Emerging Infections Program (0920-0978)

Revision

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SUPPORTING STATEMENT PART B

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1. Respondent Universe and Sampling Methods

ABCs conducts active, laboratory- and population-based surveillance and includes all cases in a defined catchment area. The total population of invasive disease surveillance is approximately 45.5 million across 10 sites. However, most areas restrict the population further for certain pathogens to ensure complete reporting and good audit data. No sample selection is involved in this surveillance study. Therefore, the data collection covers the entire target population. Because ABCs personnel submit the disease surveillance forms as a part of their job to perform a public health service, the response rate is expected to be 100%.

FoodNet conducts active population-based surveillance for eight pathogens and one syndrome among all residents of our catchment area. The population under surveillance is 50 million persons and represents 15% of the U.S. population. We identify approximately 23,000 reports of illness (all pathogens combined) each year (based on 3-year average, 2018-2020). We work with health departments in ten states to collect basic demographic and lab data on all cases but only some cases are interviewed (the number of cases interviewed depends on each state health department).

The Influenza Hospitalization Surveillance Network (FluSurv-NET) covers a population about 30 million residents who have the potential of being hospitalized with laboratory-confirmed influenza. Starting with the 2017-18 influenza season, FluSurv-NET implemented a sampling strategy for collection of clinical data using the standardized case report form on persons that meet the case definition to address the large increase of cases. To ease the burden on sites, seven readily available variables (site-assigned unique case number, state, case type, age or date of birth, sex, hospital admission date, and positive influenza test result) are submitted to CDC as soon as possible. Although timely completion of the remainder of the case report is encouraged, sites have until September 30 to complete medical chart reviews and data abstraction.

Twelve EIP sites and three sites funded through a cooperative agreement with the Council of State and Territorial Epidemiologists (CSTE) participate in the pediatric and adult influenza hospitalization project and represent 16 metropolitan areas and approximately 9% of the US population. All hospitals that accept adult and/or pediatric admissions in the catchment areas under surveillance are included for active public health surveillance so accurate population-based rates can be calculated.

Rates of laboratory-confirmed influenza-associated hospitalizations by age group, sex, and race/ethnicity and severe influenza-associated complications are calculated using population denominators from the most recent census data available for pediatric and adult populations. These rates are further used to estimate national influenza disease burden and burden averted through vaccination, both throughout each season on an annual basis.

Interim analyses of aggregate data are conducted to estimate hospitalization rates and monitor factors associated with severe influenza throughout the influenza season. Final analysis includes a seasonal summary of the epidemiologic characteristics of hospitalized cases using standard descriptive statistics. Where appropriate, univariate and multivariate analyses are conducted to evaluate factors associated with serious influenza-associated complications.

All analyses are conducted using SAS or R. Aggregate results are regularly shared with relevant CDC programs, including the ACIP, and with the public and scientific community via scientific publications.

The HAIC conducts population-based surveillance and includes all cases occurring within the population of a geographically defined area, referred to as a catchment area (i.e., surveillance area), in each participating EIP site. No sampling is involved in surveillance for candidemia or invasive *Staphylococcus aureus*. Case sampling is performed in *Clostridioides difficile* infection (CDI) surveillance and for Extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales surveillance, which is part of the select Gram-negative bacilli surveillance (MuGSI), to reduce the burden of data collection, as follows:

Application of CDI case sampling at all participating EIP sites: In sites with catchment area populations greater than 1,500,000 persons, because of the relatively high volume of positive *C. difficile* cases, sites will apply a stratified random sampling scheme, based on age and sex, after determining which positive *C. difficile* toxin specimens qualify as a CDI case for the surveillance. CDI cases will be categorized into strata based on age and sex. There will be a total of 8 strata; two sex groups (i.e., males, females) and four age categories (i.e., 1-17, 18-44, 45-64, >64). All CDI cases in the youngest age group (i.e., 1-17), regardless of sex, will undergo full case report form completion. For the other 6 age/sex strata, the EIP sites will randomly sample 1 in 4 CDI cases for full case report form completion. For all other EIP sites (i.e., surveillance populations less than 1.5 million persons), a minimum of 3 in 4 CDI cases will be randomly selected from each epidemiologic class (includes hospital-onset, long-term care facility-onset, community-onset healthcare facility-associated, and community-associated) for full case report form abstraction. Sites with relatively fewer CDI cases may choose to complete a full case report form on all CDI cases. The sampling scheme may be subject to change based on the evolving epidemiology and burden of CDI.

Application of sampling of ESBL-producing Enterobacterales at all participating EIP sites:
A case report form will be completed for the first incident case per species in a patient in a 365-day period and for all incident cases from normally sterile sites (Note: 365-day period is defined as January 1st to December 31st).

For the new data collection instrument introduced in the Revision Package "HAIC 400.14 HAIC MuGSI Kpc and NDM treatment collection form" sampling will not be performed. Treatment data will be collected from all cases that are identified as KPC- or NDM-producing CRE.

2. Procedures for the Collection of Information

Case finding in ABCs is active and laboratory- and population-based, therefore a sampling method is not used. As positive laboratory reports are essential to the case definition, the microbiology laboratories in acute care hospitals and reference laboratories processing sterile site specimens for residents of the surveillance area are the most efficient sites for case identification. In addition, some of the data of interest on cases of invasive bacterial disease is readily accessible in the microbiology laboratory. However, most data that are essential for describing

the population-based epidemiology of these diseases (e.g., age, residence within the surveillance area, outcome) may not be available in many microbiology laboratories. Therefore, a standard case report is completed on all identified cases through medical record review. The standard case report form contains questions on basic demographics, underlying conditions, vaccinations and risk factors for infection. Data collection is done differently in each surveillance area; for example, through the cooperation of on-site hospital personnel (e.g., Infection Control Practitioners or Medical Records personnel), through medical record review or clinician interview by county health department personnel, or through medical record review by surveillance personnel.

To assure complete timely reporting and collection of data, contact with microbiology laboratories must be frequent. In hospitals without computerized microbiology data, surveillance personnel should call designated microbiology laboratory contacts regularly to identify new cases and request isolate submission. Where microbiology data are computerized, electronic listings of all isolates of the pathogens of interest from normally sterile sites should be obtained on a monthly basis. If enrollment into special studies due to slow reporting falls below 90% or isolate collection falls below 85% of surveillance cases, regular calls to microbiology labs should be instituted to ensure that delayed reporting of cases does not have an adverse effect on enrollment rates into special studies or isolate collection rates.

Each area must determine what means will be used for collection of data that are unavailable in the clinical microbiology laboratory. It is essential that the method(s) selected are detailed in writing and shared with CDC and the other surveillance areas, to permit assessment of the comparability of data collection. In addition, problems with proposed methods for data collection should be identified promptly and new methods substituted, and changes documented when appropriate. In addition to formal audits of the surveillance systems, surveillance areas regularly assess the completeness of information collected for each case. If any core variables (e.g., outcome) are frequently incomplete, the data collection method should be revised to correct the problem. CDC should be notified regarding changes in data collection methods as these occur.

In FoodNet, a sampling method is not used in case ascertainment. All laboratory-confirmed cases are included in incidence rates and trends. Rates are calculated from the number of cases divided by the total population (based on US census data). Trends over time are calculated using a negative binomial regression model to account for the change in catchment area (from 5 sites in 1996 to 10 sites since 2004) and the variability in incidence between pathogens and sites. Rates are calculated overall, by pathogen, by species or serotype, and for various subpopulations including state, age groups, race, and ethnicity. Interview rates by states vary; thus, not all cases have information for every data element. A descriptive summary is compiled for laboratory practices and testing volume and is used along with other sources of data to estimate the burden of known foodborne diseases in the United States.

The FluSurv-NET conducts active public health surveillance for laboratory-confirmed influenza hospitalization cases in all age groups within selected catchment areas in 15 states. Sites prospectively identify cases by reviewing hospital laboratory, admissions, infection control practitioner databases/logs, or reportable conditions databases. This involves our surveillance site partners maintaining active contact with hospital laboratories, admissions departments, and

infection control practitioners, or review of reportable condition databases. Methods may vary slightly among surveillance areas or among hospitals within an area depending on the availability of laboratory and admissions databases. For hospitals with computerized viral laboratory data, computerized listings of all influenza positive cases in all age groups are obtained on a weekly basis throughout the influenza season. Influenza admissions also may be tracked by infection control professionals or other hospital staff serving hospital wards where influenza cases might be admitted. For hospitals in states where hospitalized influenza cases are a reportable condition, infection control practitioners review laboratory results and admission logs. Additionally, states may utilize the state health information exchange, if applicable, to identify additional influenza cases. For all potential cases identified, medical charts are reviewed by state health department appointed surveillance officers to determine whether case definition inclusion criteria are met.

Once there is verification of positive influenza test and confirmation that patient meets the case definition and inclusion criteria, sites conduct medical and laboratory chart review and data abstraction to collect detailed clinical and epidemiologic information contained in the standardized case report form. To obtain as complete an influenza vaccine history as possible sites will use the following sources, in order of priority, to collect this information: 1) review the patient's medical chart, 2) consult the state vaccination registry, 3) contact the patient's provider via fax or telephone and/or 4) contact the patient or their proxy. If providers and/or patients or proxies need to be contacted, a standardized interview will be used to obtain influenza vaccination history.

Case finding in HAIC population-based surveillance is active and laboratory-based. As positive laboratory reports are essential to the case definitions for CDI, select Gram-negative bacilli (MuGSI), invasive *S. aureus* infections and for candidemia, the microbiology laboratories in acute care hospitals, reference laboratories, and other healthcare facilities (e.g., long term care facilities, dialysis center referral laboratories, etc.) processing specimens for residents of the surveillance areas are the most efficient sites for case identification. In addition, some of the data of interest on cases of CDI, select Gram-negative bacilli and invasive *S. aureus* infections, or candidemia are readily accessible from the microbiology laboratory. However, most data that are essential for describing the population-based epidemiology of these infections (e.g., age, residence within the surveillance area, outcome) may not be available in many microbiology laboratories. Therefore, a standard case report is completed on all identified cases through medical record review. The standard case report form includes questions on basic demographics, underlying conditions, and risk factors for infection. Data collection may be performed differently in each surveillance area; depending on EIP site resources and practices; for example, through the cooperation of on-site hospital personnel (e.g., Infection Control Practitioners or Medical Records personnel), or through medical record review by EIP site personnel. In addition, for cases identified as community-associated carbapenemase-producing Enterobacteriaceae (CA CP-CRE), a health interview will be conducted using a standard phone script and questionnaire to validate the community-associated case's status and to identify other known potentially modifiable risk factors for CP-CRE acquisition. Furthermore, for CRE cases from sterile specimen sources that are identified as KPC or NDM positive the "HAIC 400.14 HAIC MuGSI KPC and NDM treatment collection form" will be collected during medical record review.

To assure complete timely reporting and collection of HAIC data on CDI, select Gram-negative bacilli (MuGSI), invasive *S. aureus* infections and candidemia, contact with microbiology laboratories must be frequent. EIP sites must demonstrate to CDC project staff a comprehensive understanding of all laboratories within their catchment areas that are performing testing for pathogens included in HAIC surveillance, to ensure complete case capture. This entails EIP site personnel communicating regularly (e.g., annually) with all healthcare facilities and providers in their catchment areas (e.g. through telephone inquiries, email communications or mailings) to ensure that they know the laboratories serving those facilities and providers (including laboratories such as large regional reference laboratories that may be located outside the catchment area) and the type(s) of microbiological testing for HAIC pathogens performed in those laboratories. In hospitals without computerized microbiology data, surveillance personnel communicate regularly with designated microbiology laboratory contacts to identify new cases and request isolate submission. Where microbiology data are computerized or where queries of laboratory automated testing instruments can be programmed, electronic listings of all isolates of the pathogens of interest identified from the body sites under surveillance (e.g., stool for *C. difficile*) should be obtained on at least a monthly basis. Regular interactions of EIP site personnel with microbiology laboratory staff members ensure that case reporting is complete and timely, and that isolate submission rates to CDC are acceptable.

Each EIP site must determine what means will be used for collection of HAIC data that are unavailable in the clinical microbiology laboratory. All sites used standardized case report forms to collect these data. It is essential that the method(s) selected by the sites are shared with CDC and the other EIP sites to permit assessment of the comparability of data collection. In addition, problems with proposed methods for data collection should be identified promptly and new methods substituted, and changes documented when appropriate. In addition to formal audits of the surveillance systems, EIP sites regularly assess the completeness of information collected for each case. If any core variables (e.g. outcome) are frequently incomplete, the data collection method should be revised to correct the problem. CDC should be notified regarding changes in data collection methods as these occur.

3. Methods to Maximize Response Rates and Deal with No response

The state public health laboratories and partnering academic institutions submit the disease surveillance forms as a part of their job to perform a public health service; therefore, the response rate is expected to be 100% for ABCs. To ensure complete, timely reporting and collection of isolates, sites frequently contact microbiology laboratories. Each site has established regular reporting procedures for each laboratory that identifies ABCs cases from surveillance area residents. This can include receiving computer-generated/electronic line lists, phone calls, and/or paper reports. In laboratories without computerized microbiology data, surveillance personnel contact the designated microbiology laboratory contacts regularly to identify new cases and request isolate submission. Where microbiology data are computerized, electronic listings of all isolates of the pathogens of interest from normally sterile sites [i.e., blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, bone, joint fluid, muscle/fascia/tendon (group A Streptococcus only), or internal body site (lymph node, brain, heart, vascular tissue, liver, spleen, vitreous fluid, kidney, pancreas, or ovary)] are obtained on a weekly or monthly basis, depending on the volume of testing by the laboratory. When a new

laboratory is added to surveillance or a laboratory changes reporting practices (e.g., paper to electronic), surveillance personnel carefully review the computer program and/or process used to generate the line list to ensure that the system will correctly identify every ABCs case. Any changes made to the ABCs case definition (e.g., addition of a source to the normally sterile site list) are communicated to the laboratories immediately. Sites then assess whether the case definition change has been successfully implemented in the laboratories. CDC also tracks performance measures for the EIP sites and provides each surveillance area with several forms of feedback monthly via Power BI Online dashboard behind SAMS.

FoodNet calculates performance standards overall and for each site twice a year to gauge progress on data completeness. Data elements that are less than 80% complete are not included in analysis. Periodic review of the performance standards is conducted and discussions are held with sites who do not meet performance standards to develop plans for improved performance.

The FluSurv-NET surveillance relies on public health reporting. A primary limitation of this activity is that case ascertainment may not be complete. To identify all laboratory-confirmed cases, all laboratories would need to be audited, not just hospital laboratories; however, because the majority of influenza positive cases will not require hospitalization, the workload in determining which of the positive cases required hospitalization would be impractical.

Another limitation of performing surveillance for laboratory-confirmed influenza is that not all patients with influenza will receive influenza diagnostic testing and not all those that are tested will be positive, even if they have influenza, due to the timing of viral shedding and specimen collection. However, because the clinical presentation of influenza is similar to that of many other illnesses, we have limited our case definition to individuals with laboratory-confirmed evidence of influenza.

For the HAIC, EIP site staff submit the case report forms and supplemental data collection tools (e.g., the MuGSI KPC and NDM Treatment Form) as a part of their job to perform a public health service, and therefore, the response rate is expected to be 100%. Performance measures that are tracked for the EIP sites include measures related to the completeness and timeliness of case report form completion and isolate submission. For the CA CP-CRE health interviews, the response rate will likely be less than 100%, since patients have to be contacted and could decline to be interviewed. To help improve the response rate, standardized interviewing techniques will be used consistently across sites, including reading each question and response exactly as written, not skipping a question, reading slowly to allow a thoughtful response, reading the entire question, keeping non-leading feedback phrases, and neutral cues or probes, and other techniques. Interviewers are also given guidance on providing consistent responses to commonly asked questions from respondents and to schedule interviews during a time that is convenient for respondents.

4. Tests of Procedures or Methods to be Undertaken

For ABCs and the FluSurv-NET, the data being collected represents standard clinical and demographic information. No tests of procedures or questions were performed.

For FoodNet, except for HUS surveillance, FoodNet does not use a standardized case report form. Each state uses their own state-specific forms from which data elements are extracted and sent to CDC. If FoodNet would like to collect new data elements, these are reviewed with sites to evaluate the feasibility of collecting such data.

For the HAIC, pilot projects were conducted for CDI (in two EIP sites), for Candidemia surveillance (in two EIP sites) and over time for various ram-negative bacilli included under MuGSI; (MuGSI) in three EIP sites for carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii* (CRE/CRAB) and for carbapenem-resistant *Pseudomonas aeruginosa; in* five sites for extended-spectrum beta lactamase producing Enterobacteriaceae (ESBL); and in nine sites for invasive *E. coli*.

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

For ABCs, Jasmine Varghese, Yunmi Chung, Sandra Pena, and Melissa Arvay are primarily responsible for data management. Statistical consultation has been provided by Nong Shang and the other Division of Bacterial Diseases statistical team members. Other members of the ABCs team at CDC or EIP sites can perform additional analyses.

For FoodNet, staff at state health departments collect the data and an extract is sent to CDC. Hazel Shah and Kennedy Houck compile the data at CDC, produce yearly reports, and are responsible for trend analysis and public datasets. Any member of the FoodNet team at CDC, sites or federal partners can perform additional analyses.

The following identifies individuals who are consulted for Influenza statistical and data analysis: Catherine Bozio Influenza Division, National Center for Immunization and Respiratory Diseases (NCIRD), CDC; principal investigator. Dawud Ujamaa and Devi Sundaresan compile the data that is sent to CDC, produce reports, and provide analytic support. Other staff in the Influenza Division is consulted as needed. Each EIP site analyzes and reports their data, as needed. Other members of the FluSurv-NET team at CDC and sites can perform additional analyses after proposing analytic plans to the Principal Investigators and completing a data use agreement as needed.

For the HAIC, statistical consultation has been provided by Jonathan Edwards, Sarah Yi, Sophia Kazakova , Kelly Hatfield, James Baggs and Rongxia Li. Data are collected by EIP personnel and by local facility staff, as described previously. Identification of the specific EIP surveillance officers and local facility staff members who participate in training and data collection activities is at the discretion of the EIP site or the facility, respectively. Analyses are prioritized by the HAIC Steering Group; major analyses are typically performed by CDC staff, while site-specific analyses or special multi-site analyses may be performed by CDC or EIP site staff. The following individuals are primarily responsible for data management and analysis, although other members of the HAIC team at CDC or in EIP sites may perform analyses.

CDI: Alice Guh

Select Gram-negative bacilli (MuGSI): Alice Guh, Nadia Duffy, Josh Brandenburg, Heather Grome

Invasive *S. aureus* infections: Isaac See, Kelly Jackson, Carly Adams, and Holly Biggs

Invasive *Candida* infections: Meghan Lyman, Sumera Jiva