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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The Centers for Disease Control and Prevention (CDC) is requesting OMB approval of a new data collection, Risk Factors for Community-Associated *Clostridium difficile* Infection through the Emerging Infections Program

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A. Justification

1. Circumstances Making the Collection of Information Necessary

Background

The Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion (DHQP), in collaboration with state public health authorities, plans to assess risk factors for community-associated *Clostridium difficile* infection through the CDC's Emerging Infections Program (EIP) and is submitting a new information collection request for a three-year data collection period.

Clostridium difficile is an anaerobic, spore-forming, gram positive bacillus that produces two pathogenic toxins: A and B. *C. difficile* infection (CDI) ranges in severity from mild diarrhea to fulminant colitis and death.[1] Transmission of C. *difficile* occurs primarily in healthcare facilities as environmental contamination by *C. difficile* spores combined with patient exposure to antimicrobial drugs creates an opportunity for infection. Traditional risk factors for CDI include antibiotic use, advanced age, and prior hospitalization.[2] CDI increasingly has been reported among young, healthy individuals residing in the community without traditional CDI risk factors.[3-6] Community-associated CDI is estimated to represent 32% of all CDI based on population-based figures from the Emerging Infections Program, [5,7,8] with an incidence of 30-40 per 100,000 population in the United States[5] . Previous reports have shown approximately 40% of patients acquiring community-associated CDI (CA-CDI) were not exposed to antibiotics,[3-6] suggesting that additional factors may contribute to infections. Other factors such as proton pump inhibitors have been raised as a risk factor for CDI in the community and on February 8, 2012 the U.S. Food and Drug Administration issued a communication advising physicians to consider the diagnosis of CDI among patients taking proton pump inhibitors. However, the data on the association of CDI with proton pump inhibitors are still controversial and studies to quantify this association are needed. In addition to the understanding of the factors that

predispose patients to CDI, further evaluation of potential C. *difficile* exposure sources in the community is necessary to guide prevention efforts.

The sources of *C. difficile* and the risks for developing CDI in previously thought to be low-risk community populations are not well defined. Although initial evaluation of only CA-CDI cases involving telephone interviews (OMB# 0920-0892, expiration date: 07/31/2014) raised several hypotheses of potential risk factors for CDI in the community (e.g., outpatient healthcare exposures, infants in the home, and proton pump inhibitor use) the magnitude of association of these risks with disease development using a control population has not been evaluated to date. [5,6,9,10] Because *C. difficile* exposure sources and risks may vary by age, we propose to conduct a matched case-control study for pediatric (i.e., 1-5 years of age) and adult (i.e., ≥ 18 years of age) populations through the Emerging Infections Program sites (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) to identify which factors put the patient at risk for CDI in the community and Can be prevented. Section 301 of the Public Health Service Act (42 U.S.C 241) authorizes the collection of these data (Attachment A).

1.1Privacy Impact Assessment

Overview of the Data Collection System

EIP staff will contact case- and control-patients for a telephone interview and collect data on paper forms. Both case- and control-patients will be initially screened for eligibility using screening questions (Attachment C, D) after verbal consent is provided (Attachment E) and, if eligible for inclusion in the study, a full adult or pediatric interview (Attachment F,G) will be performed. Data will then be entered into a password protected database on a secure limited access server, and will be destroyed 3 years after the study completion. No patient identifiers such as name, address, or phone number will be sent to CDC.

Items of Information to be collected

Information transmitted to CDC may include: state, county of residence, age, gender, race/ethnicity, medications, outpatient healthcare visits, outpatient surgical procedures, outpatient antimicrobial exposures, and food preferences (Attachment F,G). Information in identifiable Form (IIF) in the form of name, mailing address, and phone number will be collected by collaborators as part of their state health department routine activities but removed prior to data transmission to CDC. Names or other personal identifying information are not collected by CDC on data abstraction forms. There are no personal identifiers submitted to CDC for any of the forms included in this package.

2. Purpose and Use of Information Collection

The information collected will be used by CDC to identify modifiable risk factors that put patients at increased risk for developing CA-CDI . The understanding of these risk factors will inform the development of prevention strategies to reduce the burden of *C. difficile* in the community, through the Emerging Infections Program sites (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee), which is estimated to be 150,000 infections per year based on the CDC's CDI population-based surveillance data. Currently there are no guidelines on prevention of *C. difficile* in the community and this will be the first study to explore how CA-CDI can be prevented. The CDI surveillance through the CDC's Emerging Infections Program provides a unique platform to conduct this study given that all *C. difficile* positive specimens from the population under surveillance are being captured. Targeted Prevention measures to be informed by this study will be applied by outpatient healthcare providers and by persons in the community in order to improve the health and safety of the American population. This activity supports the HHS Action Plan to Combat Antimicrobial Resistance (http://www.cdc.gov/drugresistance/pdf/action-plan-2012.pdf) and CDC's Get Smart Program on Appropriate Antibiotic Use (http://www.cdc.gov/getsmart/campaign-materials/about-campaign.html).

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2.1 Privacy Impact Assessment

The information is being collected to better understand the clinical and epidemiologic characteristics of patients who developed CA-CDI and to identify modifiable risk factors for CA-CDI. The data will benefit public health by identifying prevention targets for a disease with high morbidity and which poses treatment challenges. The data will be analyzed after the study is complete and the results will be shared in scientific presentations and publications to stakeholders.

No Information in Identifiable Form (IIF) will be sent to CDC. CDC partners (i.e. EIP staff) will collect IIF about participants consistent with their usual local and state public health mandates for surveillance, and, therefore, there is a potential effect on the patients' privacy if there were a breach of security. In an effort to prevent a breach of security, project paperwork maintained by each participating site will never be submitted to CDC and will remain in a locked, secure location, available only to a minimum number of local project staff, and will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted. Each participating EIP site will destroy identifiers within 3 years after the completion of the study. IIF of any type will not be shared outside of EIP personnel.

3. Use of Improved Information Technology and Burden Reduction

This study will use paper data collection forms. Data collected through telephone interview onto these forms will then be entered into a password protected database on a secure limited access server by the EIP personnel. The information transferred to CDC will be destroyed 3 years after the study completion. A web-based interview was not feasible or possible in this study for several reasons: (1) EIP sites do not collect e-mail information on their CA-CDI cases, (2) The study requires age-matched control participants to be selected from the same county as case patients; available commercial services (Knowledge Network™) were explored and cannot reliably generate age-matched controls within the given counties in adequate numbers to reach estimated sample sizes. In addition, the types of health-related questions asked may require clarification that can only be given by an interviewer and are not

amendable to an electronic survey. In accordance with the Government Paperwork Elimination Act (GPEA), Public Law 105-277, all means to maintain records electronically have been taken.

4. Efforts to Identify Duplication and Use of Similar Information

Essential steps in reducing the occurrence of community-associated CDI include quantifying the burden and identifying modifiable risk factors associated with infection. The current EIP CDI surveillance has been essential to quantify the burden of CDI in the United States. CA-CDI risk factors have not been well evaluated and effective prevention measures in this population remain uncertain. There is not current available data that quantifies CA- CDI risk factors in adults and children. Because EIP CDI is a longitudinal surveillance system and includes multiple partners in different states, it represents a unique system to capture *C. difficile* infections that occur in the community, as opposed to those that occur during hospitalization, across a variety of geographic locations.

The information collected as part of OMB# 0920-0892, expiration date, 07/31/2014 was used to generate hypotheses of potential risk factors for CA-CDI and to inform the development of the telephone interview questionnaire for the proposed study, which will include persons with and without *C. difficile* infection.

EIP staff routinely attend local, national, and international conferences relevant to the pathogens of interest and communicates frequently with non-federal colleagues at universities and health departments, as well as colleagues within the government in order to prevent duplication of effort.

5. Impact on Small Businesses or Other Small Entities

This study will unlikely impact small business or entities as only individual people will be participating in the study and the burden of data collection will be on the surveillance officers appointed by the states.

6. Consequences of Collecting the Information Less Frequently

EIP personnel will complete data collection on cases as they are identified from laboratory reports on an ongoing basis; age-matched controls will be interviewed as soon as possible once a case is identified. Each study participant will complete only one survey. Performing data collection on cases and controls as they are identified (versus a quarterly or annual basis) is essential to avoid recall bias. The study's validity depends on the ability of cases and controls to recall exposures that may have occurred, in certain cases, months prior to the phone interview. Ongoing interviews will limit the issues with distant recall of necessary information.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

There are no special circumstances that require the information to be collected in any of the formats identified, and the request fully complies with regulations.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A. A 60-day Federal Register Notice was published in the *Federal Register* on September 4, 2013, Vol. 78, No. 171, p. 54472 (Attachment B). No public comments were received.

B. The following representatives were consulted during the development of the study methods and data collection instruments. All of the following contacts were contacted several times between March 2013 and July 2013.

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9. Explanation of Any Payment or Gift to Respondents

Upon completion of the interview, respondents will be sent a $20 gift card as a token of appreciation. Previous research has demonstrated that such tokens can enhance response rate especially in populations that may not have motivation to otherwise participate.[11,12] In our study, we are recruiting healthy controls that, unlike patients affected by a disease or condition, do not have motivation to engage in a telephone interview that require 30 minutes of their time. Furthermore, studies at CDC have successfully used such tokens of appreciation to increase participation given healthy controls have been shown to be hard to recruit.[13] Examples of CDC's studies that have used gift cards as a way to increase response rates include the "Risk Factors for Invasive Methicillin-resistant Staphylococcus aureus (MRSA) among Patients Recently Discharged from Acute Care Hospitals" (OMB#0920-0958; expiration date: 3/31/2015). Increasing response rate makes the study more cost effective to the government and less burdensome to the public because it decreases the number of contacts that need to be made with the public in order to achieve the target sample size. CDC will purchase these gift cards and send them to the sites to distribute to the cases and controls who were interviewed. Many of study patients are hard-to-reach and multiple attempts may be required. The amount proposed is not of such a magnitude to interfere with voluntary participation. A Thank You letter with the gift card will be sent to respondents.

10. Assurance of Confidentiality Provided to Respondents

This information collection request has been reviewed by the Information Collection Review Office (ICRO), who has determined that the Privacy Act does not apply as information submitted to CDC will not include IIF. Data will be treated in a secure manner, unless otherwise compelled by law. A unique identifier will be assigned to each patient to allow the reporting EIP site to link reported data back to the individual patient, however this link will not be shared with CDC. Sex, age, and race/ethnicity data will be transmitted to CDC; no other patient identifiers will be transmitted to CDC. The data management system is kept in a CDC secure limited access server.

IRB Approval

The risk factor study protocol to assess risk factors for community-associated *C. difficile* has been approved by CDC's IRB (Attachment H, I). The protocol was reviewed in accordance with the expedited review process outlined in 45 CFR 46.110(b)(1), categories 5 and 7. The IRB approved the inclusion of pregnant women under 45 CFR 46.204, Subpart B. The IRB determined that the study poses no greater than minimal risk to subjects.

10.1 Privacy Impact Assessment Information

Participation in this project is voluntary and study participants can stop the interview at any point during the interview process; they will be informed of this during the consent process. In addition, participants can refuse to answer any of the questions in the interview. Persons contacted for interview will be asked to provide a verbal consent (Attachment E in English; Attachment L in Spanish). Patients eligible for the telephone interview will be initially screened using case or control screening questions (Attachment C in English, Attachment J in Spanish, Attachment D in English, Attachment K in Spanish) to confirm eligibility. Only those subjects confirmed to be eligible to be included in the study based interview screening question will

proceed to the full adult (Atachment F in English, Attachment M in Spanish) or pediatric telephone interview (Attachment G in English, Attachment N in Spanish).

Project paperwork maintained by each participating site will remain in a locked, secure location, available only to a minimum number of local project staff, and will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the surveillance project, or for other research for which the use or disclosure of protected health information would be permitted. Each participating EIP site will destroy identifiers at the earliest opportunity, unless there is a public health or research justification for retaining the identifiers or as required to by law. Information received by CDC will also be stored in a secure, password-protected database. Information received by CDC will be provided only to those individuals at CDC with a need to know.

This information collection request has been reviewed by NCEZID who has determined that the Privacy Act does not apply. Information submitted to CDC will not include names or individually identifying numbers (such as Social Security Numbers). Patients included in the study will be assigned unique identification codes; these codes will not contain identifying information. Personal identifiers will not be transmitted to CDC.

11. Justification for Sensitive Questions

Epidemiological and clinical characteristics such as age, race, sex, geographic location, healthcare exposures, and comorbidities are likely associated with CA-CDI. The collection of these data is critical to public health in order to identify risk factors for disease that should be targeted for prevention efforts. Clinical and epidemiologic data are collected and analyzed with the purpose of contributing valuable knowledge to the field of public health. Social Security Numbers will not be collected in this study. As discussed in item A.10 above, participating individual’s privacy will be treated in a secure manner, unless otherwise compelled by law.

12. Estimates of Annualized Burden Hours and Costs

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 . We anticipate the screening questions to take about 5 minutes and the telephone interview 30 minutes per respondent in both the adult and pediatric groups. There is no reliable way to estimate how many people may be Spanish speaking but the instruments have been translated into Spanish if needed (Attachments J-N). For C. difficile the majority of cases will be non-Hispanic Caucasian just based on the epidemiology of the disease, but we cannot foresee how many control enrollments may be Spanish speaking- we are not matching on language. Also, we cannot predict how many Spanish speaking people would enroll and complete the form as we are not targeting to enroll a certain number of Spanish speakers. The forms are exactly the same – just translated into Spanish. They will take the same amount of time to complete as the English versions as a Spanish speaker will be performing the interview. Table 12-A provides details about the annualized burden and how the estimated annual burden of 201 hours was calculated.

Table 12-A. Estimated Annualized Burden Hours

Type of Respondents (adult and pediatric)	Form Name	Number of Respondents	Number of Responses per Respondent	Average Burden per Response (in hours)	Total Burden (in hours)
Case Subjects≥ 18 years of age	Screening Process	129	1	5/60	11
	Telephone interview	71	1	30/60	36
Control Subjects ≥ 18 years of age	Screening Process	142	1	5/60	12
	Telephone interview	71	1	30/60	36
Case Subject 1-5 years of age	Screening Process	141	1	5/60	12
	Telephone interview	78	1	30/60	39
Control Subjects 1-5 years of age	Screening Process	194	1	5/60	16
	Telephone interview	78	1	30/60	39
Total					201

–B. The total cost burden for respondents is estimated as follows: With a total annual burden of 201 hours, the total cost of the time to respond to the proposed study is estimated to be $4,424.01 (Table B). We used the 2012 mean average hourly wage for all occupations in the United States. This wage of $22.01 was obtained from the Bureau of Labor Statistics (http://www.bls.gov/oes/current/oes_nat.htm).

Table B: Annualized cost to respondents

Type of Respondents	Form name(s)	Total Burden Hours	Hourly Wage Rate	Total Respondent Cost
All cases and controls (adult and pediatric)	Screening and Interview	201	$22.01	$4,424.01

13. Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers

None.

14. Annualized Cost to the Government

Costs to the government include costs for surveillance officers (epidemiologists) to develop and coordinate study activities at CDC, costs for the EIP personnel to perform local study coordination and data collection, costs for a database manager, costs for photocopying data collection forms, and costs for local principal investigators to participate on regular conference calls, update IRB approvals, and ensure study progress. The costs for the government related to this study are depicted on the table below.

The data collection forms that will be completed by EIP personnel are included in attachments G, and H. Collection of data on attachments G and H will occur in a total of 298 patients annually and is estimated to take approximately 30 minutes per patient. Therefore, a total of 149 hours of work to abstract data on attachments F and G will be required annually.

There will also be costs related to photocopying of study forms and instructions at each participating site.

Table 14-1: Estimates of Annualized Costs to the Federal Government

Expense Type	Expense Explanation	Annual Costs (dollars)
Direct Costs to the Federal Government		
CDC surveillance epidemiologist (0.5 FTE)	Develop the protocol, data collection forms, training. Assist with data entry and analysis	25,764
Database manager (0.25 FTE)	Create and maintain data management system	10,000
	Subtotal, Direct Costs to the Government	35,764
Cooperative Agreement	Identification of eligible study participants, interview of participants using attachments F and G, data entry, and participation on conference calls, and submission of study protocol to local IRBs.	
	California Site Cost and Fees	22,000
	Colorado Site Cost and Fees	15,000
	Connecticut Site Cost and Fees	25,000
	Georgia Site Cost and Fees	30,000
	Maryland Site Cost and Fees	12,000
	Minnesota Site Cost and Fees	20,000
	New Mexico Site Cost and Fees	14,000
	New York Site Cost and Fees	30,000
	Oregon Site Cost and Fees	7,000
	Tennessee Site Cost and Fees	20,000

	Subtotal, Contracted Services	195,000
	TOTAL COST TO THE GOVERNMENT	230,764

15. Explanation for Program Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

CDC will provide each surveillance area with several forms of feedback including data integrity checks, patient enrollment, and summary tables. Specifically, data from multiple sites will be concatenated approximately 3 weeks after receipt at CDC.

Statistical analysis will be performed at CDC, with input of co-investigators, using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). Matched odds ratios (mOR) and *P* values will be calculated for univariate and multivariate analysis using conditional logistic regression. Variables from univariate analysis with a *P* value <0.20 will be included as candidates for the risk model. Multivariate analysis using stepwise conditional logistic regression will be performed to identify independent risk factors. A two-sided *P* value of < 0.05 will be considered statistically significant.

Results from this study will be presented at national meetings and published in a manuscript format in a peer-reviewed medical science journal. Conference abstract and manuscript will be developed as appropriate to disseminate the findings of this project.

The study will begin as soon as possible following OMB approval. This is a prospective study and based on a sample size calculation a total of 468 pediatric subjects (234 cases and 234 controls) and 426 adult subjects (213 cases and 213 controls) should be enrolled. Therefore, the

study should be completed in approximately 36 months based on the estimated annual numbers of cases.

Table D: Project Time Schedule

Activity	Time Schedule
Conduct Phone interviews	1-2 months after OMB approval
Begin transmission of data to CDC	3-4 months after OMB approval
Complete all phone interviews	36 months after OMB approval
Complete data transmission to CDC	36-38 months after OMB approval
Analysis and presentation of results	38-40 months after OMB approval

17. Reason(s) Display of OMB Expiration Date is Inappropriate

The proposed survey instrument will display the expiration date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

No exceptions to certification are requested.

List of Attachments

A:	Public Health Service Act
B:	Federal Registry Notice
C:	Screening Questionnaires- Adult
D:	Screening Questionnaires- Pediatric
E:	Verbal Consent- with and without HIPPA language
F:	Adult Interview form
G:	Pediatric Interview Form
H:	IRB protocol
I:	IRB approval letter for the CA CDI Study
J:	Spanish Version Screening Questionnaires- Adult
K:	Spanish Version Screening Questionnaires- Pediatric
L:	Spanish Version Verbal Consent- with and without HIPPA language
M:	Spanish Version Adult Interview Form
N:	Spanish Version Pediatric Interview Form

References

1. Kuijper EJ, Coignard B, Tull P, et al. Emergence of Clostridium difficile-associated disease in North America and Europe. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2006;12 Suppl 6:2-18.
2. Bartlett JG. Historical Perspectives on Studies of Clostridium difficile and C. difficile Infection. Clinical Infectious Diseases 2008;46:S4-S11.
3. Centers for Disease C, Prevention. Severe Clostridium difficile-associated disease in populations previously at low risk--four states, 2005. MMWR Morbidity and mortality weekly report 2005;54:1201-5.
4. Centers for Disease C, Prevention. Surveillance for community-associated Clostridium difficile--Connecticut, 2006. MMWR Morbidity and mortality weekly report 2008;57:340-3.
5. Kutty PK, Woods CW, Sena AC, et al. Risk factors for and estimated incidence of community-associated Clostridium difficile infection, North Carolina, USA. Emerging infectious diseases 2010;16:197-204.
6. Kuntz JL, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM. Incidence of and risk factors for community-associated Clostridium difficile infection: a nested case-control study. BMC infectious diseases 2011;11:194.
7. Karlstrom O, Fryklund B, Tullus K, Burman LG. A prospective nationwide study of Clostridium difficile-associated diarrhea in Sweden. The Swedish C. difficile Study Group. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1998;26:141-5.
8. Centers for Disease C, Prevention. Vital signs: preventing Clostridium difficile infections. MMWR Morbidity and mortality weekly report 2012;61:157-62.
9. Stevens V, van Wijngaarden E. Proton pump inhibitor use may be associated with an increased risk of Clostridium difficile infection. Evidence-based medicine 2012.
10. Chitnis AS, Holzbauer SM, Belflower RM, et al. Epidemiology of Community-Associated Clostridium difficile Infection, 2009 Through 2011. JAMA internal medicine 2013:1-9.
11. Singer E. The use of incentives to reduce nonresponse in household surveys. Survey nonresponse 2002:163-77.
12. Singer E, Nancy Gebler, Trivellore Raghunathan, John Van Hoewyk, and Katherine., McGonagle. The Effect of Incentives in Interviewer-Mediated Surveys. Journal of Official Statistics 1999;15:217-30.
13. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of Controls in Case-Control Studies: II. Types of Controls. American Journal of Epidemiology 1992;135:1029-41.