are currently available to prevent transmission of the disease. A safe, effective vaccine would offer one excellent preventive

and control measure. The presently available cholera vaccines provide limited protection for a short duration. The vaccines to be tested in this trial represent new approaches in development of cholera vaccines that offer greater chance of protection. Should these vaccines be found to be highly effective, they would offer a significant advancement in our ability to prevent cholera worldwide and would provide valuable information on the development of immunity to cholera infection.

8. This study requires only the collection of fingertip blood.

CONSENT FORM

We wish to vaccinate you/your children against cholera or tetanus. This injection will be repeated in 6 weeks. A small quantity of finger tip blood will be taken for examination before each injection and 2 weeks after.

This injection may not create any serious problem. But in some cases there may be a little pain and swelling on the spot of vaccination which is applicable to any other vaccination. Our doctors will be present to look after such problems.

It completely depends upon you whether you will be vaccinated or not. Please ask me any questions you have. Please inform me whether you give your consent to volunteer you/your children for vaccination. You may refrain from participating in this vaccination program if you so desire.

সম্মতি পত্র

আমরা আপনাকে/ আপনার পরিবারের ছেলে মেয়েকে কলেরা এবং টিটেনাস (টাকুরিয়া) এর প্রতিষেধক ইনজেকসন দেওয়ার ইচ্ছা প্রকাশ করিতেছি। এই ইনজেকসন ছয় সপ্তাহ অন্তর দুইবারে দেওয়া হইবে। আক্রান্তের ডগা হইতে এখন ইনজেকসনের আগে এবং দুই সপ্তাহ পরে এবং ছয় সপ্তাহ পরে দুইবার ইনজেকসনের আগে এবং পরে যৎসামান্য রক্ত পরিক্ষার জন্য নেওয়া হইবে।

এই ইনজেকসনে তেমন কোন অসুবিধা হওয়ার কারন নাই। তবে কাহারো কাহারো ইনজেকসনের জায়গায় সামান্য বেদনা ও একটু ফোলা ভাব হইতে পারে, যাহা যে কোন ইনজেকসনের ক্ষেত্রে প্রযোজ্য। আমাদের ডাক্তার সাহেব এই অসুবিধার ব্যবস্থা দেওয়ার জন্য সর্বদাই উপস্থিত থাকিবেন।

ইনজেকসন নেওয়া বা না নেওয়া সম্পূর্ন আপনার এক্তিয়ার। এব্যাপারে আপনার কোন কিছু জানার থাকিলে অনুগ্রহ পূর্বক আমাকে জিজ্ঞাসা করুন। এবং ইনজেকসন আপনি নিজে নিতে এবং আপনার পরিবারের অন্যকে দেওয়াইতে রাজী আছেন কিনা বলুন। আপনি ইচ্ছা করিলে এই কর্মসূচী অংশ গ্রহনে বিরত থাকিতে পারিবেন।