21 July, 1985

Principal Investigator J. Harris Trainee Investigator (if any) 20

Application No 85-023 Sponsoring Agency (if Non-ICDDR,B)

Title of Study Evaluation of Safety and Immunogenicity of Oral Rotavirus Vaccines for Use in Bangladesh

Study 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 NA
   - (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 questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Committee for review.

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

Jeffrey R. Harris, M.D.
Principal Investigator

Trainee

85-023
25/7/85

SECTION 1 - RESEARCH PROTOCOL

1. Title: Evaluation of Safety and Immunogenicity of Oral Rotavirus Vaccines for Use in Bangladesh

2. Principal Investigator: Jeffrey R. Harris, M.D.

   Co-Investigators: David A. Sack, M.D.
   J. Chakraborty, S.I.
   M. R. Khan
   Michael G. M. Rowland, M.B.B.S.
   John D. Clemens, M.D.
   Md. Yunus, M.B.B.S.
   A. M. Sarder

X

3. Starting Date: September 1, 1985

4. Completion Date: December 31, 1986

5. Total Direct Cost: $215,253

6. Scientific Program Head: This protocol has been approved by the Disease Transmission Working Group.

   Scientific Program Head's Signature David A Sack Date 18 July 198

7. Abstract Summary:

Worldwide, rotavirus is the most important cause of dehydrating diarrhea, and presumably of associated mortality, of children aged less than 2 years. Two recently developed attenuated animal strain rotavirus vaccines, the RIT 4237 and the Rhesus MMU 18006, are currently, or are soon to be, available for large-scale testing. Using the ICDDR,B Matlab Surveillance area with its well-defined population, we propose to evaluate these vaccines for safety and immunogenicity in developing country children as a preparation for a larger trial of the efficacy of one or both of these vaccines for the prevention of rotavirus diarrhea. Other vaccine-related issues we will evaluate include the effect of buffering of gastric acid on vaccine immunogenicity and vaccine secondary infection rates among household members of vaccinees. This study will be a step toward implementation of a program for routine rotavirus vaccination in developing countries.

8. Reviews: a) Ethical Review Committee _____ Date _____

   b) Research Review Committee _____ Date _____

   c) Director _____ Date _____

SECTION II - RESEARCH PLAN

INTRODUCTION

Objectives

To evaluate the safety and immunogenicity of the RIT 4237 and rhesus MMU 18006 oral rotavirus vaccines in Bangladeshi infants in preparation for a larger vaccine efficacy trial of one or both of these vaccines.

Background

Rotavirus is a common cause of diarrhea in children aged less than 2 years. In 2 village-based studies carried out in the Matlab surveillance area of the International Centre for Diarrhoeal Diseases Research, Bangladesh (ICDDR,B) in diarrhea patients aged less than 2 years, rotavirus was the third most commonly identified pathogen, after enterotoxigenic Escherichia coli and Shigella (1,2). The incidence of rotavirus diarrhea was particularly high in the second 6 months of life, peaking at 150 episodes per 1000 children per year. In a separate study in Matlab, 95% of children were found to have developed antibodies to rotavirus by the end of the second year of life (3).

More important than the role of rotavirus in causing diarrhea is its role in causing severe, dehydrating diarrhea. In one of the previously-mentioned village-based studies, 44% of rotavirus diarrhea among children aged less than 2 years resulted in at least mild dehydration (1). Because of this high frequency of dehydration, rotavirus was the most common cause of diarrhea among children who were aged less than 2 years and who presented to

the Matlab treatment center (4). Approximately 50 children per 1000 in this age group per year presented to the treatment center with rotavirus diarrhea (1). Rotavirus is an important cause of dehydrating diarrhea in the developed world as well. Studies in the United States, Japan, and Australia have shown that rotavirus causes 39% to 63% of diarrhea requiring hospitalization of children aged less than 2 years (5).

Rotavirus is also probably an important killer of young children. Diarrhea is estimated to cause approximately 20 deaths per 1000 children per year in the first 2 years of life (6), and rotavirus diarrhea with its attendant dehydration seems likely to cause a large proportion of this mortality. A Toronto series reported 21 rotavirus-associated deaths, all within 3 days of onset of illness (7). From their Matlab village-based study data, Black et al. estimated that rotavirus would have caused 5 to 6 deaths per 1000 children per year in the first 2 years of life if adequate rehydration facilities had not been available (1).

Protective immunity against rotavirus illness is induced by natural infection and appears to be intestinally-mediated. The incidence of rotavirus illness falls off quickly after the first 2 years of life, in spite of the fact that repeated asymptomatic infections continue to occur after that time (8). The best evidence for the importance of intestinal immunity comes from animal studies which have shown that passively acquired rotavirus antibody in the gastrointestinal tract protects against illness while passively-acquired serum antibody does not (9).

The ability of infection with one of the four currently recognized human rotavirus serotypes or two recognized subgroups (10) to protect against illness caused by a rotavirus of another serotype or subgroup has been unclear from epidemiologic studies. Repeat rotavirus illnesses in the same child have been well-documented and have usually been caused by members of different subgroups (11,12). Recently, however, a candidate rotavirus vaccine, RIT 4237, of bovine origin and related to human subgroup 1, induced heterologous serologic immunity (13) and in an efficacy trial provided excellent cross-protection against illness caused by subgroup 2 rotavirus (14).

Because of the assessed importance of intestinal immunity in protection against rotavirus illness and because the incidence of rotavirus diarrhea peaks in the second 6 months of life, research has centered on production of an oral, live, attenuated vaccine that is safe and immunogenic for infants 3 to 5 months of age or younger. Two animal strain attenuated vaccines are currently available or soon to be available for large-scale testing. The most extensively tested is the previously-mentioned bovine RIT 4237, which was first passaged 147 times in calf kidney cells then 7 times in African green monkey kidney cells. This vaccine was given in a single-dose regimen to Finnish infants aged 8 to 11 months, caused no symptoms, and induced a serum antibody response in 40% of the previously seropositive and 50% of the previously seronegative infants (14). In addition, it provided 50% protection against all rotavirus diarrhea and 88% protection against rotavirus diarrhea which lasted more than 24 hours (14). As noted before, the vaccine provided heterologous protective immunity. Later, a Swiss study of safety of the vaccine for infants as young as 3 months of age showed no ill effects (Juse, Andre FE. Unpublished data).. Vaccine stool shedding has

not been detected from recipients. Safety and immunogenicity studies in newborns are planned or ongoing (Appendix C).

The second candidate vaccine is the rhesus rotavirus MMU 18006 strain, which was passaged twice in primary cynomolgus monkey kidney cells, seven times in primary African green monkey kidney cells, and seven times in fetal rhesus monkey lung diploid cells. This vaccine also induces homologous and heterologous immunity with one dose but has resulted in side effects when given in high titer. A 10^{-1} vaccine dilution given with buffer induced a four-fold or greater serum antibody rise in 12 (86%) of 14 American children aged 5 to 14 months but caused fever or diarrhea on the second, third, or fourth day after vaccination in a high proportion of both these children and Swedish children aged 4 to 12 months (Levine MM, Gothefors L. Unpublished data). In Venezuela, however, 10^{-2} and 10^{-3} vaccine dilutions given without buffer induced four-fold or greater serum antibody rises in 35% to 53% and 71% to 82%, respectively, of infants aged 4 to 10 months and caused no side effects (Flores J. Unpublished data) (Appendix D). Approximately half of the recipients have shed the vaccine in their stools. Vaccine safety studies of the 10^{-2} and 10^{-3} vaccine dilutions given with buffer are planned for American infants aged 3 to 6 months, and efficacy studies of the 10^{-2} dilution without buffer are planned or ongoing for Venezuelan and Swedish infants as young as 2 months of age (Appendix E).

Rationale

We would like to carry out an efficacy trial of the RIT 4237 or Rhesus MMU 18006 oral rotavirus vaccine, or both. However, before such a large

efficacy trial can be carried out in Bangladesh, issues that remain to be resolved are the vaccines' safety and immunogenicity when given to Bangladeshi infants, the vaccines' sensitivity to gastric acid, and their propensity to secondarily infect household contacts of vaccinated children. An issue specific to the rhesus vaccine is whether the less expensive 10^{-3} dilution given with buffer can induce similar immunity to that conferred by the 10^{-2} dilution without buffer.

SPECIFIC AIMS

1. In preparation for a larger efficacy trial, to evaluate the safety and immunogenicity of the RIT 4237 and Rhesus MMU 18006 rotavirus vaccines when given to Bangladeshi infants.
2. To evaluate the effect of neutralization of gastric acid on the serologic response to these vaccines.
3. To determine the incidence of intra-household secondary transmission of these vaccines.

METHODS OF PROCEDURE

Selection of Vaccinees

The study will be carried out in approximately 49 villages of the Matlab surveillance area of the ICDDR,B, in infants aged 3 to 8 months. While infants aged 3 to 5 months comprise the actual target group, the older infants should be less affected by maternal antibody and will serve as a comparison group.

Study Design

Vaccines which will be tested include the RIT 4237 vaccine, and the 10^{-2} and 10^{-3} dilutions of the rhesus MMU 18006 vaccine. While the study will use a randomized placebo-controlled double-blind design, because of concern about inter-household secondary transmission of these live vaccines, infants will be randomized by village rather than individually. All of the approximately 1200 infants aged 3 to 8 months in the selected villages will be assigned to a vaccine group, however, it is assumed that only 60% will participate. The amount of time required for completion and analysis of the study will be approximately 16 months.

Vaccination

Vaccination will begin on February 1, 1986, after the dry season peak in rotavirus incidence and will be carried out campaign-style over a 4-week period by seven teams. Each team will consist of a recorder, the community health worker for the area being vaccinated, a porter, and a vaccinator who will also collect fingerstick blood samples. Seven groups of 100 infants will be given a single dose of vaccine or placebo. Four groups will receive one of the three vaccine types or placebo, without buffer. The other three groups will receive one of the three vaccine types, preceded by 400 mg of $NaHCO_3$. Although it will not be possible to withhold breast milk prior to vaccination, the duration from the last breastfeeding to the time of vaccination will be recorded, and mothers will be asked to withhold breast milk for 1 hour after vaccination. A fingerstick blood sample will be collected from each vaccinee at the time of vaccination and 4 weeks later.

Adverse Effects

Active surveillance of vaccinated infants for adverse effects will be carried out daily for 5 days after vaccination. Each vaccination team will be followed by two specially trained field workers. A physician will supervise all of the field workers, who will routinely ask about diarrhea, vomiting, and fever with onset after vaccination and will take daily rectal temperatures. Vaccinees with mild symptoms will be treated with antipyretics or oral rehydration solution. Vaccinees with more severe illnesses will be referred to the Matlab treatment center for physician care.

Secondary Transmission

In order to determine if any or all of the tested vaccines were transmitted to the vaccinees' household contacts, we will test the serum of these contacts for a seroresponse to the vaccines. At the time of vaccination and 4 weeks later, a fingerstick blood sample will be collected from all of each vaccinee's household contacts aged greater than 8 months and less than 5 years (average will be one household contact per vaccinee). Collection of serum from the 100 household contacts of the 100 recipients of each vaccine-buffer combination or placebo will allow us, with 80% statistical power, to detect a significant difference between these groups if 24% of the vaccine recipients' and the expected 6% of the placebo recipients' contacts (3,8) develop four-fold or greater antibody rises during the month following vaccination.

Serologic Studies

Using an enzyme-linked immunosorbent assay, we will test serum samples from all vaccinees and household contacts for antibody to both the RIT 4237 and the Rhesus MMU 18006 vaccine strains. Pre- and post-vaccination specimens will be tested together, and pairs with at least a four-fold antibody rise will be considered to show a seroresponse.

SIGNIFICANCE

Worldwide, rotavirus is the most important cause of dehydrating diarrhea, and presumably of associated mortality, of children aged less than 2 years. An effective rotavirus vaccine, therefore, could potentially have a major impact on the morbidity and mortality of children aged less than 2 years. Two promising oral rotavirus vaccines are currently available. We propose to test these vaccines for safety and immunogenicity in Bangladeshi infants as a prelude to a larger efficacy trial of one or both of these vaccines.

FACILITIES REQUIRED

No new facilities will be required for this study.

COLLABORATIVE ARRANGEMENTS

The RIT 4237 vaccine will be provided by Smith-Kline RIT of Belgium. The Rhesus MMU 18006 vaccine will be provided by Dr. Albert Z. Kapikian of the National Institutes of Health of the United States.

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ABSTRACT SUMMARY

This study will examine the safety and immunogenicity of RIT 4237 and Rhesus MMU 18006, two new oral rotavirus vaccines, in preparation for a larger efficacy trial of one or both of these vaccines.

1. Subject population - Three to 8 month-old infants in the Matlab Demographic Surveillance area. We are vaccinating 3 to 5 month-old infants because rotavirus incidence peaks in the second 6 months, and a successful rotavirus vaccine will have to be given before the age of 6 months. We are vaccinating the 6 to 8 month-old infants because they are still in the high-risk age group but serve as a comparison group less subject to the effects of maternal antibody.

2. Potential risks - Although previous studies in developed and developing countries indicate that these vaccines at the dilutions we will be using do not cause adverse reactions, the risk of mild fever and/or diarrhea exists. The risk of more severe reactions appears to be negligible.

3. Methods for protecting against or minimizing potential risks - We will monitor vaccine recipients closely for 5 days after vaccination and treat minor illnesses in the field and major illnesses at the Matlab treatment center. Previous experience indicates that adverse reactions to these vaccines would occur within the first 4 days after vaccination and would be detected by our surveillance and treatment system.

4. Methods for safeguarding confidentiality - Participants will not be identified individually in published accounts of this study.

5. a) Waiver of signed consent - We will obtain written informed consent from parents of vaccinated children and from parents of household contact children from whom we collect blood.

b) Withholding of information - We will withhold no information from the participants.

c) Compensation and/or treatment for risks - We will treat any illnesses of vaccinees in the post-vaccination period.

6. Interview procedures - No interviews will take place.

7. Potential benefits - For individuals who receive active vaccine, the very real possibility exists that they will be protected from rotavirus diarrhea, a potentially fatal illness. For society, this is a step toward implementation of routine vaccination with an effective rotavirus vaccine. An effective rotavirus vaccine should have a major impact on acute diarrheal morbidity and mortality of young children.

8. Required specimens - Two fingerstick blood specimens will be required from each vaccinee and participating household contacts.

SECTION III - BUDGET

BUDGET SUMMARY

Item	1985 Project Cost In Dollars	1986 Project Cost In Dollars
PERSONNEL SERVICES	36,335	113,576
SUPPLIES	10,980	9,240
EQUIPMENT	3,000	
TRAVEL	13,437	26,275
PRINTING AND XEROX	470	540
COMMUNICATIONS AND TELEX	500	500
COMPUTER COSTS	200	200
TOTAL DIRECT COSTS	64,922	150,331
MANAGEMENT SUPPORT COSTS (DirectCostsX31%)	20,126	46,603
GRANDTOTAL	85,048	196,934

DETAILED BUDGET

PERSONNEL SERVICES

Name and Title	% Time	Annual Personnel Cost In Dollars	1985 Project Cost In Dollars	1986 Project Cost In Dollars
International Staff				
J. Harris, Principal Invest.	80% X 10 mos	67,000	17,867	26,800
D. Sack, Co-Investigator	20% X 16 mos	112,500	7,500	22,500
J. Clemens, Co-Investigator	10% X 16 mos	paid by cholera vacc trial		
Local Personnel				
Managerial Staff				
Immunization mgr. - NOB	50% X 5 mos	6,360	530	795
Secretary grade I - GS 6	100% X 16 mos	4,280	1,412	4,280
Supply clerk - GS 3	100% X 10 mos	1,880	627	940
Supply porter	100% X 10 mos	445	148	223
Immunization Staff				
Sr. Field Res. Off. - GS 6	100% X 4 mos	4,280		1,427
Field Res. Off. (2) - GS 5	100% X 4 mos	3,040		2,027
Health Assistants (16) - GS 3	100% X 4 mos	1,880		10,027
Com. Hlth. Wrkrs. (50)	100% X 1 mo	667		2,780
Porters (8)	100% X 4 mos	445		1,187
Cold Chain Super. - GS 5	100% X 4 mos	3,040		1,013
Adverse Effects Physician - NOB	100% X 3 mos	6,360		1,590
Adv. Eff. Med. Asst. (16) - GS 3	100% X 3 mos	1,880		7,520
Census Update				
Health Assistants (17) - GS 3	100% X 0.5 mo	1,880	1,332	
Com. Hlth. Wrkrs. (50)	100% X 0.5 mo	667	1,390	
Data Staff				
Program Analyst - NOA	100% X 14.5 mos	5,520	1,150	5,520
Coding Assistants (2) - GS 3	100% X 14.5 mos	1,880	783	3,760
Data Entry Tech. (2) - GS 3	100% X 14.5 mos	1,880	783	3,760
Virology/ELISA Staff				
Sr. Research Off. (1) - GS 5	100% X 16 mos	3,040	1,013	3,040
Sr. Lab. Tech. (2) - GS 3	100% X 16 mos	1,880	1,253	3,760
Lab. Attendants (1) - GS 2	100% X 16 mos	1,640	547	1,640
Consultants				
CDC Epidemiologists X 2 (per diem X 3 mos, and airfare, no salary)				10,000
TOTAL FOR PERSONNEL			36,335	113,576

SUPPLIES

Item	Unit Cost	# Units	1985 Project Cost In Dollars	1986 Project Cost In Dollars
ELISA for Serum Rota Ab	3.00	6160 (1540 persons X 4)	9,240	9,240
Medicines	1.00	770 (770 persons X 1)	770	
Inducements	.48	1540 (770 persons X 2)	739	
Vaccine Admin. Supplies	.30	770 (770 persons X 1)	231	
TOTAL FOR SUPPLIES			10,980	9,240

EQUIPMENT

Item		
Microcomputer for field data entry, vaccination monitoring, and analysis	3,000	
TOTAL FOR EQUIPMENT	3,000	

TRAVEL

Item		
International (4 trips - airfare and per diem, at 5,000/trip)	10,000	10,000
Local (per diem - 5.56 X 3 lab persons X 90 days)		1,501
Local (per diem - 5.56 X 5 data persons X 165 days)	2,085	2,502
Local (land - 26.00/trip X 2 trips/wk X 26 wks)	676	676
Local (water - Matlab to Dhaka - 13.00/hr X 4 hrs/wk X 26 wks)	676	676
Local (water - vaccination - 13.00/hr X 7 boats X 2 hrs/boat/day X 60 days)		10,920
TOTAL FOR TRAVEL	13,437	26,275

PRINTING AND XEROX

Item		
Census Forms (.10 each X 1200)	120	
Vaccination Training Manuals (.05 per page X 1000 pages)	50	
Vaccination and Adverse Reaction Forms (.10 each X 2400)		240
Other Xerox, Pens, Paper, Office Supplies	300	300
TOTAL FOR PRINTING AND XEROX	470	540

COMMUNICATIONS AND TELEX

Item		
Postage, Telexes, Telephone	500	500
TOTAL FOR COMMUNICATIONS AND TELEX	500	500

COMPUTER COSTS

Item		
Computer time for selection and randomization of vaccine recipients from Demographic Surveillance System	200	200
TOTAL FOR COMPUTER COSTS	200	200
TOTAL DIRECT COSTS	64,922	150,331
MANAGEMENT SUPPORT COSTS (DirectCostsX31%)	20,126	46,603
GRANDTOTAL	85,048	196,934

APPENDIX A

Written Consent Statement for Potential Participants in Oral Rotavirus Vaccine Evaluation

We wish to evaluate new vaccines against rotavirus, a germ that causes diarrhea of young children. These vaccines are taken by mouth, not by injection, and have not caused serious effects when taken by volunteers in many other countries.

We will assign your child to receive a single dose of one of these vaccines or a non-vaccine preparation. Neither preparation is expected to cause any side-effects, but just in case, our doctors will visit you today and for the next five days to look after any such problems. Of course, our station at Nayergaon and our facilities at Matlab Hospital will also be available for treatment of any problem. In addition to giving your child one of these preparations, we will also take a small sample of fingertip blood from your child today and one month from today.

You may decide whether or not your child will participate. Please ask any questions that you have, and then inform me whether you consent to volunteer your child for participation. Your child may refrain from participating in this program if you desire, and the treatment that you normally receive from Matlab Hospital will in no way be affected.

I fully understand the methods and basis for this study and agree to participate.

Signature_____ Date_____

Left Thumb Imprint:

<u>পরিশিষ্ট - এ</u>

রটাভাইরাস টিকা মূল্যায়নে সম্ভাব্য অংশ গ্রহন কারীদের জন্যে
<u>লিখিত সম্মতি পত্র</u> ঃ

আমরা অল্প বয়স্ক শিশুদের পাতলা পায়খানা সৃষ্টিকারী জীবানু, রটাভাইরাস বিরোধী টিকা মূল্যায়ন করতে চাই। এই টিকা মুখে খেতে হয়, ইনজেকশনের মাধ্যমে দেয়া হয়না এবং এই টিকা গ্রহনকারী অন্যান্য বহু দেশের স্বেচ্ছাসেবীদের কোন খারাপ প্রতিক্রিয়া হয় নি।

আপনার শিশুকে একডোজ টিকা অথবা টিকা নয় এরূপ সংমিশ্রন খাওয়ানো হবে। এ দুয়ের কোনটিতে পার্শ্বপ্রতিক্রিয়া সৃষ্টির আশংকা নেই। তবুও যদি কিছু কিছু সমস্যা হয় সে জন্যে আমাদের চিকিৎসক দল আছে এবং আগামী পাঁচদিন এসে আপনাদের দেখে যাবেন। যে কোন সমস্যায় চিকিৎসার জন্যে অবশ্যই আমাদের নায়ের দাঁ ও কেন্দ্র ও মতলব হাসপাতালের সুবিধা আপনার জন্যে রয়েছে। এই টীকা বা টীকা নয় এইরূপ সংমিশ্রণ এই দুটোর যেকোন একটি সেবার সময়ে এবং একমাস পরে আপনার শিশুর আঙুলের মাথা থেকে রক্তের নমুনা সংগ্রহ করতে হবে।

আপনার শিশু এ গবেষনা অংশ গ্রহণ করবেন কিনা সে ব্যাপারে আপনিই সিদ্ধান্ত নিবেন। আপনার কোন প্রশ্ন থাকলে অনুগ্রহ করে জিজ্ঞেস করুন, তারপর আমাকে জানান আপনার শিশুর স্বেচ্ছাসেবী হিসাবে অংশ গ্রহণে আপনার সম্মতি আছে কিনা। আপনি ইচ্ছা করলে যে কোন সময় আপনার শিশুকে এই সমীক্ষা হইতে নাম কাটাতে পারেন, এতে মতলব হাসপাতালে আপনার শিশুর স্বাভাবিক চিকিৎসার কোন ক্ষতি হবে না।

আমি এই প্রক্রিয়ার পদ্ধতি এবং বিধি সম্পূর্ণ বুঝতে পেরেছি এবং এতে অংশ গ্রহণে সম্মত হচ্ছি।

স্বাক্ষর ______________________________ তারিখ ________________________

বাম হাতের টিপসহি ঃ

APPENDIX B

Written Consent Statement for Potential Participants in Evaluation of Secondary Transmission of Oral Rotavirus Vaccine

We wish to evaluate new vaccines against rotavirus, a germ that causes diarrhea of young children. It has been agreed that a young child in your household will take a vaccine or non-vaccine preparation. In addition to evaluating the effect of this preparation on the child who takes it, we would like to evaluate the effect on other young children in your household.

If you choose to allow this other young child to participate, we will take a small sample of fingertip blood from this child today and one month from today.

You may decide whether or not your child will participate. Please ask any questions that you have, and then inform me whether you consent to volunteer your child for participation. Your child may refrain from participating in this program if you desire, and the treatment that you normally receive from Matlab Hospital will in no way be affected.

I fully understand the methods and basis for this study and agree to participate.

Signature_____ Date_____

Left Thumb Imprint:

পরিশিষ্ট - বি

রটাভাইরাস টিকায় মাঠপর্যায়ে শিশুর মূল্যায়নে মতামত সংগ্রহের কাজীদের জন্যে

লিখিত সম্মতি পত্র ।

আমরা অল্প বয়স্ক বাচ্চাদের পাতলা পায়খানা সৃষ্টিকারী জীবানু রটাভাইরাস বিরোধী টিকা মূল্যায়ন করতে চাই। ইহা লক্ষ্যণীয় করা হয়েছে যে, আপনার পরিবারের একটি শিশু এই টিকা অথবা টিকা বিহীন এই সংমিশ্রন দুধে খাবে। এর সাথে আপনার পরিবারের অন্যান্য শিশুদের যে প্রতিক্রিয়া হয় সেটাও আমরা মূল্যায়ন করতে চাই ।

আপনি যদি আপনার পরিবারের অল্প শিশুকে এতে অংশ গ্রহনে সম্মত করেন তবে তার আঙ্গুলের মাথা থেকে আজ এবং এক মাস পরে ছোট একটি রক্তের নমুনা সংগ্রহ করবো ।

আপনার শিশু এ গবেষনায় অংশ গ্রহন করবেন কিনা সে ব্যাপারে আপনিই সিদ্ধান্ত দিবেন । আপনার কোন প্রশ্ন থাকলে অনুগ্রহ করে জিজ্ঞেস করুন, তার পর আমাকে জানান আপনার শিশুর স্বেচ্ছাসেবী হিসাবে অংশ গ্রহনে আপনার সম্মতি আছে কি না । আপনি ইচ্ছা করলে যে কোন সময় আপনার শিশুকে এই পরীক্ষা হইতে নাম কাটাতে পারেন, এতে ভবিষ্যৎ হাসপাতালে আপনার শিশুর স্বাভাবিক চিকিৎসার কোন ত্রুটি হবে না ।

আমি এই পরীক্ষার পদ্ধতি এবং স্থিতি সম্পূর্ণ বুঝতে পেরেছি এবং এতে অংশগ্রহনে সম্মত হলাম ।

স্বাক্ষর ---------- তারিখ ----------

বামহাতের টিপ সহি :

SmithKline-RIT
a SmithKline company

JUNE 4, 1984.

Dave

APPENDIX C

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ROTAVIRUS VACCINE RIT 4237

STUDIES IN PROGRESS

STUDY	INVESTI-GATOR	PARAMETERS STUDIED	AGE RANGE	NUMBER DOSES	NUMBER INCLUDED (FORESEEN)	END FORESEEN
RV-H-011	JUST	R/I/IN	± 3Mo	1	20 + 12C (40)+ (20C)	END MAY
RV-H-017	VESIKARI	R/I/PR/PC	3-24Mo	1	60 + 60P (300)+(300P)	III/84
RV-H-020	HADZILE-MOVIC	R/I/VE/PR	3-12Mo	1	(60)	III/84
RV-H-021	JUST	R/I/VE/PR	NEWBORNS	1	(10)	III/84
RV-H-022	VESIKARI	R/I/DR/ EM/PC	4-6Mo	1	(210)+(30P)	IV/84
RV-H-026	VODOPIJA	R/I/IN/PC	3Mo	1	(80)+(40P)+ (40C)	JUNE 84

KEY : R = REACTOGENICITY
I = IMMUNOGENICITY
VE = VIRUS EXCRETION
PC = PLACEBO-CONTROLLED
C = CONTROL (OPV)
PR = PROTECTION
EM = EFFECT OF ARTIFICIAL MIL
IN STOMACH ON "TAKE" RAT
P = PLACEBO
IN = POSSIBLE INTERFERENCE WITH OPV

APPENDIX C

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ROTAVIRUS VACCINE RIT 4237

COMPLETED STUDIES

STUDY	INVESTIGATOR	PARAMETERS STUDIED	AGE RANGE	NUMBER DOSES	NUMBER INCLUDED	STATUS
H-001	VESIKARI	R/I/VE/ST	MEDICAL STUDENTS	1	20	PUBLISHED
H-003	VIDOPIJA	R/I/VE/ST/PC	6-7 Y	1v/s2	30+ 6P	COMPLETED
H-004	VESIKARI	R/I/VE/ST R/I/VE/ST	± 2Y 8-12Mo	1	20 5	PUBLISHED
H-005	VESIKARI	R/I/PR/PC	8-11Mo	1	86+ 92P	PUBLISHED
H-008	JUST	R/I	3-9Mo	1 & 2	47	COMPLETED
H-009	VESIKARI	R/I/PR/PC	8-11Mo	2	172+172P	COMPLETED
H-010	VIDOPIJA	R/I/PC	6-12Mo	1/2/3	90+ 30P	COMPLETED
H-012	DENIS	R/PR/PC	6-12Mo	1	46+ 47P	COMPLETED
H-013	VESIKARI	R/I/EM	6-12Mo	1	43	COMPLETED
H-016	VIDOPIJA	R/I/DR	6-12Mo	3	90+ 30P	SEROLOGY

TOTAL VACCINATED 649

KEY :
- R = REACTOGENICITY
- I = IMMUNOGENICITY
- VE = VIRUS EXCRETION
- ST = SERUM TRANSAMINASES
- PC = PLACEBO-CONTROLLED
- PR = PROTECTION
- EM = EFFECT OF ARTIFICIAL MILK IN STOMACH ON "TAKE" RATE
- DR = DOSE RESPONSE (10^6, 10^7, 10^8 $TCID_{50}$)
- P = PLACEBO

ROTAVIRUS VACCINE RIT 4237

STUDIES PLANNED

STUDY	INVESTI-GATOR	PARAMETERS STUDIES	AGE RANGE	NUMBER DOSES	NUMBER FORE-SEEN	STATUS
/-H-015	DENIS	VE/VT/PC	3-12Mo	1	40	IN DISCUSSION
/-H-018	CORBEEL?	IMM.MECH.	6 Mo	1	15	-
/-H-023	PECKHAM	R/I/VE/VT/PR/PC	6Mo-3Y	1	200 + 200P	START IV/84
/-H-024	JUST	R/I/DR	3-12Mo	1	90 + 30P	START 06/84
/-H-025	CADRANEL	R/I/pH	0-3Mo	1/2/3	100	START 06/84
/-H-027	PELLER	R/I/PR/PC	0-12Mo	1	30 + 30P	IN DISCUSSION
/-H-028	GIAMMANCO	R/I/PR/PC	0-12Mo	1	TO ESTABLISH	START IV/84
-	COLL.WHO	R/I/PR/PC	<1Y	TO ESTABLISH		IV/84

USA TRIALS

-2	YOLKEN	R/I/Ig/ST/PC	2-6Mo	1	40 + 40P	III/84
	SACK (NIAID)	R/I/PR/PC	2-6Mo	2	±300	IN DISCUSSION

KEY : R = REACTOGENICITY
I = IMMUNOGENICITY
VE = VIRUS EXCRETION
VT = VIRUS TRANSMISSION
PC = PLACEBO-CONTROLLED
PR = PROTECTION
pH = EFFECT OF GASTRIC pH ON "TAKE" RATE
P = PLACEBO
Ig = STOOL IgA

SIDE REACTIONS TO RHESUS ROTAVIRUS VACCINE

Venezuelan study February-March/1985

		INOCULUM	
Maximum Rectal [a] Temperature	PLACEBO (n=19)	RRV 10^{-2} (10^5 PFU) (n= 17)	RRV 10^{-3} (10^4 PFU) (n= 18)
less than 38.1°C (< 100.6°F)	17	14	17
38.1 - 38.3°C (100.6 - 100.9°F)	0	1*	1*
38.4 - 39.0°C (101.1 - 102.2°F)	2**	2***	0
more than 39.0°C (> 102.2°F)	0	0	0

[a] 0-6 days following administration of vaccine or placebo. Temperatures taken twice daily by medical staff.

* Single temperature elevation to 38.3°C.

** [illegible]

*** [illegible]

REACTIONS TO THE RHESUS ROTAVIRUS VACCINE

Venezuelan study (February-March 1985)

	INOCULUM		
Clinical Findings	PLACEBO (n=19)	RRV 10^{-2} (10^5 PFU) (n=17)	RRV 10^{-3} (10^4 PFU) (n=18)
Diarrhea	1	1*	1**
Liquid stools (< 3/day)	2	1	2
Semiliquid stools	1	1	2
Soft stools	9	5	7
Vomiting	5	3	3
Rhinorrhea	8	9	7
Coughing	5	1	5
Bronchialitis	1	1	
[illegible]		1	

* E. histolytica identified

** Salmonella sp. identified

APPENDIX E

Rhesus Rotavirus Vaccine Studies in Infants

To Date:

LOC	AGE IN MOS	# VACC *	DILUT	BICARB BUFFER	REACTIONS	SEROCON
Umea	4-12	52 P, 54 V	-1	500 mg	Fev, diarr	------
U. of Md.	5-14	13 P, 14 V	-1	?	Fev	86%
Venezuela	4-10	17 P, 17 V	-3	? No	None	35-53%
Venezuela	4-10	17 P, 17 V	-2	? No	None	71-82%

Planned:

LOC	AGE IN MOS	# VACC & DILUT	BICARB BUFFER	SEROCONV	EFFIC
Venezuela	2-10	100 P, 100 V-2	? No	Yes	Yes
U. of Md.	3-6	30 P, 30 V-2, 30 V-3	400 mg	Yes	No
Umea	4-12	200 P, ? 200 V-2	? 500 mg	Yes	Yes

* P - Placebo, V - Vaccine