INFORMED CONSENT FORM

A Phase II Double-blind Trial to Evaluate the Safety, Immunogenicity and Effect on Infant Immune Responses of a Single Dose of Tdap in Pregnant Women in Mali

Investigators:

Centre pour le Développement des Vaccins – Mali, Bamako, Mali

[redacted]

Center for Vaccine Development, University of Maryland School of Medicine, Baltimore

[redacted]

Division of Microbiology and Infectious Diseases NIAID, NIH

[redacted]

Adult Subject Name: _____

Infant Name (*Add after birth)*: _____

What is this study about?

Pertussis is a respiratory disease caused by a germ. The disease is transmitted from person to person by coughing or sneezing. It is a very contagious disease that can affect people of all ages. It is particularly dangerous in young infants. They can have difficulty breathing and may die from the disease. The Center for Vaccine Development in Maryland and Centre pour le Développement des Vaccins-Mali are working with the National Institutes of Health (NIH) Division of Microbiology and Infectious Diseases (DMID) in the US to do research to learn if vaccinating a pregnant woman against pertussis is safe and if it will provide pertussis antibody to protect the infant, especially in the first few months of life before infants have received their own pertussis vaccines.

In this study, we plan to vaccinate 200 pregnant women with a vaccine that is routinely given to pregnant women in Mali, which protects against tetanus and diphtheria, or the experimental vaccine that is not licensed in Mali, which protects against pertussis in addition to tetanus and diphtheria. Then, we will compare the levels of antibodies (protective substances) in the blood of the babies that are born and of the women who received the vaccine against pertussis and those that received the standard vaccine.

We will follow and obtain blood from the infants of the vaccinated women to 6 months after birth, which will allow us to understand how much antibody is passed from the mothers to the baby, how long those antibodies last, and if there is any effect with infant pertussis vaccinations. We also want to know more about how well the vaccine is tolerated. 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.

Who can be in this study?
Healthy women ages 18 through 39 years, inclusive, who are 14 to 26 weeks pregnant and who intend to enroll their infants, once they are born, will be asked to participate in this study during their regular pregnancy visits to the local health center. They will be in the study for approximately 10 to 13 months. A total of 200 pregnant women will participate in this study, and about 133 will receive the experimental vaccine against tetanus, diphtheria and pertussis (BOOSTRIX) and about 67 will receive the standard vaccine against tetanus and diphtheria (Td). Td is already used routinely in pregnant women in Mali at the first prenatal visit. BOOSTRIX is recommended for pregnant woman in the US, the United Kingdom and elsewhere, and is pre-qualified (approved) by the World Health Organization (WHO), but the administration of BOOSTRIX is not the standard practice in Mali.

After you have given birth, we will confirm that you still wish to enroll your infant into the study. Only infants whose mothers have been vaccinated as part of this study may participate in this study. The study doctor will confirm that your infant is healthy after birth and may continue in the study.

What will happen in this study?
If you wish to participate, you will have 7 in-clinic visits as well as 2 home visits from field workers (FWs) through your completion of the study to follow your health and eventually the health of your infant until your infant is 6 months old. We will collect 4 blood samples and 4 breastmilk samples from you, and 3 to 4 blood samples from your infant to test your immune response to the vaccine. Even though we plan to collect breastmilk samples as part of this study, you may still participate in this study if you do not plan to breastfeed.

Visit 00
This visit will be done within the 30 days before the vaccination. During the first visit at the study clinic, we will ask you questions about your health and any previous vaccinations. We will ask you about any other medications you have been taking. We may examine you. We will also ask about the result of any examination performed by your own midwife or doctor. We may review your medical records from your own midwife or doctor for more information. We will then perform an ultrasound to date your pregnancy and observe the fetus. All this information will be reviewed to decide if you are eligible for the study. We will take your picture to make your study identification card.

Visit 01
The next visit will be done at the study clinic. We will ask you questions about your health and any previous vaccinations. We will ask you about any other medications you have been taking. We may examine you and we will measure and record your blood pressure, pulse, and temperature. We will measure your height and weight if it was not done at the previous visit. We will ask you not to eat or drink anything hot or cold within 10 minutes prior to taking temperature. We will also ask about the result of any examination performed by your own midwife or doctor. If you are confirmed to be eligible, then we will collect 6 teaspoons (30 ml) of blood to see your antibody level of protection before vaccination.

After all this is done, you will be vaccinated in your preferred upper arm with either BOOSTRIX or Td. Neither you nor the study personnel will know which vaccine you receive. This is decided randomly (like taking a grain of rice from a bag) and only the person who vaccinates you will know. After you have been vaccinated, you will be observed for 30 minutes to see if there are any immediate side effects. You will be asked to notify the study center if you develop any severe reactions after study vaccination. We will also take your address so that we may visit you at home. It is possible that visit 00 and 01 may be completed the same day.

Visit 02
The next visit will be 4 days after the vaccination and it will be a home or clinic visit. During this visit, we will ask questions about how you have felt since vaccination day. We will ask you about any other medications you have been taking.

Visit 03
The next visit will be a home or clinic visit, 8 days after the vaccination. During this visit, we will ask questions about your health since the last visit. We will ask you about any other medications you have been taking.

Visit 04
This visit will be done at the study clinic 31 days after vaccination. We will ask you questions about your health and any previous vaccinations. We will ask you about any other medications you have been taking. We may examine you and we will measure and record your blood pressure, pulse, and temperature. We will ask you not to eat or drink anything hot or cold within 10 minutes prior to taking temperature. We will also ask about the result of any examination performed by your own midwife or doctor. We will collect 6 teaspoons (30 ml) of blood to see your antibody level after vaccination.

Visit 05 (at the delivery of your baby)
The next visit to the clinic will be whenever you come to deliver your baby. At this time, we will review the study procedures required for you and your infant going forward, we will add your infant's name to this informed consent form and ask you to acknowledge your infant's participation as well as your continuing participation by signing and dating the form again.

We will record how the delivery is for you. After the delivery we will examine you and your baby. We will collect 6 teaspoons (30 ml) of blood from you and collect a blood sample (up to 6 teaspoons, or 30 ml) from the placenta (the afterbirth) to see what kind of protection you passed

on to your infant. If we cannot get blood from the placenta then we will collect ½ to 1 teaspoon (5 ml) of blood from your baby's arm within the first 3 days after birth. We will collect up to 4 teaspoons of your breast milk within the first 3 days after delivery. Blood and breast milk will help us to know your and your baby's antibody level.
We may examine you and we will obtain your blood pressure, pulse, and temperature. We will take axillary temperature, heart rate, respiratory rate, head circumference, length, and weight of your baby within 7 days after birth. We will ask you about any other medications you have been taking.

Visit 06
The next visit to the clinic will be when your infant is 6 weeks old. At this visit, we will ask you about your and your infant's health and examine both of you, and we will measure your infant's height and weight, and record birth outcomes. We will ask you about any other medications you have been taking. We will collect 1 teaspoon (5 ml) of blood from your infant's arm. We will also collect up to 4 teaspoons (20 ml) of breast milk from you.

Visit 07
The next visit to the clinic will be when your infant is 10 or 18 weeks old. Half of the infants will have a visit at 10 weeks old and the other half at 18 weeks old. This will be decided randomly, (like taking a grain of rice from a bag of rice).

At this visit, we will ask you about you and your infant's health, examine both of you, measure your infant's height and weight, and record birth outcomes, and collect a 1 teaspoon (5 ml) sample of blood from your infant's arm and collect up to 4 teaspoons (20 ml) of breast milk from you. We will ask you about any other medications you have been taking.

Visit 08
The next and final visit to the clinic will be when your infant is 6 months old. At this visit, we will ask you about you and your infant's health, examine both of you, measure your infant's height, weight, and record birth outcomes, and collect 1 teaspoon (5 ml) of blood from your infant's arm, as well as 6 teaspoons (30 ml) of blood and 4 teaspoons (20 ml) of breast milk from you. We will ask you about any other medications you have been taking. Your and your infant's participation will be complete after this visit.

Right to Withdraw
Your participation and your child's participation in this study are voluntary. You do not have to take part in this research. You are free to withdraw your consent at any time. Refusal to take part or to stop taking part in the study will involve no penalty or loss of benefits to which you and your child are otherwise entitled. If for any reason, while you are pregnant, you are no longer available for follow up prior to the end of the study or you cannot participate for another reason, then you may leave the study, but we will check on your health and will examine the injection site if it is within the 30 days after study vaccination. If, after you deliver, your infant is no longer available for follow up, then your participation will end, but we will follow you to check your health. Otherwise, your participation will end when your infant is 6 months old.

If you withdraw from this study, we will not collect any more information from you, but already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, these data will be handled the same as research data.

You will be told of any significant new findings which develop during the study which may affect your willingness to participate in the study. You may be asked to sign a revised consent form if this occurs.

Can I and my infant be removed from this research?
The investigator (study doctor), the Institutional Review Board (IRB), a committee at the University of Maryland School of Medicine and Ethics Committee of the Faculte de Medecine, Pharmacie et Odonto-stomatologie, charged with protecting the safety and rights of people taking part in research studies, or the NIH (the sponsor of the study) can remove you and your infant from the research study without your approval. You could be removed from the study for any of the following reasons:

- Reasons related only to you (for example, if you move away, if you do not agree to receive your study vaccine, if you fail to follow instructions of the research staff, or if you have a serious reaction to your study vaccine),
- Because the entire study is stopped (the sponsor, any regulatory authority, or IRB may stop the study at any time),
- If you do not later consent to any future changes that may be made in the study plan,
- If the study doctor, the IRB, the Ethics Committee, or the NIH decides that the research study is no longer in your or your infant's best interest.

If you decide to stop participating in the study, or if your participation is ended, 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 agree to have more tests.

What are my responsibilities if I take part in this research?
If you take part in this research, you will be responsible to:

- come to all your study visits as scheduled.
- contact the study staff or doctor if you have severe symptoms (not feeling well) or are hospitalized or feel concerned about symptoms.

If you agree for your child to participate in this study after his/her birth, you will be responsible for his/her usual vaccines and all other health care not related to the study.

What are the risks of being in this study?
<u>Potential Risks to Pregnant Woman and her Fetus</u>
If you receive BOOSTRIX, you may have pain, redness, and swelling at the injection site. Headache, fatigue, fainting, a slight change in heart rate, and gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain) are also possible reactions. These are mild and usually stop within 8 days following vaccination. There is no known risk to the fetus. In the very rare case that you have an allergic reaction to the vaccine, you could have: an itchy skin rash,

swelling of the face, difficulties in breathing and/or swallowing, or dizziness. If this occurs, the study doctor will treat you immediately, or you can seek help urgently at the closest health center. Similar reactions may occur after receiving the routine Td vaccine.

Obtaining a sample of blood from your arm may cause some pain, swelling, bruising, or infection at the site of the blood draw. To avoid infection, a qualified and trained staff member will collect the blood from you and your infant. The blood that is taken when your baby is delivered will be collected from the placenta (afterbirth) after the umbilical cord of the infant has been cut and after the placenta has been removed from the mother.

Breast milk will be collected by applying pressure or with a pump according to your preference. The pressure will be applied by you with your hands by placing the breast between your thumb and 2 fingers. The breast pump is a manual instrument that will be placed on the breast to extract the milk by applying pressure. If needed, we will help you use it. There is no significant risk to breast milk collection. You may experience mild tenderness from milk expression.

All women will also have an ultrasound to date the pregnancy. We will place a gel on your belly over where the baby is. We will then place a small device on the gel to see inside. This device is connected to a special monitor that lets us see the baby and take measurements to know the age of the pregnancy. This procedure is not harmful to you or the baby, but it may feel uncomfortable. If we find any problems when we perform the ultrasound, we will inform you. It is possible this news may cause you some emotional distress; there may also be additional costs to you if you choose to perform further testing based on this information.

If you or your fetus is injured directly from the study vaccine, CVD Mali will pay for the costs of medical treatment according to Malian standard of care. You will have no other form of compensation. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH or the Federal Government.

There is a small possibility that confidentiality may be lost during the study. The risk will be minimized by using an identification number rather than a name on all forms.

<u>Potential Risks to Infants</u>
As with the risks to pregnant women, there is a possibility that obtaining a blood sample from your infant may cause some pain, swelling, bruising, or infection at the site of the blood draw. To avoid infection, a qualified and trained staff member will collect the blood from your infant.

The standard of care in Mali is to vaccinate infants with the pentavalent Diphtheria and Tetanus and Pertussis and Haemophilus influenzae and Hepatitis B vaccine at 6, 10, and 14 weeks of age; this vaccination should provide protection. There is a possibility that your infant's response to the pertussis vaccine could be lower after the usual infant vaccinations because of your study vaccine.

There is a small possibility that your infant's confidentiality may be lost during the study. The risk will be minimized by using an identification number rather than a name on all forms.

What are the benefits of being in this study?
There may be no direct personal benefit of participation. If you are enrolled in this study you will receive the recommended set of pregnancy tests as routine in Mali free of charge. It is possible that pregnant women who receive BOOSTRIX will be protected against pertussis and that the protection will be shared with the infant.

Feedback on research results
We will know the results of the study after it is finished. The study team will hold meetings to inform you, your family and the community about the results.

What are the costs of being in this study?
All research testing that is done at the screening visit and after vaccination, including the ultrasound and blood tests, will be performed free of charge.

What are the payments for being in this study?
You will receive the following compensation. On the vaccination visit, you will receive a drink and sandwich and reimbursement for transportation to the health center (1000fcfa). The next visit to the study clinic (30 Days after vaccination), you will receive a drink and sandwich and reimbursement for transportation to the health center (1000fcfa). On the day of delivery, you will receive reimbursement for transportation to the health center (1000fcfa) and 3 pagnes and soap. When the infant is 6 weeks, you will come to the study clinic with him/her, you will receive a drink and sandwich and reimbursement for transportation to the health center (1000fcfa). When the infant is 10 or 18 weeks you will come to the study clinic with him; you will receive a drink and sandwich and reimbursement for transportation to the health center (1000fcfa). On the final visit, when the infant is 6 months old, you will come to the clinic with him; you will receive a drink and sandwich, soup or porridge for your baby and reimbursement for transportation to the health center (1000fcfa).

What will happen to the samples that are collected during this study?
The blood samples will be used to follow the protective response given by the vaccine you receive. These samples will be sent to the USA for testing at the University of Maryland. Any remaining samples will have your name and other personal information removed and stored in a central storage facility in the USA for approximately 15 years and could be used to study other protective responses or responses to other infections. No genetic testing will be done.

Any testing that is to be done on these samples and that is not already part of this study will only be done after getting approval from the Ethics Committee at the Faculté de Medecine, de Pharmacie et d'Odonto-Stomatologie (FMPOS), Bamako and the University of Maryland in Baltimore.

What are the alternatives to participating in this study?
You are free to decide not to enroll in this study or to stop participating at any time. Presently, pertussis vaccination is not routinely offered to pregnant women in Mali. BOOSTRIX is not for sale in Mali. You could find other vaccines containing pertussis and you can pay for the vaccination at the pharmacy. If someone becomes ill with pertussis, medical care can be obtained at the local health center. If you decide not to participate, this will not affect the care or benefits that you and your infant would normally receive at the health centers or hospitals.

How will information be kept private?
We will protect the information collected about you and your infant by keeping it in locked cabinets and machines that can only be used by personnel involved in the study, the institution that is paying for the study and the Ethics Committees in Mali and in the U.S. (these groups are responsible for the protection of people who take part in research) or their representatives. Study monitors or auditors, or the US Food and Drug Administration may inspect study records and (in the case of monitors or auditors) may have access to your medical records in order to verify the results of our research. By agreeing to participate in this study, you give permission for these parties to access your records. In the case of publication of these results, the identity of the subjects will remain private. We will only use a study number.

To help us protect your privacy, we have a Certificate of Confidentiality from the National Institutes of Health (NIH). The researchers can use this Certificate to legally refuse to give information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you.

A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you give your consent to release information to a medical care provider, an insurer, or other person to receive research information, then the researchers will not withhold that information.

The Certificate of Confidentiality only applies under US law. Therefore, all specimens and information sent to the US as part of this trial will be protected by the Certificate of Confidentiality. Information and samples remaining in Mali will not be protected by the Certificate of Confidentiality.

Long term storage for future research
It is possible that some of the blood samples will be left over after all the tests are done. If you give permission, any blood that is not used in these tests will be stored in the USA for approximately 15 years and may be used at a later time to study protective responses in infants or other infections (not genetic research). These future studies, if any, will be performed only to answer questions in the public health interest and will be submitted and approved by the ethics committees prior to starting. If you do not allow us to store blood specimens, they will be destroyed when this research is completed. This will not affect you/your child's participation in this study. Blood samples will be stored without your name or your child's name. They will be identified by study number, which can be linked to you. Your decision can be changed at any time before the end of this trial by notifying the study doctors or nurses. Please check your choice, below.

_____ I give permission that any unused part of my/my child blood samples may be stored for a probable period of 15 years after the end of the study for future projects to study infections (NOT genetic research) and to help in the development of future vaccines. These future projects will be submitted and approved by the ethics committee.

_____ I do not give permission that any unused part of my/my child blood samples may be stored for future projects (Please note that you/your child can still participate in this study whether or not you agree with this statement).

Who can answer questions about this study?
If you have any questions regarding participation or if your infant has a problem due to his/her participation in this study, you may contact at any time [redacted]
All these doctors may also be contacted at [redacted]

To learn more about the ethical approval of this study or your rights as a research subject, you can contact the Ethics committee of FMOS at [redacted]

Informed Consent Form

Name of the participant:_____

- This study aims to see if the vaccine Boostrix is safe in pregnant women and protects infants from pertussis.
- The information regarding the study has been provided to you on the information sheet.
- If you participate in this study, you will receive 1 dose of Boostrix (against tetanus, diphtheria, and pertussis) or 1 dose of Td vaccine (standard vaccine used routinely against tetanus and diphtheria).
- There will be samples of blood and breast milk collected from you, blood samples collected from your baby after birth and a blood sample from the placenta.
- You are free to participate or not in the study. If you decide that your baby may not participate or you change your mind, you can withdraw from the study at any time, this will not affect your rights to your usual medical care.
- You will sign 2 original consent forms at the time of enrollment.
- If you accept to have your baby participate at birth, you will sign the "Summary of Infant Participation" section.

_____
Subject's Signature or Fingerprint

Date: _____
____ I have read and understand the information on this form.
____ I have had the information on this form read and explained to me.

_____
Name of Witness to Consent procedures
If the subject is illiterate, or unable to sign

_____ Date: _____
Witness signature

_____ Date: _____
Signature of Investigator or Authorized Representative obtaining informed consent

_____
Printed Name of Investigator

Summary of Infant Participation
Your infant's participation will include:

- Collection of cord blood after birth. If we are unable to obtain cord blood, it is possible we will have to draw about 5 ml of blood (about a teaspoon) from your child within the first 3 days after birth.
- There will be three additional study visits when your child is 6 weeks, 10 or 18 weeks, and 6 months old. At each of these study visits we will ask you questions about your child's health and collect about 5 ml of blood from your child.

You are free to withdraw your child's and/or your participation at any time, without penalty.

Re-Consent After Birth of Child

Child name: _____

Date of birth: _____

_____
Parent's Signature or Fingerprint

Date: _____

_____
Name of Witness to Consent procedures
If the subject is illiterate, or unable to sign

_____ Date: _____
Witness signature

_____ Date: _____
Signature of Investigator or Authorized Representative obtaining informed consent

_____
Printed Name of Investigator