COVER PAGE

STUDY TITLE: Effect of Antimalarial Drugs on the Immune Response to Rabies Vaccine for Post-exposure Prophylaxis. A Randomized, Open Label, Trial in Healthy US Adults Age 18-60 Years

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Consent / Authorization Form

Background/Purpose:

You are being asked to participate in a research study because you are a healthy individual between 18 and 60 years of age.

Research studies include only those individuals who choose to take part. Please take your time to make your decision. Please ask the study doctor or the study staff to explain any words or information that you do not understand. You may also want to discuss it with family members, friends or other health care providers.

The purpose of this study is to look at the effect of taking medications that prevent malaria (antimalarials) on the ability of a person's body to develop the natural immune response to a rabies vaccine. It is thought that taking antimalarials may interfere with this natural reaction and the person may not develop the response necessary to prevent rabies after they have been exposed to it.

This is important to the US Department of Defense, the current funders of this study; because they deploy soldiers to areas that require them to take antimalarials and they have a high chance of being exposed to rabies.

The rabies vaccine used in this study is RabAvert®. This rabies vaccine is approved by the US Food and Drug Administration (FDA) and is used in this area for pre-exposure immunization in people at risk of contact with rabid animals and for post exposure prevention in people who have been bitten by a rabid or suspected rabid animal.

The antimalarial drugs used in this study are Chloroquine, Malarone and Doxycycline. These drugs are all approved by the FDA for the prevention and treatment of malaria.

We plan to enroll 100 subjects in the study, being conducted at Upstate Medical University. However, any subject withdrawing before first vaccination will be replaced.

The study is being funded by a grant from the US Department of Defense.

Study Procedures:

If you choose to participate in this study, you will be asked to read and sign this informed consent and authorization form before any study procedures are performed.

This study will last up to 3 months and will include 8-11 visits to the Clinical Research Unit (located on the Upstate campus).

At the **first visit** (screening) you will be evaluated by the study team to see if you are eligible for the study. This is called the screening visit and will include a medical evaluation. To be eligible you must:

- Be at least 18 years old and no more than 60 years old.
- Be in good health, as determined by medical history and physical examination.
- If you are a female you must have a negative urine pregnancy test result for you to be in the study. If you are of child bearing potential, you must be willing to use oral, implantable, transdermal or injectable contraceptives or another reliable method of contraception, approved by the study doctor, for the duration of the study and for 30 days after your last vaccination.
    - The study doctor or study staff will tell you the result of the pregnancy test.
    - The results of pregnancy testing must be negative in order for you to be in the study.
- Be able to give your informed consent.
- Be willing to come to the study center for all visits with the study doctor.

If you are eligible and want to continue to participate in the study, you will be randomly assigned to a study group. If you are subject 1-39 you will have a 1 in 3 (33%) chance of being randomized to the malarone, doxycycline or control (no medication) groups. If you are subject 40-100 you have a 40% chance of being randomized to the chloroquine group and 20% chance of being randomized to the malarone, doxycycline, or control (no medication) groups.

The four study groups are:

1) Group 1: subjects will take two pills of the antimalarial medication chloroquine by mouth, once per week for 6 weeks. Chloroquine will be taken on Days 0, 7, 14, 21, 28 and 35. **RabAvert® Vaccinations will be on days 14, 17, 21 and 28**. The rabies vaccine will be administered **intramuscularly (into the muscle) by needle and syringe.** There will be 25 subjects in this group.

2) Group 2: subjects will take one pill of the antimalarial medication malarone by mouth, every day for 42 days. **RabAvert® Vaccinations will be on days 14, 17, 21 and 28**. The rabies vaccine will be administered **intramuscularly (into the muscle) by needle and syringe**. There will be 25 subjects in this group.

3) Group 3: subjects will take one pill of the antimalarial medication doxycycline by mouth, every day for 42 days. **RabAvert® Vaccinations will be on days 14, 17, 21 and 28**. The rabies vaccine will be administered **intramuscularly (into the muscle) by needle and syringe**. There will be 25 subjects in this group.

4) Group 4: subjects will immediately start with the **RabAvert®** rabies vaccination on days 0, 3, 7 and 14. The rabies vaccine will be administered **intramuscularly (into the muscle) by needle and syringe**. There will be 25 subjects in this group.

Vaccination Schedule (IM = intramuscular)

Day	0	3	7	14	17	21	28	Number of subjects
Group 1 Chloroquine				IM	IM	IM	IM	25
Group 2 Malarone				IM	IM	IM	IM	25
Group 3 Doxycycline				IM	IM	IM	IM	25
Group 4 Controls	IM	IM	IM	IM				25

You will need to stay at the study site for 15 minutes after you take the antimalarial medication for the first time so this visit will be about 45 minutes.
You will need to stay at the study site for about 30 minutes after vaccination so these visits will be about one hour.

You will be asked to come back at regular intervals for follow up visits and blood draws. Most of these follow up visits will take 30 minutes. You will be provided with a schedule of the remaining visits at your Day 0 visit.

On visits following the screening visit the following tests/procedures may be done:

- Physical examination based on your signs and symptoms of any illness.
- Vital signs (temperature, heart rate, pulse and respiratory rate).
- Review changes in medications you are taking.
- Assessment of any side effects (called adverse events).
- Urine test for pregnancy at each vaccination visit (for all female subjects)
- Urine collection for chloroquine group only
- Blood draws for presence of immune response. The immune response is how your body is reacting to the medication or vaccine.
- Dispense antimalarial medication if needed with instructions or review antimalarial medication taken.
- Vaccination with rabies vaccine.

If you are in the chloroquine group, you will be asked to give a urine specimen prior to any chloroquine administration. Syracuse University will be utilizing the urine specimens collected to determine if a protein in the urine may play a role in decreasing side effects experienced while taking chloroquine and/or from long term chloroquine use. As of April 30th 2018, urine specimen will not be collected from those in the chloroquine group. Blood draws will be between 8.5 mls (less than 2 teaspoons) and 48.5 mls of blood (max amount: about 4 tablespoons). The total volume of blood drawn for the entire study will be approximately 228 - 236 mls, depending on your assigned group. For comparison, when people volunteer to donate blood, the volume is about 250-450 ml at one time. We will be using your samples to look at how different medications against malaria affect a person's immune system response to the rabies vaccine. You will be asked at the end of this document if we can keep your leftover samples for future research.

Are there things you should not do while participating in the study?

There are some restrictions if you decide to participate in this study. You should not receive any other vaccines in the 4 weeks before the first vaccination is given and in the 4 weeks after the last vaccination. If you participate in this study, you should not be involved in other vaccine studies or other clinical studies (involving drugs or other agents, or medical devices) until one month after the last visit of this study.

Risks/Discomforts:

The rabies vaccine used in this study is RabAvert®, a purified chick embryo cell vaccine (PCECV) made by Novartis Pharmaceuticals. This vaccine is currently available in the U.S. and is used for pre and post exposure to rabies. You are being given this vaccine for research purposes only (outside the FDA indication) as you do not need pre or post exposure treatment.

Overall, the vaccine is well tolerated; however, you should not receive this vaccine if you have ever had a life threatening allergic reaction to a rabies vaccine. Reactions to the current rabies vaccines are usually mild with local pain, redness, and swelling at the injection site. Some general reactions occurring less frequently are headache and fatigue.
A serious, but rare, neurological disorder called Guillain Barré (pronounced ghee-YAN bah-RAY) syndrome is a condition resulting from some viral infections in which the body damages its own nerve cells (outside of the brain and spinal cord), resulting in muscle weakness and some degree of paralysis. GBS can last for weeks to months. Most people (85%) eventually recover completely or nearly completely, but some people have permanent nerve damage, and between 3% and 4% of people who develop GBS die. Guillain-Barré syndrome has been reported as a rare event following RabAvert® vaccination but its association with vaccination is uncertain.
You may have discomfort associated with intramuscular injection of the vaccine. The injections will be in the deltoid muscle. Subjects may develop a flu-like illness with fever and body aches after vaccination. This is similar to other vaccines for viruses.

Possible reactions to the antimalarial medication chloroquine include GI upset, headache and itching (more common in Africans).

Possible reactions to the antimalarial medication malarone include nausea, vomiting, abdominal pain, headache, diarrhea, weakness, loss of appetite and dizziness.

Possible reactions to the antimalarial medication doxycycline include mild diarrhea, GI upset, mild skin rash, photosensitivity and itching. Vaginal itching or discharge may also occur. This medication may also have more severe symptoms such as headaches, fever, chills, severe diarrhea, and decreased urination.

If you are assigned to groups 1, 2 or 3, you will be given one of the above antimalarial medications for research purposes only (outside the FDA indication) as you do not need treatment (or prevention) for malaria.

Blood Draws may cause pain and/or bruising at the location on your arm where the blood was taken. On rare occasions, it may cause lightheadedness or fainting or infection.

Could you have an allergic reaction?

Sometimes people have allergic reactions to vaccines or medications. When you take the first dose of medication, you will be asked to wait at the site for 15 minutes so we can make sure you do not have a reaction to it. When you get the rabies vaccine, you will be asked to wait 30 minutes. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

- a rash
- having a hard time breathing
- wheezing
- a sudden drop in blood pressure (making you feel dizzy or lightheaded)
- swelling around the mouth, throat, or eyes
- a fast pulse
- sweating

You should get medical help right away (call 911) and contact the study doctor or study staff if you have any of these or any other side effects during the study.

For female participants of child bearing potential:

You should not participate in this study if you are pregnant or plan to become pregnant. You should also not participate in this study if you are nursing a child. All women will have a pregnancy test before beginning medication and before each rabies vaccination. If found to be pregnant, study medication will be immediately stopped and no further rabies vaccines will be given. If you are found to be pregnant we will ask that you allow us to follow you to determine the outcome of the pregnancy.

If you think you may be pregnant while taking part in the study, you must immediately call the study doctor.

Benefits:

This study is not meant to provide you with any direct benefit. We do not know if giving the rabies vaccine while taking antimalarials will allow your body to develop protective antibodies to the rabies virus. Participation in this study does not mean you are protected against rabies virus and any possible exposure to rabies virus should be treated with the standard (FDA approved) post exposure treatment regimen. The information obtained from this study may help determine if antimalarial medications taken with a rabies vaccination schedule has an effect on the overall rabies protection.

Voluntary Participation /Study Withdrawal:

Your participation in this study is entirely voluntary and you may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which you would normally be entitled. Your decision about whether or not to participate in the study will not affect your relationship with SUNY Upstate Medical University.

The Study Doctor can take you off the study without your consent if:

- He or she feels it is for your benefit and/or safety, for example if a side effect or medical condition develops during the study.
- You are unable to follow the study procedures.
- It is discovered that you do not meet the study requirements.
- If the study is stopped by the Study Doctors or other oversight committees before the end of the study.

If there are significant new findings or information that might change your mind about participating in the study, we will give you the information and allow you to reconsider whether or not to continue.

If you decide to stop taking part in this study, you should tell the study doctor. If you stop being in the study early, the study doctor or study staff may ask you some questions about being in the study. To help you leave the study safely, the study doctor may ask you to participate in more tests.

If the study is stopped early or if you choose to stop participating in the study, you are encouraged to return to the study site for these assessments:

- Physical examination.
- Injection site assessment (if you leave the study within 14 days of vaccination).
- Blood draw for presence of an immune response (if you leave the study within 14 days of study vaccination).

Alternatives:

Your alternative is not to participate in this study. All study procedures (vaccines, medications and tests) are being done for research purposes only. Rabies vaccination is not indicated for the general population. If you feel you should be treated with the rabies vaccine, you should not participate in this study and you should discuss this with your regular doctor.

Costs/Payments:

There are no costs to you for participating in this study. All costs for the required study visits, examinations, laboratory procedures and study medication will be paid by the study sponsor.

You will be paid $50 for each visit to cover your expenses, including the screening visit. Total payment for the study will be between $400 and $550 dollars depending on which group you are assigned. In the event that your participation in the study is discontinued early, you will only be paid for the visits completed.

In addition, by accepting payment for participating in this study, certain identifying information about you may be made available to professional auditors to satisfy audit and Federal reporting requirements, but confidentiality will be preserved. Please note that if you earn $600 or over in a calendar year as a research subject, you may have to pay taxes on these earnings.

Questions:

If you have any questions about the research, or in the event of a research-related injury, please contact Dr. Timothy P. Endy at (315) 459-3031. If you have any questions about your rights as a research subject, please contact the SUNY Upstate Medical University Institutional Review Board Office at (315) 464-4317.

In Case Of Injury:

In the event of illness or physical injury resulting from taking part in this research study, medical treatment will be provided at University Hospital. You will be responsible for any costs not paid by your insurance company. No other compensation is offered by SUNY Upstate Medical University. SUNY Upstate Medical University has no plans to give you money if you are injured. You have not waived any of your legal rights by signing this form.

Confidentiality of Records and Authorization to Use/Share Protected Health Information for Research:

If you agree to participate in this research, identifiable health information about you will be used and shared with others involved in this research. For you to be in this research we need your permission to collect and share this information. Federal law protects your right to privacy concerning this information.

When you sign this consent form at the end, it means that you have read this section and authorize the use and/or sharing of your protected health information as explained below. Your signature also means you have received a copy of Upstate's Notice of Privacy Practices.

Individually identifiable health information under the federal privacy law is considered to be any information from your medical record, or obtained from this study, that can be associated with you, and relates to your past, present, or future physical or mental health or condition. This is referred to as protected health information.

Your protected health information will be kept confidential. Your identity will not be revealed in any publication or presentation of the results of this research.

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.

Why is it necessary to use/share your protected health information with others?
The main reason to use and share your health information is to conduct the research as described in this consent form. Your information may also be shared with people and organizations that make sure the research is being done correctly, and to report unexpected or bad side effects you may have.

In addition, we may be required by law to release protected health information about you; for example, if a judge requires such release in a lawsuit, or if you tell us of your intent to harm yourself or others.

What protected health information about you will be used or shared with others as part of this research?
We may use and share the results of tests, questionnaires, and interviews. We may also use and share information from your medical and research records. We will only collect information that is needed for the research.

Who will be authorized to use and/or share your protected health information?
The researchers, their staff and the staff of Upstate Medical University participating in the research will use your protected health information for this research study. In addition, the Upstate Institutional Review Board (IRB), a committee responsible for protecting the rights of research subjects, and other Upstate Medical University or University Hospital staff who supervise the way the research is done may have access to your protected health information.

The researchers and their staff will determine if your protected health information will be used or shared with others outside of Upstate Medical University for purposes directly related to the conduct of the research.

With whom would the protected health information be shared?
Your protected health information may be shared with:

- Representatives from the US Department of Defense, sponsors of this research;
- Frontier Science, database management group;
- Researchers at Syracuse University, where the urine specimens from subjects in the chloroquine group will be tested
- Federal agencies that supervise the way the research is conducted, such as the Department of Health and Human Services' Office for Human Research Protections, the Food and Drug Administration (FDA) or other governmental offices as required by law.

All reasonable efforts will be used to protect the confidentiality of your protected health information. However, not all individuals or groups have to comply with the Federal privacy law. Therefore, once your protected health information is disclosed (leaves Upstate Medical University), the Federal privacy law may not protect it.

For how long will your protected health information be used or shared with others?
There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be used and analyzed for many years and it is not possible to determine when this will be complete.

Can you withdraw your authorization to collect/use/share your protected health information?
You always have the right to withdraw your permission (revoke authorization) for us to use and share your health information, by putting your request in writing to the investigator in charge of the study. This means that no further private health information will be collected. Once authorization is revoked, you may no longer participate in this research activity, but standard medical care and any other benefits to which you are entitled will not be affected. Revoking your authorization only affects uses and sharing of information obtained after your written request has been received, but not information obtained prior to that time.

Even after you withdraw your permission, Upstate Medical University may continue to use and share information needed for the integrity of the study; for example, information about an unexpected or bad side effect you experienced related to the study.

Consent for the Use of Leftover Samples for Future Research (OPTIONAL)

We would like to save any blood sample left over for future research studies, such as additional analysis. These samples will be stored (possibly indefinitely) at a designated facility and provided to scientists performing research. Your stored sample will be coded with a unique number for this study and your identity will only be known by the study site. Saving these leftover blood samples for future research is OPTIONAL and you may choose to allow us to save your samples or not to save your samples. Your decision about whether or not to allow your samples to be saved for future research will have no affect on your participation in the rest of the study. No genetic testing of any kind will be done on your leftover samples.

- ☐ I **agree** to allow my blood samples collected in this study to be saved for future related research.

- ☐ I **do not agree** to allow my blood samples collected in this study to be saved for future related research.

CONSENT TO PARTICIPATE IN RESEARCH & AUTHORIZATION TO USE AND SHARE PERSONAL HEALTH INFORMATION:

I hereby give my consent to participate in this research study and agree that my personal health information can be collected, used and shared by the researchers and staff for the research study described in this form. I will receive a signed copy of this consent form.

_____ _____
Signature of subject Date

_____
Print name of subject

_____ _____
Signature of Person Obtaining Consent/Authorization Date

_____
Printed Name of Person Obtaining Consent/Authorization