PART B OF THE SUPPORTING STATEMENT

FoodNet Non-O157 Shiga Toxin-Producing *E. coli* Study:
Assessment of Risk Factors for Laboratory-Confirmed Infections and Characterization of Illnesses by Microbiological Characteristics

Contact:
Amy McMillen
Office of Policy and Planning
National Center for Preparedness, Detection, and Control of Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Road, N.E., MS C-12
Atlanta, Georgia 30333
Phone: (404) 639-1042
Fax: (404) 639-3039
Email: auh1@cdc.gov

Collections of Information Employing Statistical Methods

1. Respondent Universe and Sampling Methods

The study will enroll patients (case-patients) and well controls. The study will attempt to enroll all case-patients in the CDC's Foodborne Diseases Active Surveillance Network (FoodNet) surveillance area during the study period who are identified by routine laboratory surveillance as having a probable non-O157 STEC infection, which is defined as a positive enzyme immunoassay (EIA) or polymerase chain reaction (PCR) test for Shiga toxin from a specimen, submitted by an ill person, that yielded no colonies suggestive of *E. coli* O157.

The number of cases to be enrolled will be dependent on the number of positive, non-recurrent and non-duplicate specimens reported from clinical laboratories in the FoodNet surveillance area from patients not meeting the following exclusion criteria.

A case will be excluded from the study if the patient (or surrogate):

1. did not have a sample from which non-O157 STEC was eventually isolated and obtained by a state public health laboratory or CDC;
2. is not reachable after 10 unsolicited telephone attempts; if time permits, these calls should be made over no fewer than five days (including at least three attempts on a weekend [Saturday 10am–9pm, Sunday 1pm–9pm] and at least three during 5-9 pm on a weekday, the remainder can be made 9am-5pm on weekdays), all within 45 days of culture date;
3. does not have a telephone number available;
4. does not speak either English or Spanish;
5. does not report illness associated with the submission of the clinical specimen from which non-O157 STEC was isolated;
6. was not a resident of the FoodNet catchment area at the time of specimen collection;
7. is part of an outbreak that has been investigated by public health officials, unless he or she is the outbreak patient with earliest known onset date;
8. lives in the same household as a confirmed case-patient who has an earlier onset date;
9. is unable to remember the date of illness onset, or the illness began more than 45 days before specimen collection date;
10. does not provide informed consent (and assent, when appropriate) to participating in the study;
11. is an inmate in a prison or other correctional facility.

In addition, three age group- and county-matched controls will be recruited for each case. Controls will be identified through randomly ordered purchased lists of phone numbers or through birth registry data as has been described in the Part A Supporting Statement.

A person will not be included as a control in the case-control study if he or she:

1. resides outside the FoodNet catchment area;
2. does not speak English or Spanish;
3. is an inmate in a prison or other correctional facility;
4. does not provide informed consent (and assent, when appropriate) to participating in the study.

The total population of FoodNet surveillance is approximately 46 million persons. The table below illustrates the population under surveillance for each FoodNet site as of 2009.

State	Surveillance sites	Estimated Population
CA	Alameda, Contra Costa, San Francisco, Counties	3,348,114
CO	Adams, Arapahoe, Boulder, Broomfield Denver, Douglas, and Jefferson Counties	2,801,318
CT	Entire state	3,518,288
GA	Entire state	9,829,211
MD	Entire state	5,699,478
MN	Entire state	5,266,214
NM	Entire state	2,009,671
NY	Albany, Allegany, Cattaraugus, Chautauqua, Chemung, Clinton, Columbia, Delaware, Erie, Essex, Franklin, Fulton, Genesee, Greene, Hamilton, Livingston, Ontario, Orleans, Otsego, Monroe, Montgomery, Niagara, Rensselaer, Saratoga, Schenectady, Schoharie, Schuyler, Seneca, Steuben, Warren, Washington, Wayne, Wyoming, and Yates Counties	4,265,336
OR	Entire state	3,825,657
TN	Entire state	6,296,254
TOTAL	---------	46,859,541

*Populations were retrieved from the U.S.Census Data, 2009 estimates

2. Procedures for the Collection of Information

All information will be collected by FoodNet surveillance officers in the ten FoodNet sites. FoodNet surveillance officers are employees of the State Health Department or state agents. Each clinical laboratory in the surveillance area routinely report cases of probable non-O157 STEC infection to FoodNet surveillance officers.

The addresses of probable non-O157 STEC infection case-patients will be reviewed to determine if they reside within the surveillance catchment area. Those patients residing outside of the catchment area will be excluded from the study and CDC will not receive any information on individuals who reside outside of surveillance catchment area.

Non-O157 STEC is reportable in all states. The Privacy Rule allows for covered entities to disclose protected health information to public authorities (including the states) without individual authorization under the provisions for public health practice. In the states where the illness is reportable, state public health statutes allow for the contact of individuals to gather information to protect public's health.

According to Federal regulations for the protection of human subjects in research under 45 CFR 46.109 and 46.111, IRBs reviewing proposed research protocol have the authority to allow researchers to contact individuals to invite them to participate in research.

Collection of information from case-patients

A FoodNet staff member or local health department staff in each site will interview case-patients by telephone as described in the part A supporting statement.

Collection of information from controls

We will attempt to enroll three age- and county-matched controls for each enrolled case. Age matching will be by the following six age strata: 0 to <2 years, 2 to <6 years, 6 to <18 years, 18 to <40 years, 40 to <60 years, and 60 years or older. These age strata were chosen to balance need for enrolling sufficient controls and the need for providing reasonable control of any potential confounding effect of age on exposure-infection associations. Because the specific age of respondents is collected, residual confounding by age, can be assessed and further adjusted for using finer increments of age in the analysis. Once a case-patient has been interviewed, controls should be enrolled as soon as possible. Controls need to be enrolled no later than 60 days after the specimen collection date for their matched case-patient.

Controls in all except the youngest age group will primarily be selected from commercially available lists of randomly ordered residential telephone numbers, by county, that include age information on household members, allowing for the rapid identification of households at which an age-matched control might be available for a given case. Controls less than two years old will primarily be selected from birth registries. Because commercially-available phone lists are unable to provide reliable age information for persons aged less than 2 years, birth registries will be used as the preferred method of selecting controls for case-patients in this age group. Sites that do not have access to birth registries will use sequential digit dialing to recruit controls aged less than two years. All of these control selection methodologies are described in the part A supporting statement.

3. Methods to Maximize Response Rates and Deal with Nonresponse

The average annual number of non-O157 STEC cases reported by the 10 FoodNet sites from 2006 through 2008 was 230. Assuming a 70% participation rate, we estimate an enrollment of 161 patients each year ([230][0.70]= 161) across all 10 sites. We estimate an enrollment of 483 controls each year ([161][3]= 483).

This project is being conducted through the FoodNet infrastructure in which each of the 10 sites has established relationships with laboratories and healthcare facilities within their defined catchment areas. Personnel at these sites have regular contact with the facilities and encourage all facilities and laboratories to participate. Audits of the clinical laboratories in the surveillance area will be performed at least monthly to identify potential unreported cases to ensure complete ascertainment of cases.

HIPAA regulation allows for the disclosure and use of protected health information for research purposes without individual authorization because criteria for a waiver were met. CDC personnel will not perform these audits. Completeness and correctness of data collected should be assessed and cross-checked regularly to identify and address issues with the data collection or the application of surveillance definitions to ensure response. CDC staff will perform site visits to the FoodNet sites on a biyearly basis to evaluate compliance with standard operational procedures.

The potential for non-response bias will assessed by comparing demographic characteristics and illnesses severity markers (hospitalization, development of hemolytic uremic syndrome, and death) between enrolled patients and non-enrolled patients using data collected through routine public health surveillance for all patients with culture-confirmed STEC infections.

A potential type of bias that could affect a study of this type is differential access to medical care between enrolled patients and controls. Because all enrolled patients will have sought care for their illness, in order to ensure that the controls recruited come from the same population as the patients did they will have to have had the ability to seek similar medical care if they had diarrhea. Matching by county of residence and age group as outlined in the study protocol should greatly limit the chances that recruited controls have less access to medical care. Other factors potentially associated with access to medical care include race and finer geographic markers of socioeconomic status like zip code of residence. It would not be possible to require matching controls to patients by race because this would make control recruitment very difficult and could hamper our ability to recruit 3 controls for each case. Furthermore, race and finer geographic detail are factors of interest with respect to infection. Published reports indicate that races differ with respect to incidence of hemolytic uremic syndrome, an important complication of STEC infections. Matching by race would prevent assessment of associations between race and non-O157 STEC infection. Matching by finer geographic units may lead to over-matching that could prevent detection of certain risk factors.

Selection bias could result through methods outlined to recruit controls. Whereas patients are not required to have land line telephones in their places of residence, all controls are. If persons

with landline telephones are less or more likely to have certain exposures as compared to some patients who may only have cell phones then bias could be introduced. However, because geographic matching is essential for a study of infections, like non-O157 STEC, for which the environment in which people live and work could be important risk factor for infection, the use of cell phone directories for control recruitment is not possible. Cell phones are mobile preventing their use for geographic matching of patients and controls. We can assess the impact of any bias by conducting analyses restricted to patients and their matched controls that have land line telephones in their homes to see how much point estimates change.

4. Tests of Procedures or Methods to be Undertaken

To understand the logistics and resources required to initiate and maintain a longitudinal, multi-site FoodNet case-control study, a pilot study was conducted at the Minnesota FoodNet site. The Minnesota Department of Health pilot study aimed to identify strengths and challenges of conducting case-control study to assess risk factors for non-O157 STEC infections. The pilot was conducted over a two year period. Investigators attempted to enroll three controls for every enrolled case-patient. Sequential digit dialing was used to recruit controls. Data were successfully analyzed using conditional logistic regression. The success of this pilot provided the sufficient confidence to conduct a similar study in all FoodNet sites. The methodology and questionnaires of the Foodnet study take into account the findings from this pilot project.

One key difference between the pilot and the FoodNet study will be the use of purchased phone-lists from Survey Sample International (SSI) for control selection. The validity of the SSI phone list methodology was evaluated against the traditional sequential digit dialing method used in Minnesota. Controls recruited in the Minnesota pilot study were divided into two groups: those whose landline telephone number were on the SSI phone lists and those whose telephone numbers were not on SSI phone lists. No statistical differences in a variety of exposures were found between these two groups of controls, suggesting that the use of SSI phone lists for controls selection will lead to findings very similar to those obtained through the established, but more time-consuming, method of sequential digit dialing.

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

Contact information for the statistician consulted for project design and data analysis is as follows:

Robert M. Hoekstra, PhD
Math Statistician
Biostatistics and Information Management Branch
Division of Foodborne, Waterborne, and Environmental Diseases
Centers for Disease Control and Prevention
1600 Clifton Rd, NE
Atlanta, GA 30333
(404) 639-4177
Email: JREdwards@cdc.gov

Data will be collected by FoodNet site personnel. Identification of the specific FoodNet personnel who will participate in data collection activities is at the discretion of the FoodNet site. Data will be analyzed by group of FoodNet CDC, USDA, and FDA staff and FoodNet site personnel.