ORIGINAL ARTICLE

Recommendations for Surveillance of *Clostridium difficile*–Associated Disease

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BACKGROUND. The epidemiology of *Clostridium difficile*–associated disease (CDAD) is changing, with evidence of increased incidence and severity. However, the understanding of the magnitude of and reasons for this change is currently hampered by the lack of standardized surveillance methods.

OBJECTIVE AND METHODS. An ad hoc *C. difficile* surveillance working group was formed to develop interim surveillance definitions and recommendations based on existing literature and expert opinion that can help to improve CDAD surveillance and prevention efforts.

DEFINITIONS AND RECOMMENDATIONS. A CDAD case patient was defined as a patient with symptoms of diarrhea or toxic megacolon combined with a positive result of a laboratory assay and/or endoscopic or histopathologic evidence of pseudomembranous colitis. Recurrent CDAD was defined as repeated episodes within 8 weeks of each other. Severe CDAD was defined by CDAD-associated admission to an intensive care unit, colectomy, or death within 30 days after onset. Case patients were categorized by the setting in which *C. difficile* was likely acquired, to account for recent evidence that suggests that healthcare facility–associated CDAD may have its onset in the community up to 4 weeks after discharge. Tracking of healthcare facility–onset, healthcare facility–associated CDAD is the minimum surveillance required for healthcare settings; tracking of community-onset, healthcare facility–associated CDAD should be performed only in conjunction with tracking of healthcare facility–onset, healthcare facility–associated CDAD. Community-associated CDAD was defined by symptom onset more than 12 weeks after the last discharge from a healthcare facility. Rates of both healthcare facility–onset, healthcare facility–associated CDAD and community-onset, healthcare facility–associated CDAD should be expressed as case patients per 10,000 patient-days; rates of community-associated CDAD should be expressed as case patients per 100,000 person-years.

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Clostridium difficile is an anaerobic, spore-forming bacillus that is responsible for a spectrum of *C. difficile*–associated disease (CDAD), including uncomplicated diarrhea, pseudomembranous colitis, and toxic megacolon, which can, in some instances, lead to sepsis and even death.[1] *C. difficile* is the most commonly recognized cause of diarrhea in hospitalized patients; it has been recommended that patients who develop diarrhea more than 3 days after admission be tested only for *C. difficile* as the possible infectious etiology for their symptoms.[2] The main modifiable risk factor for CDAD is antimicrobial use, which increases risk through an alteration in the patient's normal lower-intestinal flora and, in some instances, also selects for highly antimicrobial-resistant strains of *C. difficile*.[3] It is thought that the alteration in the complex ecology of the large bowel provides *C. difficile* an opportunity to thrive and produce disease.[1]

Recent increases in CDAD incidence and severity[4-8] have highlighted the need for standardized reporting definitions and surveillance methods.[8-10] CDAD surveillance can serve several purposes. Currently, the primary purposes, from a public health standpoint, are to guide the implementation of interventions to control CDAD in healthcare facilities (HCFs) and to monitor the impact of such interventions. These purposes may be achieved by detecting outbreaks and disease trends in individual HCFs and by comparing CDAD rates among similar institutions. To properly make such comparisons, standardized case definitions are needed. Additional public health purposes of CDAD surveillance include understanding the emergence of community disease, severe or recurrent, and disease in previously low-risk populations.

Much of the science pertaining to CDAD surveillance, both inside and outside HCFs, is still in its infancy and is evolving rapidly, as the changing epidemiology unfolds. This article is intended to put forth interim recommendations for surveillance, including case definitions. These recommendations primarily address CDAD surveillance for inpatient healthcare

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settings but also include recommendations for community settings. Thus, the intended audience of this article includes state and local public health authorities, in addition to HCF personnel responsible for infection surveillance and control.

DEFINITIONS

An HCF is defined as any acute care, long-term care, long-term acute care, or other facility in which skilled nursing care is provided and patients are admitted at least overnight.

A CDAD case is defined as a case of diarrhea (ie, unformed stool that conforms to the shape of a specimen collection container) or toxic megacolon (ie, abnormal dilation of the large intestine documented radiologically) without other known etiology that meets 1 or more of the following criteria: (1) the stool sample yields a positive result for a laboratory assay for *C. difficile* toxin A and/or B, or a toxin-producing *C. difficile* organism is detected in the stool sample by culture or other means; (2) pseudomembranous colitis is seen during endoscopic examination or surgery; and (3) pseudomembranous colitis is seen during histopathological examination. The CDAD case definition may be implemented for laboratory-based reporting systems by focusing only on criterion 1, if the laboratory routinely performs tests for *C. difficile* only on unformed stools.

A recurrent CDAD case is defined as an episode of CDAD (ie, one that meets the criteria for a CDAD case) that occurs 8 weeks or less after the onset of a previous episode, provided that CDAD symptoms from the earlier episode resolved with or without therapy. The recurrent CDAD case definition may be implemented for laboratory-based reporting systems on the basis of the following stipulations: (1) an additional positive result of a laboratory test performed on a specimen collected 2 weeks or less after the last specimen that tested positive represents continuation of the same CDAD case, (2) an additional positive result of a laboratory test performed on a specimen collected 2-8 weeks after the last specimen that tested positive represents a recurrent CDAD case, and (3) an additional positive result of a laboratory test performed on a specimen collected more than 8 weeks after the last specimen that tested positive represents a new CDAD case.

A case patient with severe CDAD is defined as a case patient who meets any of the following criteria within 30 days after CDAD symptom onset (or, in the case of laboratory-based reporting, within 30 days after the index laboratory test): (1) history of admission to an intensive care unit for complications associated with CDAD (eg, for shock that requires vasopressor therapy); (2) history of surgery (eg, colectomy) for toxic megacolon, perforation, or refractory colitis; and (3) death caused by CDAD within 30 days after symptom onset (eg, as listed on the death certificate or recorded in the medical record by a clinician caring for the patient).

CDAD case patients are further defined by their exposures (Figure), as follows.

1. A patient classified as having HCF-onset, HCF-associated CDAD is defined as a patient with CDAD symptom onset more than 48 hours after admission to an HCF.
2. A patient classified as having community-onset, HCF-associated CDAD is defined as a patient with CDAD symptom onset in the community or 48 hours or less after admission to an HCF, provided that symptom onset was less than 4 weeks after the last discharge from an HCF.
3. A patient classified as having community-associated CDAD is defined as a patient with CDAD symptom onset in the community or 48 hours or less after admission to an HCF, provided that symptom onset was more than 12 weeks after the last discharge from an HCF.
4. A patient classified as having indeterminate disease is defined as a CDAD case patient who does not fit any of the above criteria for an exposure setting—for example, a patient who has CDAD symptom onset in the community but who was discharged from the same or another HCF 4-12 weeks before symptom onset.
5. A patient classified as having unknown disease is a CDAD case patient for whom the exposure setting cannot be determined because of lack of available data—for example, a patient who has CDAD symptom onset in the community or 48 hours or less after HCF admission and for whom available medical records are not sufficient to exclude discharge from an HCF 12 weeks or less before symptom onset.

SURVEILLANCE RECOMMENDATIONS

Use of the Definitions

Depending on the purposes of surveillance, all or only some of the above case definitions may be appropriate for use. For example, if the sole purpose is to track and compare HCF-associated CDAD, indeterminate cases may not need to be differentiated from community-associated CDAD cases; instead, both indeterminate and community-associated CDAD could be reported in aggregate or not reported at all. If the

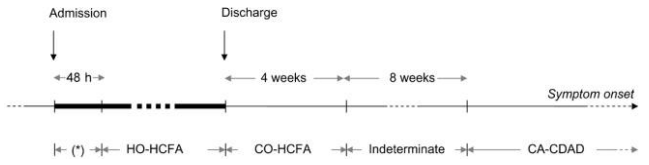

FIGURE. Time line for definitions of *Clostridium difficile*–associated disease (CDAD) exposures. Case patients with symptom onset during the window of hospitalization marked by an asterisk (*) would be classified as having community-onset, healthcare facility–associated disease (CO-HCFA), if patient was discharged from a healthcare facility within the previous 4 weeks; would be classified as having indeterminate disease, if the patient was discharged from a healthcare facility between the previous 4-12 weeks; or would be classified as having community-associated CDAD (CA-CDAD), if the patient was not discharged from a healthcare facility in the previous 12 weeks. HO-HCFA, healthcare facility–onset, healthcare facility–associated CDAD.

purpose is only to track new incident cases, reporting of recurrent cases may not be necessary (ie, use of an 8-week "lock out" period during which a patient cannot be classified as a case patient again). Finally, if the purpose is only to track disease trends in the community, only community-associated CDAD cases need to be reported.

Use of the HCF-Onset, HCF-Associated Definition Versus the HCF-Onset, HCF-Associated and Community-Onset, HCF-Associated Definitions Combined

The decision to report community-onset, HCF-associated cases in addition to HCF-onset, HCF-associated cases should be made by HCFs and surveillance systems on the basis of their ability to categorize cases correctly and the capacity of the reporting infrastructure. The scientific background and rationale for including community-onset, HCF-associated cases is provided in the Appendix. However, there are additional principles that should be considered for use of the HCF-onset, HCF-associated case definition alone or in combination with the community-onset, HCF-associated case definition.

1. If interfacility comparisons are to be made, they should be made using only the same definitions (ie, the HCF-onset, HCF-associated case definition alone or in combination with the community-onset, HCF-associated case definition).
2. Community-onset, HCF-associated cases should be attributed to the reporting period during which the case patient was discharged from the HCF before CDAD symptom onset. For example, if a patient was discharged on June 25 and was readmitted with CDAD on July 12, the case should be assigned to June. Because of the need to assign community-onset, HCF-associated cases to the previous inpatient stay, HCFs and surveillance systems that choose to use this definition should make allowance for a 1-2 month delay in finalizing case numbers and rates for the reporting period.
3. Community-onset, HCF-associated cases should be attributed to the HCF from which the patient was last discharged, providing the patient was an inpatient of that HCF for more than 48 hours. In essence, inclusion of community-onset, HCF-associated cases in CDAD reporting is a form of postdischarge surveillance that, for success in most surveillance systems, assumes that the majority of patients who develop symptoms of CDAD soon after discharge return to the same HCF for care. However, it is anticipated that some surveillance systems could also successfully track community-onset, HCF-associated case patients discharged from different HCFs by identifying the HCF from which the patient was last discharged in the case report. If this is possible, another category could be assigned for such case patients—namely, patients with community-onset, HCF-associated from another facility CDAD. A name or identifier of the other facility from which the patient was last discharged may also be reported in some systems.
4. Reporting of community-onset, HCF-associated cases should only be performed in addition to reporting of HCF-onset, HCF-associated cases; rates of each type of case should be calculated and tracked independently. The rate of HCF-onset, HCF-associated cases is considered the minimum surveillance required for healthcare settings. Tracking and feedback of each rate independently will allow comparison of rates of HCF-onset, HCF-associated CDAD with data from HCFs and surveillance systems that do not track rates of community-onset, HCF-associated CDAD.

Denominators for and Expression of CDAD Rates

Rates of HCF-onset, HCF-associated cases and rates of community-onset, HCF-associated cases should be expressed, for feedback and comparative purposes, as case patients per reporting period (ie, per month, for most HCFs and surveillance systems) per 10,000 patient-days. The calculation of this rate is [number of case patients per reporting period / number of inpatient days per reporting period] × 10,000 = rate per 10,000 inpatient-days.

Because this rate reflects the per-day patient risk of *C. difficile* transmission and disease risk factors (eg, antimicrobial exposures), it is the most useful across different types of HCFs with varying average lengths of patient stay. These rates are also useful for comparison of disease incidence between wards or units within an HCF in which such ward- or unit-specific denominators are available.

For those systems designed to track community-associated CDAD, rates should be calculated and expressed as case patients per 100,000 population during the reporting period (ie, usually person-years). Rates of severe CDAD should be expressed as a percentage of the CDAD cases that occurred during the reporting period along with the absolute number of severe cases.

Additional Recommendations

Cases may be reported either as individual events or in aggregate as the count of cases per reporting period, along with recommended denominator data. Individual case reports offer the opportunity to collect additional data that could allow future refinement of case definitions, answer important research questions, or suggest the underlying risk of CDAD in different patient populations (eg, to determine the age distribution of case patients). It may also be useful to collect HCF-level data on a periodic basis. For example, the type of diagnostic test(s) used, the volume of tests ordered, the number of prescriptions of oral metronidazole and vancomycin, the overall antimicrobial use in the HCF, and the age distribution of the patient population. Although possibly too burdensome to collect on an ongoing basis, these data could assist in the creation of more-meaningful comparisons of rates.

CONCLUSIONS

In summary, although the data to support the above-outlined definitions are far from complete, early evidence suggests that these definitions may help to direct surveillance and reporting

initiatives. Additional studies are urgently needed to answer several questions. For example, what proportion of probable CDAD cases are currently diagnosed and treated empirically and, therefore, will not fulfill the laboratory, endoscopic, or histopathologic criteria outlined above? Although the experience at one hospital suggests that 1% of cases or fewer are diagnosed using the endoscopic or histopathologic criteria,[11] it is unknown whether, in some hospitals, these criteria are necessary to capture most cases.[12] Are there significant differences in CDAD rates, depending on the diagnostic tests and the testing algorithms used? Do rates based on HCF-onset, HCF-associated cases alone correlate with rates based on HCF-onset, HCF-associated cases and community-onset, HCF-associated cases combined across a number of HCFs? Can typing of *C. difficile* strain be used to better define the epidemiology of CDAD cases occurring soon after discharge from HCFs? Even before these questions can be answered, it is expected that the principles set forth here will improve methods for surveillance and will lead to a better understanding of how best to prevent *C. difficile* transmission and the development of CDAD.

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APPENDIX

RATIONALE FOR REPORTING COMMUNITY-ONSET, HCF-ASSOCIATED CDAD IN ADDITION TO HCF-ONSET, HCF-ASSOCIATED CDAD

Inpatient stay in an HCF is a recognized risk factor for CDAD. For example, recent reports suggest that rates of CDAD in acute care facilities range from 3 to 25 case patients per 10,000 patient-days, with most rates for facilities where CDAD is endemic being between 5 and 10 case patients per 10,000 patient-days.[10,13-15] In contrast, rates of CDAD among persons living in the community without recent healthcare contact are 8-25 case patients per 100,000 person-years.[16-19] Although some reports suggest that the risk of CDAD among patients without recent HCF exposure may be increasing,[20,21] the majority of CDAD cases still involve persons with ongoing or recent HCF exposure.[9,21-24] One study showed that, whereas the risk of developing CDAD was 1,300-fold greater in acute care facilities than in the community, the density of antimicrobial usage was only 37-fold greater in acute care facilities.[19] Although some of this increased risk in HCFs is related to the advanced age of patients, the severity of illness, and the types of antimicrobials used, it also points to the propensity for persons to be newly exposed to *C. difficile* organisms in HCFs, where there is a concentration of symptomatic patients with CDAD.[25]

In addition to an increased risk of CDAD, HCF exposure is associated with an increased risk of *C. difficile* colonization. Rates of asymptomatic colonization with *C. difficile* range from 7% to 11% among asymptomatic adult inpatients of acute care facilities[25,26] and from 5% to 7% among elderly patients in long-term care facilities.[27,28] In at least 2 studies, the risk of colonization was shown to increase during hospitalization, suggesting a cumulative daily risk of exposure to the healthcare environment.[25,29] Although 2 recent reports from Japan suggest that rates of carriage among asymptomatic adults without recent HCF exposure may be higher than previously thought,[30,31] these studies either involved culture of specimens from the same patient on multiple occasions, suggesting transient colonization,[30] or involved the use of newly developed molecular methods that have not been similarly applied to patients in HCFs.[31] Historically, rates of carriage among asymptomatic adults without recent HCF exposure were found to be generally less than 2%.[32,33] A recent study involving infants and very young children, in whom rates of asymptomatic carriage are known to be higher than in adults,[32] suggested that person-to-person transmission is responsible for carriage.[34]

Although the usual incubation period from exposure to onset of CDAD symptoms is not known with certainty, persons who remain asymptomatically colonized with *C. difficile,* compared with persons colonized with other multidrug-resistant pathogens, over longer periods of time appear to be at decreased, rather than increased, risk for development of CDAD.[25,35-37] The protection afforded by more longstanding colonization may be mediated by the boosting of the body's serum levels of antibody to *C. difficile* toxins A and B.[35,36] However, protection is also observed in humans and animal models when colonization occurs with nontoxigenic strains.[37,38] Whatever the mechanism of protection afforded by asymptomatic colonization, it is the patient who is newly exposed to *C. difficile*, rather than the patient already colonized with *C. difficile,* who is at an increased risk for development of CDAD during stay at an HCF.

The period between exposure to *C. difficile* in an HCF inpatient and the development of CDAD was estimated in 1 study to be less than 7 days.[39] This is to be distinguished from the increased risk of CDAD that can persist for many weeks after cessation of antimicrobial therapy because of prolonged perturbation of normal intestinal flora.[40] Despite ear-

lier evidence of a relatively short incubation period (ie, less than 7 days), more recent evidence suggests that CDAD acquired in HCFs may have its onset after discharge.[9,22,24] Although CDAD symptom onset may occur in patients as many as 2-3 months after discharge,[9,24] limited data suggest that the majority of patients with delayed-onset cases have CDAD symptom onset within 4 weeks after discharge.[22]

The likelihood that HCF transmission is responsible for these delayed-onset cases is suggested by several epidemiologic observations. First, as elucidated by close questioning, some of these patients had their earliest symptom onset before discharge.[22] Second, the incidence among persons recently discharged from HCFs appears to be much higher than the incidence among persons without recent HCF exposure. Third, when compared with outpatient control subjects who were also recently discharged, patients with CDAD onset after discharge had longer lengths of previous inpatient stay, suggesting a longer period of exposure during which transmission could have occurred.[9] Finally, a significant correlation has been observed over time between the number of HCF-onset, HCF-associated case patients and the number of community-onset, HCF-associated case patients recorded monthly within a single HCF (Centers for Disease Control and Prevention, unpublished data). There is less correlation between these numbers if HCF-associated case patients include patients who were transferred to another HCF, suggesting that inpatient stay at another HCF carries with it an independent, increased risk of *C. difficile* exposure. This supports the recommendation that case patients be attributed to the last HCF facility from which the patient was discharged.

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