Investigator Studies Program (MISP) Protocol and Procedures

Section #1 - MISP Protocol Identification

Study Title:	The title of the protocol should include study design, indication and, where applicable, dosage, dosage form, and comparative agent(s). **Single oral dose of azithromycin1 gm with or without amoxicillin2 gm to prevent peripartum infection and sepsis in laboring high-risk women: 3-Arm RCT**
Request Date:	**11/20/2015; Updated 6/13/2017; 10.1.2017; 11.28.17; 10/20/2018**
Institution Name	**University of Alabama at Birmingham/Cameroon Health Initiative**
Investigator Contact Information: – Full address – Phone No. – Fax No. – e-mail address	**Alan T.N. Tita, MD, PhD** **Professor, Department of Obstetrics and Gynecology** **Director, Center for Women's Reproductive Health & Maternal-Fetal Medicine Division** **10270K Women & Infants Center** **1700 6th Avenue South** **Birmingham Alabama 35233** **Phone: 205-934-9616** **Fax: 2059759858** **Email: atita@uab.edu**

Section #2- Core Protocol	
2.1 Objectives & Hypotheses	**Primary Objective**: To test the effectiveness of a single adjunctive oral dose of a) 1g of azithromycin and b) 1g of azithromycin + 2g of amoxicillin, each compared to c) usual care alone (placebo group)in reducing maternal peripartum infections and sepsis in at-risk laboring women in a LIC setting. **Hypothesis #1**: A single, oral dose of a) 1g azithromycin or b) 1g azithromycin+2g amoxicillin given for prolonged labor or prolonged membrane rupture in term pregnant women will reduce the risk of peripartum infections and sepsis. ~~**Secondary Objectives**: 1. To collect and story specimens to estimate the prevalence of mycoplasma and ureaplasma in the genital tract, placenta and chorioamnion and assess whether their presence is associated with peripartum infection in LICs.~~ ~~**Hypothesis #2**: The presence of genitalureaplasma and mycoplasmas in the placenta and chorioamnion of laboring women will be strongly associated with maternal peripartum infections (similar to our findings in the US).~~
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Maternal bacterial infection and sepsis during pregnancy and the puerperium accounts for approximately 10% of the global burden of maternal deaths. This places it among the top 5 causes.[1] The appropriate use of antibiotic prophylaxis for cesarean delivery and antiseptic agents are among the most effective preventive interventions as highlighted by the recent WHO guidelines for maternal peripartum infections (access guidelines at: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/peripartum-infections-guidelines/en/).[1] Cesarean delivery is the strongest risk factor for maternal peripartum infection including endometritis, wound infection and sepsis (increasing risk by at least 5 to 10 times compared to vaginal delivery).[2] Antibiotic prophylaxis, preferably prior to incision, in particular, among several strategies, effectively reduces the risk of infection and associated high health care and personal costs.[1,3-5] In a recently completed multicenter US randomized clinical trial (abstract attached), we have demonstrated a further 50% reduction in the risk of maternal peripartum infection by adding a single 500mg intravenous dose of azithromycin to the standard prophylactic regimen (a single intravenous dose of cefazolin 1-2g or ampicillin) in the highest-risk group of women who undergo cesarean delivery following labor or membrane rupture for at least 4 hours(see trial registration at: https://clinicaltrials.gov/ct2/show/NCT01235546?term=tita&rank=2). This work builds on, and is supported by, over 20 years of research on maternal infections at UAB and elsewhere.[6-17]Azithromycin provides coverage against the most common pathogens identified in association with peripartum infections including genital mycoplasmas and ureaplasmas (when specific methods are utilized to identify them). In sum, the use of a single dose of cefazolin or ampicillin for cesarean delivery is associated with a 50% reduction in risk of infection/sepsis. Adding azithromycin to this standard regimen further reduces post-cesarean infection risk by 50%. It is unknown whether the effect of azithromycin alone would be similar to azithromycin plus cefazolin or ampicillin. While the role of antibiotic prophylaxis for cesarean delivery is well-established, in most low income countries, the fraction of maternal infection

and sepsis attributable to cesarean delivery is minimal because of the low cesarean delivery rate of 5-10% or lower (compared with 20-30% or higher in the US and many high income countries).[18] Therefore, strategies that address maternal peripartum infection and sepsis in the developing world should focus on identifying and preventing (or treating) infection in high-risk women who have a vaginal birth (or abortion). There is an increased risk of infection in women who undergo prolonged labor ≥18-24 hours (at least 2 fold) or membrane rupture ≥8-12 hours (2-3 fold in our study) compared to women who do not experience these risk factors. These risk factors identify a large group of women who are at the highest risk for maternal peripartum infections (chorioamnionitis and endometritis) and sepsis after a vaginal delivery. Indeed, the recent WHO Guidelines articulated the following among research priorities: **what are the benefits of initiating prophylactic antibiotics after prolonged rupture of membranes?**[1]Furthermore, a recent JHPIEGO consultative meeting on enhancing the focus on maternal infections suggested that "**Attention to identification and prompt management of prolonged labor and prolonged rupture of membranes is critical to reduce disease and death due to maternal sepsis**".

Therefore, drawing from our findings with the azithromycin-based extended antibiotic prophylaxis strategy for cesarean delivery in the US, we propose to adapt the intervention and evaluate the role of a single oral dose of azithromycin (with or without oral amoxicillin) to prevent maternal peripartum infection and sepsis in women planning a vaginal delivery who have prolonged labor (≥18 hours) or prolonged membrane rupture (≥8 hours). The current global standard of care (including at the proposed study sites) is that antibiotics are not given solely for these risk factors.

Azithromycin is available as a generic agent. It has a bimodal half-life of up to 70 hours in the non-pregnant population; although it is not as well studied in the pregnant population. Azithromycin covers a broad spectrum of bacteria (including gram-positive cocci, genital ureaplasmas and mycoplasmas and certain gram-negative bacilli and anaerobes) that are associated with maternal infections, which are often polymicrobial (chorioamnionitis, endometritis and perineal wound infection) and sepsis. Amoxicillin mirrors the standard penicillin or cephalosporin recommended for prophylactic use for cesarean delivery and is also commonly available in LICs as a generic agent.[1]The use of single prophylactic doses minimizes the likelihood of antimicrobial resistance (although this will need to be monitored). Azithromycin is currently recommended to <u>treat or prevent</u> several infections in pregnancy including gonorrhea (1g po), chlamydia (1 g po) and mycobacterium avium complex prophylaxis (600mg twice/week or 1.2 g weekly po). It is sometimes used for perioperative <u>prophylaxis in patients at risk</u> for endocarditis (500mg po). Considering our success with 500mg IV for cesarean prophylaxis, the 40% bioavailability of oral azithromycin and the approved doses for treatment of infections, we will use 1g po of azithromycin for the proposed intervention. Similarly, amoxicillin has a bioavailability of 80-90% and is used to treat several infections at doses of 500mg-2g po. Considering that ampicillin is used at a dose of 1-2g for cesarean prophylaxis, a 2g optimal dose of amoxicillin will be used for the study intervention.

The best approach to this evaluation in order to influence future uptake into clinical practice is a randomized trial of these simple regimens vs. the usual standard of care (including antibiotic prophylaxis after 18 hours of

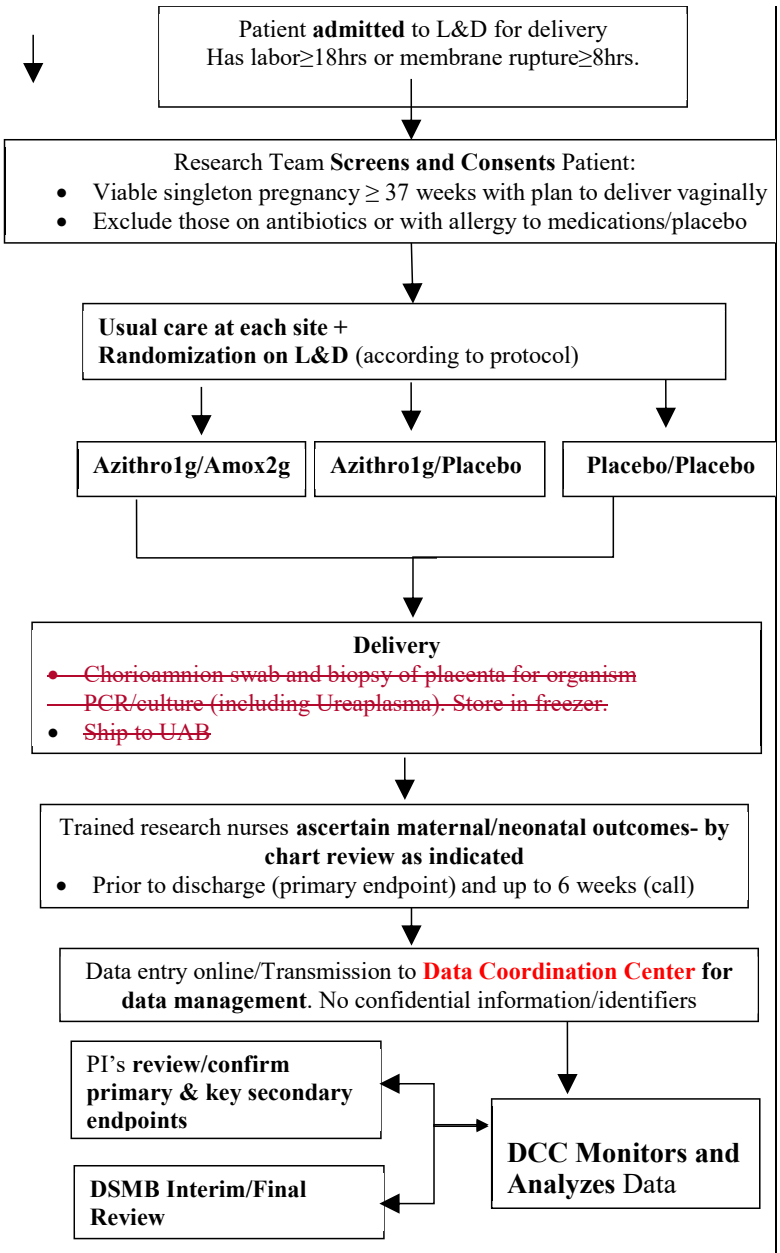
	membrane rupture). The key primary outcomes will include any maternal bacterial infection (sepsis, chorioamnionitis, endometritis, or other wound infection) and/or maternal death prior to discharge from the hospital. **The primary endpoint is the incidence of maternal peripartum infections that lead to sepsis and death. For this study we will assume an effect size of 50% which mirrors the minimum effect size observed with standard antibiotic prophylaxis for cesarean delivery. The baseline risk of infection with prolonged membrane rupture or labor is not well defined and ranges from 15-30%. We assume a baseline risk of 20% for the composite and this test of concept will also help better quantify baseline risks.**
2.3 Study Design	Study design:3-arm randomized controlled trial. The investigational regimens are 1g of azithromycin and 1g azithromycin+2g amoxicillin; the common control arm is usual care at sites + placebo. We will design placebo for each, amoxicillin and azithromycin, with the assistance of the CBCHS Central Pharmacy, using identical capsules containing each antibiotic or matching placebo (non-antimicrobial agent e.g. starch) to accomplish blinding: 1 g azithromycin/placebo for amoxicillin, 1 g azithromycin/2 g amoxicillin vs. placebo for azithromycin /placebo for amoxicillin. Study location:~~4~~ 6 hospitals with approximately 8,000 deliveries in total per year in Cameroon. These hospitals belong to (or are affiliated with) the CBCHS, a well-established major local partner of our UAB Cameroon Health Initiative (CHI UAB). CHI UAB is collaboration between a multidisciplinary group at UAB (multiple schools and departments) and major health organizations in Cameroon including the CBCHS, major medical schools and the Ministry of Health to improve health care through research, education and service delivery. CHI UAB has a dedicated in-country program coordinator based at the CBCHS with a background in laboratory sciences (MSc) and public health (MPH). The CBCHS is a very well organized system with 7 major hospitals and over 80 health care units providing maternity care in 6 of the 10 regions of Cameroon. ~~We will start at BBH, MBH, BHM and Mboppi and add a 5th site later if necessary.~~ Inclusion criteria: Pregnant women with singleton pregnancy in labor at term ≥37 weeks who plan to deliver vaginally and have a) prolonged membrane rupture (≥ 8 hours) or prolonged labor (≥18 hours)**The study is restricted to those at term because those who are preterm may be more likely to receive antibiotics for other reasons and per recommendations.* Exclusion criteria: Evidence of chorioamnionitis or other infection requiring antibiotics at time of eligibility, allergy to azithromycin or amoxicillin or any ingredients in the placebo, or plan for cesarean delivery prior to enrollment.Interventions:1g po Azithromycin/ placebo for amoxicillin, 1g po Azithromycin+ 2 g po Amoxicillin, and placebo for amoxicillin/placebo for azithromycin. Subjects will be stratified by enrollment site. Outcomes: The **primary endpoint is the percentage of women that develop maternal peripartum infection or death ~~prior to discharge from the hospital~~up to 6 weeks postpartum** defined as one or more of: a) Chorioamnionitis: Fever (>100.4°F/38°C on two occasions 30 minutes apart or ≥102°F/39°C on one occasion) in addition to one or more of the following: fetal tachycardia >160bpm, maternal tachycardia>100bpm, uterine tenderness or purulent lochia prior to delivery, or diagnosis by a clinician.

b) Endometritis: Fever (>100.4°F/38°C on two occasions 30 minutes apart or ≥102°F/39°C on one occasion) in addition to one or more of uterine tenderness or purulent lochia or diagnosis by a clinical provider.
c) Sepsis–a clinical diagnosis of infection in association with standard clinical criteria suggestive of a sepsis syndrome.[19]The WHO Definition: Suspected or confirmed infection plus signs of mild to moderate organ dysfunction (tachycardia, low BP, tachypnea, altered mental status, and reduced urinary output) will be used. The specific identification criteria put out by WHO will be used. Other components of peripartum infection also include ~~chorioamnionitis, endometritis or~~ wound infection and abscess as defined in the manual ~~and~~ will be ascertained ~~as defined below~~.
d) Maternal death due to any reason

Other endpoints: will include the following:
~~a) the incidence of Ureaplasma and mycoplasma colonization of the placenta and chorioamnion (PCR and culture testing of a specimens obtained after delivery from all participants)~~
a~~b~~) The incidence of the primary endpoint (above) ~~within 6 weeks of delivery~~prior to discharge from the hospital.
b~~c~~) Maternal readmission for any reason within 6 weeks of delivery
c~~d~~) Neonatal morbidity requiring prolonged hospital stay >3 days.

Sample size: It is estimated that up to15-30% of women who have prolonged labor or membrane rupture will have one or more infections included in the primary endpoint. We assume a baseline risk of 20%. To demonstrate a 50% reduction in peripartum infections in the high-risk group of laboring women (of the same order as the minimum effect size observed in high risk group who have cesarean) with each of the antibiotic prophylaxis regimens (azithromycin alone and azithromycin+amoxicillin compared separately to placebo with 80% power and two-sided alpha of 0.025 for each comparison (0.05 total), 241 women per group are needed. Thus, approximately 750 women will be needed for the 3-arm comparison.
All enrolled will ~~have specimen collection from the placenta and chorioamnion and will~~ be followed for outcome ascertainment up to 6 weeks postpartum. Of note, the oral regimens will include an identical placebo capsule with the azithromycin and 2 placebo capsules for the no treatment group.

2.4 Study Flowchart



2.5 Study Procedures

1. Screening: Routine care at each hospital will be given to patients by their clinical maternity providers who will be blinded to the study interventions.

	Trained research staff in maternity outcomes reporting at each center (also blinded to study medications) will be responsible for all screening and research data abstraction from patient medical records with the help of clinical investigators and staff. Each hospital will have a designated investigator physician. Research nurses will undergo centralized specific training to screen and ascertain study outcomes. Screening will occur on labor and delivery in the selected CBCHS units and will be conducted by dedicated trained study staff with the assistance of clinical staff. The screening form will be used and completed for each patient screened. Potential subjects will be approached by trained research staff for written consent in English or French. Patients who cannot read will have the consent form read to them. Those that indicate they do not understand will be excluded. Study subjects will be randomized only after eligibility criteria have been confirmed and the patient has consented to participate by signing the informed consent form. The randomization form will be used to complete randomization *2. Randomization and Drug allocation concealment:* Enrolled subjects will be randomly assigned in a 1:1:1 ratio to one of the two prophylactic oral regimens or to no treatment/placebo using either a web-based randomization sequence with varying block sizes and stratified by study site. Alternatively, considering challenges to internet access, a computer-generated randomization scheme with appropriate sequence of use of the interventions will be confidentially maintained in the pharmacy at each site and used to accomplish the random allocation of consecutive patients. *Blinding:* As previously discussed we will plan to accomplish blinding with placebo by working with the CBCHS central pharmacy to accomplish identical capsules with and without the active medications. These medications will be packaged according to the predefined sequence into opaque envelopes containing the designated medication. All packages will have capsules that represent azithromycin or placebo and amoxicillin or placebo. The envelopes will be stored in sequential order until a patient is ready for randomization, 3. Medication distribution: The allocated therapy will be provided by the pharmacy staff. Clinical supplies will be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location for use in study participants as above. Clinical supplies will be dispensed in accordance with the protocol. The pharmacy is responsible for keeping accurate records of the clinical supplies, the amount dispensed for use by the patients, and the disposition at the end of the study. The allocated therapy will be provided by the pharmacy staff to study staff for distribution. **The patient is considered randomized once the medication is dispensed from the pharmacy and sequential number posted on the patient specific randomization form. The study medication will be initiated immediately (prior to delivery).** ~~On labor anddelivery,achorioamnion swab will be collected by trained research staff into storage tubes with appropriate medium and stored in a dedicated study freezer. Maternal blood will also be collected into the tube provided and frozen as well. Specimens will be shipped to UAB and kept in a biorepository~~

~~for future testing (shipped in batches as boxes get full). Of note all CBCHS facilities have back-up generators to ensure continuous power.~~

Data Collection: Research staff will use data collection forms to collect patient information including contact information, characteristics and clinical outcomes. In addition to outcomes at time of discharge, participants will be followed-up at 6 weeks in person at their postpartum visit or by phone. They will be asked about any post-delivery problems and admissions for them or their baby and records will be reviewed to validate the outcomes. Complete baseline and outcome data will be collected by trained study nurses by direct interview and chart review using the forms provided. Contact and other confidential information will be known only to the local staff at each site. No confidential information will be entered into the database.

Outcome adjudication: We will review and validate primary outcomes centrally in a blinded fashion – 2 investigators will review de-identified records to confirm that the pre-defined criteria are met and agree on the diagnosis. Any initial disagreement will be resolved by consensus of the reviewers. If necessary a final adjudication will be made by the study PI.

Data Management: A study statistician and data manager located at UAB will be responsible for coordinating overall data management for the trial. A designated in-country site PI will be responsible for day-today supervision of data management, with everyone using the same standardized data collection tools. Data management at each site includes procedures for data entry, data editing, and compilation; data transmittal and quality control, data verification, confidentiality and security. Data will be collected and managed with Research Electronic Data Capture (REDCap), an established, secure web-based data capture and management tool developed at Vanderbilt University and supported by the Data team at UAB. We have been able to use REDCap for remote capture of data entered in Cameroon into the database at UAB in our ongoing survey of infection practices. Data quality will be assessed monthly by the data manager, and remedial measures, including re-abstraction of data and retraining of staff and edits will be used as needed to enhance data quality.

Overview of study management: Dr. Tita will be PI and will coordinate with and local project director, Pr. Tih to provide local study oversight in collaboration with other team members of CHI UAB and the Weltys. Mrs. Rahel Mbah will be project coordinator. Physicians at each site will be designated as site PIs and the central pharmacy will be responsible for packaging medications. The CHI-UAB research assistant team will help with implementation at each site. The study will be discussed every 2 weeks at UAB during the CHI UAB Meeting with the Weltys. Dr. Tita will correspond with Mrs. Mbah on a weekly basis and she will oversee the research assistants. Dr. Tita or a team member investigator from the US will visit Cameroon every 4-6 months and tour all sites to ensure the proper implementation. UAB has established a subcontract to CBCHS for management purposes.

6. Study Administration

This study will be conducted at ~~4~~ 6 hospitals with approximately 8,000 deliveries in total per year in Cameroon. These hospitals belong to (or are affiliated with) the CBCHS, a well-established major local partner of our UAB Cameroon Health Initiative (CHI UAB). CHI UAB is collaboration between a multidisciplinary group at UAB (multiple schools

and departments) and major health organizations in Cameroon including the CBCHS, major medical schools and the Ministry of Health to improve health care through research, education and service delivery. CHI UAB has a dedicated in-country program coordinator based at the CBCHS with a background in laboratory sciences (MSc) and public health (MPH). The CBCHS is a very well organized system with 7 major hospitals and over 80 health care units providing maternity care in 6 of the 10 regions of Cameroon. We will start at BBH, MBH, BHM and Mboppi and add a 5th site later.

Table 1: Study sites, key investigators and roles

Clinical Sites	Members	Role
UAB	Alan Tita, MD, PhD	PI/PD
	Akila Subramaniam, MD, MPH	Co-I
	Lorie Harper, MD	Co-I/DSMB
	Jodie Dionne-Odom, MD	Co-I
	Jeff Szychowski, PhD	Biostatistician
	Robin Steele, MPH	Data Manager
	Victoria Chapman, RN, MPH	Analyst
	Wally Carlo, MD	DSMB
CBCHS	Pr. Pius Tih, PhD, MPH	Cameroon PD
	Rahel Mbah, MSc, MPH	Coordinator
	Leopold Tchokote, MD	Co-I MBHD
	Dr. Datouo	Co-I MBH
	Edward Ndze	Pharmacist
	Edith Welty	Co-I
	TBN	Co-I BHM
	TBN	Co-I BBH
UB	Gregory Halle-Ekane, MD	Co-I and ObGyn

Overview of training: Dr. Tita will oversee the training of staff and clinical providers at all sites in coordination with Ms. Mbah. As relevant training will cover the ethical conduct of research, study overview (why is the study being done?), training in implementing study procedures, training in collecting and entering date into database, training in reporting of adverse events. Mrs. Mbah will be invited to come to the US to receive a 1 week training in the conduct of clinical research prior to the start of the study and she will be expected to train and supervise the assistants with research. Our staff are already familiar with data collection at CBCHS facilities and entry into our database with over 1000 enrolled in the Moyo evaluation and 220 in the GBS study as well as 140 in a malaria study in Mutengene.

- Screening and randomization will occur as previously described together with specimen collection.
- **Maternal outcomes will be ascertained in the hospital following (on an ongoing basis until discharge) and at the follow-up 6 weeks after delivery.**

	• **Patients will be educated about the signs and symptoms of infection and other study outcomes and encouraged to notify the provider or come to the hospital after discharge with any concerns. If possible, records of visits (to any hospital or health facility) prior to the routine postpartum call will be obtained and reviewed to ascertain study outcomes (treating providers may also be called if clarifications are needed).** • **All newborn outcomes will be ascertained until hospital discharge and with 6 week follow-up or death through review of hospital discharge records supplemented by maternal questionnaire at 6 week phone follow-up. Readmissions and related diagnoses for infants will be validated through history and record review.** • **Several data collection forms will be used during these processes, including forms for maternal outcomes, newborn outcomes, NICU outcomes, and postpartum clinic/hospital outcomes. Data on these forms devoid of personal identifiers will be securely sent to the DCC through web-based entry.** • **As a validity check a second abstraction of all study forms will be performed on a random sample of 5% of all subjects by a different research staff and compared for concordance (inter-rater agreement).** **4.5. Follow-up** • Through discharge and then up to 6 weeks as previously described. **4.5.1 Withdrawals:** Patients who withdraw from the study after randomization will be excluded from further follow-up. Outcomes ascertained up until the time of withdrawal will be reported in intent to treat fashion. Those who withdraw prior to the 6-week window for ascertaining the primary outcome will be accounted for by randomizing an equal number of additional patients.
2.6 Study Duration	3 years
2.7 Statistical Analysis and Sample Size Justification **Data Management**	Data management: A study statistician and data manager located at UAB will be responsible for coordinating overall data management for the trial. A designated in-country site project director and staff will be responsible for day-today supervision of data management, with everyone using the same standardized data collection tools. Data management at each site includes procedures for data entry, data editing, and compilation; data transmittal and quality control, data verification, confidentiality and security. Data will be collected and managed with Research Electronic Data Capture (REDCap), an established, secure web-based data capture and management tool developed at Vanderbilt University and supported by the Data team at UAB. We have been able to use REDCap for remote capture of data entered in Cameroon into the database at UAB in our ongoing survey of infection practices. Data quality will be assessed monthly by the data manager, and remedial measures, including re-abstraction of data and retraining of staff and edits will be used as needed to enhance data quality.

	Analyses: Data analyses will follow the CONSORT guidelines. Analyses will be by intention-to-treat in which subjects will be analyzed in the group to which they were randomized, regardless of whether or not they received the assigned intervention. Analyses will be performed at the Center for Women's Reproductive Health, University of Alabama at Birmingham. The key analyses for this study are the comparisons reflected by the primary and secondary aims. The primary analysis will compare the incidence of the composite peripartum infection outcome between each of the active groups and the control groups – a chi-square p-value as well as the relative risk and 95% CI will be computed for each comparison. The secondary outcomes will be similarly compared. Student's t-test comparisons of continuous outcomes will be done. Standard comparisons of covariate characteristics at baseline between groups will be done. It is anticipated that the randomization scheme will balance the groups for these covariates; however, secondary analyses of relevant outcomes using logistic regression adjustments will be implemented to account for any suggested confounding. A secondary comparison will examine the 2 active groups relative to each other. ~~The data from the ureaplasma/mycoplasma testing will be similarly compared with the understanding that the baseline colonization rate will be reflected by the findings in the no-treatment/placebo group.~~ *Sample Size Calculation, Primary Outcome:* This has been previously presented above and is shown here as a reminder. Sample size: Up to15-30% of women who have prolonged labor or membrane rupture will have one or more infections included in the primary endpoint. We assume a baseline risk of 20%. To demonstrate a 50% reduction in peripartum infections in the high-risk group of laboring women (of the same order observed in high risk group who have cesarean) with antibiotic prophylaxis with 80% power and alpha of 0.025 per primary comparison (0.05 total), 241 women per group are needed. Thus 750 women will be needed for the 3 arm comparison. ~~In a sub-study of our US trial 1/3 (30%) of patients had colonization with ureaplasma or mycoplasma. For the cohort of 600, a sample size of 195 will be needed to estimate a prevalence of 25% (±5%) with 95% confidence. Thus, we will have sufficient study population to estimate the prevalence of colonization with ureaplasmas by PCR methods and to assess its role as a risk factor for infection. Testing of the 200 receiving placebo/placebo will provide baseline prevalence whereas the results from the antibiotic-exposed groups will allow us to explore whether the prevalence of ureaplasma/mycoplasma colonization is influenced by the exposure between randomization and delivery (when specimens are collected and stored in appropriate media).~~
2.8 Specific Drug Supply Requirements	The study drugs and identical placebos will be provided with the assistance of the CBCHS Central pharmacy which is responsible for procuring and supplying medications to over 90 CBCHS facilities in Cameroon. Medications will either be purchased through the CBCHS Central Pharmacy or at a certified pharmacy in the US. The CBCHS pharmacy investigator will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. Clinical supplies will be received by a designated person at the study site, handled and stored safely

	and properly, and kept in a secured location for use in study participants. Clinical supplies will be dispensed in accordance with the protocol. The pharmacy is responsible for keeping accurate records of the clinical supplies, the amount dispensed for use by the patients, and the disposition at the end of the study.
2.9 DSMB and Adverse Experience Reporting	Detailed information concerning adverse events (AEs) will be collected and evaluated throughout the trial. An AE is any event that is serious, deemed related to the study and/or unexpected in nature, severity, or frequency. Reporting of these events will be as follows: • For any maternal, fetal or neonatal deaths or other life-threatening events: • An Adverse Event Report will be sent by fax/email within 24 hours of knowledge to the DCC, who will assure that the event is reported to the DSMB as indicated. • A copy of the patient's medical record should be made (with all of the patient identifiers removed or completely obscured) in case it is later required by the Data and Safety Monitoring Board (DSMB). These will be reviewed by the site study physician and Dr. Halle Ekane who will make the determination regarding information to submitted on the form and relatedness. • Any other events that are serious and/or unexpected in nature, severity, or frequency. • Promptly complete an Adverse Event Report and send to the DCC. The DSMB will review all AEs and other interim safety data and will provide a report to the study leadership and the IRBs. **DSMB)** will be constituted to assist with safety monitoring. **The DSMB will review safety (safety outcomes will include drug reactions, perinatal death and maternal death or severe morbidity warranting prolonged maternal or neonatal hospital stay or readmission.** Institutional Review Board (IRB) approval for the study will be obtained at UAB and CBCHS IRBs. Adverse events will be reported locally to the IRB, to the UAB IRB and to the DSMB. DSMB members will have expertise in Epidemiology/Statistics, OB/maternal-fetal medicine (Dr. Lorie Harper, MD) and pediatrics/neonatology (Dr. Wally Carlo) and will be appointed prior to study starting enrollment. Given the small size of the study, no stopping rules for effectiveness have been developed. However the DSMB may recommend to stop for safety. Given our experience with the prior study of azithromycin in the US, this is a low-risk study and we anticipate few severe adverse events
2.10 Itemized Study Budget	See attached separately
2.11 References	1. WHO. WHO recommendations for the prevention and treatment of maternal peripartum infections. World Health Organization, Geneva; 2015http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/peripartum-infections-guidelines. 2. Gibbs RS. Clinical risk factors for puerperal infection. Obstet Gynecol. 1980;55(5 Suppl):178S-184S.

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2.12 Publication Plan	We plan at least 2 abstracts to reputable international obstetric meetings (e.g. SMFM, ACOG or FIGO) and 2 manuscripts within 6-12 months of completion of the primary data collection to high impact journals such as the New England Journal of Medicine, JAMA, the Lancet or BMJ.
2.13 Curriculum Vitae	Attached separately

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