STUDY TITLE - DMID 21-0018: Efficacy of Immunization with 4C-MenB in Preventing Experimental Urethral Infection with Neisseria gonorrhoeae
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University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

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IRB Study # 21-0498

Title of Study: DMID 21-0018 - Efficacy of immunization with 4C-MenB in preventing experimental urethral infection with *Neisseria gonorrhoeae*

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CONCISE SUMMARY

The purpose of this research study is to test whether a vaccine that protects against some bacteria that cause infections of the blood or brain (Bexsero™) may also help protect against related bacteria that cause gonorrhea. The study will also compare the effect of Bexsero™ to the effect of the flu vaccine and the tetanus vaccine on gonorrhea infection. It is not expected that flu vaccine or tetanus vaccine will be effective against gonorrhea.
Gonorrhea is a highly contagious sexually transmitted infection that can cause infection in the genitals, rectum, and throat. It is very common, especially among sexually active young people ages 15-24 years. You can get gonorrhea by having vaginal, anal, or oral sex with someone who has gonorrhea. A pregnant person with gonorrhea can give the infection to their baby during childbirth. Gonorrhea infection is caused by the Neisseria gonorrhoeae bacterium, also known as gonococcus.

If you agree to be in this study, you will receive 4 doses of vaccine, 2 doses of Bexsero, 1 dose of influenza vaccine (flu shot), and one dose of tetanus booster vaccine. You will be randomly assigned to receive either 2 doses of Bexsero™ or a combination of the flu and tetanus vaccines as your first two vaccines. After the first two vaccines, you will be given a dose of the bacteria that cause gonorrhea delivered through a small tube inserted in the opening of your penis. You likely will develop gonorrhea from this exposure which can lead to symptoms of penile discharge or discomfort or pain with urination. There is a rare possibility the bacteria will spread causing infection of the testis, blood, or joints. After the dose of bacteria, you will have daily visits for up to 10 days with the study doctor; you will be treated with antibiotics as soon as possible if symptoms develop or at day 10 if no symptoms develop to prevent developing later infection. After receiving your antibiotic treatment, you will be given the final two vaccine doses from the study.

You will have up to 17 in-person visits and 4 telephone check-in visits during their participation. You will also provide blood samples at four separate visits and up to 24 urine specimens. Your total participation in this study will last for up to a total of 40 weeks.

Other risks associated with participation in this study include risks associated with vaccines including discomfort at or around the injection site; flu-like symptoms such as fever, muscle aches and pains, or tiredness; and allergic reactions such as hives, itchy rash, shortness of breath. Risks of taking the blood samples are discomfort and/or bruising; infection, excess bleeding, clotting, or fainting are also possible.

IF YOU AGREE TO PARTICIPATE IN THIS STUDY, YOU MUST NOT HAVE VAGINAL, ORAL, OR ANAL SEX EVEN WITH A CONDOM OR ALLOW CONTACT BETWEEN YOUR PENIS AND ANOTHER PERSON'S MOUTH, VAGINA, ANUS, EYES, OR UNPROTECTED SKIN FROM THE TIME YOU RECEIVE THE GONORRHEA BACTERIA DOSE UNTIL YOU HAVE HAD A NEGATIVE TEST FOR GONORRHEA (WHICH MAY BE UP TO 17 DAYS AFTER DOSING). THIS IS IMPORTANT TO PREVENT YOU FROM GIVING THE GONORRHEA BACTERIA TO ANOTHER PERSON.

If you are interested in learning more about this study, please continue reading below.

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary.

You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill (UNC-CH). If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help to develop new products, such as drugs.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or study staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The group B meningitis vaccine (trade name Bexsero™) is currently approved for use by the United States Food and Drug Administration (FDA) and recommended by the Centers for Disease Control and Prevention (CDC) to prevent life threatening infections of the brain or bloodstream. The purpose of this research study is to test whether Bexsero™ also protects from gonorrhea, a sexually transmitted infection. The information we learn by doing this study may also help us to develop a vaccine that specifically protects individuals against gonorrhea infection.

The bacteria that cause gonorrhea (*N. gonorrhoeae*) are highly related to some bacteria (serogroup B *N. meningitidis*) that can cause meningitis, an infection of the fluid around the brain. Because the two types of bacteria are similar, it is hoped that the vaccine that protects against meningitis will protect against gonorrhea, as well.

Bexsero™ is not FDA-approved for protection from gonorrhea, therefore, its use in this study is considered investigational, but receiving the vaccine will provide you with protection against *N. meningitidis*. The use of the flu and tetanus vaccines are not expected to protect against gonorrhea but will help protect against flu and tetanus. Both flu and tetanus vaccines are approved by the FDA and recommended by the CDC for all adults.

In addition to receiving vaccine during this study, you will also be given a dose of *N. gonorrhoeae*, the germ that causes gonorrhea. After receiving that dose of the germ, you will be examined for 10 days to determine whether you become infected, and you will receive an antibiotic that cures the infection if you develop symptoms of infection. Even if you have no symptoms, you will receive an antibiotic at the end of 10 days to prevent late onset of infection.

Some participants will receive the meningitis vaccine before the dose of bacteria and some will receive it after, so to ensure you receive the vaccine, you must complete the entire study.

Every participant will also receive vaccines for influenza (the "flu shot") and tetanus (the "tetanus booster"). These vaccines are administered on visits you do not receive the meningitis vaccine. The effect of the Bexsero™ will be compared to two doses of FDA-approved control vaccines, namely one dose of the influenza vaccine (FLULAVAL™, FLUARIX™, FLUZONE™, AFLURIA™ or AFLURIA SOUTHERN HEMISPHERE™) and one dose of Td vaccine (TDVAX™ or TENEVAC™), both given according to label instructions and CDC recommendations.

You are being asked to be in the research study because you are a healthy young individual assigned male sex at birth. This study is limited to individuals assigned male sex at birth, because infections with *N. gonorrhoeae* in individuals assigned female sex at birth are more likely to lead to serious complications.

Are there any reasons you should not be in this study?

You should not be in this study if any of the following apply to you:

You must agree to refrain from vaginal, oral, and anal sex for the duration of the study even if you wear a condom until you have been treated and the **test proves the infection has been cured. Importantly, if you have sex after gonorrhea bacteria are introduced into your system before your test results confirm that you are free of infection, you could transmit gonorrhea to your sexual partner. Because your partner is not being monitored for infection, as you are in this study, your partner could fail to receive timely treatment for the infection and be at risk for passing the infection back to you or to others in the community. Additionally, infection in the vagina, oral cavity or anus can have more severe consequences than infection in the penis, so your partner could be placed at a more significant health risk than you assume by participating in this study if you were to pass this infection to them.** It is important that you understand that failure to follow the instructions regarding abstinence from sexual activity with another person could potentially subject you to civil liability: you could be sued and have to pay damages.

You must also agree to comply with these additional needs of this study:

- carrying a cell phone to allow research staff to contact you when you are away from the research unit, if necessary
- returning to the research unit for scheduled study visits within the allowable study window
- returning to the research unit within 1 week after the conclusion of the study for a final examination and test of cure

Other reasons you should NOT join this study:

1. you are a student or employee under the direct supervision of any of the study investigators mentioned in the header above

2. you are less than 18 years old or 36 or older
3. you have ever received any vaccine directed against group B meningitis.
4. you have received any vaccine in the last 28 days or need to schedule a vaccine other than those provided in the study prior to completion of the study
5. you have any abnormality in the urinary tract or have had genitourinary surgery
6. you have ever had an infection with *Neisseria meningitidis*
7. you have a weakened immune system such as complement deficiency, antibody deficiency, Chronic Granulomatous Disease or HIV infection
8. you have a history of abnormal bleeding
9. you have a history of seizures
10. you have a history of cancer, except basal cell carcinoma of the skin more than 5 years ago
11. you are currently using drugs in a way that might interfere with your ability to safely participate in the study
12. you have a history of a psychiatric disorder, including depression, not controlled by medication
13. you have any medical conditions which would preclude safe participation in this trial
14. you are allergic to antibiotics such as penicillin, cefixime, ceftriaxone, or ciprofloxacin, or to lidocaine or latex
15. you have received chemotherapy within the last year
16. you are taking steroids, except for topical application
17. you are taking other immune suppressive medications
18. you are on any of the following medicines and cannot stop taking them on the day you receive treatment with the study antibiotic:
    - Tizanidine - Zanaflex
    - Theophylline - Theo-24, Elixophylline, Theochron
    - Warfarin - Jantoven, Coumadin
    - Probenecid - probalan
    - Aspirin - Ecotrin, Enteric Coated Aspirin, Buffered Aspirin
    - Sulfinpyrazone - anturane
    - Aminoglycoside antibiotics - gentamicin (gentak), tobramycin (tobrex), amikacin (Amikin, Amiglyde-V, Arikayce)
    - Glyburide -(Diabeta or Glynase PresTabs)
    - Cyclosporine - (Gengraf, Neoral, or Sandimmune)
    - Phenytoin - (Dilantin)
    - Methotrexate - (Otrexup, Rasuvo, or RediTrex)
    - Diuretics such as furosemide (Lasix), bumetanide (Bumex), torsemide (Demadex) or ethacrynic acid (Edecrin)
    - Antacids, multivitamins, or other dietary supplements containing magnesium, calcium, aluminum, iron or zinc
    - Other medications used to treat ulcers such as sulcrafate and Videx® (didanosine) chewable/buffered tablets
    - Caffeine-containing medications, including common pain-relievers such as Anacin, BC Fast Pain Relief, Excedrin or more than 2 caffeinated beverages (coffee, tea or sodas)

How many people will take part in this study?
Approximately 140 people will take part in this research study at UNC-CH.

How long will your part in this study last?
Your participation in this study will last for approximately 14-40 weeks (3½-10 months).

What will happen if you take part in the study?

Screening Visit
If you agree to be in the study today, we will:

- Explain the study procedures
- You will complete a brief questionnaire, and we will review any incorrect answers to be sure you understand the study. Then, you will be asked to sign this consent to confirm your willingness to continue in the study.
- Ask for your contact information
- Obtain demographic data (birthdate, race, ethnicity, sex assigned at birth)
- Ask you about your medical history, including medicines you are taking or have taken
- Ask you whether you have had a recent fever or other symptoms of a new infection
- Take your vital signs [weight, heart rate, blood pressure, temperature, and respiration (breathing) rate]
- Perform a limited physical exam
- Ask you a series of health-related questions to confirm your eligibility for the study
- Draw blood sample (total collection volume is up to 60 mL or about 4 tablespoons) and collect a urine sample to determine whether we can detect any abnormalities or immunodeficiencies that would make you ineligible for the study. More specifically, your urine will be used to test for a range of disorders, such as urinary tract infections, kidney disease, and diabetes. Your blood will be used for a complete blood count, and for tests to look for evidence of liver disease, kidney disease, normal immune function against bacterial infection, and infection with HIV or syphilis.
- Provide you with study contact information.
- Provide you with reimbursement.
- Schedule Visit 2.

The screening visit will last about 1½ hours.

Enrollment/Entry Visit (Visit 2)

The following procedures will be carried out:

- The results of the tests from the screening visit will be reviewed with you at this study visit. We will ask you about any side effects from the procedures carried out at the screening visit.
- You will have the opportunity to re-review the informed consent form with the study coordinators and discuss again the risks involved. You can opt out of the study if you wish.
- If you decide to continue, you will be enrolled in the study and be randomly assigned by a computer-generated random assignment to one of two study groups (like flipping a coin): one group will receive the meningitis vaccine before undergoing the experimental gonorrhea infection, and the other group will receive control vaccines before the experimental gonorrhea infection. The control vaccines are: the flu vaccine and a booster vaccine for tetanus and diphtheria. Both control vaccines are safe and approved for use by the FDA and recommended by the CDC. You will not know which group you were assigned to. This is called blinding (or masking). If needed for your safety, the study doctor can find out to which group you have been assigned.
- We will update your medical history and medications you are currently taking.
- Take your vital signs [heart rate, blood pressure, temperature, and respiration (breathing) rate].
- You will be asked to give approximately 60 mL or 4 tablespoons of blood to study your immune responses prior to receiving the vaccine.
- You will be asked to provide a urine sample.
- Then, you will receive the vaccine assigned to you. The vaccine will be administered as an injection in the deltoid region of the upper arm.
- Provide you with study contact information.
- Provide you with reimbursement.
- Remind you that 48h after your vaccine injection we will contact you by telephone to ask whether any side effects from the vaccine have occurred**.**
- Schedule the in-person visit 4. You will be given a choice to schedule visit 4 anytime between 28 and 56 days after this visit (excluding weekend days)

The enrollment (entry) visit will last about one to two hours.

Telephone Contact (Visit 3)

- Approximately 48h after your vaccine injection at enrollment (visit 2), we will contact you by telephone to ask whether any side effects from the vaccine have occurred.

This phone call will last about 15 minutes.

Second immunization (Visit 4)

Between 28 to 56 days after visit 2, you will return to the research unit. The following procedures will be completed:

- Ask you about side effects experienced after the first immunization.

- Update your medical history and medications you are currently taking.
- Take your vital signs [weight, heart rate, blood pressure, temperature, and respiration (breathing) rate].
- Draw blood sample (total collection volume is up to 60 mL or about 4 tablespoons).
- You will be asked to provide a urine sample.
- Administer the vaccine according to the group you were assigned to by an injection in the deltoid region of the upper arm.
- Schedule Visits 6 (24-138 days after visit 4) and 7 (28-140 days after visit 4).
- Provide you with reimbursement.

This visit will last about one to 1 ½ hours.

Telephone contact (Visit 5)

- Approximately 48h after your vaccine injection at visit 4, we will contact you by telephone to check whether you're feeling well and whether any side effects from the vaccine have occurred.

This phone call will last about 15 minutes.

Evaluation visit for proceeding to experimental gonorrhea infection (Visit 6)

24 – 138 days after visit 4 and within one week before you receive the experimental gonorrhea infection, you will return to the research unit. The following procedures will occur:

- We will ask you about any side effects since the last time we saw or spoke to you.
- Update your medical history and medications you are currently taking.
- Take your vital signs [weight, heart rate, blood pressure, temperature, and respiration (breathing) rate].
- Draw blood sample (total collection volume is up to 60 mL or about 4 tablespoons) to study immune responses to the vaccine and to gonorrhea.
- Perform a limited exam.
- Ask you to provide a urine specimen to test for gonorrhea, chlamydia and trichomonas and to store for research tests.

This visit will last about 1½ hours.

Inoculation (Delivery of bacteria to the penis, Visit 7).

You must abstain from all sexual activity from this point of this study until visit 18, which may be as long as 17 days from visit 7. This means that you should not allow your penis or discharge from your penis to contact another person's mouth, vagina, anus, eyes or unprotected skin until you have been treated with antibiotics and tested for gonorrhea. It is important that you understand that you could injure your sexual partner by passing this infection to them without them being monitored or treated for the infection. This could

potentially lead to civil liability due to that injury (you could be sued and have to pay damages) if you engage in sex after gonorrhea bacteria are introduced into your system before your test of cure results confirm that you are free of infection.

On this visit, occurring 2-5 days after Visit 6 , the following procedures will take place:

- You will be return to the research unit at the scheduled day and time.
- Your vital signs will be obtained signs [weight, heart rate, blood pressure, temperature, and respiration (breathing) rate].
- The results of the previous urine tests for sexually transmitted infections will be reviewed with you by the study physician; if there is a positive test result, you would not be eligible to enroll in the study, and you would be referred for treatment to a provider of your choice.
- If all test results are negative, a brief re-examination will be performed and study staff will review your medical history and medications.
- To begin the study, the inoculation procedure (dose) involves the placement of live gonorrhea germs in the opening tip of the penis through a plastic tube inserted about 2 inches. (The researcher will show you the catheter before we begin).
- You may experience discomfort during the procedure.
- The purpose of this inoculation is to give you a gonococcal infection. You will receive a solution containing live bacteria that are expected to cause infection in up to 80% of people.
- The primary symptoms of this infection include burning with urination, and a discharge of pus from the penis.

This visit will last about 3 to 4 hours.

Post-inoculation evaluation (Visit 8-17)

- You will be asked to return to the research unit daily for up to 10 days after inoculation (except weekend days, unless you need or request antibiotic treatment) for examination by a physician, nurse practitioner, or physician's assistant for signs or symptoms of gonorrhea.
- You should collect the first void urine each day (i.e., the first pee of the morning) and bring it with you to the daily visits. We will provide you with sterile collection cups. You will be asked to provide another urine sample when you arrive to the research unit.
- If you develop a discharge of pus from the penis or other symptoms of infection, you will be treated for gonorrhea with antibiotics.
- Even if you do not develop signs or symptoms of infection, you will be treated with antibiotics on the tenth day after inoculation.
- Before treatment on the last day, a penile swab and a urine sample will be collected.
- **Schedule the next visit.**
- **You will be reminded not to have sex or have your penis contact another person's mouth, vagina, anus, eyes or unprotected skin until you return and are cleared by a negative test for gonorrhea.**

Regardless of whether you were infected or not, you must still not have sex until after you receive negative results from a test for gonorrhea.

These visit will last 30 minutes to one hour.

Unscheduled post-inoculation evaluation and treatment visit

- On weekend days or between daily scheduled evaluation visits (8-17) after your inoculation you may contact the study physician, nurse practitioner, or physician's assistant using the contact telephone number provided to you at study entry (that is also provided after inoculation visit) to request evaluation and treatment.
- If you request an unscheduled evaluation and treatment, you will be asked to return to the research unit for examination within 12 hours by a physician, nurse practitioner, or physician's assistant for signs or symptoms of gonorrhea.
- If you have developed a discharge of pus from the penis or other symptoms of infection, you will be treated for gonorrhea with antibiotics.
- Before treatment, a penile swab and a urine sample will be collected.
- **Schedule the next visit.**
- **You will be reminded not to have sex even with a condom or have your penis contact another person's mouth, vagina, anus, eyes or unprotected skin until you return and are cleared by a negative test for gonorrhea.**

Regardless of whether you were infected or not, you must still not have sex until after you receive negative results from a test for gonorrhea.

This visit will last about one hour.

Follow up visit (Visit 18)

Within 1 week (3-7 days) of antibiotic treatment, you must return to the research unit for an examination and provide urine for testing to be sure the gonorrhea germs have been cleared from your system. **You must not have sex or have your penis contact another person's mouth, vagina, anus, eyes or unprotected skin until you return and are cleared by a negative test for gonorrhea.**

At this visit, you will also receive a vaccination, according to your randomization group.

This visit will last about one to 1 ½ hours.

You will receive compensation.

Follow-up telephone call (Visit 19)

Approximately 48h after your vaccine injection at visit 18, we will contact you by telephone to check whether you're feeling well and whether any side effects from the vaccine have occurred.

This phone call will last about 15 minutes.

Follow up visit (Visit 20)
Between 28 to 56 days after visit 18, you will return to the research unit. Thus, the study period for this visit could occur between study day 89 and study day 271, depending on when your prior visits have occurred. The following procedures will be completed:

- Ask you about side effects experienced after the first immunization.
- Update your medical history and medications you are currently taking.
- Take your vital signs [weight, heart rate, blood pressure, temperature, and respiration (breathing) rate].
- Administer the vaccine according to the group you were assigned to by an injection in the deltoid region of the upper arm.
- Provide you with reimbursement.

This visit will last about one hour.

Follow-up telephone call (Visit 21)
Approximately 48h after your vaccine injection at visit 20, we will contact you by telephone to check whether you're feeling well and whether any side effects from the vaccine have occurred.

This phone call will last about 15 minutes.

Specimens
You will be asked to give up to 60 mL (4 tablespoons) blood samples at various points during the study. Blood will be drawn by a trained phlebotomist using a sterile needle inserted into a vein in your arm. The blood draw procedure will be conducted a total of four times over the entire time you participate in the study. Samples of up to 50 mL of urine (about 10 teaspoons) will be collected during the study. Up to 24 urine samples will be collected during the study. The blood and urine samples will be used to study the immune response to infection with the gonorrhea germs.

How will the specimens be collected?
Blood will be collected from a vein in your arm using a sterile needle and blood collection device. White blood cells and plasma (the fluid part of the blood) will be separated and stored in individual tubes labeled only with the collection date and your study ID number.

Urine will be collected into a sterile container. The sample will be split into small volumes and stored in individual tubes labeled only with the collection date and your study ID number.

What will happen to the specimens?

Specimens collected on this study will be retained in a specimen repository or "biobank" and will be stored indefinitely in a freezer in the laboratory of Dr. Duncan, located in the Medical Biomolecular Research Building on the UNC-CH campus. Specimens will be destroyed if they are discovered to be degraded or no longer useful for future testing. Only Dr. Duncan and other approved study investigators will have access to the link between the study ID number and individually identifiable information. The specimens will be used only for studies that have been approved by a human subjects protection committee, and no information will be released to other researchers that could enable them to connect any subject's name to the specimens.

You will be asked in a separate consent form if you allow us to store your specimens for as-yet-undesignated tests in the future that do not include genetic testing. If you decide not to allow your specimens to be stored for future testing, you may still participate in the main study.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will benefit personally from being in this research study by receiving safe and approved vaccines for meningitis, flu and tetanus and diphtheria. You may discover a previously unrecognized medical condition as a result of examinations and testing for this study. The long-term goal of this research is to develop a gonococcal vaccine, which would greatly benefit society.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following risks and/or discomforts to you. You will be given vaccines. The risks associated with the vaccines in this study are listed below.

Risks associated with intramuscular administration of BEXSERO™ include:

- Pain at the injection site
- Muscle aches
- Redness at the injection site
- Fatigue
- Headache
- Swelling at the injection site
- Nausea
- Joint pain

Risks associated with intramuscular administration of flu vaccine (FLULAVAL™, FLUARIX™, FLUZONE™, AFLURIA™ and AFLURIA SOUTHERN HEMISPHERE™) include:

- Pain at the injection site
- Redness at the injection site
- Swelling at the injection site

- Fatigue
- Headache
- Muscle aches/arthralgia
- Fever
- Malaise
- Sore throat
- Reddened eyes
- Cough
- Chills
- Chest tightness
- Facial swelling

Risks associated with intramuscular administration of the tetanus and diphtheria vaccine (TDVAX™ or TENEVAC™) include:

- Pain at the injection site
- Redness at the injection site
- Swelling at the injection site
- Itching
- Swelling in your legs and arms
- Fever
- Malaise
- Muscle aches
- Joint pain
- Rash
- Nausea
- Infection of the skin

You will be asked to provide blood samples, which will be obtained by venipuncture (sticking a needle into a vein in your arm). **Risks of venipuncture include:**

- Acute pain and discomfort
- Development of a bruise
- Formation of a blood clot in the vein that has been stuck.
- Infection
- Rarely, blood donors become faint while blood is being obtained.

A solution containing the gonorrhea germs will be delivered through a small catheter to the urethra (tube in the penis through which the urine runs). **Possible risks to urethra include:**

- There may be some discomfort associated with the delivery of live gonorrhea germs in the anterior urethra at the tip of the penis through a small plastic tube.
- You may experience mild irritation or itching for several minutes after the procedure.

- There is a possibility of urethral injury from insertion of the catheter, but this has not happened in our previous studies.
- Other discomforts include irritation associated with urethral examinations and urethral swab specimen collection (only one urethral swab is obtained during the study).
- There may be some pain associated with intramuscular antibiotic injection.

In the days following delivery of the bacteria, you may develop gonorrhea, which includes the following symptoms:

- Burning
- Itching in the penis, especially with urination
- Discharge of pus from the penis

Infection and Systemic Effects

- While gonorrhea in men is usually a mild illness, serious adverse complications from untreated gonorrhea can include infection of the epididymis (the long coiled tube that connects the testicle with the tube leading to the urethra) and testicles, either of which could lead to sterility.
- Another complication involves the development of urethral strictures (bridges of tissue across the urethra) which would require surgery to correct.
- Systemic complications include infection of the blood, joints, heart valves, or brain lining (meningitis). Systemic complications are serious and perhaps permanent complications are possible. The risk of these complications, however, is remote, based on the large number of natural infections (more than 500,000 each year in the United States alone). More than 200 volunteers have participated in the experimental infections at UNC to date, and several hundred in other institutions in the United States. No serious complications have been reported in the medical literature from investigators conducting these trials. It is believed that prompt treatment will minimize any risk of complications. However, you must agree to receive an antibiotic injection or pill to treat gonococcal infection. The gonorrhea bacteria used to cause infection are killed by antibiotics, and all subjects previously infected in this research have been cured.
- Although you may withdraw from the study at anytime, if you withdraw after receiving the gonorrhea bacteria, you must be treated with antibiotics and tested for gonorrhea to ensure that you are not at risk for advancing gonorrhea infection and that you cannot pass the infection on to others. This treatment and testing will be provided by the study team without charge. If you decline this care, you can seek this medical care through your own physician or a public health clinic at your own expense. If you do not receive this care, you will be at risk for developing worsening gonorrhea infection and have the potential to pass the infection to others.

Although the bacterial product has been extensively tested for purity, it is still possible that it may contain other infectious agents that could infect you. This has happened in only two trials in the past (~2.5% of the time). If this occurs, the trial will be stopped, and you will receive an

antibiotic pill or injection to treat potential gonococcal infection and infection with the contaminating bacteria.

Possible side effects from antibiotic treatments such as cefixime, ceftriaxone with lidocaine or ciprofloxacin:

- Allergic reactions, including serious shock
- Itching
- Skin rash
- Nausea
- Vomiting
- Headache
- Upset stomach or indigestion
- Dizziness
- Abdominal discomfort/pain
- Sensitivity to sunlight or ultraviolet light
- Diarrhea
- Colitis (severe diarrhea and inflammation of the colon)
- Abnormal liver function tests

An FDA safety review has shown that fluoroquinolones (including ciprofloxacin) when used systemically (i.e., tablets, capsules, and injectables) are rarely associated with disabling and potentially permanent serious side effects that can occur together. These side effects can involve the tendons, muscles, joints, nerves, and central nervous system. For these reasons, ciprofloxacin will only be used in the unlikely event of a treatment failure with other antibiotics (this has never happened before in this study). Possible side effects from ciprofloxacin treatment include:

- Rare complications include central nervous system events, including,
  - seizures
  - confusion
  - tremors
  - hallucinations
  - depression
  - nervousness
  - anxiety
  - difficulty sleeping
  - paranoia (thinking and feeling like you are being threatened in some way, even if there is no evidence, or very little evidence, that you are)
  - nightmares
- Nerve problems in your extremities, such as pain, burning, tingling, numbness, and/or weakness
- Tendon problems, such as Achilles tendon rupture

Some risks or discomforts may be unforeseeable. Any side effects will be treated promptly. If treatment failure occurs (which has not happened to date), you will receive an alternative effective antibiotic. **Following inoculation (receiving the gonorrhea bacteria) you must refrain from sexual activity or having your penis contact another person's mouth, vagina, anus, eyes or unprotected skin until antibiotic treatment and a molecular detection test confirms that gonorrhea is no longer present in the penis. It is important that you understand that spread of this infection to another person could be harmful because those persons may not be under daily medical supervision and monitoring as you are during your participation in this study. It is important that you also understand that infection of a female partner or partner who was assigned female sex at birth with gonorrhea would put her at risk of bad health outcomes including pelvic inflammatory disease and infertility.**

Legal Risks

Failure to follow the instructions regarding abstinence from sexual activity with another person could subject you to civil liability: you could be sued and have to pay damages.

Once you are enrolled in this trial, you may withdraw at any time. However, even after withdrawal from the study, you must receive antibiotic therapy, and return for follow-up testing. You could potentially transmit gonorrhea to a sexual partner. You will be cleared from the study only after molecular detection test results from a urine specimen taken during your return visit to the clinical research unit are available and demonstrate absence of infection. Study investigators will contact you by phone approximately two weeks after the end of the trial to determine whether unexpected complications resulted from this protocol.

Although the gonococcal bacteria you will be exposed to are normally transmitted during sex, this experimental infection is ***not*** considered a sexually transmitted infection, and you are not at increased risk of other sexually transmitted infections as a result of your participation in this study. Experimental gonococcal infections are ***not*** considered reportable communicable diseases and are ***not*** reported to the HIV/STD Surveillance unit of the North Carolina Department of Health and Human Services. However, you should understand that if the test for gonorrhea, chlamydia or HIV from specimens obtained at the study visit before the experimental procedures begin is positive, this will be reported to the North Carolina state health department as required by law.

Research study records describing the bacteria, or the course of experimental infection will ***not*** be entered into your medical records. You may truthfully answer "no" to future questions about prior sexually transmitted infections. Although gonorrhea is normally sexually transmitted, this experimental infection is not sexually transmitted and does not reflect risk-taking behaviors.

Breach of Confidentiality

There may be a risk of breach (loss) of confidentiality. The study team has put in place measures to protect your privacy and keep your information confidential to minimize this risk.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

Will you receive any other clinical results?

No analyses providing clinically relevant results are anticipated as part of this research; in rare cases, you may be offered the opportunity to receive information about the results of research in which the specimens were used (for example, findings that would affect your medical care).

How will your privacy be protected?

No subjects will be identified in any report or publication about this study. We may use de-identified data and/or specimens from this study in future research without additional consent.

Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Paper records from this study will be stored in a locked filing cabinet in the Principal Investigator's office. Only investigators directly involved in the study will have access to individually identifiable data. This includes research staff, hospital staff, and nurses on the research unit. Any data to be shared with other investigators will be identified only by a study ID number. This includes monitors from the FDA and the study sponsors at the NIH. The information linking the study ID number and individual identifiable information will be stored in password-protected electronic file saved within a secure server.

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

You will be asked to sign a separate form ("HIPAA authorization") to allow researchers to review your medical records.

What is a Certificate of Confidentiality?

This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers 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 proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

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 an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

By signing this informed consent document, you agree that some of the information generated by participating in this study and/or a copy of the consent form may be included in your medical record and that this information may be viewed by other physicians or caregivers who provide healthcare services to you. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study. Additionally, the information may be shared with your medical insurance plan if the research services provided are billed to your insurance.

Under North Carolina law, researchers are required to report information about the abuse or neglect of a child or disabled adult to local or state authorities.

The study team would like to message you by (text messaging and/or e-mail), however you may say “no” to receiving these messages and still participate in this study. If you say “yes”, messages may contain personal information about you and may be sent or received by the study team’s personal electronic devices or in a method that is not able to be encrypted (protected) and there is the risk your information could be shared beyond you and the study team. This information may include information such as reminders and notifications to contact the study team.

If you wish to stop receiving unprotected communication from the study team or have lost access to your device, please notify the study team using the study contact information on the first page of this addendum to the consent. After the study is complete and all research activities finished, or you withdraw from the study or request to stop receiving unprotected communication, you will no longer receive un-encrypted (un-protected) messages specific to this study.

_____Yes, I consent to the study team utilizing:

Cell phone number _____

Email address _____

If my phone number or email address changes, and I want to continue receiving unencrypted messages, I will notify the study team and provide them with my new information but will not be required to sign this document again.

_____No, I do not consent to receive un-protected communication from the study team.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. If you are hurt, become sick, or develop a reaction from something that was done as part of this study, the researcher will help you get medical care, but neither the University of North Carolina at Chapel Hill nor the sponsor, National Institutes of Health (NIH), has set aside funds to pay you for any such injuries, illnesses or reactions, or for the related medical care. Any costs for medical expenses will be billed to you or your health insurance company. You may be responsible for any co-payments and your insurance may not cover the costs of study-related injuries.

If you think you have been injured from taking part in this study, call the Principal Investigator at the phone number provided on this consent form. They will let you know what you should do.

By signing this form, you do not give up your right to seek payment or other rights if you are harmed as a result of being in this study.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. However, you must receive antibiotics prior to clearance from the study. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

If you withdraw or are withdrawn from this study, all data collected up until the point of withdrawal will be retained; however, no additional information will be collected unless you provide additional written permission for further data collection at the time of your withdrawal.

Will you receive anything for being in this study?

You will receive payment for taking part in this study:

1. If you are screened and excluded from the study, you will receive $30.00 for each screening visit after completing the visit.

2. If you are enrolled in the study, you will receive $20.00 for vaccination and specimen collection visits (visit 2, 4, 6, and 20) after completing each visit.

3. If you begin the study and complete the inoculation procedure, but withdraw prior to completion of the study, you will receive $50.00 for each attended visit (Visits 7-18) and you will not be eligible to participate in the study at another time. This is provided at the test of cure visit that occurs 3-7 days after you are treated.

4. If you begin the study, undergo inoculation procedure, and complete the study visits through your test of cure follow-up visit, you will receive $1000.00. Compensation for this phase of the study is uniform even though the number of visits you will have between the inoculation visit (Visit 7) and test of cure visit (Visit 18) will vary depending on whether and when you develop active infection (between 1 and 10 visits). Compensation for this phase of the study is provided upon completion of the test of cure visit (Visit 18).

5. You will receive vouchers for parking at each study visit, as needed.

6. You will receive 4 vaccine doses, all of which are US FDA approved, reduce your risk of having harmful effects resulting from the infections they are approved to prevent, and commercially available in the United States.

Total compensation: Minimum of $30.00, maximum of $1110.00 after completion of all study visits; plus parking vouchers during the study for visits if conducted at UNC main campus.

In-person study visits that are outside of the scheduled visits noted above will be compensated at $20 per visit.

You will not receive anything for allowing us to store your specimens beyond the compensation offered for participation in the main study.

Your name, address, and U.S. tax payer identification number (SSN or ITIN) are required to process payments and/or to report taxable income to the IRS. You must complete a W-9 (for U.S. persons) or W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents (for non-resident aliens) in order to receive payment for participation.

U.S. person participants must complete Form W-9 in order to receive payment for participation. If payment by UNC equals or exceeds $600 per calendar year for U.S. persons, UNC will report the amount to the Internal Revenue Service on Form 1099. Nonresident alien participants must complete Form W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents in order to receive payment for participation. Payments to

nonresident alien participants may be subject to tax withholding and are generally reported to the Internal Revenue Service on Form 1042-S. This information will not be linked to any of the study data and will only be used for payment purposes.

If you do not provide your SSN or ITIN, or complete the appropriate documentation noted above, we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?

If you enroll in this study, you will have some tests and procedures that are only part of the research study. The costs of these research tests and procedures will be paid by the sponsor. You will be responsible for transportation to the UNC Global Clinical Research North (GCRN) or Clinical and Translational Research Center (CTRC). However, you will not have to pay for parking since you will receive parking vouchers during the study.

What if you are a UNC student?

Participation in this study will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?

Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?

This research is funded by the National Institutes of Health (NIH) (the sponsor). This means that the research team is being paid by the sponsor for doing the study. In addition, the spouse of Dr. Alex Duncan, the principal investigator on this study, is employed by GlaxoSmithKline (GSK), Inc., the manufacturer of one of the vaccines used in this study.
If you would like more information, please ask the researchers listed in the first page of this form.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research subject?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the UNC-CH Institutional Review Board (IRB) at 919-966-3113 or by email to IRB_subjects@unc.edu.

Emergency Contact Information:

In case of emergency during your participation in this study, call the nurse on duty in the clinical research unit at 919-966-4744 and leave a call-back number where you can be reached.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

Signature of Research Participant | Date

Printed Name of Research Participant

Signature of Research Team Member Obtaining Consent | Date

Printed Name of Research Team Member Obtaining Consent