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DETECTION OF HEALTHCARE-ASSOCIATED INFECTIOUS DISEASE OUTBREAKS WITH A SPECIAL LOOK AT CLOSTRIDIUM DIFFICILE INFECTION IN LONG-TERM CARE FACILITIES

Almea Matanock

Almea Matanock

Candidate

Biomedical Research Education Program

Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

James Cheek, Chairperson

Deirdre Hill

L. Olivia Hopkins

Erin Crotty Phipps

Fares Qeadan

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BY

ALMEA MATANOCK
BA
MD

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DETECTION OF HEALTHCARE-ASSOCIATED INFECTIOUS DISEASE OUTBREAKS WITH A SPECIAL LOOK AT *CLOSTRIDIUM DIFFICILE* INFECTION IN LONG-TERM CARE FACILITIES

By

Almea Matanock

B.A., Human Biology, Brown University, 2003

M.D., University of New Mexico, 2009

M.S., Biomedical Sciences, University of New Mexico, 2017

ABSTRACT

Healthcare-associated infections (HAI) are a major cause of morbidity and mortality and a public health priority. However, standard procedures and comprehensive guidelines for HAI outbreak detection and response are still needed. This hybrid thesis describes what is known about HAI outbreaks in the introduction, reviews the HAI outbreaks reported to New Mexico Department of Health (NMDOH), in the first paper, and then in the second paper examines how established methods for detecting infectious disease outbreaks perform in identifying *Clostridium difficile* infection (CDI) outbreaks in long-term care facilities (LTCF) in Bernalillo County, New Mexico, and finally, it closes with our overall conclusions at this time from this work. Our main findings are that gastrointestinal illness, most commonly norovirus, in LTCFs is most likely to be reported and that in LTCFs the least complex threshold method performs with the highest sensitivity and specificity in detecting possible CDI outbreaks.

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Chapter 1: Introduction

Every day, one in 25 patients in acute care health facilities have a healthcare-associated infection (HAI) (1). A variety of pathogens ranging from very common norovirus to rare, but increasing carbapenem-resistant Enterobacteriaceae cause HAIs. Additionally, HAIs also put healthcare personnel at risk. A particularly important problem is when HAIs cause an outbreak. In an outbreak HAIs can spread rapidly, cause health facilities to close, and be a sign of infection-control issues. Investigating HAI outbreaks can uncover underlying systemic problems and guide interventions that may globally improve infection control processes. Response to a particular outbreak has the potential to reduce outbreaks of other HAIs through improvement in infection control practices. For example, recommendations for improved respiratory protection during intubation procedures, raised in an investigation of an influenza outbreak, would likely protect healthcare personnel from other pathogens that are transmitted by droplets.

In the U.S., there are well-established surveillance systems, such as the National Healthcare Safety Network (NHSN), for tracking the incidence of particular pathogens, such as *Clostridium difficile*, and particular sites of infections such as central line-associated blood stream infections (CLABSI). Surveillance systems can assist in the detection of outbreaks. However, without standard definitions and response practices, HAI outbreaks cannot be compared or evaluated and may go undetected. For some infections, thresholds for investigation have been developed and implemented as general infection control guidance (e.g. ≥2 cases of influenza like illness in a long term care facility in 72 hours (2)). However, for many HAIs there is no specific definition or described threshold for investigating what might possibly be an outbreak.

The total number of HAI outbreaks is unknown because not all outbreaks are recognized and likely only a portion of those recognized are reported. Approximately 35 HAI outbreaks/year are reported to the New Mexico Department of Health (NMDOH). However, lacking is a general description of these outbreaks. Understanding the characteristics of these outbreaks including pathogens, size, number of case fatalities, and effect on health facility operations, will improve our response to them. Additionally, describing what is reported, may help us be able to see outbreak types and characteristics that are not as commonly recognized. Our specific aim with the first paper and part of the project is to evaluate the characteristics of HAI outbreaks reported to NMDOH in the past 5 years, 2011–2015.

The second paper and project explores different methods for developing thresholds for HAI outbreak detection. Specifically, we examined *Clostridium difficile* infection (CDI) incidence in long-term care facilities (LTCF) with the aim of estimating the potential number of possible CDI outbreaks and developing a method for detection of possible CDI outbreaks in this setting.

Chapter 2: Healthcare-Associated Infectious Disease Outbreaks Reported to New Mexico Department of Health

Abstract

Background: Healthcare-associated infections (HAI) are a major cause of morbidity and mortality. However, HAI outbreaks have not been systematically well studied. Here we describe HAI outbreaks reported to New Mexico Department of Health (NMDOH).

Methods: We conducted a retrospective descriptive analysis of HAI outbreaks, defined as two or more epidemiologically linked HAIs at a healthcare facility, reported to NMDOH. Characteristics included descriptions of the healthcare facilities, outbreaks, and responses.

Results: During 2011–2015, 135 HAI outbreaks were reported to NMDOH, and 93% occurred in long-term care facilities (LTCF). Excluding 2 outbreaks that lasted >1 year, the median outbreak length was 11 days (range 1–72 days) with a median of 4 days (range 0–61 days) from recognition to reporting. Gastrointestinal illness was most common (101 [75%]). The most common pathogens identified were norovirus (n=72;53%), influenza (n=20;15%), and *Clostridium difficile* (n=4;3%). There was a median of 26 cases/outbreak (range 2–234) with more patients than staff affected. In 58 (44%) of outbreaks, the affected unit was closed, which in 88% of the cases were entire facility closures.

Conclusions: Reported HAI outbreaks are most common in LTCFs, relatively short in duration, and affect both patients and HCPs in noticeable numbers.

Background

A national point-prevalence survey conducted in 2011 estimated that on any given day 1 in 25 patients in acute care health facilities has a HAI (1). In a survey of infection preventionists, 35% reported that their health facility had investigated an outbreak in the past year (3). Cases occurring as part of outbreaks in are only a fraction of all HAI cases. However, when HAI outbreaks occur they can spread rapidly, be a sign of underlying systemic infection control issues, and put patients, healthcare personnel (HCP), and visitors at risk of infection. Investigation of outbreaks can lead to insights about disease transmission, demonstrate the effectiveness of certain interventions, and be the impetus for implementing infection control measures that might have lasting impact on not only the outbreak HAI, but other HAI that are transmitted similarly (4).

Examination of HAI outbreaks has been primarily pathogen focused (5-9) and of infection control measures (10-16), with reviews about some special settings within healthcare such as neonatal intensive care units (17). However, few studies have reviewed all HAI outbreaks (surveillance data (18), survey (3), systematic reviews (4, 10)). Further description of HAI outbreaks is needed to focus response and prevention efforts. Our primary aim in this study was to describe the characteristics of and response to HAI outbreaks investigated by NMDOH.

Methods

We used a retrospective descriptive analysis of HAI outbreaks reported to NMDOH during 2011 to 2015 (5 years). We defined a HAI outbreak as two or more

epidemiologically linked healthcare-associated infections, as defined as a symptomatic illness from a pathogen or its toxin which can be related to a medical procedure or to exposure to the healthcare facility environment in HCPs, patients, or visitors of the healthcare facility (18). Our unit of measure was HAI outbreaks. We describe the characteristics of the healthcare facilities, the outbreak, and the response to the outbreak including pathogen, mode of transmission, primary site (i.e. blood stream, gastrointestinal, etc.), size of outbreak, type of facility, unit and facility closures, changes in equipment, and treatments.

We extracted the information from electronically saved narrative outbreak reports. We created a standardized form for data abstraction, which we piloted with the first nine outbreaks abstracted. All data were directly abstracted into Microsoft Excel 2013 (Redmond, WA). We analyzed the data to assess descriptive characteristics of outbreaks. All analyses were performed using SAS v9.3 software (SAS Institute, Carey, NC). The protocol was internally reviewed and deemed public health practice.

Our hypotheses were that the majority, >50%, of the HAI outbreaks reported to NMDOH would have one following characteristics:

(a) Caused by an unusual pathogen defined as any pathogen other than norovirus, *C. difficile*, *Staphylococcus aureus,* or influenza

(b) Include HCP cases defined as at least one outbreak case in an HCP

(c) Occure in a short period of time defined as the entire outbreaks duration of ≤14 days

(d) Include case fatality defined as any case deaths attributed to the outbreak

We thought these characteristics would be the ones most likely to cause identification and prompt reporting of HAI outbreaks. We test these four hypotheses using a one sample, one right sided proportion z-test. Each hypothesis translates to testing the null and alternative H_0: $p \leq 0.50$ versus H_1: $p > 0.50$.

Results

Outbreak characteristics: there were 135 HAI outbreaks reported to NMDOH in 2011 to 2015. The 135 outbreaks were reported from 69 health facilities with a median of 2 outbreaks per facility (range 1–6) in the 5 year period. Long-term care facilities represented 93% of reports. Bernalillo County, the home of the largest New Mexican city Albuquerque, where a third of the state's population resides, was the source of 48% of reports.

Gastrointestinal illness was the most common syndrome (101 [75%]) followed by respiratory combined with influenza-like illness (28 [21%]). The remaining 6 outbreak reports included bacteremia, skin and soft tissue infection, urinary tract infection, or unknown. Where a specific pathogen was identified, norovirus was most common (72 [53%]) followed by influenza (20 [15%]), and then Clostridium difficile (4 [3%]) (Table 2.1). Methicillin-resistant *Staphylococcus aureus* (MRSA), pertussis, carbapenem-resistant Enterobacteriaceae (CRE), *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and Group A *Streptococcus* (GAS) represented 1 outbreak each during the 5 year period.

Duration of an outbreak was defined as the time from the first case to the last case. Excluding the 2 outbreaks that lasted more than 1 year, the median outbreak length was 11 days (range 1–62 days). The median was 4 days (range 0–61 days) from the

recognized start of the outbreak to when it was reported. Among gastrointestinal outbreaks, *C. difficile* lasted somewhat longer than norovirus on average (median 18 days [range 10–71] vs 12 days [range 2–72]) (Table 2.2). Unidentified gastrointestinal outbreaks were on average shorter (median 5 days [range 1 –25]) than norovirus, but had a very similar range. Among the respiratory outbreaks, influenza was shorter than the other respiratory illnesses (median 8 days [range 1–34]) vs 23 days [range 13–44]).

In the 127 outbreaks with case counts, there was a median of 26 cases per outbreak (range 2–234). Of note, the outbreak reports commented on the fact that all cases were not always captured, especially HCP cases. There were no visitors included in case counts. However, visitors were thought to be the index case in 3 outbreaks (2%). Patients were noted as the index case or were the first recognized cases in 33 (24%) outbreaks and HCP in 19 (14%) outbreaks. However, it is not certain from the outbreak reports how the true first case of disease entered into the facility. There were 103 outbreaks reporting patient cases (median 19 total case per outbreak [range 0–110]) and 95 outbreaks reporting HCP cases (median 8 total cases per outbreak [range 0–212]). Zeros are included of the range from outbreaks where either patient or HCP cases were not reported. Since we suspect that the total number of cases reported underrepresents the total number of cases experienced, we report the average number of deaths not the case fatality rate as typically presented. *C. difficile* outbreaks were associated with the highest mean case fatality (2.7 deaths per outbreak [range 0–8]) followed by influenza (1.1 deaths per outbreak [range 0–3]). There were more case deaths than increases in level of care during *C. difficile* outbreaks (2.7 deaths per outbreak [range 0–8] vs 1.7 cases whose level of care was increased per outbreak [range 0–5]).

Outbreak response: In 58 (44%) outbreaks the unit was closed, of which 88% (51/58) entailed closure of the entire facility. Patient isolation was initiated by the facility or recommended by NMDOH in 82 outbreaks (61%). Change in equipment was recommended in 51 outbreaks (38%) which most commonly consisted of using disposable service for meals during gastrointestinal outbreaks. There were some specific recommendations when the outbreak was thought to be transmitted by equipment including using single dose vials, disposable or sterilizable equipment, to clean procedural equipment, and designated equipment for patients in isolation. In 14 of 20 influenza outbreaks (70%) vaccine was offered to eligible, unvaccinated, HCPs and in 10 of 20 influenza outbreaks (50%) vaccine was offered to eligible, unvaccinated, patients. We were not able to determine the timing of interventions during the outbreak nor were we able to tell from the reports which intervention were fully implemented.

Hypothesis testing: We expected that outbreaks with HCPs cases, caused by unusual pathogens (pathogens other than norovirus, *C. difficile*, influenza, and *S. aureus*), occurring in a short period of time (defined as ≤14 days), or with case fatalities would lead to identification and prompt reporting in more than 50% of reported HAI outbreaks (see methods section). The results indicate that outbreaks with HCP cases (84%, $p<0.05$ [95% Confidence Interval (C.I.) 0.77–0.92]) and outbreaks that occurred in ≤14 (62%, $p<0.05$ [95% C.I. 0.53–0.71]) were reported >50% of the time (Table 2.3), consistent with hypotheses (b) and (c). Outbreaks caused by unusual pathogens or with case fatalities were not common characteristics of reported outbreaks (sample proportion was less than 50%).

Discussion

HAI outbreaks reported to NMDOH were relatively short in duration, occurred in LTCF, affected both patients and HCPs, and caused gastrointestinal illness, which was mostly commonly from norovirus. Our findings agree with previous reports (3, 18). We had few outbreaks of unusual pathogens that were typically detected by astute clinical microbiologists or clinicians who had seen ≥2 cases among their patients. None of these methods is very systematic in identifying outbreaks, especially in lager healthcare systems where different diagnostic laboratories might be used or patients are not necessarily followed by the same provider. Strengthening systems approaches, including automatizing recognition of pathogens across multiple laboratory and provider networks, might lead to better HAI outbreak recognition. Detection of HAI outbreaks caused by rare pathogens, pathogens that cause less acute disease, or those that are endemic in the healthcare setting might particularly benefit from system wide approaches. Examples of this includes hepatitis B (HBV) and hepatitis C (HCV) that are transmitted in the healthcare setting and cause HAI outbreaks, but that without robust detection methods, may go unnoticed (19, 20).

We expected that LTCF would be one of the more common facilities reporting HAI outbreaks. However, we did not expect that almost all outbreak reports would be from LTCFs. Several factors may explain why there is a higher than expected proportion of LTCFs. The first is that other facility types may not see it necessary to report. One example would be a large acute care facility that is able to manage the outbreak on their own. In LTCFs the person assigned to infection prevention often has other clinical or administrative duties and so may reach out to NMDOH more readily for assistance.

Additionally, in LTCFs the person assigned to infection prevention may not have formal training in infection prevention. A second theory is because of patients relatively long length of stay in the same physical location HAI outbreaks in LTCF may be more likely to be identified. A third possibility is that specific characteristics of LTCF promote infections. Three possible unique characteristics of LTCF that might promote the spread of infectious disease include: 1) communal patient activities, especially dining, that might promote transmission, 2) high patient to HCP ratios, and 3) shared HCPs who work in multiple facilities, who may transmit infection between facilities. There were notes about shared HCPs possibly introducing infection from one facility to another in the NMDOH reports we reviewed. This has been documented in previous gastrointestinal outbreaks as well (21). Even when HCPs are not sick themselves fomites that are shared between facilities could potentially transmit infection. As more facilities come under single corporate management, this issue could increase. It highlights the importance of infection control not only to protect those in the facility where the outbreak is occurring, but also in associated facilities.

In general outbreaks were reported shortly after they were identified, with a median of 4 days. However, the time of detection of the outbreak may not account for initial cases. We observed this in three ways: (1) investigations did not always look back in time past the first reported cases to identify earlier occurrences, (2) often the outbreak started with many cases instead of growing exponentially as would be expected for many of the infectious diseases reported, and (3) case definitions often did not include visitors who may be the true index cases in facilities, especially for pathogens which are known to cause community outbreaks. Visitors might be particularly important to the way that

infections are introduced into LTCFs. With low patient turn over in LTCFs, patients are a less likely way of circulating acute community disease. Additionally, in LTCF, family members often provide care and assistance, but are without training or personal protective equipment. While there is guidance for influenza vaccination for patients and HCPs (2), this is not usually extended to family members or other visitors. Additionally, while reminders about hand and respiratory hygiene are often recommended to be posted during outbreaks, these interventions might be helpful in preventing outbreaks as well.

Other gastrointestinal outbreaks, where a pathogen could not be identified, might have a short duration because only the end of the outbreak was identified. Alternatively, they may have been caused by viruses that were not tested for but cause a syndrome like norovirus. In a review of the gastrointestinal outbreaks, in LTCF reported in the literature, 69% of outbreaks were caused by a virus, 83% of which was norovirus (57% of the total), and bacterial infections were implicated in 31% of outbreaks (22). Other respiratory outbreaks also had a similar profile to influenza with two exceptions, the level of care increased more often than in influenza, but there were fever case deaths on average. Among the other respiratory outbreaks 1 of the 8 was confirmed as pertussis.

The limitations of this study stem from the fact that our data source is outbreak reports. Reports were commonly missing data elements and in some instances, there was no report. Missing data prevented us from looking at associations between variables. For example, we wanted to explore further if HCP cases might be associated with larger patient case counts (10). However, HCP cases were frequently noted in the reports to be missing. Furthermore, HCP screening, prophylaxis, treatment, and exclusions were infrequently documented. Additionally, missing data made drawing conclusions difficult

for some variables. For example, we believe that the proportion of outbreaks where isolation was documented as a control measure more likely to reflect the completeness of reporting on that measure as opposed to actual implementation. Likewise, rarely were patients notified that they could have been potentially exposed. Notification may not be well documented. However, isolation of both symptomatic and exposed individuals can serve an important role in interrupting person to person transmission of disease.

In few instances, even when the outbreak was well documented, the causes and magnitude were still not entirely clear. In this category were 3 outbreaks that had more than one pathogen identified. These were two norovirus outbreaks that also had *C. difficile* cases identified and one respiratory outbreak there were multiple possible pathogenic causes, but no single unifying one.

Table 2.1: Characteristics of Outbreaks Classified by Syndrome and Pathogen (n 135), 2011–2015

Outbreak Type[1]	Number	(%)	Median Duration in Days	(Range)
Norovirus[2]	72	(53.3)	12	(2–72)
Clostridium difficile	4	(3.0)	18	(10–71)
Other Gastrointestinal	25	(18.5)	5	(1–25)
Influenza	20	(14.8)	8	(1–34)
Other Respiratory	8	(5.9)	23	(13–44)

Not included in the table are 6 single outbreaks whose syndromes included skin and soft tissue, urinary tract infection, bacteremia, mixed urine and respiratory and pathogens included MRSA, pertussis, CRE, *P. aeruginosa*, *B. cepacia*, and GAS

[2]Includes two norovirus outbreaks with *C. difficile* cases

Table 2.2: Case Information by Outbreak Syndrome or Pathogen (n 135), 2011–2015

Outbreak Type[1]	Median Case Counts (Range)											
	Total		Confirmed		Patients		Healthcare Personnel		Increased Level of Care[3]		Deaths[3]	
Norovirus[2]	34	(5–234)	3	(1–10)	22	(0–110)	13	(0–212)	2.6	(0–78)	0.1	(0–2)
Clostridium difficile	10	(6–15)	7.5	(2–15)	7.5	(1–15)	2.7[3]	(0–8)	1.7	(0–5)	2.7	(0–8)
Other Gastrointestinal	22	(3–91)	—	—	17	(3–78)	7	(0–24)	0.6	(0–2)	0.1	(0–1)
Influenza	12	(3–49)	3	(1–9)	11	(0–49)	4	(0–19)	1.5	(0–6)	1.1	(0–3)
Other Respiratory	12.5	(7–50)	1	(0–12)	13	(11–50)	8	(1–31)	3	(1–9)	0.5	(0–3)

[1]Not included in the table are 6 single outbreaks whose syndromes included skin and soft tissue, urinary tract infection, bacteremia, mixed urine and respiratory and pathogens included MRSA, pertussis, CRE, *P. aeruginosa*, *B. cepacia*, and GAS
[2]Includes two norovirus outbreaks with *C. difficile* cases
[3]Mean used in replace of median when median equal to zero

Table 2.3: Outbreak Identification Indicators and Results for Testing Hypotheses (a)–(d)

Outbreak Characteristics	**n/N ($\hat{p}$, 95% CI)**	**p value**
Unusual pathogen[1]	6/135 (0.04, 0.01-0.08)	p>0.05 (Hypothesis a)
HCP cases	80/95[2] (0.84, 0.77-0.92)	p<0.05 (Hypothesis b)
Occur in short time period (≤14 days)	69/112[2] (0.62, 0.53-0.71)	p<0.05 (Hypothesis c)
Case deaths	11/90[2] (0.12, 0.05-0.19)	p>0.05 (Hypothesis d)

[1] Unusual pathogens were defined as those other than norovirus, *Clostridium difficile*, influenza, and *Staphylococcus aureus*

[2] Outbreaks without this information recorded in New Mexico Department of Health report were excluded

Chapter 3: *Clostridium difficile* Infection Outbreak Detection Methods in Long-Term Care Facilities

Abstract

Background: Clostridium difficile infections (CDI) are a major cause of healthcare-associated infections resulting in morbidity and mortality for patients. Healthcare-associated CDI cases are reportable and outbreaks in this setting have been recognized. However, methods for detecting CDI outbreaks have not been well studied or standardized. Our aim is to estimate the potential number of CDI outbreaks in LTCFs and develop a better working detection method.

Methods: We used retrospective laboratory confirmed incident CDI cases from long-term care facilities (LTCF) in Bernalillo County, New Mexico. We applied 4 previously described infectious disease detection algorithms (Epidemic Threshold [ET], Moving Percentile Method [MPM], Cumulative Sum [CUSUM], and Exponential Weighted Moving Average [EWMA]), to estimate periods of possible CDI outbreaks. To assess the performance of the 4 algorithms, we compared them to reported outbreaks, 3 expert infection preventionists' opinions about what could be a possible outbreak, and clusters observed in the data and defined by a new simple heuristic rule (≥3 cases averaged over any 3 consecutive week period with at least 2 weeks between clusters).

Results: In 2012 –2015, for the 14 LTCFs included in this study, the weekly incidence ranged from 0.16–11.24 per 10,000 resident days. All 4 methods detected the 1 reported CDI outbreak. ET had the highest sensitivity and specificity in detecting expert visually identified possible outbreaks (EVIPO) (sensitivity 98.0%, specificity 99.0%, accuracy 98.9%) and clusters (sensitivity 89.6%, specificity 99.3%, accuracy 98.3%).

Conclusions: ET, the simplest method, had the highest sensitivity and specificity in detecting possible CDI outbreaks. However, when case counts were low with many weeks of zero incidence, the use of the new simple heuristic rule to identify clusters might be sufficient in deciding whether to trigger an investigation for possible CDI outbreaks.

Background

Healthcare-associated infectious disease (HAI) are a major cause of morbidity and mortality, targeted as a public health priority. *Clostridium difficile*, an anaerobic Gram-positive and spore-forming bacterium which causes toxin-mediated gastroenteritis, is an intractable cause of HAI. CDI is due to a combination of environmental factors and host susceptibility (23). An increasing trend of CDI burden in long-term care facilities (LTCF) has been observed in the past two decades (24). The increased CDI risk in LTCF residents is likely due to advanced age, extended length of stay, frequent hospitalizations, and exposure to antibiotics (23, 25).

Among populations already at great risk for CDI, outbreaks can be difficult to detect. There are multiple reasons why CDI outbreaks are difficult to detect including that CDI is endemic, that the risk increases with typical healthcare-associated interventions, and that it is environmentally stable making the epidemiologic link between cases harder to define. Additionally, there are is no defined threshold or standard definitions for CDI outbreaks. Reported outbreaks likely do not accurately represent the proportions of different types of HAI outbreaks or the magnitude of the issue (18, 26). In part this is because what is reported in the literature is more unusual than the routine HAI outbreaks.

However, the other issue faced by infection preventionists and others working in public health is that HAI outbreaks can go undetected. Therefore, having better detection methods to prevent exponential spread, address infection control issues, and improve patient outcomes is imperative. Investigation of outbreaks can lead to insights about disease transmission, demonstrate the effectiveness of certain interventions, and be the impetus for implementing infection control measures that might have lasting impact on not only the outbreak, but other HAI that are transmitted similarly (4).

Healthcare-associated CDI cases, that are reportable to the New Mexico Department of Health (NMDOH) (27) and Centers for Medicare and Medicaid Services (CMS), require reporting through the National Health Safety Network (NHSN) for acute care facilities. Additionally, CMS is piloting reporting of CDI cases through NHSN in LTCFs. However, we are not aware of any widely-accepted thresholds or algorithms used to detect outbreaks. Additionally, definitions for estimated periods of transmission to aid in detecting and investigating possible CDI outbreaks are not standard.

This study aims to estimate the number of possible CDI outbreaks and develop better detection methods. Using routinely collected surveillance data from LTCF in Bernalillo County, New Mexico, we applied previously described infectious disease detection algorithms used in other settings and for other infectious diseases (28-31). For comparison, we also asked local infection preventionists to review epidemic curves for potential outbreaks and review CDI outbreaks among the LTCFs reported to the NMDOH.

Methods

Data sources: We used open access CMS data to obtain facility-level information including annual bed counts, resident days, and average length of stay (32). Since 2011, the New Mexico Emerging Infections Program (NM EIP) has been conducting laboratory-based surveillance for LTCF-onset (LTCF-O) CDI cases in Bernalillo Country (33). We obtained the CDI case counts from the NM EIP data. Reported CDI outbreaks from the LTCFs in the NM EIP catchment area were reviewed at NMDOH.

For data completeness, we used data from 2012–2015. Facilities with greater than 1 year of missing resident days were excluded. For the 2 facilities that had a single missing year of resident days, we used an average of the other 3 years for the imputation. Facilities without all 4 years of CDI case count data were excluded. We included incident CDI cases defined as stool specimen positive for *C. difficile* by identification of toxin by Enzyme Immunoassay (EIA) or Nucleic Acid Amplification Tests (NAAT) obtained from a patient without a *C. difficile* positive stool specimen in the previous 8 weeks at the time of stool collection. Recurrent cases (defined as a positive stool specimen 2–8 weeks after a prior positive) and repeat tests from incident or recurrent cases (defined as tests positive within 2 weeks of the initial test for an incidence or recurrent case) were excluded.

Data analysis: Weekly incidence was calculated using NM EIP facility case counts and an estimated weekly facility resident days. We estimated the weekly resident days from the annual resident days reported to CMS, assuming a >80% occupancy capacity year-round. We then applied the following methods for outbreak detection to the weekly CDI incidence:

1. Epidemic Threshold (ET) (29): Using the weekly non-zero incidence, we calculated the 95% upper confidence interval (UCI) for each facility. The 95% UCI was then compared to the weekly incidence. When the weekly incidence exceeded the 95% UCI, it was noted as a possible outbreak week.
2. Moving percentile method (MPM) (30): For stability in the calculations, we used 2012 to establish a baseline mean from which we took the 95^{th} percentile. Advancing forward, a new 95^{th} percentile was calculated each week through the subsequent years in each facility. When the weekly incidence exceeded the 95the percentile, it was noted as a possible outbreak week.
3. Cumulative sum (CUSUM) (34): A one sided CUSUM was calculated by facility using the mean incidence and the square root of the mean squared successive difference as an estimate of the standard deviation (28, 34). We used standard values for delta=1, and k=0.5, the reference, allowance, or slack value. Values of k=0.5 and h=4 or 5, the upper bound/threshold value, generally work to detect shifts in the mean of 1 standard deviation (30, 34). We choose h=2 given the generally low incidence of CDI in our data. In national detection algorithms for gastrointestinal pathogens such as *Salmonella* spp., h=0.5 and delta=0.5 have been used (28).
4. Exponentially weighted moving average (EWMA) (34): For this method, we used facility mean and variance, to calculate the Upper Confidence Interval, which for this method is the detection threshold (EWMACHART statement SAS). The only parameter we defined was the weight, λ. Suggested values are $0.05 \leq \lambda \geq 0.25$ (34). Smaller λ are able to detect smaller changes in incidence (34). However, since this is a weight, a smaller λ weight may take longer to react to a change (34). Knowing that

we had both of these scenarios, relatively small changes in incidence and long periods of zero incidence, we choose a λ of 0.15.

Methods 1–4 (ET, MPM, CUSUM, and EWMA) were compared to CDI outbreaks reported to NMDOH (one pure CDI outbreak and two norovirus outbreaks with CDI cases) as the gold standard using sensitivity and specificity analysis. Since there was only one pure CDI outbreak, we used two additional comparisons as the gold standard. Our first method was expert visually identified outbreaks (EVIPO). To obtain the expert opinion, the epidemic curves of weekly incidence in each facility was reviewed by 3 local infection preventionists. They noted on the graphs which weeks they thought could be possible outbreaks. When any 1 of the 3 denoted a week as a possible outbreak, we defined it as positive by this method. Our second method was to define clusters in the data. In reviewing the epidemic curves, we developed a simplified definition of a cluster of CDI. The definition of a cluster is ≥3 cases averaged over any consecutive 3 week period with at least 2 weeks of zero incidence between clusters. The remainder of the weeks were divided by the average cluster length for a comparable "non-cluster" time to calculate specificity. Our cluster definition was designed to capture longer time periods of elevated incidence as well as weeks with very high incidence. Our cluster definition was inspired roughly from the "rule of three" (35). In our data, a weekly CDI incidence of zero was common. The "rule of three" states that the 95% confidence interval can be estimated to be 3/n when the usual occurrence is 0/n. However, instead of choosing a 1 week period with three cases, we broadened the definition to ≥3 cases averaged over any consecutive 3 week period to account increased incidence that didn't rise to 3 cases in a

single week, but was elevated and often this elevation lasted for a longer period of time. We considered any of the four methods to have detected a cluster if at least one week was flagged during its time period. We used the number of weeks flagged outside of clusters divided by the total number of non-cluster periods to estimate the proportion (p) of non-cluster periods misclassified. The latter calculation could be used to quantify the specificity of detection according to 1-p.

Data was maintained Microsoft Excel 2013 (Redmond, WA). Analyzes were performed in both using SAS v9.3 (SAS Institute, Carey, NC) and Microsoft Excel 2013 (Redmond, WA) software. The protocol for this study was reviewed by the University of New Mexico Health Sciences Human Research Review Committee (HRRC 00016856).

Results

The 14 facilities included in this study had a median 120 beds, a median length of stay of 94 days, and a median annual occupancy capacity of 89.7% with only one facility <80%. Mean weekly incidence ranged from 0.16–11.24 per 10,000 resident days (Table 3.1). During 2012–2015, there was a range of <10–64 cases in the 4 year period with 2 facilities having case counts <10. In the other 12 facilities, incidence and clusters were spread over the course of years. By our definition of a cluster as ≥3 cases in any consecutive 3 week period with at least 2 weeks between clusters, there were 77 clusters over the 4 years with a median length of 3 weeks (range 1–21). These same two facilities with case counts <10 also did not have any clusters of CDI cases. Our experts visually detected 49 possible outbreaks (EVIPO) in the 4 years with a median length of 6 weeks (range 1–29).

The accuracy for detecting both EVIPO and clusters was >85% for all methods (Table 3.2 and Table 3.3). ET had the highest sensitivity and specificity in detecting EVIPO (sensitivity 98.0%, specificity 99.0%, accuracy 98.9%) and clusters (sensitivity 89.6%, specificity 99.3%, accuracy 98.3%). Our experts were not quite as sensitive in detecting clusters, but specificity remained high (sensitivity 91.8%, specificity 89.6%, accuracy 72.7%). The lowest sensitivity was using in the EWMA.

ET and MPM detected periods of higher incidence, which is equated to ≥2 cases per week. CUSUM and EWMA also captured most of these high incidence periods, but also detected some periods of ongoing low incidence (Figure 1). MPM, EWMA, and especially CUSUM stayed elevated for a prolonged period of time after a period of higher incidence. Both ET and CUSUM detected clusters with sensitivity and specificity >80% (Table 3.3).

We reviewed 3 outbreaks that were reported to NMDOH with CDI cases in the 14 facilities, 2012–2015. Two of these were norovirus outbreaks with 2 recognized CDI positive cases each at the time. In both facilities, there were >2 CDI cases in the weeks around the time of the outbreak report in the surveillance data. The 3rd CDI outbreak report represents a purely CDI outbreak. It described 9 CDI cases, including several individuals with a history of CDI as well as recent admissions to the facility, in a 23 day period. All detection methods identified this outbreak. ET detected as possible outbreaks the CDI cases included in the norovirus outbreaks. MPM detected as possible CDC outbreak one of the norovirus outbreaks with CDI cases. In the other norovirus outbreak with CDI cases, MPM detected the 2 weeks prior as possible outbreak. CDI incidence was higher during these 2 weeks than during the norovirus outbreak. CUSUM and

EWMA only detected 1 of the 2 norovirus outbreaks with CDI cases. With only 1 pure and verified CDI outbreak further comparisons were not made.

Discussion

ET defined as the upper 95% confidence interval calculated without zero incidence was most sensitive in detecting reported outbreaks, defined clusters, and possible outbreaks visualized by expert infection preventionists reviewing the epidemic curves. This is a relatively simple statistic that can be calculated at the facility level. In the facilities included in this study the upper 95% confidence interval of the incidence equated to 1–2 cases per week for all facilities except 1 of the 14 facilities that had an ET of 2–3 cases per week. A more simplified heuristic rule such as a threshold of 2 cases per week or our cluster definition of ≥3 cases in a 3 week period would not require any calculations to be implemented, but would also not be generalizable to facilities with higher case counts, which is why we approached this using weekly incidence.

Reviewing the epidemic curves visually demonstrated to us that ET was more sensitive than the other methods in this relatively low incidence data because the threshold did not change. Prior studies demonstrated that more stable methods with fewer parameters (e.g. ET and MPM) perform better than more complex ones (e.g. CUSUM and EWMA) (29, 30). However, specific outbreak parameters such as size and baseline incidence affected methods' performance. The other methods, MPM, CUSUM, and EWMA, varied in their threshold level which made them less sensitive. Additionally, because their threshold stayed elevated for a prolonged period after a cluster when the incidence had returned to zero, the specificity of these methods was also low.

There were few reported outbreaks to compare to our detection methods. We believe this is the essence of why it is important to develop further guidance for outbreak detection. To compare methods, we asked experts to review the weekly epidemic curves, which might be one approach that facilities could take. We defined what appeared to be clusters. However, with the retrospective data available to us these clusters could not be verified as true outbreaks. We observed that long duration, relatively low incidence periods were not captured by the cluster definition. Even in reported clusters that are thought to be outbreaks, confirming linkage between cases is difficult since microbiologic information beyond the diagnosis is not often available and *C. difficile* can persist in the environment for many weeks (36, 37).

Reviewing CDI outbreaks from facilities throughout NM reported to NMDOH in 2011–2015, we observed a median outbreak duration of 18 days with 10 cases per outbreak and 2.7 deaths per outbreak. Using 49 EVIPOs and 77 clusters in our 14 facilities over 4 years, we calculate 0.9–1.4 outbreaks per facility per year. Extrapolated to the 15,600 LTCFs in the United State, this is 14,040–21,840 possible CDI outbreaks (38). Even if only a quarter are true outbreaks and only a quarter of the cases and deaths are prevented by recognizing these outbreaks, this could still potentially be 8,775–13,650 cases and 2,306–3,587 deaths averted.

Without investigating of the EVIPO or clusters, we cannot say if they truly represent outbreaks. However, the aim of this project is to develop a trigger for investigating what might be an outbreak. Including some periods that could be outbreaks, but turn out not to be upon investigation, is expected for a detection system. Ideally a detection system should have very high sensitivity. Overall, we had very high sensitivity

with all methods except EWMA. We also had high specificity, which is likely elevated by large periods of zero incidence. Even the methods with responsive threshold, MPM, CUSUM, and EWMA, detected only a relatively small portion of the non-cluster time. Therefore, the number of non-cluster periods not detected (true negatives) is very high and leads to high specificity.

The other methods, in particular CUSUM, could potentially have better sensitivity by optimizing the parameters. We did this to some extent, but only within values used in previous studies. With more verified outbreaks (e.g. in a setting where outbreaks were defined and reported or in a study done prospectively investigating cases detected by various methods) parameters could realistically be further optimized. Additionally, the stability of MPM would improve with additionally data points added to the development of the baseline.

There were several limitations to this study. First, we had to develop several assumptions in our calculations for comparison—a) we assumed that facilities with >80% occupancy capacity that annual resident days could be divided evenly over the course of the year to produce a weekly incidence and b) that undetected periods were equivalent to detected periods in defining non-cluster time periods. Secondly, as discussed, we did not have enough detected, investigated, and verified outbreaks to compare our methods to. Third, even when CDI outbreaks are investigated, it can be difficult link cases together because *C. difficile* can last for a long time in the environment, can colonize individuals who remain asymptomatic, but can transmit CDI, and rarely is microbiologic information available (36, 37, 39).

Table 3.1: Facility Description, Cases Counts, and Weekly Incidence, 2012–2015

Facility	Case Count			Weekly Incidence per 10,000 Resident Days		
	Mean	Standard Deviation	95% Confidence Interval LowerUpper	Mean	Standard Deviation	95% Confidence Interval Lower Upper
A	1.00	0.00	..	1.34	6.39	0.48 2.21
B	1.35	0.58	1.19 1.50	7.75	14.66	5.76 9.73
C	1.20	0.54	1.07 1.34	11.24	19.41	8.61 13.87
D	1.30	0.58	1.15 1.44	4.64	7.99	3.56 5.72
E	1.22	0.42	1.08 1.36	3.21	7.58	2.19 4.24
F	1.25	0.57	1.11 1.40	4.75	8.28	3.63 5.87
G	1.24	0.55	1.09 1.39	4.14	8.00	3.06 5.22
H	1.33	0.56	1.09 1.57	2.44	7.48	1.42 3.45
I	1.33	0.61	1.14 1.52	3.67	8.30	2.55 4.80
J	1.00	0.00	..	0.16	1.36	-0.02 0.35
K	1.44	0.58	1.24 1.64	5.02	9.51	3.73 6.30
L	1.45	0.54	1.17 1.73	2.50	7.14	1.53 3.47
M	1.19	0.60	0.97 1.41	1.45	4.00	0.91 1.99
N	1.26	0.54	1.09 1.42	1.07	2.37	0.75 1.39

Table 3.2: Detection of *Clostridium Difficile* outbreaks with Expert Visual Identified Possible Outbreaks (EVIPO) as the gold standard

Detection Method	**EVIPO Detected /Total EVIPO**[1]	**Sensitivity**	**Specificity**	**Accuracy**
Epidemic Threshold (Upper 95% Confidence Interval)	48/49	98.00	99.01	98.85
Moving 95th Percentile (MPM)	30/35[2]	85.71	98.51	96.93
Cumulative Sum	38/49	77.55	88.18	86.58
Exponentially Weighted Moving Average	20/49	40.81	98.89	90.15

[1] Where any 1 of 3 experts identified a period as possible outbreak

[2] For the MPM method, the number of identified outbreaks by the gold standard method (EVIPO) was 35 because the year 2012 was excluded to establish a baseline mean for the 95th percentile

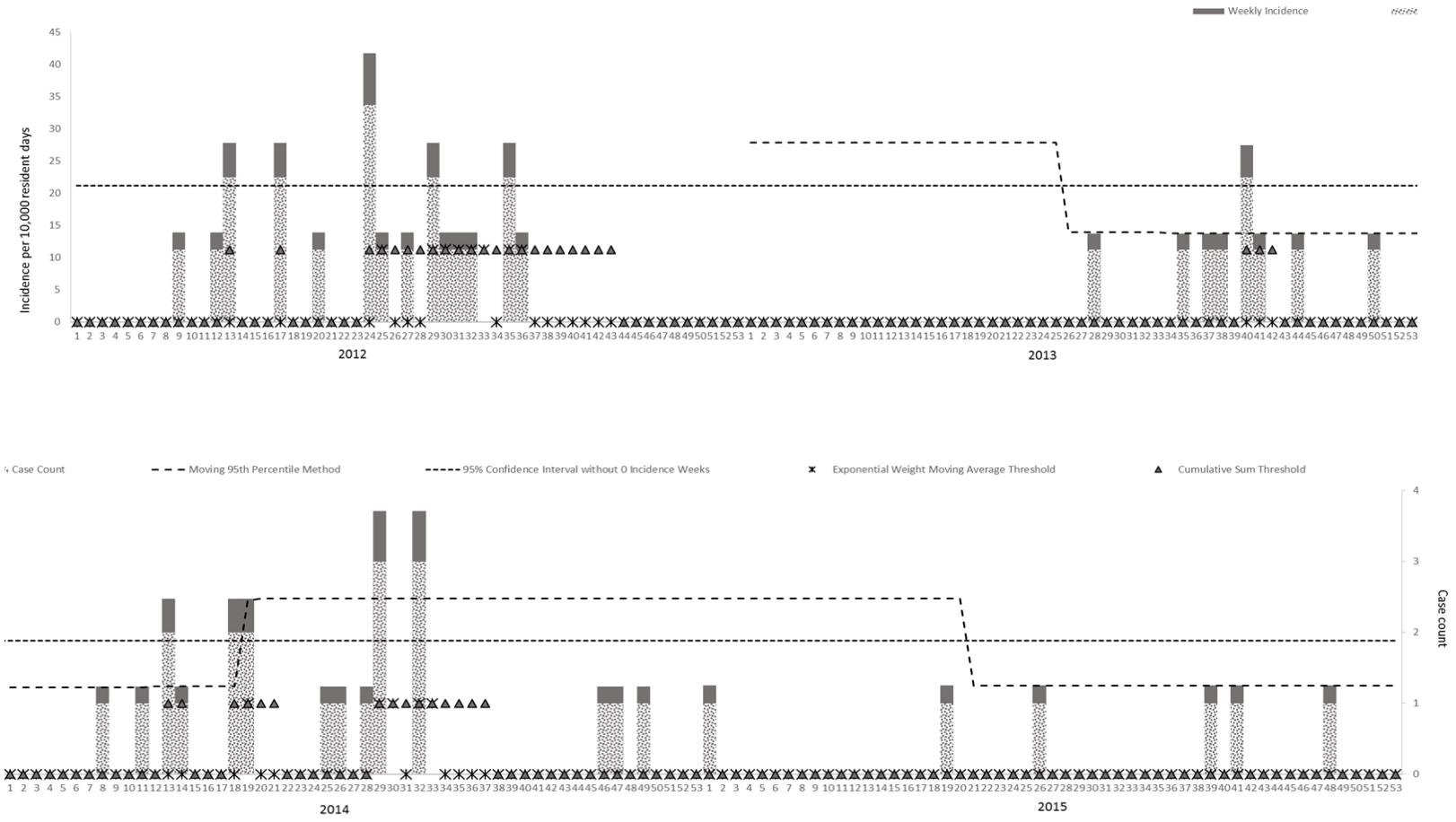
Table 3.3: Detection of *Clostridium Difficile* outbreaks with Cluster as the gold standard

Detection Method	**Detected Clusters /Total Clusters**	**Sensitivity**	**Specificity**	**Accuracy**
Epidemic Threshold (Upper 95% Confidence Interval)	69/77	89.61	99.34	98.34
Moving 95th Percentile (MPM)	35/47[1]	74.47	98.46	96.31
Cumulative Sum	62/77	80.52	87.19	86.40
Exponentially Weighted Moving Average	25/77	32.47	98.85	91.37
Expert Visual Identification of Possible Outbreaks (EVIPO)[2]	56/77	72.73	91.79	89.62

[1] For the MPM method, the number of identified outbreaks by the gold standard method (EVIPO) was 35 because the year 2012 was excluded to establish a baseline mean for the 95th percentile

[2] Where any 1 of 3 experts identified a period as possible outbreak

Figure 1: Detection Method Thresholds by Weekly *Clostridium Difficile* Infection Incidence per 10,000 Resident Days and Cases per Week in One Example Long-Term Care Facility, 2012–2014



Chapter 4: Conclusions

Reported HAI outbreaks are most commonly in LTCF, relatively short in duration, and affect both patients and HCPs. This HAI outbreak profile is very commonly reported to public health authorities. Streamlining response procedures, especially for common pathogens, could assist facilities and public health officials in day to day operations, coordinate response, and improve the study and subsequent understanding of which infection control measures are most effective. Additionally, we think there is a need to develop detection methods for HAI outbreaks that may be less easily recognized. Reliance on astute HCPs to identify outbreaks is likely to cause gaps in our ability to detect outbreaks, especially in more complex health systems.

To understand detection more systematically, we examined CDI incidence in LTCFs for possible outbreaks using established methods for outbreak detection. We determined that the simplest method, ET—the upper 95% confidence interval, appears to have the best sensitivity and specificity in detecting possible CDI outbreaks. This is the first step to increasing detection of possible HAI outbreaks. However, using the new heuristic rule to identify clusters might be sufficient in deciding whether to trigger investigations for possible CDI outbreaks in a setting with relatively low incidence. Detection of CDI outbreaks potentially would mean thousands of averted cases and would allow for advancements in our understanding of environment and individual risk factors. Ultimately, we hope that this would lead to better outbreak detection and control.

This work comes at a time when NMDOH is updating and standardizing investigation procedures for commonly investigated diseases in the healthcare setting. Additionally, the Association of State and Territorial Health Officials (ASTHO) and the

Council of State and Territorial Epidemiologists (CSTE), along with other partners have recently created a HAI outbreak detection and response council to develop improved guidance for HAI outbreak identification and response (40). We hope that this project can assist in informing this effort.

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