Risk Factors for Community-Associated *Clostridium difficile* Infection through the Emerging Infections Program

Request for OMB Approval of a New Data Collection

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Table of Contents for Part B:

B. COLLECTION OF INFORMATION EMPLOYING STATISTICAL METHODS

Part B. Collections of Information Employing Statistical Methods

1. Respondent Universe and Sampling Methods

Cases will be identified through routine Emerging Infections Program (EIP) *Clostridium difficile* infection surveillance (0920-0892, Expiration 07/31/2014). All identified community-associated *C. difficile* infection (CA-CDI) cases within the study age ranges (1-5 years and ≥ 18 years) will be eligible for enrollment. An EIP staff member or local health department staff in each participating site will interview case-patients by telephone. Each site will attempt to enroll every patient within the designated age ranges that meets the EIP surveillance definition of a CA-CDI case. EIP or local health department staff will contact patients to determine study eligibility and, for those who are eligible, offer participation in the study.

Case Definition**:** A case of CA-CDI will be defined as a positive *C. difficile* specimen either by toxin or molecular assay collected as an outpatient or within 3 days after hospital admission in a surveillance area resident aged 1 to ≤ 5 years or ≥18 years who did not have a prior positive *C. difficile* assay and a documented overnight stay in a healthcare facility in the twelve weeks prior to specimen collection.

The numbers of CA-CDI cases by EIP site and age group is shown below.

CA-CDI Cases age ≥ 18 years by Month and EIP Site

	Month of Year											
Site	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
CA	19	24	30	20	24	24	22	26	31	19	17	26
CO	27	24	26	31	29	35	31	37	42	37	38	34
CT	27	26	39	40	29	25	32	23	41	30	33	33
GA	37	34	32	27	31	39	51	43	32	41	29	38
MD	32	33	49	35	33	29	39	30	35	31	38	48
MN	17	23	24	17	26	19	20	18	23	24	25	18
NM	19	20	18	27	28	27	22	19	41	33	34	33
NY	49	39	36	54	44	46	53	51	63	52	45	48
OR	2	1	2	2	2	4	2	2	1	5	1	2
TN	7	11	6	14	9	13	9	19	17	11	19	20

CA-CDI Cases in ages 1-5 years by EIP site and Month

	Month of Year											
Site	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
CA	2	1	-	1	-	1	-	-	-	3	-	-
CO	4	2	5	6	1	9	5	5	4	6	6	3
CT	1	-	2	-	3	1	-	3	2	-	-	1
GA	10	7	1	11	1	3	4	6	5	7	6	9
MD	-	1	2	5	5	1	1	4	1	1	2	2
MN	2	3	3	4	3	1	1	5	4	4	2	5
NM	1	-	-	3	2	-	1	-	2	-	-	3
NY	5	6	4	3	4	-	1	3	4	6	4	1
OR	-	-	1	-	-	-	-	-	-	-	-	-
TN	3	1	1	2	-	-	-	3	2	-	3	1

Eligible Case:

All residents aged 1 year to 5 years and ≥ 18 years in the surveillance areas with a positive *C. difficile* stool by either toxin or molecular assay and without documentation of a prior positive *C. difficile* assay will be eligible for investigation.

Inclusion Criteria for Cases:

1. An eligible CDI case**,** and
2. Stool specimen collected as an outpatient or within 3 days after admission, and
3. No report of overnight stay in a healthcare-facility during telephone interview

Each person can be enrolled as a case only once during the study period. A person enrolled as a case cannot serve as a control. In order to limit patient's difficulty in recalling exposures, patients will be interviewed as soon as possible after the illness is identified.

Exclusion Criteria for Cases:

1. Patient did not have a sample from which a positive *C. difficile* toxin assay or a positive *C. difficile* molecular assay was obtained, or
2. Ever reports a *C.difficile* diagnosis prior to the current specimen collection date, or
3. Had an overnight stay in a healthcare facility in the 12 weeks prior to specimen collection documented in the medical record or reported during interview, or
4. Is not in the age group of 1 year to 5 years and ≥ 18 years at the time of stool collection, or

5. Is not reachable after 8 unsolicited telephone attempts on at least 6 different dates using a valid telephone number. At least one attempt on a weekend and between 5-8 pm on a weekday should be made, or
6. Cannot be interviewed within 90 days after positive *C. difficile* stool collection date, or
7. Does not have a telephone number available, or
8. Does not speak either English or Spanish, or
9. Does not report diarrheal illness (at least 3 watery / loose stools in a 24 hour period) associated with the submission of the clinical specimen from which *C. difficile* was detected, or
10. Is deceased or incapacitated (i.e. a proxy will not answer for the case subject), or
11. Was not a resident of the EIP catchment area at the time of specimen collection, or
12. Does not provide informed consent to participating in the study, or
13. Is an inmate in a prison or other correctional facility.

Eligible Control

One control will be identified for each case included in the study. Eligible controls will be matched to cases by age group and gender and will be randomly selected from commercially available lists of residential telephone numbers or from birth registries (i.e. for subjects between 12 and 24 months of age) A person cannot serve as a control more than once in the study.

Inclusion criteria:

1. An eligible control, and

2. Resident of the EIP catchment area at the time of matched case's positive *C. difficile* stool collection, and
3. Age is within the same age- and gender-strata as the matched case-patient. The age strata are as follows:

CHILDREN AGE GROUP	**ADULT AGE GROUP**
12-23months	18–29 years
24-47months	30-39 years
48-60 months	40-49 years
	50-59 years
	60-69 years
	>70 years

Exclusion criteria:

1. Resides outside the EIP catchment area at the time of matched case's *C. difficile* specimen collection, or
2. Is not in the age group of 1 year to 5 years and ≥ 18 years at the time of matched case's stool collection, or
3. Is not reachable after 8 unsolicited telephone attempts on at least 6 different dates using a valid telephone number. At least one attempt on a weekend and between 5-8 pm on a weekday should be made,
4. Reports a history of *C. difficile* diagnosis, or
5. History of diarrhea (at least 3 watery / loose stools in a 24 hour period) during the 12 weeks prior to the matched case patients Illness Onset date/ Specimen Date, or

6. Reports an overnight stay in a healthcare facility in the 12-weeks prior to the specimen collection date / or onset of illness date of the matched case subject, or
7. Cannot be interviewed within 90 days after matched case's positive *C. difficile* stool collection date, or
8. Is deceased or incapacitated (i.e. a proxy will not answer for the control subject), or
9. Does not speak English or Spanish, or
10. Is an inmate in a prison or other correctional facility, or
11. Does not provide informed consent to participating in the study.

A patient may not serve as a control more than once in the study. We will attempt to enroll one age-matched control for each enrolled case. Age matching will be by the following six age strata: 12 months to 23 months, 24 months to 47months, and 48- 60 months; for adults: 18 to 29 years, 30 to 39 years, 40 to 49, 50-59,60-69, > 70 years. Once a case-patient has been interviewed, controls should be enrolled as soon as possible. Controls need to be enrolled no later than 90 days after the specimen collection date for their matched case-patient.

For the adult component of the study, we intend to enroll 142 subjects ≥ 18 years of age annually, 71 cases and 71 matched-controls. In order to reach our target annual enrollment, EIP staff will have to contact 129 potential cases and 142 potential controls per year. Based on previous EIP studies, we expect a 35% refusal rate and 10% ineligibility rate for cases, whereas for controls we expect a 45% refusal rate and 5% ineligibility rate. For the pediatric component of the study, we intend to enroll 156 subjects between 1 and 5 years of age annually, 78 cases and 78 matched-controls. In order to reach our target annual enrollment, the sites will have to contact 141 potential cases and 194 potential controls. Based on previous CDC's studies, we estimate a 35% refusal rate and a 10% ineligibility rate among cases, and, a 55% refusal rate and a 5% ineligible rate among controls. Data collection will take place over 36 months in order for

the EIP sites to reach the study targeted sample size of a total 426 subjects enrolled in the adult arm of the study and 468 in the pediatric arm of the study .

2. Procedures for the Collection of Information

EIP surveillance officers are employees of the State Health Department or state agents. This staff will receive training by CDC and the EIP study principal investigator in study methods, data security, and patient confidentiality. All staff will undergo necessary ethics training by participating institutions as required by local policies.

Over the 36-month study period, study personnel at each site will prospectively identify through routine CA- CDI surveillance eligible cases to be enrolled in the study. Cases and controls who meet study inclusion criteria and who provide verbal informed consent (refer to attachment E) will be interviewed. The Adult or Pediatric Phone Interview (refer to attachment F,G) will include details on outpatient healthcare visits, outpatient surgical procedures, outpatient antimicrobial exposures, emergency room visits, co-morbidities, and other medications. Data from these completed forms will be entered into a password protected database on a secure limited access server by the EIP site. No patient identifiers such as name, address, phone number, medical record number, or social security number will be sent to CDC.

Power Calculation:

A sample size calculation for a 1:1 matched case-control study was done using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). For the adult study group, a conservative sample size calculation was performed using a power of 0.80, an alpha of 0.05, and an estimated prevalence of exposure to infants in diapers in adult control-patients of 10.2% to detect a matched odds ratio of 2 for cases compared to controls. The exposure to infants in diapers was used as risk factor because prior studies have suggested that infants may serve as a source for CDI because their high *C. difficile* colonization rate. The estimated prevalence of exposure to infants in diapers was based on census household data for children less than 4 years of age present in homes (10.2%). Based on these numbers a total sample

size of 426 would be required (Table). For the pediatric study group, a conservative sample size calculation was performed using a power of 0.80, an alpha of 0.05, and a prevalence of gastric or jejunostomy (G-J) tubes in pediatric cases of 19% to detect a matched odds ratio of 2 for cases compared to controls. G-J tube usage was chosen as the variable of interest in children because previous studies on hospital-associated CDI have demonstrated an association with this method of feeding; the estimated prevalence in cases was noted in these studies.[1] Based on these numbers a total sample size of 468 would be required (Table). In order for us to reach the target samples, 36-months of data collection will be necessary; see Part A.

Table: Sample Size Calculations for Adult and Pediatric Study Groups

Study Group	Power	Alpha	Odds Ratio	Cases	Controls	Total
Adult	0.80	0.05	2	213	213	426
Pediatric	0.80	0.05	2	234	234	468

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

In order to maximize response rates EIP sites will attempt up to 8 phone contacts with cases and controls. These attempts will include weekends [Saturday 10am–8pm, Sunday 12pm–8pm] and weekdays [10am-8pm] in order to maximize the potential of reaching participants.

There will also be a small gift card ($20) for participants who complete the phone interview. This is intended to convey our appreciation for contributing to this important study.

Each participating site will track response rates among eligible case- and control-patients. Basic demographic information such as age, gender and race will be recorded for all eligible

subjects and used later to compare characteristics between respondents and non-respondents in order to test for any potential response bias.

4. Tests of Procedures or Methods to be Undertaken

To assess study feasibility and resources required for this prospective multi-site study, a pilot evaluation at one EIP site (Minnesota) will be performed in 8 case patients. Prior to launching the study, we will field an eight-case test of the phone interview instrument. This will be identical to the instrument that will be used in this study with the exception of a few additional questions to assess overall clarity of questions and respondent's opinions on any aspects of the interview that were not clear. The purpose of the pilot test will be twofold: (1) to assess ease of use of the forms for those conducting interviews, and (2) to identify areas of the interview that were either unclear or difficult to understand.

In addition, the development of the current interview questionnaire used lessons learned during the interview of CA-CDI cases under OMB# 0920-0892, expiration date: 07/31/2014 using a different questionnaire.

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:

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Data will be collected by EIP personnel, as described previously. Identification of the specific EIP surveillance officers who will participate in training and data collection activities is at the discretion of the participating EIP sites.

References

1. Sandora TJ, Fung M, Flaherty K, et al. Epidemiology and risk factors for Clostridium difficile infection in children. The Pediatric infectious disease journal 2011;30:580-4.