Phase II, randomized, double-blind, placebo-controlled study of the safety and immunogenicity of the recombinant live attenuated tetravalent dengue virus vaccine admixture TV005 (TetraVax-DV TV005) in healthy adults, adolescents, and children in Dhaka, Bangladesh

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International Centre for Diarrhoeal Disease Research, Bangladesh
Voluntary Consent Form (Adult)

Protocol No. PR-15097	Version No. 2.7	Date: 27-07-2016

Protocol Title: Phase II, randomized, double-blind, placebo-controlled study of the safety and immunogenicity of the recombinant live attenuated tetravalent dengue virus vaccine admixture TV005 (TetraVax-DV TV005) in healthy adults, adolescents, and children in Dhaka, Bangladesh

Investigator's Name: Dr. Rashidul Haque

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b) and The University of Vermont, USA

Purpose of the research: Over two billion persons are at risk of dengue infection world-wide. While some people who get dengue do not get sick, others can become more ill and may even die. There are 4 strains of dengue virus (types 1, 2, 3, and 4). Dengue was first seen in Bangladesh in 2000 and testing shows that 80% of people in Dhaka have been exposed to dengue.

Vaccines are medicines that are given to people to prevent against disease. We want to test a vaccine that would protect against all 4 strains of dengue virus. This vaccine is called TetraVax DV TV005. This vaccine was developed by scientists at the National Institutes of Health in the United States. This experimental vaccine has been tested in volunteers in the United States. We will draw your blood throughout the study to see how well this vaccine prevents against dengue. We will also use blood tests to measure the safety of the vaccine and will watch for side effects.

This study will include 192 people from Mirpur, Dhaka. The ages of study participants will range from 1 year old to 50 years old. One in four people in the study will be randomly assigned to get a placebo instead of the experimental vaccine. A placebo is a dummy test vaccine that does not have the active ingredients of the experimental vaccine. The experimental vaccine or placebo is an injection given under the skin.

This study will be done in collaboration with the icddr,b and the University of Vermont. Research ethics committees at the icddr,b and at the University of Vermont have reviewed this research study.

It is up to you decide whether you want to be part of this study. Participation in this study is **voluntary** and you can decide to stop participating in the study at any time. Any decision that you make will not affect the care that you receive or the benefits to which you would otherwise be entitled. Please ask questions about the study and discuss the study with anyone you think can help you make a decision about participating in the study.

Why are we inviting you to participate in the study? We are inviting you to participate in this study because we are trying to understand the safety and efficacy of TetraVax-DV TV005 in healthy adults, adolescents, and children in Dhaka, Bangladesh.

What is expected from the participants of the research study? The entire study is approximately 37 months including screening. If you agree to be in the study, you may expect the following:

Screening:

1. The study will be explained to you and you will sign the informed consent if you want to be in the study. We will give you a copy of this signed form.

2. Study staff will review criteria to confirm that you are eligible to be in the study.
3. You will be interviewed by a staff member who will collect information regarding your medical history. This will include a menstrual and contraceptive history and/or history of surgical sterilization for women of reproductive age.
4. A physical exam will be performed. Please note that the physical exam will include an examination of the skin though every effort will be made to maintain modesty.
5. A urine sample will be collected to test for pregnancy in women of reproductive age. A positive pregnancy test would exclude you from participation in this study. Pregnancy counselling will be conducted for all women of reproductive age.
6. A blood sample will be collected for routine laboratory tests which will include a test for Hepatitis B and C (liver diseases). If you test positive for Hepatitis B and/or C, then you cannot participate in the study. We would refer you to an appropriate medical provider who will provide further testing, counselling and follow-up care as needed.
7. After all information has been reviewed, we will notify you whether or not you qualify for the study. If you decide to participate, you will be asked to return to the clinic within the next 30 days to receive the experimental vaccine or placebo.
8. This screening visit is expected to last approximately 2 hours.

Day of Dose (Day 0):

1. Your medical history and the inclusion/exclusion criteria of the study will be reviewed again on the day that you are scheduled to receive the vaccine or placebo.
2. A blood sample and urine pregnancy test (for women of reproductive age) will be performed. Vital signs will again be measured.
3. A physical exam will be performed.
4. If all tests and inquiries are satisfactory, you will receive a dose of the experimental vaccine or placebo. You will be asked to stay at the clinic for at least 30 minutes following the injection for observation.
5. Instruction will be provided about future visits. You will be provided a thermometer to monitor for fevers for the first fifteen days of the study.
6. This day 0 appointment is expected to last approximately 3 hours.

Home visits/telephone surveillance:

1. With the exception of days with a scheduled clinic visit, study staff will visit your home daily for the first fifteen days of the study. At each of these visits, study staff will take your temperature. They will ask you about any medications you may have taken that day and will ask you additional questions about possible side effects. Each visit is expected to last less than 15 minutes. Study staff may call your telephone if you are not able to be contacted in-person.
2. After the first fifteen days of the study, study staff will either visit your home or contact you by telephone once a week until your study day 180 visit. They will ask you questions about any fevers, side effects and medications taken. This surveillance is expected to last less than 15 minutes.
3. Between the day 180 visit and completion of the study at 3 years, a member of the study staff will contact you once a month by phone to assess for hospitalizations, fevers greater than 2 days and certain other events.

Follow-up Visits:

1. You will need to return to the clinic for eight scheduled follow up appointments over the three years following vaccination. You will have visits scheduled on Days 7, 14, 28, 56, 180, 360, 720, and 1080 following vaccination. Each of these visits are expected to last less than one hour.
2. At each visit, you will provide a blood sample for research and/or safety measures, your vital signs will be measured, questions will be asked about your medical history, and you will have a physical exam.

3. At study days 28 and 56, women of reproductive age will have a urine pregnancy test performed.

Unscheduled Visits:
Should you develop a fever (equivalent to an oral temperature ≥38ºC) that persists for more than one day during the three years following vaccination, you will need to go to the clinic for an unscheduled visit. You may need to provide another blood sample of approximately 2 mL (less than ½ teaspoon) to check for dengue fever. Study staff will continue to monitor you until your fever resolves.

Additional contact with study staff:
You are expected to contact the Investigator, or their designee, immediately should you develop any signs or symptoms that you believe may be serious or if you are hospitalized (an overnight stay in the hospital or emergency ward) during the course of the study. You may contact the study staff as indicated below.

Total blood draw amounts:
A total of 257 mL (approximtely 17 tablespoons) of blood will be drawn from screening through study completion for safety and research measures. No more than 30 mL (2 tablespoons) will be drawn at a single visit. Note that additional blood may be drawn beyond this amount if a study doctor finds it is necessary for additional safety monitoring.

Photography:
There are times throughout the study that study staff may take a photograph of you, such as if a rash develops. The photo(s) are stored in an electronic file without your name and will not show your face or reveal private body parts.

Withdrawal from the study: There are several reasons why you may be removed from the study once you have received the vaccine or placebo. These reasons will be reviewed in detail at your screening visit and again at the time of vaccination (day 0). You may be removed from the study if you do not follow these instructions. Additionally, you may be removed from the study if:

- A study investigator believes it is in the best interest of the volunteer to be removed from the study.
- The research project is ended by the funding organization or a regulatory body.

You may decide that you no longer want to be in the study at any time without penalty or consequence. Medical costs incurred following your withdrawal and unrelated to study participation become your responsibility. All information and samples collected from you prior to your withdrawal may continue to be used in this research unless you specify that your samples are to be destroyed.

What are the risks to participating in the study? Sometimes things happen to people in research studies that may hurt them or make them feel bad. These are called risks. The risks of participating in this study include those caused by drawing blood, risks from the experimental vaccine, and risks to confidentiality.

This is a test vaccine and it is not fully known what may happen. The components of this vaccine have already been tested in volunteers in the United States without significant adverse side effects and with none of the volunteers developing a dengue-like illness at any time. The effects of the vaccine on unborn infants and on breastfeeding children are not known, so you must take precautions to make sure you do not become pregnant, and you should not plan to become pregnant during the first 28 days after receiving the vaccine. You will be excluded from participation in the study if you are pregnant or lactating at the time of study

screening or vaccination. The study staff will go over pregnancy prevention requirements and methods and you may not participate if you cannot agree to follow these carefully.

If you receive this experimental vaccine, your risk of developing severe dengue following a second infection with a dengue virus may be increased. It is not known whether this is a true risk or how long this risk might last, but it may be for the rest of your life.

There are risks from receiving vaccination such as pain, tenderness, itching or swelling at the site where the injection was given. You could have an allergic reaction (hives or trouble breathing). Sometimes people can die from allergic reactions. You will be observed for 30 minutes following vaccination to check for signs of an allergic reaction.

The most common side effects of vaccination with TetraVax-DV TV005 included rash and feeling tired. The rash is most commonly seen on the trunk and the arms. It does not hurt and typically goes away in a week. Approximately 4 out of 10 volunteers who have received TetraVax-DV TV005 have developed a rash. Feeling tired is also common after vaccination; it was noted in approximately 1 out of 3 volunteers who received TetraVax-DV TV005. Other possible side effects include the following: headache, eye pain, sensitivity to light, muscle aches or joint pains. You may also get a low white blood cell count, low platelets (cells that help the blood clot) or elevated liver function tests.

From blood draws, you may have pain where the needle is inserted, have a bruise where blood is taken, or have bleeding at the site of the blood draw. There is a very small risk of developing an infection, but our study staff will make efforts to reduce this risk.

Since the information we collect for this study could be used to identify you, we will take great care to protect this information as described below under privacy, anonymity, and confidentiality.

You will be provided with any significant new findings discovered over the course of the research that may affect your willingness to continue participating in the Study.

What happens if you are injured? If you are injured or become ill as a direct result of participating in this research project, the study staff will provide medical care for that injury or illness. This medical care will be at no cost to you. You will not be provided with any further compensation in the event of injury or illness.

What are the benefits to participating in the study? There is no direct benefit to you for your participation in this study. If you are in this study, you will get free medical examinations and laboratory tests that are a part of the study protocol. You will be offered primary care by the study clinic through your day 180 visit. By taking part in this study, you are helping to make better dengue vaccines that may help other adults and children from getting dengue fever.

Privacy, anonymity and confidentiality: We will keep all information collected about you confidential and locked in a secure place. No one except study staff, the icddr,b Ethical Review Committee, local regulatory authorities in Bangladesh, and the United States Food and Drug Administration (FDA) will have access to this information. Monitors under contract to National Institute of Allergy and Infectious Disease (NIAID) may have access to your research file in order to monitor all aspects of the study in accordance with the appropriate regulations. Your name and identity will not be disclosed in the process of analysing or publishing the results of this study; however, because the genetic information we are

collecting is potentially identifying, we cannot guarantee absolute confidentiality, although we will make every effort to preserve confidentiality.

If you sign this form, you have given us permission to share certain information with authorized people and groups. If you decide to withdraw your permission and end this agreement, please contact Dr. Rashidul Haque at the address/number below. He, or his study staff, will help you with this process. Please note that any study information already obtained will continue to be used.

Your participation in this research study is voluntary. However, you will not be able to participate in this study if you do not sign this form.

Clinical Trials Registration: Information about this study 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.

Storage and Future use of sample: Some of your samples may be shipped to University of Vermont, USA for analysis. If you agree, we will store blood samples collected during this study for five years in both icddr,b and the University of Vermont. Unused samples will be destroyed. We may use these samples in the future for other research purposes, including genetics research. If such research is conducted by us or by our collaborators, appropriate approvals from respective authorities will be secured at that time. Should samples be used in the future, your privacy and anonymity would be maintained. If you consent now to having your samples used in the future but later change your mind, you may contact us and the samples will be destroyed.

Right not to participate and withdraw: You are the only person who can decide whether you will participate in this study. You have the right to withdraw yourself from the study at any time without giving a reason. An alternative to participating in this study is to not participate.

Are there any costs? It will not cost you any money to be in this study.

Principle of compensation: Study participants who enrol will be compensated with 500 taka per study visit, including the screening visit and scheduled visits. The compensation is to help offset travel expenses to the clinic site for study visits, and for loss of income for visits during work hours. Food will also be provided at each scheduled clinic visit. The participants shall also be provided best possible, free treatment, for research-related injuries.

Answering your questions/ Contact persons: We will happily provide you further information about the study, now or at a later time point. You may communicate with the principal investigators of the study or their designated person via the contact address given below. Please contact the Principal Investigator in the event of a research-related injury.

Name of your Principal Investigator	**Dr. Rashidul Haque**
Address:	Centre for Vaccine Sciences , icddr,b, Mohakhali, Dhaka - 1212
Telephone number:	+880- 0173093859

Office hours telephone number:	+88 02 9827001-10 ext.3483
Name of study staff:	**Dr. Masud Alam**
Address:	House#28, Avenue:1, Bloc: E, Section:12, Mirpur, Dhaka-1221
Telephone number:	+88 02 9827001-10 ext.3482; 01711-570550

If you have any complaints or questions about your rights as a research volunteer, you may contact:

Name of the icddr,b IRB Contact:	**Mr. M.A. Salam Khan**
Address	IRB Secretariat, icddr,b, Mohakhali, Dhaka-1212 Cell: +880- 01711428989, Office: +880-2-9827001-10 Ext. 3206, +880-2-9886498

I have read this consent form or someone explained it to me. I freely agree to the study.

_____ _____
Printed name of participant Date

_____ _____
Signature or left thumb impression of participant Date

_____ _____
Printed name of the witness Date
(if applicable)

_____ _____
Signature or left thumb impression of the witness Date
(if applicable)

_____ _____
Printed name of the PI or his/her representative Date

_____ _____
Signature of the PI or his/her representative Date

I agree to allow stored blood to be used in future studies.

Yes ☐

No ☐

(NOTE: In case of representative of the PI, she/he shall put her/his full name and designation and then sign.)