Serologic Survey for *Vibrio cholerae* Infection in Haiti with Assessment of Risk Factors for Asymptomatic, Mild, Moderate, and Severe Disease

Supporting Statement for an Emergency Clearance Request: Section B

(Revised 1/14/11)

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B. Collection of Information Employing Statistical Methods.

1. Respondent Universe and Sampling Methods

These studies aim to describe, with high internal validity, the range of outcomes of intense exposure to *V. cholerae* in single communities. As such, we have designed the studies to maximize the prevalence of positive antibody tests to *V. cholerae*. The results of these studies will reveal, for the highly affected communities in which the studies are conducted, both the proportion of persons asymptomatically infected with *V. cholerae* (those who are seropositive but do not develop clinical cholera) as well as proportions with and risk factors for severe disease. Because they use single-site designs, these studies will not be directly representative of the country as a whole, but their results, applied in context, will provide useful information to decision-makers and public health officials in Haiti. Although the range of intensity of *V. cholerae* exposure may vary across the country, the health and genetic background of the host population as well as the environmental, water, sanitation, and water hygiene conditions are fairly uniform, country-wide. Additionally, while there are several known risk factors for the development of severe disease (including blood group O and use of stomach acid-suppressing medications), it is expected that the percentage of infected individuals who develop severe disease will be relatively similar across Haiti.

We acknowledge that caution is needed when applying information from one community to a broader population; however, logistical difficulties ranging from security, transportation, blood handling and storage, and lack of accurate census data constrain the design of the studies. Additionally, current estimates for progression to severe disease are derived generally from Asian populations with endemic, rather than epidemic, cholera caused by a different *Vibrio cholerae* strain. There is substantial variation in severity rates between the El Tor and classical *Vibrio cholerae* strains; the *Vibrio cholerae* causing the epidemic in Haiti is a hybrid between the two strains and its propensity for causing severe disease is unknown. The estimate provided from this study then, while not directly representative of the entire population, would still provide useful information not otherwise available, and will aid in projections and resource allocation.

Proposal 1: In the cross-sectional study design, the study area in Haiti will be chosen in conjunction with the MSPP shortly before survey implementation and the precise geographic area will be selected based on the following criteria: a) an area with high cholera activity in the preceding 3–6 weeks (which is the time period when *V. cholerae* antibody testing is most accurate), and b) where the logistics of carrying out the study are feasible. Much of the Haitian population resides in densely-populated rural areas that are grouped into areas of several hundred households. The study area will be selected to encompass a community using local census data, if available, or a geographical grid to include approximately 3000 people or 500 households.

Previous cholera surveys in Haiti have shown response rates of nearly 100% and average household sizes of six. All residents over the age of two years residing in the 500 households within the selected census study area will be asked to participate. The entire population of the study area has been selected because it will allow for calculations of the relative percentages of community residents that develop positive antibody titers, and symptomatic and severe disease. This approach will also help ease logistical challenges, improve quality control, and minimize the impact on the study results of regional differences in medical care. This type of study design has been used previously to examine the impact of epidemic

cholera (1).

Proposal 2: In the prospective study design, the study team will select a Haitian hospital that is actively experiencing a high burden of cholera cases, again using the best available up-to-date in-country knowledge of logistics, feasibility, and disease burden. The team will then identify approximately 300 patients who are currently hospitalized with cholera and reside within a defined catchment area, and administer the serologic survey to these patients. With the patients' permission, they will proceed to the patients' households and attempt to enroll all household contacts over the age of 2 years for an estimated aim of 900 contact participants enrolled. No randomization will occur. Similar to the cross-sectional study, this study design favors the inclusion of participants with a high likelihood of cholera exposure (and thus antibody responses) over a randomized sample of a broader population that would likely have lower seroprevalence and fewer data suited to this analysis. Previous studies have used this study design to examine the spectrum of cholera illness, and many of these studies inform the current cholera severity estimates (2-4).

2. Procedures for the Collection of Information

Proposal 1: To calculate the sample size needed to determine the pattern of cholera severity using the cross-sectional study design, we estimated that approximately 75% of residents would have positive antibody titers to *V. cholerae*, 5% of persons with positive antibody titers would develop severe disease, with a sampling error for severe disease of 1.5%, resulting in a sample size of approximately 400 households including 2400 individuals. Expected confidence intervals of less than 1.5% for severe disease with an alpha of 0.05 and a power of 80% were chosen to achieve a high degree of confidence for an estimate of severe disease within a Haitian community. Because this study involves a blood test, the response rate is expected to be somewhat lower than previous surveys and is estimated to be 80%. The number of selected households will be increased to 500 to recruit 2400 participants. This sample size will allow for exploration of associations between severe disease given *V. cholerae* exposure and individual risk factors for severe disease, including blood type O and *Helicobacter pylori* infection.

Proposal 2: To calculate the sample size needed to determine the pattern of cholera severity using the prospective study design, we estimated that approximately 75% of household contacts would have positive antibody titers to *V. cholerae*, 5% of persons with positive antibody titers would develop severe disease, with a sampling error for severe disease of 1.5%, resulting in a sample size of approximately 900 contacts from the households of 300 hospitalized patients. Expected confidence intervals of less than 1.5% for severe disease with an alpha of 0.05 and a power of 80% were chosen to achieve a high degree of confidence for an estimate of severe disease within a Haitian community. Because this study involves a blood test and a follow up survey, the response rate is expected to be somewhat lower than previous surveys and is estimated to be 80%.

In each study design, seven teams of Haitian phlebotomist and enumerator pairs will undergo training on the questionnaire and study design and will then attempt to visit all households within the study area. The enumerators will read the questions aloud to participants in Creole and record their answers on personal digital assistants (PDAs) or pencil-and-paper forms if PDAs are unavailable. Parents or guardians will answer questions on behalf of children age 11 years and younger to maximize response accuracy. Children ages 12-17 years may

answer questions themselves with permission of their parent or guardian. Data will be entered into a Microsoft Access 2007 database with data validation checks and analyzed using SAS software version 9.2. Copies of data will be maintained by the MSPP and CDC investigators in secure files and on secure computers.

3. Methods to Maximize Response Rates and Deal with Nonresponse

Response rates in recent cholera surveys in Haiti have approached 100%, though the rate will likely be lower in this study because of the blood draw. The study team will attempt to maximize response rates through advance coordination with local officials and community leaders. Individuals who decline to have their blood drawn will be asked to complete the questionnaire. Their responses will be compared to participants who did have blood drawn. Households with absent family members will be visited by the survey teams more than once to maximize participation.

4. Tests of Procedures or Methods to be Undertaken

Most questions used in this survey have been used previously in the cholera response in surveys that met non-research determination. The survey questionnaire in Creole will be pilot tested prior to study implementation.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

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The Division of Foodborne, Waterborne, and Environmental Diseases at the National Center for Emerging and Zoonotic Infectious Diseases at CDC and the MSPP will supervise collection of the data and perform analysis.

Note the person(s) who:
1) Designed the data collection: Brendan Jackson
2) Will collect the data: Haitian local employees under the supervision of Brendan Jackson with other DFWED and CDC Haiti staff
3) Will analyze the data: Brendan Jackson, Ciara O'Reilly, Eric Mintz, Barbara Mahon, John Copeland, and Mike Hoekstra

References

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