Attachment 1.

85-044 (11)

Date 10/12/85

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator J D Clemens (ICDDR,B)

Trainee Investigator (if any) 2

Application No. _____

Supporting Agency (if Non-ICDDR,B) UNDP

Title of Study GASTRIC ACID AS A DET[illegible] OF DISEASE SUSCEPTIBILITY

Project status:
(X) New Study, limited to oral cholera vaccine trial
( ) 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.

(PTO)

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

J D Clemens
Principal Investigator

Trainee

85-044

Section I — Research protocol

Title	Gastric Acid as a Determinant of Disease Susceptibility in a Population Immunized With Oral Cholera Vaccine and as an Interactive Risk Factor for Clinical and Asymptomatic Cholera in an Unvaccinated Populaion
Principal Investigators	F. P. L. Van Loon J. D. Clemens
Starting date	June 1986 as it is linked to the on going vaccine trial
Completion date	June 1987
Total direct costs	$ 191722
Scientific Programme	This protocol has been approved by the Disease Transmission Working Group.

Scientific Programme Head

Approved by Van Cijfloon 19/12/85

Abstract Summary

Although hypochlorhydria (HC) is a recognized risk factor for severe cholera little is known about the relationship between HC and the efficacy of oral cholera vaccine nor about the interaction between HC and other recognized risk factors in modifying an individual's susceptibility to cholera. In this study, which is linked to the ongoing field trial of oral cholera vaccine in Matlab, we will perform two analyses. Firstly, using the non-invasive magnesium breath hydrogen test to measure gastric acidity, we will measure gastric acid output in vaccinated individuals who became ill with cholera and in vaccinated individuals who did not contract cholera despite intimate exposure to a family contact with cholera . This comparison of vaccine "failures" with vaccine "successes" will allow assessment of the role of HC in modifying vaccine efficacy, and will, in conjunction with other data collected on these individuals in the trial (nutritional status, ABO blood type, serological immunity, age, sex) enable us to construct a multivariate assessment of factors, determining vaccine success or failure. A second analogous case control comparison will be performed for unvaccinated subjects contracting cholera, or not contracting cholera despite known exposure. This latter analysis will enable a reassessment of the role of HC as a risk factor when considered in relation to other known risk factors.

REVIEWS:

(a) Ethical Review Committee: ----------

(b) Research Review Committee: ----------

(c) Director: ----------

Introduction

That gastric acidity plays a key role as a barrier against cholera has been recognized since the late sixties (2,3,4,5,6). Next to other risk factors like ABO blood type, it is being considered that hypochlorhydria predisposes to cholera (7,8,9,10). From the spring of 1985 onwards, the ICDDR,B has conducted a large scale field trial of the two new oral cholera vaccines in its Matlab field studies area (1,16). In this population all children aged 2-15 years and all non-pregnant women older than 15 years living in selected portions of the Matlab field area receive either oral B-subunit/whole cell (BS/WC) cholera vaccine, whole cell cholera vaccine (WC) or a placebo preparation containing killed K12 strain E coli in a randomized, double-blind fashion. In this this population we are planning to carry out a non-invasive study of gastric acidity by means of the magnesium breath hydrogen test.

In this study, we would like to evaluate several issues not previously considered. Firstly, does the increased susceptibility to cholera rendered by hypochlorhydria reduce natural barriers to a sufficient level that oral vaccination, with resulting small intestinal immunity, is inadequate to protect against cholera? Secondly, among non-vaccinated individuals, does hypochlorhydria contribute to the risk of cholera of all grades of severity, or merely to the risk of severe cholera ? Moreover, how do other possible risk factors for cholera, such as ABO blood type, serological immunity and nutritional status modify the risk imposed by hypochlorhydria ?

General Aims

(1) To elucidate the role of gastric acid as a modifier of oral cholera vaccine efficacy and as a risk factor for cholera.

(2) To evaluate interactions between gastric acid output and such other risk factors for cholera as serological vibriocidal and antitoxic antibody levels, ABO blood type, and nutritional status in modifying vaccine efficacy and in altering the basic risk of cholera.

Specific Aims

1. To compare gastric acid output, as assessed via a non-invasive breath test, in vaccinated "cases" demonstrated to have acquired clinical cholera and in vaccina
demonstrated to have acquired clinical cholera and in vaccina

"controls" who were not infected with cholera despite documented intimate exposure to a case of cholera.

2. To perform a multivariate assessment of contribution of the following factors to the prediction of cases and controls, as defined in "1": gastric acid output, ABO blood type, nutritional status, vibriocidal and anti-toxic serological antibodies.

3. To compare gastric acid output, assessed via a non-invasive breath test, in 3 sets of non-vaccinated "cases"-- one with cholera gravis, one with mild-to-moderate clinical cholera, and one with asymptomatic chol
to-moderate clinical cholera, and one with asymptomatic chol

infections-- with a control group consisting of non-vaccinated individuals intimately exposed to a cholera case but not infected by the case.

4. To perform a multivariate assessment of the contribution of the risk factors noted in (2) to differentiating each of the three case groups from the control group described in (3).

Methods

1.1 Statement of hypothesis #1

Our first hypothesis is that "hypochlorhydria", defined as gastric acid output more than 2 SD below the standard, contributes significantly to vaccine failures among persons receiving 3 doses of oral B subunit-cholera (BS-WC) or whole cell only (WC) cholera vaccines.

1.2 General Approach

We will test this hypothesis using a case-control design. "Cases" will be individuals receiving 3 doses of vaccine and developing clinical cholera > 7 days after the third dose. "Controls" will be individuals receiving 3 doses of vaccine, but not developing clinical cholera or asymptomatic infection despite exposure to a family member with cholera. Gastric acid output, as assessed with the non-invasive magnesium-hydrogen breath test, will then be compared in the 2 groups, permitting an assessment of the role of hypochlorhydria in producing vaccine failures. Moreover, the interrelationship between gastric acid output and other cholera risk factors in predicting vaccine failures will be examined.

1.3 General Eligibility Requirements

Subjects will be eligible if they received 3 complete

doses of BS-WC or WC oral cholera vaccine.

1.4 Selection of Cases

Cases will be eligible persons developing "clinical" cholera (defined as cholera infection associated with at least 3 loose stools a day) and detected through the treatment centre or family study surveillance mechanisms of the cholera vaccine trial. In the latter (see Appendix), family contacts of cholera cases detected in the treatment centres are cultured and queried about symptoms daily for 7 consecutive days to detect mild and asymptomatic cases. We expect that about 40 eligible cases will occur in the trial, of which 35 will participate in the study.

1.5 Selection of Controls

Controls will be eligible persons who are not infected with cholera in the family studies. Four controls will be selected for each case and matched by age at exposure within four brackets (2-5 years, 6-10 years, 11-15 years, > 15 years), by the particular vaccine received, and by the time since administration of the vaccine.

1.6 Assessment of Gastric Acid Output (Appendix 2)

The magnesium breath hydrogen test is a non invasive method to determine the gastric acidity. This test is extensively being used and appreciated as accurate and safe both in animals and humans of all ages. Application of the device within the ICDDR,B has been cleared by both the Ethical Review Committee and the Research Review Committee (14) In brief, its basis is the reaction of magnesium with gastric hydrochloric acid to release hydrogen gas that is

immediately absorbed into the bloodstream and then exhaled by air. Thus, low gastric acidity is reflected in hardly any hydrogen production and so no increase in breath hydrogen. After informed consent the non absorbed and non toxic metallic magnesium (150 mg. orally in a single dose) will be given as a powder to overnight fasting individuals half an hour after gastric acid stimulant pentagastrin administration (6 ug./kg s.o). The pentagastrin stimulation test is a standard procedure in hospital setting carried out without medical supervision. Pentagastrin elicits reproducible gastric secretory response comparable to those induced by histamin or betazol but offers several advantages: it only requires a single subcutaneous or intra-muscular injection and side-effects are usually minor and transient. These may include various gastrointestinal phenomena such as nausea borborygmi; and the urge to defecate and circulatory effects including flushing tachycardia, faintness and dizziness. Allergic reactions are rare. Gastric secretion begins within 10 minutes and such responses occur within 30 minutes. The diagnostic dose is 6 ug/kg administered by subcutaneous injection (15) Collection of exhaled breath, belch and hydrogen measurement take place by use of gas collection bags and a gas-chromatograph , and correction will be made for excess hydrogen. During the experiment subjects are asked to report on any physical discomfort. Data will be analyzed and compared with the normal values (3,11,12,13).

1.7 Assessment of Additional Risk Factors for Cholera

As part of the ongoing cholera vaccine trial acute phase blood specimens are obtained from treatment centre patients and from patients detected in the field. These specimens are evaluated for vibriocidal antibodies using the microtechnique and for anti-cholera toxin (CT) antibodies with ELISA. The bloods are also typed for ABO antigens. Blood obtained on Day 1 of the family studies are processed in a similar fashion. Nutritional status (height and weight) data are obtained at discharge for all treatment centre patients and on day #1 for all family study participants.

1.8 Sample Size

Assuming that the 33% prevalence of hypochlorhydria seen in cholera gravis among non-vaccinees increases to 50% in vaccine failures, the above numbers of cases and controls will detect a > 4-fold relative risk of vaccine failures in hypochlorhydric individuals with > .9 power, assuming a p value of .05 (2-tailed).

1.9 Analysis

The basic analysis will evaluate the association between HC and vaccine failures with odds ratios, which approximate relative risks under the rare disease assumption. Separate analyses will be performed by the type of vaccine received and adjustment for potential confounding variables (e.g., age, antibody titres, ABO blood type, nutritional status) will be performed using logistic

regression.

To evaluate the relative importance of several possible determinants of vaccine failure, we will evaluate the five factors -- acid output, ABO blood type, nutritional status, baseline serum vibriocidal antibody titre, and baseline serum anti-CT titre using the backwards stepwise elimination algorithm for logistic regression, taking case-control status as the dependent variables. The logistic model will also permit evaluation of interactions between risk factors.

2.1 Statement of hypothesis #2

The second hypothesis is that hypochlorhydria may increase the risk not only of cholera gravis but also of mild-moderate cholera and of asymptomatic cholera infections, and that its effect may be modified by additional risk factors for cholera.

2.2 General Approach

In this case-control study, 3 groups of "cases" will be chosen:

a. an unvaccinated group with cholera gravis (severe dehydration) identified from treatment centres.

b. an unvaccinated group of mild-moderate cholera identified from treatment centres and from family studies.

c. group of asymptomatic excretors of V. cholerae, identified from family studies.

A single control group consisting of unvaccinated subjects who did not develop cholera infections despite intimate exposure to a family with clinical cholera will also be

selected. Gastric acid output will be ascertained for each group and values for gastric acid output in each case group will be compared with that for the control group to assess the role of hypochlorhydria in elevating the risk of severe, non-severe, and asymptomatic cholera. Moreover, the interrelationships between gastric acid output and other putative cholera risk factors in increasing the three types of cholera infections will be examined.

2.3 General Eligibility Requirements

Subjects will be eligible if they received neither BS-WC nor WC oral cholera vaccine.

2.4 Selection of Cases

A. Group I: cholera gravis (N=28). This group will be selected from eligible persons diagnosed with cholera at a treatment centre and having severe dehydration (WHO criteria).

B. Group II: mild-moderate cholera (N=65). This group will consist of eligible subjects with diarrhoea (> 3 loose motions/day) associated with cholera but with non-severe dehydration. They will be selected from treatment centre patients and family study participants.

C. Group III: asymptomatic cholera (N=162). This group will consist of eligible subjects infected with V. cholerae but not exhibiting diarrhoea as defined above. They will be selected from family studies.

2.5 Selection of Controls

Controls will be eligible persons not infected by V. cholerae in the family studies. Because this group will be

the control group for each of the three case groups, no suitable matching strategy can be used, and they will be selected by simple random sampling.

2.6 Assessment of gastric output

see section 1.6

2.7 Assessment of additional risk factors for cholera

see section 1.7

2.8 Sample size

Assuming a 5% rate of hypochlorhydria in the control group, the above samples of cases and controls will detect with > .8 power ($p < .05$, 2-tailed) the following increased relative risks of subjects with hypochlorhydria:

> or = to 3-fold for asymptomatic cholera;
> or = to 5-fold for mild-moderate cholera;
> or = to 9-fold for cholera gravis.

2.9 Analysis

Analysis of the separate contribution of hypochlorhydria to cholera risk and of the relationships of this risk to that contributed by serological antibodies, ABO bloodtype and nutritional status will follow the procedures outlined in section 1.9.

Significance

To maximize the yield of scientific information from an expensive, large-scale field trial, such the one currently in progress at ICDDR,B, it is desirable not only to determine vaccine efficiacy, but also to assess determinants of vaccine failures so that future vaccine development can proceed in a way that accounts for biological barriers to effective vaccination.

The present study will evaluate hypochlorhydria in the context of other possible reasons for vaccine failures, and will make use of the enormous epidemiological "data bank" on cholera created by the trial to reexamine hypochlorhydria as a risk factor for cholera and its interrelationships with other risk factors.

REFERENCES

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BUDGET

		% effort	Total Project Cost 1986	1987
31	Local Salaries			
	Medical Officer	100%	2,760	2,760
	Health Assistants (2)	100%	1,740	1,740
	Coding Assistant	100%	870	870
	Data Entry Technician	100%	870	870
32	International Salaries:			
	Principal Investigator I	60%	25,945	25,945
	Principal Investigator II	25%	-	14,373
36	International Travel:			
	For presentation of paper Air ticket and per diem			4,000
37	Supplies and Materials:			
	Drugs		1,000	1,000
	Hospital supplies		500	500
	Stationery		100	100
	Freight charge		960	-
42	Printing of forms, reprints and others:			1,00
43	Printing of forms, reprints and others:			1,00
48	Inter-departmental service:			
	Computer services		-	3,000
	Transport services		965	965
	Water transport		12,300	12,300
	Xerox and mimeograph		250	250
	Patient hospitalization		14,135	14,135
	Medical illustration		-	1,000
	Telex		25	25
	Total operating cost (Direct):		62,420	84,833
	Administrative cost 31%		19,350	26,298

BUDGET SUMMARY

		US Dollar
31	Local salaries ..	12480
32	International salaries ..	66263
36	International Travel ..	4000
37	Supplies and materials ..	4160
43	Printing of forms reprints and others	100
48	Interdepartmental service ..	59350
	Total =	146353

Total operating cost (direct)	= US $	146353
Administrative costs	= US $	45369
GRAND TOTAL	= US $	191722

Consent Form

Gastric acid as a modulating factor in oral cholera vaccine efficacy and its relative risk for cholera.

You have been a participant in the oral cholera vaccine trial, conducted in the Matlab field area of the International Centre for Diarrhoeal Disease Research, Bangladesh.

For better understanding of the role of gastric acid in the effectiveness of the vaccine, you are requested to volunteer in a linked study that will measure your gastric acid production.

If you agree, you will be hospitalised overnight in a fasting state. Early in the morning you will get an injection of pentagastrin under the skin to stimulate the acid output and half an hour later you will get some magnesium to drink. Then you will be asked to breath into a collectiion bag. We don't expect any harm of the procedure.

Pentagastrin may cause a slight transient abdominal discomfort 10 minutes after injection as well as an urge to defaecate and dizziness, but it is routinely used in gastric acid measurement.

Magnesium has been reported not to have any side effect in this dosage that is lower than the daily requirement.

The breath test is largely used as a common diagnostic.

Your hospitalisation will be free of costs, as well as your transport to end from the centre. You are free to withdraw from the research at any time.

You may realise that the procedure in this stage serves just a research purpose and is not beneficial for you individually but may help to improve the vaccine development that will favour large populations.

Please place your signature below if the procedure has clearly been explained to you and you have agreed to join the study.

_____

Signature of the Investigator

Date: _____

_____

Signature of the Subject
or Guardian

Date: _____

অনুমতিপত্র

কলেরা ভ্যাকসিনের কার্যকরিতার উপর এবং কলেরায় গ্যাস্ট্রিক এসিডের প্রভাব।

আপনি আই ডি ডি আর বি'র অতলব ফিল্ড এলাকায় বসে থাকার কলেরা ভ্যাকসিনের যে পরীক্ষা করা হয়েছে তাতে অংশগ্রহন করেছেন।

গ্যাস্ট্রিক এসিড কলেরা ভ্যাকসিনের কার্যকরিতার উপর কি প্রভাব বিস্তার করে তা দেখবার জন্য আপনাকে একটি পুনর্মাত্রিক গবেষনায় স্বেচ্ছায় অংশগ্রহন করতে অনুরোধ জানাচ্ছি। এই গবেষনায় আপনার গ্যাস্ট্রিক এসিড উৎপাদন ক্ষমতা নির্নয় করা হবে।

আপনি পরিক্ষায় অংশগ্রহনে সম্মত হলে আপনাকে হাসপাতালে ভর্তি করা হবে এবং রাত অভুক্ত থাকতে হবে। পরের দিন সকালে আপনাকে চামড়ার নীচে পেনটাগ্যাসট্রিনের ইনজেকশন দেয়া হবে যাতে আপনার এসিড উৎপাদন উদ্দীপিত হবে তবে আধঘন্টা পরে আপনাকে কিছু ব্যাকলেসিয়াম খেতে দেয়া হবে। তারপরে আপনাকে একটি ট্যাপে শ্বাসপ্রশ্বাস নিতে বলা হবে। যাতে আপনার কোন প্রকার ক্ষতি হবার সম্ভাবনা নেই।

পেনটাগ্যাসট্রিন ইনজেকশন দেবার দশমিনিট পরে সাময়িক পেটে ব্যথা হতে পারে এবং বমিবমি ভাব বা পায়খানায় যাবার ইচ্ছা হতে পারে। কিন্তু এতদসত্বেও গ্যাসট্রিক এসিড পরিমাপের জন্য পেনটাগ্যাসট্রিন ইনজেকশনই ব্যবহার করা হয়ে থাকে।

আপনাকে যে পরিমান ব্যাকলেসিয়াম দেয়া হবে, যা দৈনিক প্রয়োজনের চেয়েও কম, তাতে কোন পার্শ্ব প্রতিক্রিয়ার সম্ভাবনা নেই।

স্বাস্থ্যপ্রশ্নাদের এই পরীক্ষা রোগনির্ণয়ের জন্য অত্যাবশ্যক প্রমাণিত হয়ে আছে।
হাসপাতালে আসার জন্য এবং পরীক্ষার সুরুতে ও শেষে যাতায়াতের জন্য আপনাকে কোন অর্থ ব্যয় করতে হবে না। আপনি ইচ্ছামত যে কোন সময়ে পরীক্ষা থেকে নিজেকে প্রত্যাহার করে নিতে পারেন। আপনার মনে হতে পারে যে এই অবস্থায় এই সকল পরীক্ষা কেবল গবেষনার খাতিরেই ব্যবহৃত হবে এবং এতে করে ব্যক্তিগতভাবে আপনার কোন লাভ হবে না তবুও ভ্যাকসিন উদ্ভাবন ত্বরান্বিত করতে এই পরীক্ষা বিশেষভাবে সাহায্য করবে যাতে দেশের বৃহত্তর জনগোষ্ঠির কল্যান সাধিত হবে।
যদি আপনাকে সমস্ত প্রক্রিয়াটি ভালভাবে বুঝিয়ে বলা হয়ে থাকে এবং আপনি যদি এই গবেষনায় অংশগ্রহন করতে রাজী থাকেন তবে নিম্নে আপনার স্বাক্ষর দিন।

____________________ ____________________

গবেষকের স্বাক্ষর

তারিখ __________

রোগী বা অভিভাবকের স্বাক্ষর

তারিখ __________

APPENDIX I

Minimal Morbidity List

	Description	Detailed List No.	Possible Diagnosis
1	Fever with skin eruptions	010-012	Measles, Chickenpox, Smallpox
2	Fever with neck rigidity, vomiting, skin rash	024	Meningitis
3	High fever, intermittent, with chills and prostration	030, 031	Malaria
4	Fever, unqualified	039	
5	Yellow skin, yellow whites of eyes	046	Jaundice
6	Skin sores and ulcerations, unqualified	049	
7	Diarrhoea and vomiting, massive dehydration, watery stools	050	Cholera
8	Diarrhoea, abdominal pain, mucopurulent and bloody stools	060	Amoebic dysentery
9	Diarrhoea, unqualified	069	
10	Abdominal pain, rigidity of abdominal wall	070	Acute abdomen
11	Other abdominal apin or swelling	071, 072	
12	Chronic cough with loss of weight, blood in sputum, slight fever	080, 081	Tuberculosis
13	Acute cough, fever, chest pain, shortness of breath	082	Pneumonia
14	Nose and throat discomfort, watery discharge, cough, fever	090	Common cold, Upper respiratory infection
15	Breathing difficulty, shortness of breath, chest pain, swollen ankles	100	Heart disease