United States Army Medical Research Institute of Infectious Diseases

CONSENT TO PARTICIPATE IN RESEARCH

Title of Protocol: An Exploratory, Pilot Study of the Safety and Immunogenicity of Reduced Doses of the US Yellow Fever Vaccine (FY19-26)

Principal Investigator: Phillip R. Pittman, M.D., MPH

You are being asked to participate in a research study. As you think about your decision, you should consider all of the information in this informed consent form.

The table below summarizes some **key** things to think about. After reading this summary, if you think you might be interested in participating, read the rest of the consent form for more details about the study.

RESEARCH SUMMARY	
Voluntary Participation	You do not have to take part in this research. It is your decision. You can also choose to stop participating at any time during the study.
Purpose	The purpose of this study is to evaluate whether lower doses of the Yellow Fever (YF) vaccine offer similar protection to the FDA approved vaccination dose.
Duration	You will be in this study for about 14 months.
Procedures	As part of this study, you will • be randomized to 1 of 3 groups • have a physical exam, provide medical history and medication information, and have blood drawn for lab tests (including pregnancy test for women) • receive the study YF vaccine • return for 12 follow-up visits over 12-13 months • keep a diary of symptoms for 28 days after the vaccination
Drugs/Devices	The drug used in this study is the FDA-approved yellow fever vaccine, YF-VAX®
Risks	The **main** risks from being in this study are: • related to receiving the YF vaccine (headache, tiredness, muscle aches; injection site pain, tenderness, redness, and swelling) • related to having blood drawn (bruising and swelling) Steps to lessen the risks are described later in this consent form.

Benefits	You are not expected to receive any direct benefit from taking part in this study. If you receive the full dose of YF-VAX® you are considered protected from Yellow Fever disease.
Payment	You will receive $50 for each blood draw. You will receive additional compensation ($200) for completing vaccination day activities, but if you are active duty or a Federal employee you **must be on leave or off-duty** to receive this additional compensation.

INTRODUCTION

You are being asked to participate in a research study conducted at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) by Phillip R. Pittman, M.D., M.P.H. because you have not previously received the Yellow Fever vaccine.

You do not have to take part in this research. It is your choice. It is important that you understand this research study so that you can make a decision regarding whether you wish to participate in the study or not. This process is called informed consent. To make your decision, you will need to consider all of the information provided here and ask questions about anything you do not understand. You may want to talk with your family, friends, or others to help you decide if you want to be part of this study. When you feel that all of your questions have been answered, you will be asked if you agree to be part of the research or not. If you agree, you will be asked to sign this consent form. You will be given a copy of this form to keep.

WHY IS THIS RESEARCH BEING DONE?

YF disease is a viral hemorrhagic fever that is a re-emerging infectious disease and is likely to continue to be a threat to deploying military forces well into the future. The African yellow fever epidemic coupled with manufacturing limitations on vaccine production constraints has led to a worldwide shortage of yellow fever vaccine. The current YF vaccine shortage has highlighted the need to pursue alternative solutions to extend existing vaccine supplies, with the most rational solution being dose-sparing strategies. Understanding the safety and biologic/immunologic responses to this vaccine is key to the warfighter's immune readiness and the readiness of the Department of Defense to perform its mission. It is essential that the war fighter is provided an effective method of protection from yellow fever virus infection when deployed in an endemic area.

The purpose of this research study is to examine whether lower doses of the Yellow Fever vaccine (YF –VAX®) (1/5th) and 1/10th provides the same protection as the current FDA approved vaccination dose.

WHO IS ELIGIBLE TO PARTICIPATE?

You must meet all of the following general criteria to participate:

- Be in good general health with **NO** acute or chronic medical conditions.
- Be male or non-pregnant, non-breastfeeding female.
- If female of child bearing potential, have a negative pregnancy test and be willing to use a reliable form of contraception for the duration of the study after vaccination.
- Be between the ages of 18-50 years old.
- You have no history of the following diseases or having received a vaccine, licensed or investigational, at any time for any of them: yellow fever, Japanese Encephalitis (JE), St. Louis Encephalitis, Tick Borne Encephalitis (TBE), West Nile, Dengue, and Zika virus.
- You have **NO** history of immunosuppression, by any cause--primary or acquired immunodeficiencies, transplantation, malignant neoplasm, lymphoma, leukemia, thymoma, mysthenia gravis, radiation, and immunosuppressive or immunomodulating drugs.
- You have a negative blood test for human immunodeficiency virus (HIV) antibody screen, hepatitis B surface antigen (HBsAg) and hepatitis C antibody.

- You have **NO** clinically significant abnormal laboratory tests. (generally ≥ 2 times the upper limit of normal).
- You **DO NOT** have any known hypersensitivity (allergic reaction) to any vaccine, eggs or egg products, or allergy to any component of the YF-VAX® (sorbitol, gelatin) or latex.
- You have **NOT** taken corticosteroids or other immunosuppressing agents for two weeks or longer. Low-dose corticosteroid topical products and nasal sprays used on occasion (according to circumstances) are permissible.
- You do **NOT** anticipate receipt of/or donation of blood or blood products for 2 months after your Yellow Fever vaccination.
- You do **NOT** anticipate receiving any other vaccine within 28 days before or after your Yellow Fever vaccination. COVID-19 vaccination or Influenza vaccination will be permitted but not within 14 days of your Yellow Fever vaccination.
- You have **NOT** received any other investigational vaccine or investigational drug within 28 days before or after vaccination with Yellow Fever vaccine.
- You are willing to comply with all follow-up visits, testing, adverse event reporting, and completion of diary card.

WHAT WILL HAPPEN DURING THIS RESEARCH?

After signing the consent document, you will be scheduled for a screening visit to confirm your eligibility to participate in the study. The screening visit will include:

• Obtaining your medical history information.

• Reviewing your vaccination history.

• Sign a separate consent to test for HIV.

• A physical examination and vital signs (temperature, heart rate, breathing rate and blood pressure).

• Reviewing your current medications.

• Counseling on pregnancy, and reviewing acceptable contraceptive methods and recent menstrual history if applicable.

• Blood draw for baseline laboratory tests, hepatitis serology, HIV, and pregnancy test if applicable (about 2 1/2 tablespoons).
• Collecting a urine sample.

Blood tests that are HIV, hepatitis B or C positive are required by law to be reported to the Maryland Health Department. The test results reported to Maryland Health Department will contain the participant's name, contact information, including address and telephone numbers, and the type of testing that was done. If the participant is in the military, study staff are required to report the same kind of information to military preventive medicine service. As a result, this information may end up in your military medical record and may be reported to your chain of command. The study doctors will discuss their health results face-to-face (and notify their primary doctor at their request).

After completing the screening portion of the study and with approval by the study physician to participate in the study, we will randomly assign you to one of three groups: Group 1 will receive the current FDA approved YF vaccine dose; Group 2 will receive 1/5th YF vaccine dose;

and Group 3 will receive 1/10th YF vaccine dose. We will inform you of your group assignment when you return for your yellow fever vaccination. You will **not** have a choice as to which group you are assigned.

Your vaccination will be given into your non-dominant upper arm preferably (given to you with a short needle as a small shot under the skin) by medically trained staff. After the vaccination, you will remain in the clinic area for at least 30 minutes to be sure that you are not experiencing any side effects from the vaccine that would impact your safety. Study medical staff will examine your vaccination site before you leave.
You will also be given a diary card to complete daily for 4 weeks to keep track of all signs or symptoms you had after receiving the Yellow Fever vaccine. A physician investigator will determine if they are related to the vaccine or not.

Study participants who receive the full vaccine dose will be given proof of vaccination documentation for their medical record.

You will return for 11 follow-up visits after you receive the study vaccination (see Study Event Table on next page). At some of these visits, we will examine your vaccination site for any reactions and we will ask you about any vaccine related side effects. At other visits, we will ask about your general health, obtain your vital signs, and/or ask about any medications that you may have taken. At each follow-up visit, we will collect a blood sample from you. No genetic tests on your blood will be performed in this study. You will have a physical exam at the end of your study participation. Follow-up visits should take between 15 and 30 minutes.
A research team member will work with you to schedule each blood draw/clinic visit at your convenience. We will notify you by either telephone or email to remind you of your appointment for each scheduled visit.

TABLE: STUDY EVENT SCHEDULE

Study Event	Screening	Day of Vaccination	Post-Vaccination Day										
	Days -60 to -1	0	2	3	5	6	7	10	14	28	90	180	365
Informed Consent	X												
Eligibility Criteria Review	X	X											
Medical History	X												X
Medication Review	X	X					X		X	X		X	X
Physical Examination	X												X
Vital Signs	X	X	X				X			X			X
CLIN LABS													
Complete Blood Count (CBC) with Differential	X						X		X				
Comprehensive Metabolic Panel (CMP)	X						X		X				
Urinalysis	X												
Hepatitis Panel	X												
HIV Antibody Screen	X												
Serum/Urine Pregnancy Test for Females of Childbearing Potential	X	X											
RESEARCH LABS	X	X	X	X	X	X	X	X	X	X	X	X	X
Amount of Blood (mL)	38	17	9	17	9	9	30	17	30	9	9	9	9
Additional Tests on Last 40 Subjects													
PBMC's		X					X		X	X	X		X
Microbiome		X	X				X		X	X	X		X
Amount of Blood (mL)		42					42		42	42	42		76
Approx. Total Amt. of Blood ((mL)	38	59	9	17	9	9	72	17	72	51	51	9	85
YF-VAX® Administration		X											
Injection Site Observation		X	X				X			X			
Adverse Event Review		X	X	X	X		X			X	X	X	X

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will take approximately 14 months.

WHAT PRECAUTIONS DO I NEED TO TAKE?

The risks from the YF-VAX® vaccine to a pregnant woman and her unborn child are unknown,

but may be dangerous. To avoid pregnancy, unless you have had your uterus removed, you should either abstain from sexual relations or practice a method of birth control such as, use of male condoms, birth control pills, or an intrauterine device. If you become pregnant by accident during the course of the trial, we will follow you until you give birth to your child.

Individuals who receive less than the full dose of YF-VAX® should receive a full dose of YF-VAX® before deploying or traveling as a tourist to an endemic area. There is no increased risk to receiving the additional vaccine dose.

HOW MANY PEOPLE WILL BE IN THE STUDY?
Up to 150 individuals will be screened in order to randomize 90 eligible individuals to one of three groups.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Potential Risks Related to Yellow Fever Vaccine

Very common side effects after vaccination include: headache, tiredness or weakness, injection site reactions (pain, tenderness, redness, swelling), and muscle pains. Other common symptoms include: fever, stomach problems, and joint pain.

Less common side effects after vaccination include: include an abnormal sensation, typically tingling or pricking ("pins and needles") and flu-like illness, injection site blisters and syncope (fainting).

The most serious two adverse reactions following YF vaccine occur in individuals over 60 years old. These are (1) Yellow Fever Vaccine-Associated Acute Viscerotropic Disease (YEL-AVD) affecting vital organs similarly to yellow fever infection, and (2) Yellow Fever Vaccine- Associated Acute Neurotropic Disease (YEL-AND) affecting the brain and nerves. This study limits the age range to 18-50 years of age. Therefore, these two complications are unlikely to occur in this age group.

As with any vaccination, there is a possibility of an allergic reaction, such as rash, itching or hives on the skin, swelling of the lips or face, swelling of the throat, fast pulse, sweating, feeling of dread, difficulty breathing, sudden drop in blood pressure causing dizziness or lightheadedness, and inability to breathe without assistance. YF-VAX® will not be administered to anyone with a history of acute hypersensitivity to eggs or egg products due to a risk of anaphylaxis (a severe potentially life-threatening allergic reaction).

Emergency medical equipment is located in the USAMRIID Division of Medicine clinic to handle emergencies. In the event you experience a medical emergency, transport to an emergency care facility will be arranged.

Potential Risks and Discomforts Related to Blood Draw

You may experience discomfort at the site of the needle stick and may sustain swelling and/or bruising at the site. Occasionally, some individuals become lightheaded (rarely to the point of fainting) and/or develop tachycardia (fast heart rate) during a blood draw. If this occurs, the blood draw will be stopped and you will be given an opportunity to lie down and relax until recovered.

There is also a small risk of infection occurring at the blood draw site or thrombophlebitis (vein swelling). This risk will be minimized by having only qualified personnel perform blood draws and by following standard infection control procedures.

Potential Risks Related to Confidentiality of Information

Investigators at USAMRIID will receive the results of the clinical and research lab tests; however, no results will be recorded in your medical record. All data and medical information obtained about you will be considered privileged and held in confidence. You will not be identified by name in any published report or in any presentation of the results. However, complete confidentiality cannot be promised, particularly if you are active-duty military, because information bearing on your health may be reported to appropriate medical and/or command authorities.

Unknown Risk

There is the possibility of risks that are unknown or that cannot be foreseen based on current information. As previously stated, the risks from the YF-VAX® vaccine to a pregnant woman and her unborn child are unknown, but may be dangerous. However, there is no known risk of the vaccine effect on reproduction for male subjects.

WHAT ARE THE POSSIBLE BENEFITS FROM BEING IN THIS RESEARCH?

You may benefit from participating in the study by learning about your health from the screening tests. *If you are in the group that receives the full dose of YF-VAX® you will be considered protected from Yellow fever disease per FDA*.

WILL RESEARCH RESULTS BE SHARED WITH ME?

The results of all screening labs, vaccine titers and safety labs (CBC, CMP) will be shared with you.

WHAT ARE MY OTHER OPTIONS IF I DO NOT PARTICIPATE IN THIS STUDY?

The only alternative is not to participate in the study.

WILL I HAVE TO PAY FOR ANYTHING IF I TAKE PART IN THIS RESEARCH?

There are no anticipated costs related to participating in this research study. Travel costs to the research site will not be compensated.

WILL I BE PAID TO TAKE PART IN THIS RESEARCH?

You will receive $50 for each study blood draw on the same day the blood sample is obtained. If you complete all blood draws, the total amount you will receive will be $650.

Study participants who complete vaccination day activities will be compensated an additional $200.00 for an overall study participation total of $850. If you are Active Duty or a Federal Employee, you must be on leave or off duty during your study visit in order to qualify for the $200.

We are required to have your name in order to compensate you for your participation. This

information and the payment amount will be kept secure and confidential. This information will not be associated with this study or your research data.

If you are paid a total of $600 or more as a research participant, USAMRIID is required to report the payment to the Internal Revenue Service as miscellaneous income. This may require you to claim compensation that you received for participation in research as taxable income.

WHAT HAPPENS IF I AM INJURED AS A RESULT OF TAKING PART IN THIS RESEARCH?

If at any time you believe you have suffered an injury or illness as a result of participating in this research, please contact Phillip R. Pittman, M.D., 301-619-2997 or e-mail at phillip.r.pittman.civ@mail.mil.

If you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty military, dependent of active duty military, retiree), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to care for your injury at DoD hospitals or clinics, but care for your injury may be limited to a given time period, and your insurance may be billed. It cannot be determined in advance which DoD hospital or clinic will provide care. If you obtain care for research-related injuries outside of a DoD hospital or clinic, you or your insurance will be responsible for medical expenses.

For DoD healthcare beneficiaries and non-DoD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights. If you believe you have sustained a research-related injury, please contact the Principal Investigator (PI). If you have any questions, please contact the PI (Phillip R. Pittman, M.D., 301-619-2997).

HOW WILL YOU PROTECT MY PRIVACY AND THE CONFIDENTIALITY OF RECORDS ABOUT ME?

All data and medical information obtained about you as an individual will be considered privileged and will be held in confidence. You will not be identified by name in any published report or in any presentation of the study results. Authorized representatives of the following groups may need to review your research and/or medical records as part of their responsibilities to protect human participants:

- Headquarters, US Army Medical Research and Development Command Institutional Review Board (HQ, USAMRDC IRB)
- USAMRIID Office of Human Research Oversight (OHRO),
- DoD and other Federal offices charged with regulatory oversight of human research.

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Your blood samples and any paperwork attached to them will not be labeled with your name. Instead, you will be assigned a unique subject identification number (SIN). Samples and research-specific laboratory slips will be labeled only with this SIN, sample designation information (the test to be done on the sample), and the date your blood was drawn. Your de-identified samples (without your name or any identifiers) will be sent to the Centers for Disease Control, Ft. Collins Branch, CO, and Emory University for testing as part of this study. We will

keep a link between your name and your SIN at USAMRIID that will be stored separate from all laboratory data and in a secure location. Only the PI and designated study team members will have access to this link. The link will be destroyed after the closure of the research study by the IRB.

Once information that personally identifies you is removed from your data, then your data may be used for future research studies or given to other researchers for future research studies without your permission to do so.

Complete confidentiality cannot be promised for military personnel, because information bearing on your health may be reported to appropriate medical or command authorities.

Blood samples that we are collecting under this study could be useful in other health research studies to further our understanding of the immune response to YF-VAX®. These samples may also have some commercial value. Should your sample(s) lead to the development of a commercial product, the U.S. government will own it and may patent and license the product. USAMRIID will not provide you with compensation for any future research use or commercial value that the samples you have given may be found to have, and you will not be notified of future uses of your sample(s).

Please indicate your decision to permit the use of your left over samples by initialing beside the appropriate statement below:

_____(By initialing here) I give permission for my leftover sera samples to be used for future research studies to further the understanding of the immune response to YF-VAX®.

_____(By initialing here) I **DO NOT** give permission for my leftover sera samples to be used for future research studies to further the understanding of the immune response to YF-VAX®.

HIPAA AUTHORIZATION

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires that researchers obtain subjects' permission (called an *authorization*) to use protected health information about them that is either created by or used in connection with this research. This authorization has no expiration date. By signing this consent form, you are agreeing, for the purpose of conducting this research study, to the use of your protected health information—including results of blood tests and vaccination history as documented in your medical record or in other databases—by the principal investigator and his research staff. Your protected health information may also be viewed by authorized representatives of the USAMRIID OHRO, the HQ USAMRDC IRB, the US Army Human Research Protections Office and other DOD offices charged with oversight of human research.

If you choose not to authorize these uses and the disclosure of your protected health information by signing this form, you will not be eligible to participate in this research study.
However, your decision not to sign this consent form will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits. You may also change your mind and withdraw (or "revoke") this authorization at any time by sending a written notice to the principal investigator. If you withdraw this authorization, no further health information about you will be collected by or disclosed to the investigators conducting this study. However, the

revocation of this authorization cannot alter any disclosure of your protected health information made prior to the revocation. Additionally, even if you revoke this authorization, investigators working on this protocol may still use or disclose health information that they have already obtained about you, as necessary, to maintain the integrity or reliability of the current research study.

Your individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting of abuse or neglect, judicial proceedings, health oversight activities, and public health measures.

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 results. You can search this Web site at any time.

WHAT IF I DECIDE NOT TO PARTICIPATE IN THIS RESEARCH?

It is your choice whether you want to participate in this research. You can choose not to be in the study now or stop taking part in this research at any time without any penalty or loss of benefits to which you are entitled. Deciding not to participate now or withdrawing at a later time does not harm, or in any way affect, your future relationships with USAMRIID.

WHAT COULD END MY PARTICIPATION IN THE RESEARCH?

Your participation in this study may be discontinued at any time if conditions are such that your safety or health may be compromised by further participation as determined by a physician investigator, if you do not meet the eligibility criteria, or if you fail to show up for scheduled blood draws. If for any reason you are withdrawn from the trial, you will be compensated for any blood draws which occurred up until point of withdrawal from the trial.

WHAT IF ANY NEW INFORMATION IS FOUND OUT?

Any new findings that occur during this research study that might affect your decision to participate in the study will be discussed with you.

If new information is provided to you, the investigators may obtain your consent to continue participating in this study.

WHO SHOULD I CALL IF I HAVE QUESTIONS OR CONCERNS ABOUT THIS RESEARCH?

If you have questions about the research at any time, you should contact Phillip R. Pittman, M.D., M.P.H., USAMRIID, 1425 Porter Street, Fort Detrick, MD 21702-5011, 301-619-2997, phillip.r.pittman.civ@mail.mil **(for questions about the study or to revoke in writing the HIPAA Authorization).** You may also contact
Study Coordinator: Lawrence Korman, R.N., C.C.R.P., 301-619-6008, lawrence.korman2.civ@mail.mil **(for questions about the study).**

If you have questions regarding your *rights as a research participant*, you may contact the HQ USAMRDC IRB Office at 301-619-6240 or by email to usarmy.detrick.medcom-usamrmc.other.irb-office@mail.mil or the Office of Human Research Oversight, USAMRIID, 1425 Porter Street, Frederick, MD 21702, 301-619-4926, usarmy.detrick.medcom-usamriid.mbx.ohue@mail.mil.

By signing below, I agree that I have been provided time to read the information describing the research study in this consent form. The content and meaning of this information has been explained to me. I have been provided with the opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily consent to participate in this study.

By signing this form, I have not given up any of my legal rights as a research participant.

SIGNATURE OF RESEARCH PARTICIPANT

Printed Name of Participant

_____ _____

Signature of Participant Date

SIGNED CONSENT OBTAINED/RECEIVED BY:

_____ _____

Printed Name Date Received