



# **COVID-19 prevalence during pregnancy and pregnancy outcomes in 8 low and middle-income sites: A Global Network Study**

## **Protocol**

Robert L. Goldenberg<sup>1</sup>, Sarah Saleem<sup>2</sup>, Masum Billah<sup>3</sup>, Patricia L Hibberd<sup>4</sup>, Nancy F Krebs<sup>5</sup> Tracy Nolen<sup>6</sup>, and Elizabeth M. McClure<sup>6</sup> on behalf of the Global Network for Women's and Children's Health Research investigators\*

<sup>1</sup>Columbia University, New York, NY

<sup>2</sup>Aga Khan University, Karachi, Pakistan

<sup>3</sup>ICDDR,B, Dhaka, Bangladesh

<sup>4</sup>Boston University, Boston, MA

<sup>5</sup>University of Colorado at Denver, Denver, CO

<sup>6</sup>RTI International, Durham, NC

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## Abstract

### Background

There is limited information regarding coronavirus infections that occur during pregnancy, especially in low and middle-income countries (LMIC). To date, there are many unanswered questions related to COVID-19 infection in pregnant women especially from LMICs. This is due to many factors, including the few reported cases; the lack of sufficient testing to understand the extent of the infection in the population as a whole; the impact of asymptomatic infection on the pregnancy and its outcome; women don't have access to authentic knowledge and that COVID-19 is epidemiologically distinct from SARS and MERS, making extrapolation difficult.

### Methods

In 8 LMIC sites, we will determine the prevalence of COVID-19 infection during pregnancy using antibody testing at or near to delivery and determine the association between COVID-19 exposure during pregnancy and maternal, fetal and neonatal outcomes. Additionally, we aim to explore knowledge, attitudes and prevention practices regarding COVID-19 during pregnancy.

Over a 24-month period, approximately 170 women per month from each site will be asked to complete a questionnaire and provide a blood sample at or near delivery, which will be tested for COVID-19 antibodies; quality control will be provided by RTI. Through the data that are routinely collected by the Global Network's Maternal Newborn Health Registry (MNHR), we will evaluate fetal, neonatal, and maternal outcomes.

The Global Network's COVID-19 study will be an important contribution to the understanding of the prevalence of COVID-19 among pregnant women as well as the association between COVID-19 and pregnancy outcomes in LMICs.

# Global Network Study Investigators

## Site Investigators

### **Site 02 (Democratic Republic of Congo)**

**Carl Bose, M.D.**

Principal Investigator  
University of North Carolina School of Medicine  
Chapel Hill, North Carolina  
[cbose@med.unc.edu](mailto:cbose@med.unc.edu)

**Antoinette Tshetu, MD, PhD, MPH**

Senior Foreign Investigator  
Kinshasa School of Public Health  
[antotshe@yahoo.com](mailto:antotshe@yahoo.com)

### **Site 03 (Zambia)**

**Wally Carlo, MD**

Principal Investigator  
University of Alabama at Birmingham  
Birmingham, Alabama  
[Wcarlo@PEDS.UAB.EDU](mailto:Wcarlo@PEDS.UAB.EDU)

**Elwyn Chomba, MBChB, DCH, MRCP**

Senior Foreign Investigator  
University Teaching Hospital  
Lusaka, Zambia  
[echomba@zamnet.zm](mailto:echomba@zamnet.zm)

### **Site 06 (Guatemala)**

**Nancy Krebs, MD**

Principal Investigator  
University of Colorado School of Medicine  
Denver, Colorado  
[Nancy.krebs@cuanschutz.edu](mailto:Nancy.krebs@cuanschutz.edu)

**Manolo Mazariegos, MD**

Investigator  
INCAP  
Guatemala City, Guatemala  
[mmazariegos@incap.int](mailto:mmazariegos@incap.int)

### **Site 07 (Bangladesh)**

**William Petri, MD**

Principal Investigator  
University of Virginia  
Charlottesville, Virginia  
[wap3g@virginia.edu](mailto:wap3g@virginia.edu)

**Rashidul Haque, MD**

Senior Foreign Investigator  
ICDDR,B  
Dhaka, Bangladesh  
[rhaque@icddr.org](mailto:rhaque@icddr.org)

### **Site 08 (Belagavi, India)**

**Richard Derman, MD, MPH**

Principal Investigator  
Thomas Jefferson University  
Philadelphia, PA  
[Richard.Derman@jefferson.edu](mailto:Richard.Derman@jefferson.edu)

**Shivaprasad S. Goudar MD, MHPE**

Senior Foreign Investigator  
KLE Academy of Higher Education and Research  
Belgaum, India  
[sgoudar@jnmc.edu](mailto:sgoudar@jnmc.edu)

### **Site 09 (Pakistan)**

**Robert L. Goldenberg, MD**

Principal Investigator  
Columbia University  
New York, New York  
[rlg88@columbia.edu](mailto:rlg88@columbia.edu)

**Sarah Saleem, MD**

Senior Foreign Investigator  
Aga Khan University  
Karachi, Pakistan  
[sarah.saleem@aku.edu](mailto:sarah.saleem@aku.edu)

### **Site 11 (Nagpur, India)**

**Patricia L. Hibberd, MD, PhD**

Principal Investigator  
Boston University  
Boston, Massachusetts  
[plh0@bu.edu](mailto:plh0@bu.edu)

**Archana Patel, MD, DNB, MSCE, PhD**

Senior Foreign Investigator  
Lata Medical Research Foundation  
Nagpur, India  
[Dr\\_apatel@yahoo.com](mailto:Dr_apatel@yahoo.com)

**Site 12 (Kenya)**

**Ed Liechty, MD**

Principal Investigator  
Indiana University School of Medicine  
Indianapolis, Indiana  
[eliecht@iupui.edu](mailto:eliecht@iupui.edu)

**Fabian Esamai, MBChB, MMed, MPH, PhD**

Senior Foreign Investigator  
Moi University School of Medicine  
Eldoret, Kenya  
[fesamai2007@gmail.com](mailto:fesamai2007@gmail.com)

**National Institute of Child Health and Human Development (NICHD)**

**Marion Koso-Thomas, MD, MPH**

Medical Officer, Global Network for Women's and Children's Health  
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)  
[kosomari@mail.nih.gov](mailto:kosomari@mail.nih.gov)

**RTI International**

**Elizabeth M. McClure, PhD**

Principal Investigator, Data Coordinating Center  
RTI International, Durham, NC  
[mcclure@rti.org](mailto:mcclure@rti.org)

**Tracy Nolen, DrPh**

Senior Statistician, Data Coordinating Center  
[tnolen@rti.org](mailto:tnolen@rti.org)

**Nalini Peres-da-Silva, BS**

Potocol Manager, Data Coordinating Center  
[nperesdasilva@rti.org](mailto:nperesdasilva@rti.org)

## Abbreviations

ANC: Antenatal Care

CI: Confidence Intervals

DCC: Data Coordinating Center

DMC: Data Monitoring Committee

DMS: Data Management System

DRC: Democratic Republic of Congo

GN: Global Network for Women's and Children's Health Research

LMIC: Low/middle income countries

MNHR: Maternal Newborn Health Registry

NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development

QA: Quality assurance

RR: Relative risks

WHO: World Health Organization

## Statement of the problem

### 1.1 Introduction

The first reports of a pneumonia of unknown cause surfaced from Wuhan, China in late December of 2019. After cases multiplied and reached most countries, the World Health Organization declared COVID-19, a novel coronavirus, a public health emergency of international concern on January 30, 2020. As of March, cases were found in every country of the world. To date, more than nine million cases and nearly 500,000 deaths have occurred. The WHO maintains the risk assessment of COVID-19 at “very high”<sup>5</sup>. While high-income countries have been among those most affected at the start of the pandemic, concern prevails about how low- and middle-income countries (LMICs), with fragile health systems and poverty will face the pandemic<sup>6,7</sup>. Very few data are available about the prevalence of COVID-19 infection in many LMICs, and especially regarding the prevalence of COVID-19 infection among pregnant women in these settings.

There are also limited data regarding the impact of coronavirus infections on pregnancy, especially in LMICs. Results from one study of SARS-CoV in 20 pregnant women suggested that SARS appears to be associated with a higher risk of serious adverse outcomes compared with risks observed with COVID-19 to date. One-third of pregnant women with SARS-CoV required mechanical respiration and the case fatality rate was 15%. In one published report of MERS, another coronavirus, on 11 pregnant women, there was a case fatality rate of 27%. There was little or no evidence of maternal to fetal transmission with either virus. Although there are limited reports, COVID-19 seems to be associated with fewer serious adverse pregnancy outcomes compared to SARS and MERS<sup>1</sup>. However, a review performed in the United Kingdom found that premature delivery was found in almost half of women hospitalized with COVID-19<sup>1</sup>. Reports assessing the vertical transmission of COVID-19 have shown mixed results<sup>2,3,4</sup>.

To date, given the few reported confirmed cases, the lack of sufficient testing to understand the extent of the infection in the population, and the unknown impact of both symptomatic and asymptomatic infection on the pregnancy outcomes, there are many unanswered questions related to COVID-19 infection in pregnant women especially from LMICs where access to authentic information is limited. Because COVID-19 is epidemiologically distinct from SARS and MERS, extrapolation is difficult from the experience of prior coronavirus outbreaks.

### 1.2 Study objectives

To determine the prevalence of COVID-19 antibodies in pregnant /recently delivered women in 8 Global Network sites (in DRC, Kenya, Zambia, Bangladesh, India [2 sites], Pakistan and Guatemala) and its association with pregnancy outcomes.

### 1.3 Study aims

- To determine the prevalence of COVID-19 antibodies in recently delivered women in 8 Global Network sites using antibody testing.

- To compare the maternal, fetal, and neonatal outcomes of COVID-19 antibody positive women vs. antibody negative women including low-birthweight, preterm birth, fetal growth restriction, stillbirth, and neonatal mortality.
- To assess knowledge, attitudes and practices of pregnant women related to COVID-19 and its prevention during pregnancy.

## 1.4 Rationale

The risk of spontaneous abortion, stillbirth, neonatal mortality, and preterm birth are important questions to address in pregnant women infected with the COVID-19 virus, as are the rates and types of congenital infections and malformations, and fetal growth restriction. This is especially true among the fetuses and newborns of infected mothers in LMICs. Each of these outcomes is likely associated with the gestational age at which the mother develops the infection.

To understand the overall scope of the COVID-19 pandemic, we believe that using a screening antibody at delivery or in the post-partum period will be the most efficient way to obtain this information. If this test is performed in a population of women at delivery, over time, we will be able to assess the extent of the COVID-19 pandemic in these locations and the trends in the proportion of the pregnant population infected with COVID-19. Also, with evidence of COVID-19 positive antibodies at the end of pregnancy, we will assess the clinical history during pregnancy to help determine if there was evidence of an acute respiratory infection, when it occurred, and its severity. In addition, we will be able to compare those pregnancies with evidence of COVID-19 positive antibodies to those with negative antibodies to answer a number of questions related to associated outcomes such as mean birthweight and low-birthweight, mean gestational age and preterm birth, fetal growth restriction, and other outcomes such as stillbirth, neonatal mortality, and congenital anomalies. The antibody testing will be used as a surrogate for COVID-19 infection.

Another component of this study will be to determine mothers' knowledge, attitude and practices related to COVID-19 in pregnancy. Knowledge will be assessed by questions related to methods of prevention, symptoms, transmission, and methods of detection and sources of care for COVID-19 or place to contact with disease symptoms. Attitudes toward the disease will include questions related to willingness or unwillingness to receive testing, or care. Concerns related to fear of social exclusion, being under lockdown/home isolation will be explored since anecdotes suggest people often hide symptoms or do not test because of these issues. We will also explore issues related to women's practice related to COVID-19 such as if fears will cause women to not attend prenatal care or deliver at health facilities. We will explore the use of protective measures such as using a mask, social isolation, etc. These issues will be explored during a prenatal care visit or by telephone if that appears to be the better option.

The Global Network sites are uniquely poised to answer these and other important questions related to COVID-19 during pregnancy in a number of low-resource settings. Since 2008, the Global Network has enrolled and completed follow-up of approximately 60,000 pregnancies each year across 8 sites in Africa, Asia and Latin America, focusing on outcomes such as preterm birth, fetal growth restriction, and maternal, fetal and newborn mortality.



## 1.5 Prior COVID-19 research

The SARS-COV-2, the virus which causes COVID-19, is highly contagious, with a  $R_0$  between 2 and 3.5<sup>8,9</sup> ( $R_0$  denotes the average number of secondary cases of an infectious disease that one case would generate in a completely susceptible population). An important issue related to prevalence is that a significant proportion of infections have been found to be asymptomatic. Initial studies performed in China reported up to 80%<sup>8</sup> of infections to be very mild or asymptomatic. A large review of children who had contact with infected persons in China found 15% of infected children to be completely asymptomatic<sup>10</sup>. Among quarantined passengers and crew on a cruise ship who were infected with SAR-COV-2, 17.9% were asymptomatic. Based on a study performed in Santa Monica, California that detected antibodies, researchers estimated that up to 4% of the general population could have already been infected. Because asymptomatic cases can actively excrete the virus, they pose a challenge to infection control as well as to understanding disease outcomes on a population basis.

Studies of different populations have repeatedly found that the groups at highest risk of unfavorable outcomes include people over 65, more likely to be male and with preexisting medical conditions such as hypertension, diabetes, cardiovascular disease or chronic lung disease<sup>11,12</sup>. There is limited information about the impact of COVID-19 on infants and children, but troubling data have emerged recently on a late onset inflammatory disease associated with COVID-19 infection in children.

There are two types of tests that are either currently available or will soon be available to confirm that a person has an active COVID-19 infection or has had a COVID-19 infection in the past. The first type is a direct test, such as PCR, that actually determines if the virus is present. This can be performed on nearly any fluid or tissue collected. Currently, many PCR tests targeting the viral genome are used to determine the presence or absence of COVID-19 on nasal or oropharyngeal swabs, but these tests can only be used to determine which people (or which tissues) are presently infected. Once the disease is cleared and the subject recovers, the test can no longer confirm that COVID-19 was present or was the cause of the illness. The second type of test is an indirect IgG antibody test that is likely to turn positive at about 10 days into the course of a COVID-19 infection. These tests likely will remain positive long after the infection is over, but the duration of a positive antibody test after the infection has cleared has not been determined. There are recent reports of people with a previous history of COVID-19 infection who are antibody positive who appear to acquire the disease again or remain infected. IgM tests have been used to indicate recent or active infection among neonates, but their value is unclear. Thus, the direct viral test (PCR) is useful for documenting an active infection, while the antibody test documents a history of infection but provides no information about when the infection occurred. IgG antibody tests are less useful in documenting active infection.

## Method and Procedures

### 2.1 Study design

This will be a prospective, population-based, cohort study conducted within the Global Network's Maternal and Newborn Health Registry (MNHR)<sup>13</sup>, a population-based observational study which enrolls approximately 60,000 pregnant women per year across 8 Global Network sites.

## 2.2 Study population

For screening purposes, all women in the MNHR will be eligible to be screened for the COVID-19 study at time of enrollment into the MNHR. This study will follow the same inclusion and exclusion criteria as the MNH Registry (MNHR) to screen:

Inclusion criteria:

- Pregnant women intending to deliver within study cluster

Exclusion Criteria:

- Decline to provide consent to include data in the study

While it seems preferable for sites to focus on women who plan to deliver at a health facility, sites will be able to recruit cluster women who plan to deliver at home or elsewhere provided arrangements are established to draw blood to test for COVID-19 antibodies at or following delivery. Similarly, the site may elect to routinely collect the maternal blood samples away from the delivery location, as long as procedures are in place to ensure the samples are collected and maintained appropriately.

## 2.3 Study intervention

Trained MNHR study staff will perform the following additional procedures with consenting MNHR study participants as follows:

Each woman will be asked to provide a blood specimen of approximately 3-5 cc at or near delivery (at delivery or 14 days after) to be tested for COVID-19 antibodies. The person collecting the specimen will be a trained member of the registry staff. The study will use one standardized testing protocol across all sites. Due to the rapid advancements in testing protocols, the final testing protocol and specific antibody test will be determined closer to study launch, with the aim to use the best quality test that is feasible at the time the study is initiated. Tests will be run at each site as soon as the logistics of testing allow. We expect each site to be able to perform their own analyses using a standardized assay kit, with central quality support provided by RTI International.

One questionnaire (Appendix 1) will be administered around the time of delivery (as close as possible to delivery but within two weeks of delivery if at all possible) to determine significant events during the pregnancy with a focus on symptoms of COVID-19 infection including cough, shortness of breath or breathing difficulty, fever, chills/shaking, muscle pain, headache, sore throat, and loss of taste or smell, based on the WHO criteria.<sup>14</sup> The questionnaire will also address the timing of the occurrence of her symptoms. We will also ask about symptoms that may have occurred prior to the pregnancy but after January 2020 to capture potential COVID-19 infections predating the pregnancy.

Information related to any COVID-19 tests performed, other significant illnesses and hospitalizations, and contacts with others infected with COVID-19 will also be collected. We will also ask about COVID-19 related symptoms at the time the sample is collected.

A second questionnaire addressing knowledge, attitudes and practice related to COVID-19 prevention, detection and treatment can be administered at any time during the pregnancy and can be administered to all women in the MNHR, even if they are not part of the antibody study (Appendix 2). The KAP questionnaire will continue to be collected as long as blood specimens are being collected and tested for COVID-19 antibodies.

Using the MNHR case report forms, we will obtain information related to pregnancy outcome including stillbirth, preterm birth (<37 weeks gestation), birthweight (g), neonatal mortality (neonatal deaths <28 days), and fetal growth restriction. We will obtain infant's hospital course and medical illnesses, hospitalizations as well as death until 28 days of age. Infants and mothers' outcomes to 42 days post-delivery will be also obtained as we do for all MNHR enrollees.

## **2.4 Primary and secondary outcomes**

- Prevalence of COVID-19 antibody positive results during pregnancy.
- Fetal/neonatal outcomes: spontaneous abortion, stillbirth, birth weight (g), and fetal growth restriction, early (7-day) and late (28-day) neonatal death, cause of death, congenital infections, and malformations
- Maternal outcomes: rate of infection, timing of infection, types of symptoms, death, cause of death
- Knowledge, attitudes, and practices of pregnant women related to COVID-19 infection during pregnancy

Definitions for outcomes will be consistent with the MNHR protocol.

## **Statistical considerations**

### **3.1 Sample size and data analyses plans**

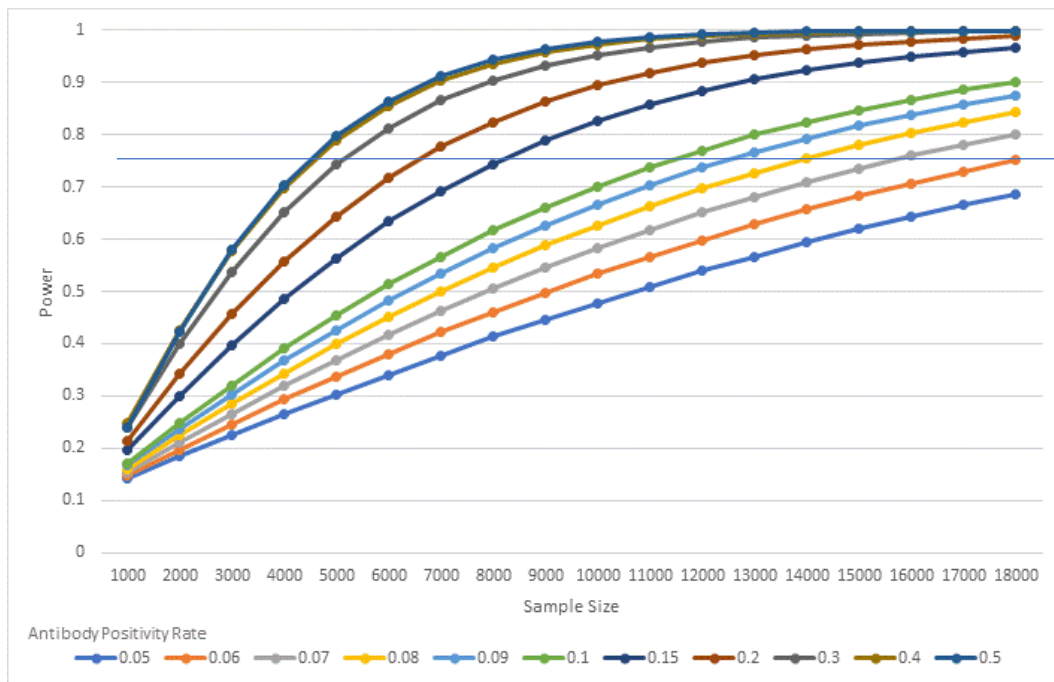
Given the many unknowns about the COVID-19 pandemic in LMICs, estimating an appropriate sample size for different study outcome comparisons is difficult. The percent of women who will become infected during their pregnancy is unknown and there will likely be high variability across sites. Thus, it is important to have a sufficient sample size to a) obtain a precise within site estimate of COVID-19 prevalence (i.e., antibody positivity), and b) estimate the association of maternal, fetal, and neonatal outcomes with COVID-19 infection status across sites.

With respect to prevalence estimation, a sample size of 2,000 per site provides 0.84 probability of obtaining a 95% confidence interval with a half-width of 0.01 if the true underlying prevalence is 0.05. This same sample size also provides high probability (>0.99) of obtaining a 95% CI with half-width of 0.02 for a true underlying prevalence of 0.25 and with a half-width of 0.03 for a true underlying prevalence of 0.50.

For assessing the association between maternal, fetal and neonatal outcomes with antibody status based on Global Network data, a number of outcomes of interest have a prevalence of about 3% in our sites (i.e., stillbirth, neonatal death, congenital anomalies).

The power to detect a relative risk (RR) of 1.5 for women with positive antibody results compared to those who were not based on a two-sided chi-square test with  $\alpha=0.05$  and assumed antibody positivity rates are portrayed in Figure 1 for a range of sample sizes. With 2,000 participants per site at 8 sites resulting in a total sample size of 16,000 participants, there is 80% power to detect a RR of 1.5 if the underlying antibody positivity rate is at least 8%. While we expect prevalence of COVID-19 to vary by site, an overall rate of 8% across all sites is assumed to be reasonable.

Figure 1. Statistical Power for an outcome with a baseline prevalence of 3% and a RR=1.50 at various levels of antibody positivity



Thus, for the purpose of this study, testing women over the study period would allow us to determine COVID-19 prevalence trends over time. With the sample size target of 2,000 in each site, we will have sufficient power to estimate the impact of COVID-19 maternal infection on several important pregnancy outcomes. Each of the 8 sites will aim to recruit and conduct COVID-19 antibody testing for a minimum of 2,000 mothers (approximately 170 per month) for the study period. While the initial study was planned for a one-year period, with the ongoing COVID-19 pandemic, the study will be extended until at least June 2022. With the extension, each site will continue to enroll approximately 170 women monthly at or immediately after delivery to reach a sample size of approximately 24,000.

Because the sites will vary in terms of the number of potentially eligible pregnant women, RTI will work with each site to develop a sampling scheme that will reflect the population of pregnant women and distribute the recruitment evenly across the year. We are also aware that some sites may not be able to reach the goal of 170 recruited women per month. However, each site should aim to enroll as close to that target as possible for the duration of the study. We also realize that the extent and timing of the COVID-19 pandemic in each site is unknown and there

will be every effort made to accommodate this study to the situation at each site. For that reason, we will evaluate recruitment for each site monthly in order to make the appropriate adjustments and adjust the time frame of the study accordingly.

At the time the initial batch of antibody testing is completed, if the prevalence of positive results is markedly low at any given site, it is unlikely meaningful information will be obtained with respect to antibody positivity and its association with maternal, fetal, neonatal outcomes. As such, the study subcommittee will have the ability to stop enrollment for a site if antibody testing is not yielding positive results. Specifically, if no positive results have been identified in the first 500 participants at a site, a review by the protocol committee will be triggered as the probability of the final prevalence exceeding 2% is <0.01%.

The statistical analyses plan (SAP) includes details of analytic strategies that will be employed for this observational study.

### **3.2 Available population**

It is our intent to conduct the COVID-19 study within the existing MNHR clusters in the GN sites. Currently, each site has approximately 3,000 – 6,000 pregnant women enrolled each year in the MNHR.

### **3.3 Estimate of projected recruitment time**

The recruitment period will be 12-24 months at each site. Due to differences in the approval process, the start date may vary across the study sites.

### **3.4 Risks and benefits**

This study does not pose significant risks to study participants. Minor risks could include discomfort while providing a blood sample or answering questions on the questionnaire. In addition, participants could feel distressed at learning the results of their tests (positive or negative previous SARS-COV-2 infection). Finally, in some settings there may be stigma associated with positive COVID-19 infection. To minimize the risk, all interviews about symptoms are confidential. The antibody testing will be conducted as part of the research study and the participant may determine whether she wishes to know the results.

### **3.5 Ethical considerations**

The knowledge, attitude and practice questionnaire will be incorporated into the routine MNHR questions and procedures. As such we will encourage completion at an early MNHR visit. However, we will be flexible about timing so that the questionnaire may be completed either during prenatal care or near delivery based on the convenience for the subject and staff. The date the questionnaire is completed will be collected so we will also be able to determine whether the time in the pregnancy the data is collected influences the results.

All women delivering within our sampling frame will be approached for consent for antibody sampling by trained MNHR staff. Only women who provide informed consent (sample consent, Appendix 3) will be enrolled in the COVID-19 antibody protocol.

All the Global Network sites will report data to the Global Network Data Coordinating Center (DCC), located at RTI International. The data will be used to evaluate protocol adherence and site performance (e.g., recruitment, loss to follow-up, data quality). The DCC will provide standardized progress reports to NICHD and the site investigators on a monthly basis to monitor outcome variables and adverse events.

The Data Monitoring Committee (DMC) appointed by NICHD will oversee the conduct of this study at their bi-annual meetings. The DMC reports are made available to all participating institutions.

## Data management and quality control

### 4.1 Data Management Overview

As this study is being conducted as an addendum to the GN's MNHR, COVID-19 study data will utilize the same DMS as the MNHR. The data will be collected in the local language electronically on forms programmed in Android Tablets in the RedCap Application. Personal identifying information will be recorded on MN00 (Screening Form) only. This information will be retained at the site only and will not be transmitted to the DCC. Data describing each mother and infant will be identified using a MNHR ID number only. Directly identifying information is not going to be entered into REDCap based EDC system.

Precision and accuracy of actual data collected will be checked by chart review (random 5%) and internal procedures using the computer program. Monthly audits and incomplete data reports will be performed by a review team). Data editing and error resolution will be performed monthly. Some of these activities may be shared with RTI.

### 4.2 Data Entry, Quality Checks and Transmission

Data entry will be performed on Android tablets with the RedCap mobile application installed. Using RedCap, study staff will prospectively enter the data from study participants. The RedCap DMS checks to make certain that entered values are acceptable, that all required fields are entered, and that items are consistent with other related items in the database.

Validity checks will test for:

- required fields
- range checks
- skip checks, and
- consistency checks between multiple variables.

All fields that are required to have a value will be checked to ensure they are not blank. Skip logic has been programmed into RedCap as needed.

All validity checks performed at data entry will be repeated on the database once it reaches RTI. Additional edit checks, such as across-form consistency checks will be performed as well. Detailed information about edit check failures will be sent back to the appropriate data collection site. Data collection staff will be responsible for entering and updating/correcting all patient

records on the computer. Additional detail on the quality review and editing process is contained in the study Manual of Procedures (MOP).

### **Transmission of Data to the Data Coordinating Center**

Data entered into offline REDCap mobile app should be uploaded to RTI REDCap server on a daily basis or as soon as there is a reliable WIFI connection. Strict confidentiality will be maintained for all data collected, and patient identifiers will not be available to RTI or the US PI.

### **Security**

REDCap is a secure web application for building and managing online and offline data collection. REDCap software is 21 CFR Part 11, FISMA, and HIPAA-compliant. RTI International will assume responsibility for configuring RedCap database for Global Network institutions. All REDCap data are encrypted and password protected at all times (at rest and during transmission). Data can be collected either in an online web-based environment or by using the offline RedCap mobile application for sites without access to internet. The Android tablets will be stored in secure locations (i.e. lockboxes) which are only accessed by authorized study staff.

### **4.3 Data Quality Reports**

After each data collection period (generally one month), the data center will produce a summary report including the following:

- number of patients that were included in the study in that period
- missing data rates
- inconsistent data rates

Additional data items may be included as determined by the MNHR investigators.

Appendix 1. Study collection form: Signs and symptoms



Appendix 2. Study collection form: Knowledge, attitudes and practices

## Appendix 3. Sample Study Consent Form

### **Global Network for Women's & Children's Health Research COVID-19 Study**

**INVESTIGATORS:**

[LIST SITE INVESTIGATORS]

**SPONSOR:**

The *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD)

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You are being asked to participate in a research study related to COVID-19 for pregnant mothers. This study is funded by the U.S. National Institutes of Health. This form provides you with information about the study so that you can decide whether you would like to participate. A member of the research team will describe the study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part. You may also request that the research staff read the form to you.

**What is the purpose of the study?**

The purpose of this study is to learn about coronavirus (COVID-19) infection during pregnancy and if there are risks of the infection for the woman and her baby.

**Who will be in the study?**

A total of up to 30,000 women will be enrolled in this study from eight sites in sub-Saharan Africa, South Asia, and Latin America. In [insert site name], up to 8,000 women will be enrolled.

You qualify for this study if you are a pregnant woman in the community.

**What will happen if I join this study?**

If you agree to participate, we will ask you some questions about your health and about your understanding of the coronavirus.

While you are at the health facility to deliver your baby, the study team will also collect:

- Information about your labor and delivery
- Information about your baby, such as birthweight and health status at the time of delivery
- A blood sample of 1 to 2 teaspoons full will be collected either in the facility at delivery, or afterward in a location convenient to you

It will take no more than 30 minutes to complete the consent form, and answer questions for the study.

After you are discharged from the health facility, a member of the study team will visit you at 6 weeks after delivery as part of the registry.

To ensure that we have accurate and complete information about the health of you and your baby, we will access and collect information from the medical records at the health facilities where you and your

baby have received care. By agreeing to participate in this study, you are also agreeing to give permission for the study staff to access your medical records. We will take precautions to protect the information that is collected from your medical records. Only study staff will have access to this information. To further protect you and your baby, all of your information will be coded with a number in place of your name.

The local research staff have been selected because of their skills, knowledge, and familiarity with your community. The research staff are here to support you during the study and should be contacted between visits if you have any questions or concerns.

### **What are the risks and discomforts**

You may feel temporary discomfort when a blood sample is collected, but this will only last a few seconds. To minimize this, we will ensure research staff are well trained in the procedure.

Another possible risk of participating in this study is that your name and personal information may be seen by persons who are not part of the project. To prevent this, you will be given an identification number that will be used in place of your name on all study documents.

Information from this research study will be retained by [local institution] and RTI International in the United States (U.S.) and in the future may be included in a de-identified public use database managed by NICHD Data and Specimen Hub (DASH) in compliance with the U.S. National Institutes of Health (NIH) Public Access Policy. De-identified means that you and your baby will not be individually identified by name or other personal identifiers in the database. Your full name or any address details will not be included. Information released will not identify you or your baby's participation in this research study.

### **What are the benefits of participating?**

You will not receive any money from participating in this study, but your participation may provide important information that can be used in the future to prevent infection in mothers and babies. We will also provide the results of the blood sample test about whether you may or may not have been infected with COVID-19 at some time prior to the test.

If new information about coronavirus in pregnancy becomes available during this study, this information will be given to you by [Insert name of Senior Investigator] or his/her staff.

### **Will I have to pay for anything?**

It will not cost you anything to be in the study.

### **Is my participation voluntary?**

Taking part in this study is voluntary. You have the right to refuse to participate or to withdraw your participation at any time. If you refuse or decide to withdraw, you will not lose any benefits or rights to which you are entitled. These actions will not have any negative effect on the health care you receive from your local health providers. You will still receive your normal medical care.

### **Can I be removed from this study?**

You will be withdrawn from the study if the research staff thinks that your participation may cause harm to you or your baby. The research staff may also remove you from the study for other reasons at their discretion. Also, the sponsor may stop the study at any time.

**What should you do if you have additional questions?**

If you have questions about this study or a project-related injury, you should contact [investigator contact]. If you have questions about your or your baby’s rights as a project participant, please contact [insert ethics committee contact].

If you have any questions about the study, please call [insert senior investigator].

**Agreement to be in this study**

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I know that being in this study is voluntary and I choose to be in this study. I understand I will get a copy of this consent form.

Signature (or thumbprint): \_\_\_\_\_ Date: \_\_\_\_\_  
*(Mother)*

Print Name: \_\_\_\_\_  
*(Mother)*

Signature (or thumbprint): \_\_\_\_\_ Date: \_\_\_\_\_  
*(Parent/Guardian/Husband)*

Print Name: \_\_\_\_\_  
*(Parent/Guardian/Husband)*

## Appendix 4. Budgetary assumptions

Table 1 provides estimated costs per site\*

Table 1. COVID-19 Supplement to the MNHR Estimated Site budgets

|  | Number    |          |                    |
|--|-----------|----------|--------------------|
| Antibody test kits   | 2,000     | \$15.00  | \$30,000.00        |
| Supplies to obtain blood samples (i.e., gloves, vials)               | 2,000     | \$2.00   | \$4,000.00         |
| Copies of study forms  | 2,000     | \$1.00   | \$2,000.00         |
| Personal protective equipment for MNH staff that will obtain samples | 2,000     | \$2.50   | \$5,000.00         |
| Lab staff to perform assays  | 12 months | \$500.00 | \$6,000.00         |
| Shipment of antibody test kits to sites                              |           |          | \$1,000.00         |
| <b>TOTAL</b>   |           |          | <b>\$48,000.00</b> |

\*Assumes that costs of data collection and data entry will be absorbed by the existing MNH registry staff

Table 2. COVID-19 Supplement Extension to the MNHR Estimated Site budgets

|  | Number   |          |                   |
|--|----------|----------|-------------------|
| Supplies to obtain blood samples (i.e., gloves, vials)               | 1,000    | \$2.00   | \$2,000.00        |
| Personal protective equipment for MNH staff that will obtain samples | 1,000    | \$2.50   | \$2,500.00        |
| Lab staff to perform assays  | 6 months | \$500.00 | \$3,000.00        |
| <b>TOTAL</b>   |          |          | <b>\$7,500.00</b> |

## Appendix 5. COVID-19 Total Antibody ELISA Test

- ZEUS ELISA SARS-CoV-2 IgG Test System test will be used for the study to retrospectively test for COVID-19 antibodies from blood samples
- Determines if any the Immunoglobulin G (IgG) is present in a blood sample
- Reports as a single “Positive” or “Negative” result which will be collected on MN25 COVID-19 Specimen Tracking log.
- RTI will continue to work with Zeus Scientific and Global Network sites to import the ZEUS ELISA SARS-CoV-2 IgG test systems into the GN countries

## Appendix 6. Protocol Version Control

| Version |  | Date      | Comments   |
|---------|--|-----------|--|
| 1.0     |  | 7/1/2020  | Original version circulated for IRB/ERC review                             |
| 1.1     |  | 8/1/2020  | Addition of data management section<br>Table of contents and abbreviations |
| 1.2     |  | 8/30/2021 | Increased sample size to 24,000<br>Extended study period through June 2022 |

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