Protocol No. 18003	Version No.: 3.0	Date: 06 November 2019

Title of the Research Project: A Phase 1 Double-Blinded, Placebo-Controlled, Dose Escalating Study to Evaluate the Safety and Immunogenicity of Double Mutant Heat-Labile Toxin LTR192G/L211A (dmLT) from Enterotoxigenic *Escherichia coli* (ETEC) by Oral, Sublingual, or Intradermal Vaccination in Adults Residing in an Endemic Area.

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International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b),68, Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka 1212, Bangladesh

PURPOSE OF THE RESEARCH

BACKGROUND

Enterotoxigenic *Escherichia coli* (ETEC) is a germ (bacteria) that causes moderate-to-severe diarrhea for many children in Bangladesh and other developing countries. It also affects many travelers to developing countries. ETEC is estimated to cause approximately 400 million diarrheal episodes and 380,000 deaths each year in the world. Scientists at a company in the United States called PATH Vaccine Solutions (PVS) have made an experimental vaccine against ETEC called dmLT Vaccine. This vaccine is not yet approved for use; however, the U.S. Food and Drug Administration (FDA) and the Directorate General of Drug Administration (DGDA) of Bangladesh have permitted its use in this research study. This study is sponsored by the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID), of the United States.

The purpose of this study is to test an ETEC vaccine (dmLT vaccine) in healthy adults aged 18-45 years in Bangladesh to find out if it is safe to give to people who are regularly exposed to ETEC and if the vaccine is acceptable. To do this, the researchers will compare the adults receiving the dmLT vaccine to the adults receiving placebo (a harmless substance). Depending on which Cohort (group) you are in, you will receive the study product (vaccine or placebo) either orally (by mouth), sublingually (under the tongue) or intradermally (into the skin). It is hoped that information from this study can be used to develop a vaccine that will help protect people from getting sick with ETEC. In addition to testing different ways to give the vaccine, we will test lower to higher amounts of the vaccine, this is called dose-escalation.

The vaccine and placebo are not pills or tablets; they are clear solutions (like water). For the oral Cohort, you will be instructed to drink 120 mL (or a little over half a cup) of a baking soda solution-like buffer and then drink 30 mL (about 2 tablespoons) of vaccine or placebo. For the sublingual Cohort, you will be instructed to rinse your mouth and then we will put 0.1 mL (less than a teaspoon) of vaccine or placebo directly under your tongue. For the intradermal Cohort, we will place 0.1 mL (less than a teaspoon) of vaccine or placebo into the skin by a needle and syringe.

This consent form contains important information to help you decide whether to be a part of this research study.

- Being in a study is your choice or voluntary
- If you join this study, you can still stop at any time

- No one can promise that a study will help you
- Do not join this study unless all of your questions are answered

After reading and discussing the information in this consent form you should know:

- Why this research study is being done
- What will happen during the study
- Any possible benefits to you
- The possible risks to you
- Other options you could choose instead of being in this study
- How your health information will be treated during the study and after the study is over
- Whether being in this study could involve any cost to you
- What to do if you have problems or questions about this study

WHY INVITED TO PARTICIPATE IN THE STUDY?

How many people will take part in the study??
Approximately 135 adults will participate in this study.

Who can participate in the study? You have been asked to join this study because you are a healthy male or non-pregnant female, age 18-45 years old. For the purpose of our research study, we need healthy adults to participate in study activities.

Who should not be in the study?
You cannot take part in this study if:

- You have received or will receive any other investigational drug or vaccine throughout the study period.
- You have any significant chronic medical or psychiatric conditions or are on certain medications.
- You were recently ill or on antibiotics.
- You are pregnant or breastfeeding.
- There may be other reasons why you cannot participate in this study, and the study doctor or study personnel will review these with you

METHODS AND PROCEDURES:
If you would like to join the study, you will be evaluated by study staff to check if you meet conditions to take part in the study, including your medical history, physical exam, and blood tests (including hepatitis B and hepatitis C testing). We will take a blood sample (about 3 teaspoons) for laboratory testing. If you are a woman, a urine pregnancy test will be done at screening and before each vaccination is given to make sure that you are not pregnant. If these screening tests show that you can take part in this research study, you will be informed and given an appointment for the enrolment and vaccination day. If you are a woman of childbearing age you must agree to use a hormonal or barrier method of birth control during the study. Abstinence is also acceptable.

All participants will be asked to collect a stool sample at screening and before vaccination. You will be given a container and instructions on how to collect this stool sample. You will need to bring this sample to the field clinic within 8 hours of collection.

You will be randomized (like a flip of a coin) to receive either the experimental dmLT vaccine or placebo either orally, sublingually, or intradermally on three separate occasions, depending on the Cohort you are in.

In each Cohort, you will have an 80% (4 out of 5 people) chance of receiving the vaccine, and a 20% (1 out of 5 people) chance of receiving the placebo. Neither you nor the doctors and study team members who will take care of you will know whether you have received the study vaccine or placebo.

You will be informed which route of vaccination group (oral, sublingual, intradermal) you are in prior to your first vaccination visit. If you are in a Cohort with oral route, you will be asked to have nothing to eat or drink for 90 minutes before and after vaccination. If you are in a Cohort with sublingual route, you will be asked to have nothing to eat or drink for 30 minutes before and after vaccination. If you are in a Cohort with intradermal route, you will be asked to stay at the clinic for 30 minutes after vaccination for observation, but there is no restriction on eating or drinking. If you are required to fast, this fasting time begins when you arrive at the clinic; thus, oral Cohorts will stay in the clinic for at least 4 hours and sublingual Cohorts will stay in the clinic for at least 2 hours.

You will be given a thermometer and a memory aid (record for temperature and symptoms) to take home and record your body temperature, any symptoms you may have, and medicines you may take for seven days after each vaccination. You will be asked to return the memory aid to the study staff at your next visit. If necessary, a research staff member will visit your household to help in the completion of the memory aid.

There are 9 study visits after screening. If you are in a Cohort with oral or sublingual study drug, you will be asked to come to study visits on Days 1, 8, 15, 22, 29, 36, 57, 114, and 209 to see how you are feeling, a brief physical examination, and collection of blood and stool samples (except stool samples will not be collected on Days 114 and 209). If you are in a Cohort with intradermal study drug, you will be asked to come to study visits on Days 1, 8, 22, 29, 43, 50, 71, 128 and 223 (except stool samples will not be collected on Days 128 and 223) to see how you are feeling, a brief physical examination, and collection of blood and stool samples. There will be three days that you will receive the vaccine (study days for vaccination): for oral and sublingual Cohorts it is Days 1, 15, and 29; for intradermal Cohorts it is Days 1, 22, and 43. The vaccination visits may take 2-5 hours and the follow-up visits will take 1-2 hours. Your total study participation will be between 8-9 months long.

About 1- 4 teaspoons (6-22 ml) of blood will be taken from your arm with a needle at every study visit. We may ask for additional blood tests if you get sick. Your arm will be cleaned before taking blood and new needles will be used each time that blood is collected.
Both saliva (spit) and stool samples (5-6 g) will be collected at each visit, except at screening and the last two visits. For the oral or sublingual Cohorts, these visits are Days 1, 8, 15, 22, 29, 36, and 57. For the intradermal Cohorts, these visits are Days 1, 8, 22, 29, 43, 50, and 71. You will be given stool containers and instructions on how to collect your stool at home. If you experience diarrhea (≥3 loose stools in a day) or a bloody loose stool after receiving the study product, you should notify us as soon as possible. You should also notify us if you have difficulty breathing, skin rash, or any painful skin changes, or an allergic reaction. We will provide instructions for another collection of your stool or a research staff member may come to your home to collect the stool specimen.
Immunological and cellular assays will be done in laboratory in Dhaka and in other foreign laboratories (Center for Vaccine Development (CVD), University of Maryland School of Medicine, and NIH, USA).

Study Days	
Oral and **Sublingual** Cohorts	**Intradermal** Cohorts
Day 1 – Vaccination #1	Day 1 – Vaccination #1
Day 8 – follow-up	Day 8 – follow-up
Day 15 – Vaccination #2	Day 22 – Vaccination #2
Day 22 – follow-up	Day 29 – follow-up
Day 29 – Vaccination #3	Day 43 – Vaccination #3
Day 36 – follow-up	Day 50 – follow-up

Day 57 – follow-up	Day 71 – follow-up
Day 114 – follow-up	Day 128 – follow-up
Day 209 – follow-up	Day 223 – follow-up

RISK AND BENEFITS

What are the risks/discomforts?

Oral and Sublingual dmLT Vaccine Risks: There is a small chance of getting diarrhea, abdominal cramping or discomfort, gas or bloating, nausea, vomiting, and/or decreased appetite after receiving oral and sublingual dmLT vaccine. There is also the possibility of facial nerve weakness and/or irritation of the tongue or oral cavity with the sublingual route of administration.

Intradermal dmLT Vaccine Risks: dmLT vaccine has been given to only a few humans intradermally. Like with any vaccine, however, you may expect to experience swelling, redness, pain, and/or bruising at the injection site. Additional risks may include pruritus (itchiness), induration (hardness of the skin), plaques (raised skin), hypopigmentation (light colored skin), hyperpigmentaton (dark colored skin), vesicles (fluid-filled bump on skin), and rash. If you get one of these findings near the area where you got the vaccine shot, we will take a photo of the skin daily until it appears stable or improves.

Other Risks of the study: Like with any vaccine, there is a small possibility that you may have an allergic reaction due to vaccination. These reactions may be mild, limited to a rash, or severe and life threatening and requiring intensive medical care in a hospital. We will be watching you in the clinic for at least 30 minutes after you get the vaccine.

Blood Collection: Minor bruising or bleeding and a slight risk of infection are possible at the site where blood is drawn. Some people feel faint at the sight of blood. You will get brief pain during collection of blood. Due to these risks, we will use a disposable syringe and needle and also other precautions to avoid such risks. In the event you develop any such problem, we will provide their appropriate treatment at our costs.

There is a risk of loss of privacy should an unauthorized person get your personal health information. We will make every effort to protect your privacy by doing such things like using password-protected computers and keeping your study records in locked cabinets and/or rooms with limited access.

If during the screening process, we discover you have a medical problem, you will be referred to a specialist for your medical care.

There may be other risks that at this time are not known. If new information about the safety of the vaccine becomes available, you will be informed.

Pregnancy:

Women are asked not to become pregnant during the study and for 28 days after the last dose of study vaccine because the effects on an unborn baby are not fully known. If you are a woman, and would like to be in the study, you must be willing to have a urine pregnancy test done at the screening visit and before getting each study vaccine. The results of the urine pregnancy test must be negative before we give you the study vaccine.

If you are pregnant or breast-feeding a baby, you cannot take part in this research study. If you are pregnant or think you are pregnant during the study, it is important that you tell the study doctor as soon as possible. If you do become pregnant during the study, the doctors will not give you anymore vaccinations but with your permission, we will continue to follow your health status until the end of your pregnancy. However if your child is born with abnormality after you have taken the study agent, no particular compensation will be provided by the National Institutes of Health (NIH), U.S. federal government or icddr,b. We will refer you/your child to a specialist for further management.

Are there benefits to being in this research study? You may not receive any direct benefit from the dmLT vaccine being tested in this study. However, you will receive medical care or referral according to the local standard of care anytime you are sick while enrolled in the study. If you receive the vaccine, you might get protection from ETEC diarrhea. Also, participating in this research study may benefit society by helping to test a vaccine to prevent ETEC infections.

What other options are there?
You do not have to take part in this study. Instead of being in this study you may choose not to take part in this study. This is not a treatment study. If you choose not to be in this study, you can still get your normal medical care.

PRIVACY, ANONYMITY AND CONFIDENTIALITY
Information about your participation in this study will remain private. In any reports, participants will be referred to by study number only but your name will not be used in the report and the information that we learn about you will not be shared with anybody except the authorized study investigators. Access to study files and other identification will be limited to members of the study staff, sponsors and its representatives, ethics committee members, members of the data and safety monitoring boards, and regulatory authorities in the U.S (FDA) and Bangladesh. All files with information that could identify you will be kept in locked cabinets for a minimum of two years; this time could be longer if the vaccine continues to be developed for marketing. However, we also would like to inform you that disclosure of information is subjected to the laws of Bangladesh. In publishing results of our study, we will not use your name or identity. If you do not come to the clinic for scheduled follow-up visits, study staff may attempt to contact you at your home and will identify themselves as part of the icddr,b research study staff. If you agree, we may take your photograph. This photograph may be published in news media or publication or icddr,b website for the purpose of this study. You can say no and you can still be in the study

The authority to collect this information is under 42 USC 285f (a U.S. law about health information dissemination).

This research is covered by a Certificate of Confidentiality from the U.S. National Institutes of Health (NIH). The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. The Certificate cannot be used to refuse a request for information from personnel of the U.S NIH that is needed for auditing or program evaluation by the U.S. NIH which is funding this project or for information that must be disclosed in order to meet the requirements of the U.S. Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web-site will not include information that can identify you. At most, the web-site will include a summary of the results. You can search this web-site at any time.

FUTURE USE OF SAMPLES AND INFORMATION

We intend for your blood, stool, and saliva samples to be stored indefinitely for future research purposes. We will store all leftover specimens after the study is completed, and may use them for future research, but they will not carry your name or identity. So, these specimens will be coded and only the research staff will be able to un-code the specimens to link them back to you. These samples will be stored at the DMID Clinical Agents Repository (CAR) in the United States. These samples may be used in the future for other tests related to ETEC and/or the dmLT vaccine. The stool samples may be tested for the microbes contained within them. Before using such unnamed samples for any future study, we would first obtain permission from the Ethical Review Committee of icddr,b. We will not be doing genetic testing on your specimens and we will not sell your specimens.

You may decide against storage of leftover samples. If you decide that you do not want your blood, stool, or saliva stored, the samples will be discarded at the end of the study. If you decide at some time in the future that you wish to have your remaining blood, stool, or saliva discarded, please contact Dr. Firdausi Qadri (telephone +8802 9827001-10, Extension 3465) and a study team member will confirm your decision. You can still participate in the study whether or not you choose to have your samples stored.

RIGHT NOT TO PARTICIPATE AND WITHDRAW

Rights as a participant of a research study: Participation in this study is voluntary, and you are the one to decide for and against your participation. If you decide against your participation, it will involve no penalty or loss of benefits to which you are otherwise eligible, and you may stop participating at any time during the study without penalty or loss of benefits to which you are otherwise eligible.

Right to withdraw: You will be able to withdraw from the study at any time without showing any reason and you are also able to refuse collection of any or all laboratory samples for the study. If you decided to withdraw from the study early, we will ask for you to complete an early termination visit. If you withdraw from this study, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. The study team may also choose to withdraw you from the study or from receiving all 3 doses of the study product for your safety or for non-compliance. The study team will inform you of the reason if this happens. If you do not receive all 3 doses of the study product you will be asked to continue with follow-up assessments through 6 months after the last dose of vaccine. The study doctor may also decide to take you off of this study at any time if it is in the best interest of your health or the study is ended early for any reason.

FUNDING, COSTS AND COMPENSATION

Who is funding this study

The National Institutes of Health (NIH) is funding this research study. This means that the University of Maryland School of Medicine is receiving payments from the NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from the NIH for conducting this study.

What are the costs and compensation for being in this study?

There will be no costs to you for being in this study. You will not have to pay to get the study vaccinations. There are no costs for the physical exams, laboratory testing, or clinic visits. They will be included as part of the study.

To make up for the time you spend away from work and home to be in the study, you will be given 500 Taka for each scheduled clinic visit. This will be paid to you on the day of the visit. Payments will be made only for any follow-ups that you complete. You will also get follow-up medical care after enrollment at the Mirpur Field Clinic. If you become sick while enrolled in the study, we will provide medical care or a referral for care at our cost. Treatment for diarrhea and for other illnesses will be free of charge, according to the standard of care that is available in Dhaka, even if you withdraw from the study. Once you are enrolled in the study and until the study is finished, with the exception of true emergencies, you can seek medical care or advice from the Mirpur Field Clinic. You should take no medications except those given at this clinic or prescribed by study doctors. If you need to get medical treatment from another clinic or hospital, please let the study staff know this.

What happens if I am injured because I took part in this study?

In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health (NIH) or U.S. federal government. If any harm is caused to you as a result of taking the study product, then we will provide medical care as available to you. In the event of unwanted reaction to the vaccine you should report that to the field clinic of this study or communicate with people listed at the end of this consent below for their management. You may be evaluated at an unscheduled clinic visit or a member of the study staff may make a home visit for your evaluation.

Who do I contact if I am injured as a result of being in this study?
Name of investigator: Dr. Firdausi Qadri
Address of investigator: Senior Director, Enteric and Respiratory Infections, Infectious Disease Division, icddr,b, Mohakhali, Dhaka 1212. Telephone: 9840525-32 , Extension No. 3465

PROVIDING ANSWERS TO YOUR QUESTIONS
If you want to know more about our study and your rights as a participant of a research study, you may contact the following investigators or the ethics committee at a suitable time, either meeting with them personally or by contacting them over telephone, at the following addresses:

Name of investigator: Dr. Firdausi Qadri
Address of investigator: Senior Director, Enteric and Respiratory Infections, Infectious Disease Division, icddr,b, Mohakhali, Dhaka 1212. Telephone: 9840525-32 , Extension No. 3465

Dr. Taufiqur Rahman Bhuiyan, Dr. Farhana Khanam, Mucosal Immunology & Vaccinology, Infectious Disease Division, icddr,b, Mohakhali, Dhaka 1212.
Telephone: 9840525-32, Extension No. 3460

Name of local Ethical Review Committee: icddr,b , Coordination Committee Secretariat
Local Ethical Review Committee contact: Mr. M.A. Salam Khan, Telephone: 9886098, Extension No. 3206

If you agree to your participation in this study, please put your name and signature or your left thumb impression on the space indicated below. Thank you for your cooperation.

PERMISSION TO STORE AND USE LEFTOVER SPECIMEN FOR FUTURE RESEARCH

_____ YES: I give permission for storage and future use of my leftover blood, saliva and stool specimens The samples will not have my name on it and I cannot be identified.

_____ NO: I am not giving permission for storage and future use of my leftover blood, saliva and stool specimens. Destroy my unused samples at the end of this study.

CONSENT FOR TAKING PHOTOGRAPH

I am giving consent to take my own photograph so that it could be used to publish in news media/publication/icddr,b website for the purpose of this study: Yes ☐ No ☐

DECLARATION BY STUDY PARTICIPANT

The investigators/ study staff have explained to me the purpose, procedures, risks and benefits of participating in this study, the rights of research participants, and the confidential handling of the information and records including personal information of me, and I have fully understood them. I understand that I may withdraw myself at any time without giving any reason, I have been told that I shall also be able to get further information in future, and that the name and/or identity of me will not be used in dissemination of the findings of this study and/or in publishing them in reports/journals. Based on the above, I voluntarily agree to enroll into this study.

Name of participant (print): _____

Signature or thumbprint of participant: _____ Date _____

DECLARATION BY WITNESS

I confirm that I witnessed the consent process, that all questions and concerns have been addressed, and that the participant agrees to enroll in this study.

Name of witness (print): _____

Signature of witness: _____ Date _____

Name of investigator/designee (print): _____

Signature of investigator/designee: _____ Date _____

Note- A signed and dated copy/photocopy of this document will be given to you.