Supporting Statement B for

Human Influenza Surveillance of Health Care Centers in the United States and Taiwan (NIAID)

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B.1 RESPONDENT UNIVERSE AND SAMPLING METHODS

The respondent universe will be separately identified for each data collection effort based on the setting being studied.

The estimated respondents per year are 3005 subjects. Below are estimated demographic data on the US subjects for the studies conducted under this generic clearance. This protocol intends to enroll based on previous years' demographic data. Enrollment will occur in at-risk settings globally and may enroll in locations across the US as well as Taiwan, Nicaragua, Chile, Argentina, Egypt, Bangladesh, China, Cambodia, and Vietnam. The NIH will determine countries to be enrolled in the studies based on the presence of known animal influenza outbreaks or novel strains in the area and/or the severity of the human influenza season in the region.

United States*	Total
Male	850
Female	650
African American	400
Caucasian	750
Hispanic	200
Asian	150
Total	1500

***At the sites outside the United States, demographic information is not pertinent to generalizability. Sites outside the United States account for the remainder of the respondents (~1500)**

This study will be inclusive of all individuals who meet the Subject Inclusion/Exclusion Criteria, regardless of religion, sex, or ethnic background. We are using a convenience sample to examine the relationships between at-risk settings and influenza transmission, as well as identify the types of influenza that are transmitted to humans, but do not expect results to be generalizable. We expect the study will enroll more men than women in the human-animal interface studies due to the demographics of workers in farms and slaughterhouses. We expect to enroll more women than men in household transmission studies due to the demographics of households in the countries where those studies will occur. We anticipate a retention and completion rate for the follow-up visit of at least 85% based on our historical experience.

B.2 PROCEDURES FOR THE COLLECTION OF INFORMATION

This generic clearance provides the needed samples and data for numerous protocols that rely upon it (as described in the Supporting Statement A). Hence, there is not a specific sample size calculation for this surveillance population, but low-end sample size calculations have been performed for the laboratory analysis associated with serologic and immunologic studies.

Immunologic analysis will be performed on all patients with positive PCR influenza tests. Each protocol will enroll 50-200 PCR influenza positives subjects each year depending on the setting – we expect more positives in hospital and household settings than in human-animal interface settings.

Immunologic outcomes will be assessed based on disease severity in hospital and household settings, with an estimated breakdown of 5% severe disease, 40% moderate disease, and 45% mild disease in each season. With these distributions we will accrue 60 patients (in the smallest or severe group) over the course of 6 influenza seasons a sample size sufficient to permit analysis and characterization of differences between the groups. Changes in multiple factors that correlate with disease will be the primary analysis.

In hospital and household settings, serologic analysis will be performed on 200 patients including: 1) Those with no clinical symptoms (N=100); 2) those with ILI and evidence of lower airway disease defined as diagnosis of pneumonia (N=40); 3) those who ILI and severe disease resulting in ICU admission, mechanical ventilation or death (N=10) and; 4) randomly selected ILI samples from the remaining subjects (N=50). Serologic analysis will be performed on groups 1-4. Based on our estimated prevalence data from our population, we anticipate that 20 of these (i.e. 20% of those from groups 2-4) will have positive PCR influenza tests. With these numbers, we anticipate that serologic analysis of each of the 4 groups will permit us to detect the added value of serologic testing when combined with PCR for identification of influenza infections. By definition, changes of four fold or greater in antibody titer at 28 days post infection compared to the titer at time of presentation is considered to be a positive response to influenza infection and will be used as the criteria for judging a positive result. In human-animal interface settings, serologic analysis will be performed on all individuals to identify possible prior exposure to influenza.

In household settings, a sample size of 211 households is needed to detect a relative transmission risk of 1.5 with 80% power and a 5% type I error rate given an average household size of 6.4 persons, a secondary influenza attack rate of 24%, and within-household correlation of 0.3,. Assuming a withdrawal rate of 5%, a total of 299 households will be needed for an individual study. This sample size yields 99% power with a type I error of 5% to detect a secondary attack rate of 0.24 ± 2%.

Influenza virus genome sequencing will be performed on all influenza positive samples collected from both the immunological and serological study groups. Specific genotypes will be correlated with the clinical disease descriptions described above.

The following bullet points explain what information/data will be collected from subjects by a fully trained staff member known as a research coordinator (RC). All subjects will be enrolled for up to 3 weeks after their eligible study start date.

- Enrollment
    - Screening to determine eligibility
    - Written consent
    - Enrollment questionnaire including basic demographic data, vaccination history, co-morbid illness, initial vital signs and history of present illness.
    - Collection of serum sample
    - Collection of nasopharyngeal swab sample
    - Collection of nasopharyngeal wash sample (Taiwan only)
    - Test for influenza
    - If influenza positive, then collect nasopharyngeal wash sample

- Follow up visit #1-4 (most studies will involve one follow up visit, up to four are possible if an individual is determined to be influenza positive in the initial test)
    - Follow up questionnaire to assess clinical course
    - Collection of serum sample
    - Medical record review to assess clinical course

Quality Management Plan:

This protocol has a DMID-approved quality management plan and a DMID-approved site specific quality management plan. These approved plans outline in detail the plan for quality control and quality assurance of all data entered in a 21CFR11 compliant database.

All data collection is the responsibility of the research coordinator and must be captured correctly, and consistent between all research coordinators across sites. The data manager is responsible for ensuring data integrity of his staff by the methods outlines in the quality management plan which include, but are not limited to the following:

- Quality control is the 100% real-time review of day-to-day operations, including all study-related documentation and measurement of the conduct of the protocol in real-time by delegated personnel in the field and associated centers. By front-loading quality management into the daily operations of protocol implementation with real time controls for assuring errors are detected and corrected early, unnecessary or duplicate efforts and resources are minimized, data and protocol timelines are efficiently managed. All source documents must be reviewed by the clinical team and data entry staff, for assuring accuracy and completion. QC Tools include: Form 12A, Form 13A, and Form 15A.

- Quality Assurance is the periodic, **retrospective**, and systematic examination of the study processes by selecting a **review frequency** and **specified sample size** (10 %), of records and key areas representing the total work effort. Research processes and systems reviewed for assurance include, *but are not limited to* determining eligibility, informed consent form and process, source data verification, study database quality control efforts, clinical laboratory processes (including processing, documenting, and shipping clinical specimens), and timely reporting of protocol deviations. Site visits conducted by a CEIRS contractor and/or DMID may occur for the purposes of oversight of Administrative and Clinical Site performance. Issues identified from these sources should be considered toward process improvements. QA Tools include: Forms 12A, 14A, and 15A.

B.3 METHODS TO MAXIMIZE RESPONSE RATES AND DEAL WITH NON-RESPONSE

Subjects are informed in detail what the study requests of them prior to enrolling the subject so the subject is made aware of all effort and benefits to them. Subjects are reminded they are in no way required to participate, and may withdraw at any moment. Follow-up/ response rates for the current emergency exemption collection conducted for the 2015-2016 influenza season is 91%.

In order to maximize the collection of all data points, fully trained staff (research coordinators) who are familiar with the acute care environment will verbally ask each subject to respond to the listed

structured questions in a step by-step manner. After completion of the structured clinical data form, research coordinators will immediately review the subject's past medical history with what is reported in the medical record. Any discrepancy between subjects report and the medical record will be brought to the subject's attention and corrected on the enrollment form as appropriate based upon the subject's report. No data points will be left blank on a data collection form. If unknown or not applicable values exist, they should be marked as "999" to indicate a value does not exist. Quality assurance checks on data entry will be carried out according to our QA/QC plan which was reviewed and approved by experts from NIAID. Our quality control plan allows us to estimate an 85% successful response rate. Methods to assure reliable follow-up include collection of multiple contact numbers for subjects, return phone call reminders, and flexible scheduling of return visits and/or phone follow-up calls to fit the patients' schedules within a 3 week period has resulted in a 91% successful follow-up/ response rate at the Johns Hopkins University location.

B.4 TEST OF PROCEDURES OR METHODS TO BE UNDERTAKEN

The research teams design the content and format for collection of samples and key data elements based on prior successful influenza studies. Those methods have been found to permit accurate and reliable collection of samples and reporting of data. The study coordinators will be directly trained by the PI and regular oversight will be provided by a Senior Coordinator (trained by the PI) to ensure consistency with procedures associated with the study.

B.5 INDIVIDUALS CONSULTED ON STATISTICAL ASPECTS AND INDIVIDUALS COLLECTING AND/OR ANALYZING DATA

Each data collection team will obtain input from physicians, researchers, and statisticians.