# SpatioTemporal Clustering of in-Hospital *Clostridioides difficile* Infection (CDI)

Shreyas Pai, MS, Department of Computer Science, University of Iowa, Iowa City, IA USA

Philip M. Polgreen, MD, MPH, Departments of Internal Medicine and Epidemiology, University of Iowa, Iowa City, IA USA

Alberto Maria Segre, PhD, Department of Computer Science, University of Iowa, Iowa City, IA USA

Daniel Sewell, PhD, Department of Biostatistics, University of Iowa, Iowa City, IA USA

Sriram V. Pemmaraju, PhD, Department of Computer Science, University of Iowa, Iowa City, IA USA

For the CDC MInD-Healthcare group

Corresponding Author: Philip M. Polgreen, MD MPH, University of Iowa. Carver College of Medicine, 200 Hawkins Dr., Iowa City, IA 52242, phone: 319-384-6194; fax: 319-354-; email: Philip-polgreen@uiowa.edu

The work described in this manuscript was presented, in part, at IDWeek 2018, San Francisco, CA, October 4, 2018, poster #509: Spatio-Temporal Clustering of CDI Cases at the University of Iowa Hospitals and Clinics.

Running head: Spatiotemporal clustering of in-hospital CDI

Word Count: 2847

**Abstract**

**Objective:** To determine if *Clostridioides difficile infection* (CDI) exhibits spatiotemporal interaction and clustering.

**Design:** Retrospective observational study

**Setting:** The University of Iowa Hospitals and Clinics

**Patients:** 1,963 CDI cases, January 2005-December 2011

**Methods:** We extracted location and time information for each case and ran the Knox, Mantel, and mean and maximum component size tests for time thresholds $T = 7$, 14, and 21 (days) and distance thresholds $D = 2$, 3, 4, and 5 units (1 unit = 5-6 meters). All tests were implemented using Monte Carlo simulations, with random CDI cases constructed by randomly permuting times of CDI cases, 20,000 times. As a counterfactual, we repeated all tests on 790 aspiration pneumonia cases, since aspiration pneumonia is a complication without environmental factors.

**Results:** Results from the Knox test and mean component size test reject the null hypothesis of no spatiotemporal interaction with p-value < 0.0001, for all values of $T$ and $D$. Results from the Mantel test reject the hypothesis of no spatiotemporal interaction with $p$-value < 0.0003. The same tests show no such effects for aspiration pneumonia. Results from the maximum component size tests show similar trends, but are not consistently significant, possibly because CDI outbreaks attributable to the environment were relatively small.

**Conclusion:** Our results clearly show spatiotemporal interaction and clustering among CDI cases and none whatsoever for aspiration pneumonia cases. These results strongly suggest that environmental factors play a role in the onset of some CDI cases. However, our results are not inconsistent with the possibility that there were many genetically unrelated CDI cases during our study period.

## Introduction

*Clostridioides difficile infection* (CDI) is one of the most common healthcare-associated infections as well as the leading cause of healthcare-associated diarrhea.[1,2] Accordingly, CDI is an important cause of excess morbidity and mortality,[2,3] and cases of CDI increase the cost of healthcare.[4] Exposure to antibiotics is the major risk factor for CDI.[5,6] However, additional individual-level risk factors have been identified, including advanced age,[7-9] greater underlying severity of illness,[5,6] increased levels of co-morbidities,[5,6] and medications designed to decrease gastric acid levels.[10]

In addition to individual-level-risk factors, the environment, especially in hospitals, has been implicated as a risk factor for CDI. In general, *CDI pressure*, the increasing risk of CDI acquisition with increasing numbers of CDI patients, has been documented at both the ward[11] and hospital levels.[12] More specifically, evidence for underlying environmental CDI contamination include reports of *C. difficile* spores on high-touch surfaces in healthcare settings,[13,14] patients' skin,[15,16] and the hands of healthcare workers.[17,18] In addition, *C. difficile* contamination increases in rooms occupied by patients with symptomatic CDI: thus, room assignments (e.g., patients placed in a room with previous occupant who had CDI) are also associated with increased risk of CDI acquisition.[19] Evidence that the environment is a contributor to increased risk for CDI has led to infection-control recommendations for disinfection, isolation, and hand washing with soap and water especially in outbreak settings.[20]

The emphasis on the environment's role in CDI has recently been subject to scrutiny. Whole-genome sequencing studies have shown that, at least in non-outbreak settings, a substantial proportion of *Clostridioides difficile* isolates are not genetically related.[21] Other work on screening asymptomatic patients for *Clostridioides difficile* carriage report that colonization established before hospitalization may also be an important risk factor for subsequent cases of hospital-based CDI.[22,23] These results raise questions regarding the proportion of CDI attributable to the healthcare environment.

One effective approach to quantify the environment's contribution to CDI is to measure the *spatiotemporal interaction and clustering* of CDI cases, because such spatiotemporal clustering suggests that environmental factors may be contributing to the spread of CDI. This approach has been widely used outside hospital settings to understand risk factors for several infectious diseases.[24] However, applying this approach within the hospital is challenging due to the lack of fine-grained spatial data that is necessary to estimate distances between pairs of in-hospital CDI cases. In this paper, we present an analysis to determine if the CDI cases observed at the University of Iowa Hospitals and Clinics (UIHC) exhibit spatiotemporal interaction and clustering after adjusting for effects that are either purely spatial or purely temporal.

**Methods**

Our analysis is based on a fine-grained dataset we have assembled on operations at the University of Iowa Hospitals and Clinics (or UIHC, a 700-bed comprehensive academic medical and regional referral center in Iowa City) from Jan 2005 through Dec 2011. The dataset contains both architectural and in-patient data, such as admission-discharge-transfer records, diagnostic codes, and clinical test results. We construct the set of *CDI cases* for in-patients by extracting (i) the date of positive CDI diagnosis and (ii) the patient's room in the hospital at the time of positive CDI test. CDI diagnosis was via laboratory test; *C. diff* toxin test was used during [Jan 2005, April 2008], *C.diff* toxin A and B test during [May 2008, Dec 2009], and *C. diff* toxin PCR test afterwards. Formally, a CDI case can be viewed as a triple ($p$, $r$, $d$), where $p$ is a patient, $r$ is a room in the hospital, and $d$ is a day in the time period [Jan 2005, Dec 2011] such that patient $p$ tested positive for CDI on day $d$ while occupying room $r$. There are a total of 1,963 CDI cases in our dataset.

To determine if CDI cases exhibit spatiotemporal interaction and clustering, we need to accurately estimate the distance between pairs of rooms in the hospital. Starting with architectural drawings, we "discretized" the UIHC hospital space and constructed a *hospital graph*. The results from this discretization process have also been reported elsewhere.[25] Each room in the hospital is represented by a *node* (larger spaces, such as hallways, are subdivided into smaller room-sized sized polygons, represented as individual nodes), and *edges* (or *hops*) are added between pairs of nodes corresponding to spatial units between which direct physical passage is possible. Each edge (hop) corresponds to a walking distance of 5-6 meters. Edges respect architectural barriers (e.g., walls), so two adjacent rooms that do not share a doorway are not connected by an edge. There are 18,961 nodes and 23,442 edges in the hospital graph. The hospital graph imposes a distance metric on the UIHC space and distances along shortest paths in this graph correspond to shortest walking distances in the UIHC space, as shown in Figure 1.

Our analysis is based on spatiotemporal interaction and clustering tests, all of which correct for solely spatial or solely temporal effects. Three of these tests are performed using a *CDI case proximity graph*, which consists of nodes representing CDI cases and edges connecting two nodes if they occur within $T$ days and within distance $D$ in the hospital graph of each other, where $T \geq 0$ and $D \geq 0$ are integer parameters (see Figure 2).

The *Knox test* compares the observed number of pairs of CDI cases that occur both within $T$ days and within distance $D$ of each other to the distribution of the number of pairs of cases within these time and distance thresholds of each other, conditioned on the absence of spatiotemporal interaction.[26] In other words, we compare the number of edges in the *observed* CDI case proximity graph, denoted $CPG_{(T,D)}^{CDI,obs}$, to the distribution of the number of edges in a random CDI case proximity graph denoted $CPG_{(T,D)}^{CDI,rand}$. To calculate this distribution, we ran Monte Carlo simulations with the time stamps of cases randomly permuted. Note that permuting the time stamps leaves purely spatial correlations and purely temporal

correlations intact while disrupting the joint spatiotemporal structure. We use extensions of the Knox test to explicitly test for other aspects of spatiotemporal structure. To test for burstiness, an important facet of infection diffusion involving periods of significant activity followed by periods of inactivity, we implement the *mean component size* test.[27,28] A *component* in the CDI case proximity graph is a maximal set of cases that are all reachable from each other via paths composed of edges in the graph. A graph can have many components and in the mean component size test, we compare the mean size of components in $CPG_{(T,D)}^{CDI,obs}$ to the distribution of mean component size of $CPG_{(T,D)}^{CDI,rand}$. As in the case of the Knox test, we use Monte Carlo simulations with the time stamps randomly permuted to calculate these expectations. The *maximum component size* test is similar; details appear in Appendix A. Finally, we also perform the *Mantel test*,[30] which computes the Pearson correlation between the spatial and temporal distance matrices of the CDI cases and compares this with the correlation between a randomly permuted spatial distance matrix and the (unpermuted) temporal distance matrix. The motivation for this test is that if the two observed distance matrices have high correlation, then randomization will result in correlation that is consistently smaller.

As a counterfactual experiment – and as a "stress test" for our approach – we repeat all of the tests just described on *aspiration pneumonia*, a complication which occurs when food, stomach acid, or saliva are inhaled into the lungs. Since aspiration pneumonia is not infectious, we expect to see very different results for aspiration pneumonia than CDI. For the 6-year period time-period between January 2007 and December 2013, there were 790 aspiration pneumonia cases reported at UIHC. Unlike CDI, however, hospital records associate aspiration pneumonia with a hospitalization rather than a precise date of onset. We therefore use hospital prescription data to get a "proxy" for an onset date. Starting from the list of antibiotics commonly used to treat aspiration pneumonia,[31-33] we define the onset of aspiration pneumonia as the first time one of these antibiotics (see Table 1) is prescribed for a patient diagnosed with aspiration pneumonia. This method yields a total of 535 distinct aspiration pneumonia cases with associated time

stamps; patient rooms are then determined based on the time stamps and used to construct the observed aspiration pneumonia case proximity graph $CPG_{(T,D)}^{AP,obs}$.

**Results**

Preliminary inspection reveals that CDI cases do exhibit some spatial clustering; certain medical units such as General Medicine, Cancer, and the MICU have many more CDI cases than others, such as Neurology. There may also be spatial patterns in CDI cases due to number of beds per room: of the 709 patient rooms at the UIHC, 342 are singles, 280 are doubles, 68 are triples, and 19 are quads or larger. We have verified that our UIHC CDI cases do not exhibit seasonality, even though case counts at the regional and national level do.[34] Finally, one important temporal variation in the number of CDI cases is due to a change in the CDI test from *C. diff* toxin A and B to *C. diff* toxin PCR in December 2009, which significantly increased apparent CDI rates. However, since our tests control for purely spatial and purely temporal correlations, this should not affect our results. No substantial or hospital-wide changes to infection control policies (e.g., contact isolation policies or room cleaning policies) were known to have occurred during the study period.

We ran the Knox test with time thresholds $T$ = 7, 14, and 21 and distance thresholds $D$ = 2, 3, 4, and 5. Results for $T$ = 14 (Figure 3, left) show that the observed number of pairs of CDI cases that are simultaneously close to each other, both in space and in time, are consistently larger than all of the corresponding expected values obtained in simulation ($p < 0.0001$ in all cases). For example, for $T$ = 14, $D$ = 2, the observed value is 287 (shown by the blue dot) and the value obtained in simulation has distribution shown by the box whisker plot (mean 157.902, std. dev. 12.5193). This is a rejection of the null hypothesis of no spatiotemporal interaction among CDI cases. The results are strikingly different for aspiration pneumonia (Figure 3, right). In all four shown cases for $T$ = 14, the observed number of aspiration pneumonia case pairs that are proximate both in space and time is *no greater* than the expected

number of proximate aspiration pneumonia case pairs over the 20,000 time permutations. These results indicate a clear spatiotemporal interaction for CDI, but none whatsoever for aspiration pneumonia.

We next present results from the mean component size and the maximum component size tests on $CPG_{(T,D)}^{CDI,obs}$ for $T$ = 7, 14, and 21 and $D$ = 2, 3, 4, and 5. For $T$ = 14 and all $D$ = 2, 3, 4, and 5 (see Figure 4, left) the observed mean component sizes are larger than the corresponding mean component sizes *for all 20,000 permutations* (thus, by definition, $p$ = 0 in all cases). For example, for $T$ = 14, $D$ = 2 (Figure 4, left) the observed mean component size is 1.11661 (shown as a blue dot) and this value is larger than the complete distribution (shown as box whisker plot) of mean component sizes (mean 1.06513, std. dev. 0.00571) obtained via simulations. This is a rejection of the null hypothesis (with $p$-value < 0.0001) that there is no spatiotemporal clustering of CDI cases. In contrast, for aspiration pneumonia, the observed mean component sizes in $CPG_{(T,D)}^{AP,obs}$ mostly appear in the lower half of the estimated distribution of mean component sizes of random $CPG_{(T,D)}^{AP,rand}$ (see Figure 4, right). These results imply that there is significant spatiotemporal clustering of CDI cases, but none for aspiration pneumonia, at least as measured by mean component sizes in the case proximity graphs. Results for the maximum component size test appear in Appendix A.

Finally, we apply the Mantel test, comparing the correlation of the temporal distance matrix with the spatial distance matrix for the observed data to the distribution of correlations obtained from randomly permuting the spatial (but, not temporal) distance matrix, 20,000 times. For CDI (Figure 5, left), the Pearson correlation coefficient of the temporal distance matrix and the spatial distance matrix is far to the right of the mean correlation obtained by permuting the spatial distance matrix, rejecting the null hypothesis of no spatiotemporal correlation with $p$-value < 0.0003. In contrast, the corresponding test for aspiration pneumonia (Figure 5, right) yields an observed Pearson correlation coefficient of 0.007, not far from the mean (0.006) of the distribution of correlations with one matrix randomly permuted ($p$ = 0.452).

Our tests yield substantively similar results for $T = 7$ and $T = 21$ with $D = 2, 3, 4$ and 5. These results are summarized in Appendix B.

**Discussion**

The importance of hospital design and room assignments have been previously cited as factors in the transmission of infectious diseases. [19,35,36] However, only a small number of studies in the literature have focused on spread of infections and outbreaks within healthcare facilities.[24] Such studies are hampered by the difficulty of defining spatial relationships inside healthcare institutions, where architectural features, (e.g., walls, elevators, nurses' stations) make it complicated to compute distances between cases. Indeed, one peripheral contribution of this paper is to point a way forward, using distances computed from readily available CAD drawings of healthcare facilities.

Our results help bridge two categories of CDI investigations – those that implicate the environment in the spread of CDI[11,19] and those that report that a substantial proportion of CDI cases are genetically unrelated,[21] thereby discounting environmental factors. Our results, obtained from a variety of spatiotemporal statistical tests, provide compelling evidence that there is spatiotemporal interaction as well as clustering among CDI cases at the UIHC. These results suggest that environmental factors are in play. On the other hand, our case proximity graphs contain many connected components (for various $T$, $D$ values), each with a relatively small maximum size component. Specifically, over all $T$ and $D$ values considered, the largest maximum component size is 13 (about 0.66% of the number of cases). Thus, our results are not inconsistent with the possibility of many genetically unrelated cases, with relatively small outbreaks.

Our results hold despite routine infection control precautions in place at the UIHC. For example, CDI patient rooms may undergo extra terminal cleaning, sometimes with Ultraviolet germicidal irradiation. All patients admitted with diarrhea are placed in contact isolation, but spread throughout the hospital

depending on their primary diagnosis. We verified that this placement does not cause additional spatiotemporal interaction or clustering by checking that our results hold even if we define CDI cases as patients with positive CDI test *at least 48 hours after admission* (see Appendix D).

In future work, we plan to use whole-genome sequencing to investigate whether genetically related strains of CDI are more common within space-time CDI clusters than among cases that did not cluster. It is worth noting that there is at least one investigation[37] that reports that clusters of genetically related CDI cases did not correspond to clusters of CDI case identified by spatiotemporal tests. However, a much closer look at this connection (or lack thereof) is needed. More specifically, this particular study[37] was done in the somewhat unique environment of a pediatric hospital; results in other hospitals may be different. Results may also vary in time: during periods when CDI is endemic, environmental factors may be insignificant, whereas during periods of outbreak they may be significant. Another direction of future work is incorporating connections between patients via shared healthcare workers.[38] Thus, joining clusters detected from case proximity graphs to staffing records could help us better understand and quantify the role of healthcare workers in the transmission of healthcare associated infections.

Our work has several limitations. First, due to the retrospective nature of this study, we do not have the ability to perform genetic sequencing of CDI cases within and outside of clusters. This is a future extension of our work. Second, there are other sources of information that we did not fuse into this investigation, e.g., staffing patterns, patient trajectories through the hospital. However, in future work, such covariates could be incorporated into space-time tests. Finally, onset of CDI infectivity may precede the date of positive CDI test. It may be important to incorporate this type of uncertainty, to obtain more robust spatiotemporal tests.

In conclusion, through a variety of statistical tests, we have shown that CDI cases at the hospital during the period from January 2005 to December 2011 exhibit significant spatiotemporal interactions and clustering. In contrast, aspiration pneumonia cases in a similar time frame do not show any spatiotemporal interactions or clustering behavior. Together, these results strongly suggest that environmental factors play a significant role in the onset for some cases of CDI. Finally, in addition to CDI, our approach could be extended to other infections within the hospital and even non-infectious outcomes with localized environmental factors (e.g., falls, medication errors).

**Acknowledgements**

Financial Support: This project is funded by CDC MInD-Healthcare via CDC cooperative agreement U01CK000531.

Potential Conflicts of Interest: All authors report no conflicts of interest relevant to this article.

Thank You Notes: The authors acknowledge feedback from other University of Iowa CompEpi group members, especially Talal Riaz, for help with creating and visualizing hospital graphs.

| Antibiotic | Count |
|---|---|
| Piperacillin/Tazobactam | 427 |
| Metronidazole (Systemic) | 154 |
| Clindamycin (Systemic) | 94 |
| Meropenem | 88 |
| Moxifloxacin | 86 |
| Ceftriaxone | 83 |
| Ampicillin Sod/Sulbactam Sod | 57 |
| Cefotaxime | 5 |
| Imipenem/Cilastatin | 2 |

**Table 1:** Most frequently prescribed antibiotics, sorted by frequency, for patient visit records marked with the aspiration pneumonia complication code during the 2007-2013 time period. A total of 790 patient visits were coded with aspiration pneumonia; because some patients were prescribed more than one antibiotic from the list, the sum of the prescriptions (996) exceeds the number of aspiration pneumonia codes.

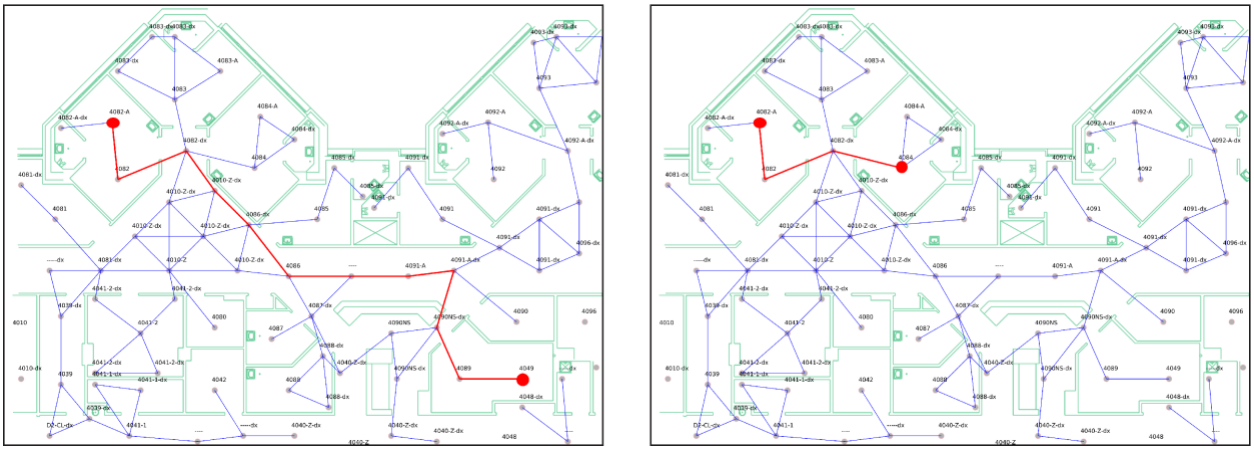

**Figure 1.** Each path in the hospital graph from a node *s* to a node *t* corresponds to a valid walking route in the hospital from the spatial unit corresponding to node *s* to the spatial unit corresponding to node *t*. For example, the top-left figure shows two rooms, 4082-A and 4084, whose shortest path distance in the UIHC graph is 11 hops (a hop is an edge in the hospital graph). The top right figure shows rooms 4082-A and 4049, whose shortest path distance in the UIHC is 3 hops.

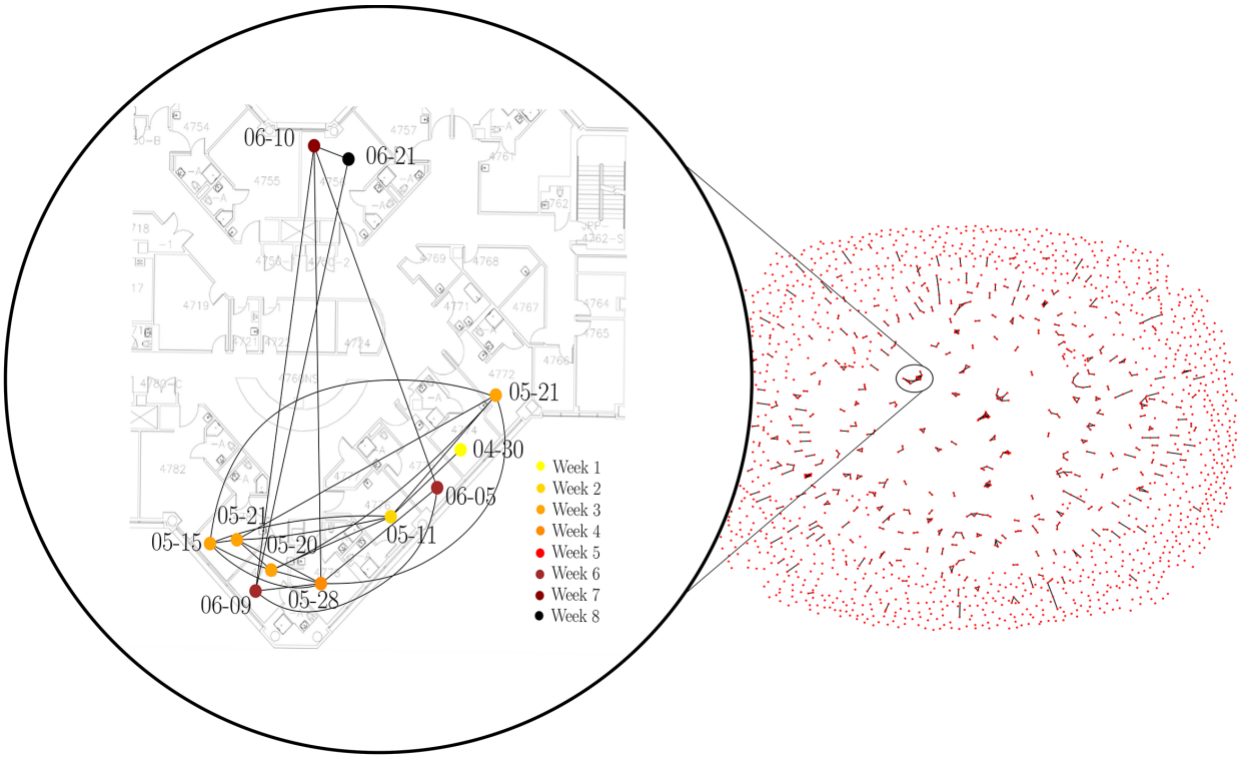


**Figure 2**. $CPG_{(14,5)}^{CDI,obs}$: CDI case proximity graph for $T$ = 14 days and path length of $D$ = 5 ($\leq$ 30m). The graph contains 1,963 nodes, corresponding to CDI cases at the UIHC during time period from January 2005 to December 2011. Its 682 edges correspond to pairs of cases occurring with 14 days and distances of no more than 5 hops ($\leq$ 30 m) from one another. The resulting CDI case proximity graph contains 1,519 components, 1,229 of which are single nodes. The mean component size is 1.29 and the maximum component size is 11. A component of size 11 is enlarged and shown on the left. The CDI cases in this component occurred over a roughly 2-month period (30 April to 21 June, 2010) in the GMed (4JPE) unit; 9 of these cases occurred in a "pod" of 7 adjacent patient rooms, whereas 2 occurred in a single patient room in a separate "pod."

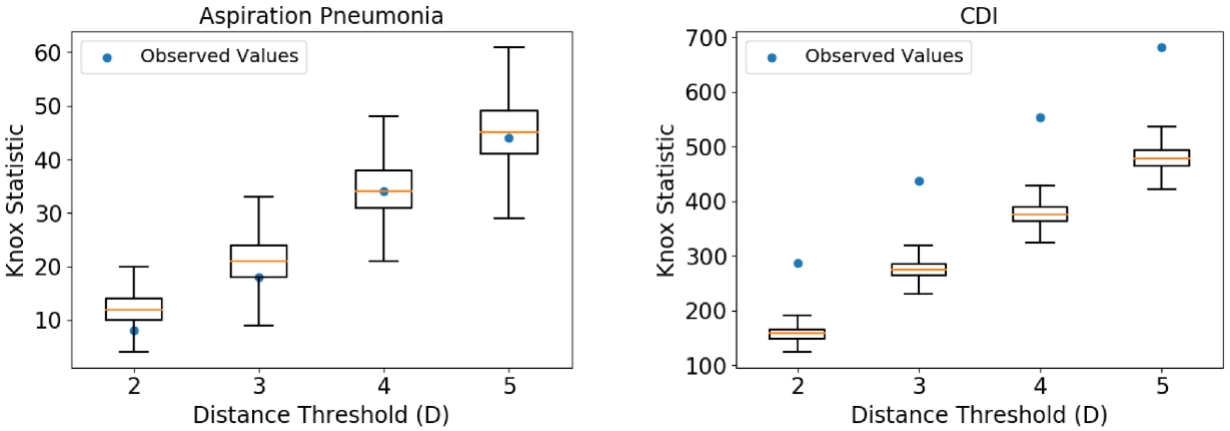


**Figure 3.** The Knox test for CDI (right) and aspiration pneumonia (left) are shown for time threshold $T$ = 14 days, and distance threshold $D$ = 2, 3, 4, and 5 hops. The test results were derived from 20,000 random permutations of the time stamps of the cases. The boxplots show the distribution of the Knox test statistics and the blue dots corresponds to the Knox test statistics on the observed data. There is a striking difference in the results for CDI and aspiration pneumonia.

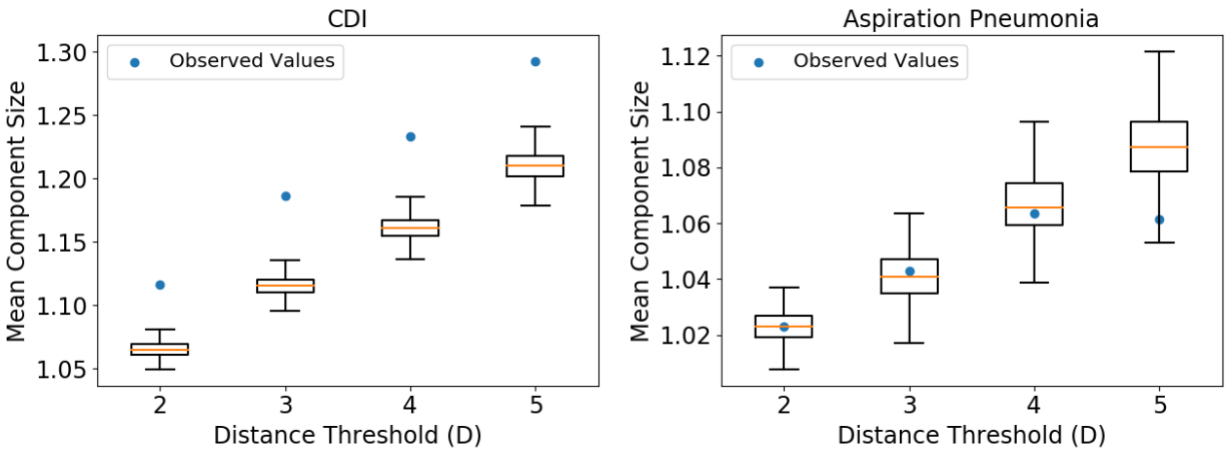


**Figure 4.** The mean component size test for CDI (top left) and for aspiration pneumonia (top right) are shown for time threshold $T$ = 14 days, and distance threshold $D$ = 2, 3, 4, and 5 hops. The test results were derived from 20,000 random permutations of the time stamps of the cases. The boxplots show the distributions of the test statistics obtained from the random permutations and the blue dots corresponds to the test statistics on the observed data.

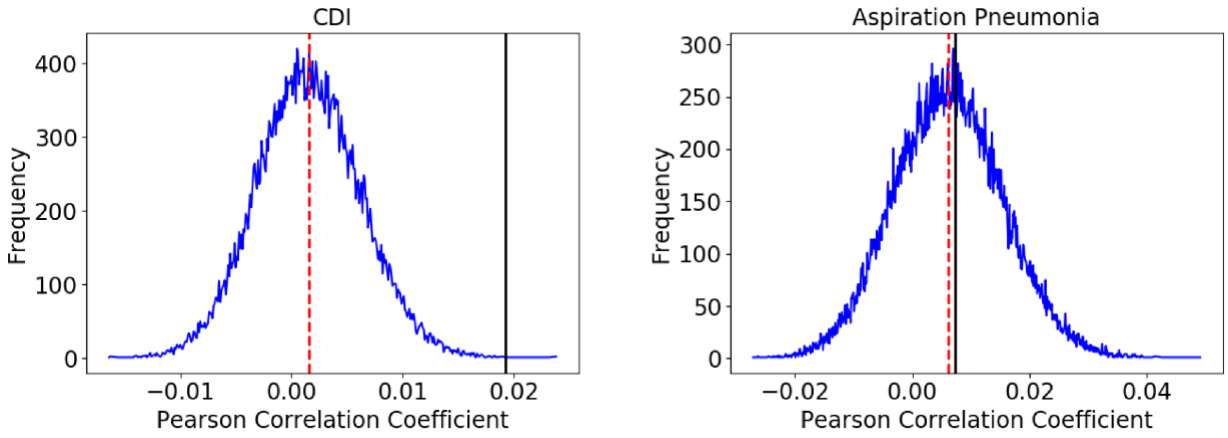


**Figure 5.** The figure on the left shows the Pearson correlation coefficient (0.01924, black line) for the spatial and temporal distance matrices of CDI cases in comparison with the distribution of correlation coefficient (mean is the red line), when one of the matrices is permuted randomly. The plot is the result of randomly permuting the matrix 20,000 times. The figure on the right shows the results of the same computation for aspiration pneumonia cases.

## References


**1.** Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *The New England journal of medicine* 2014;370:1198-1208.

**2.** Evans CT, Safdar N. Current Trends in the Epidemiology and Outcomes of Clostridium difficile Infection. *Clinical infectious diseases* 2015;60 Suppl 2:S66-71.

**3.** Kwon JH, Olsen MA, Dubberke ER. The morbidity, mortality, and costs associated with Clostridium difficile infection. *Infectious disease clinics of North America* 2015;29:123-134.

**4.** Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. *Clinical infectious diseases* 2002;34:346-353.

**5.** Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. *Clinical infectious diseases* 2011;53:42-48.

**6.** Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. *Antimicrobial agents and chemotherapy* 2013;57:2326-2332.

**7.** McDonald LC, Owings M, Jernigan DB. Clostridium difficile infection in patients discharged from US short-stay hospitals, 1996-2003. *Emerging infectious diseases* 2006;12:409-415.

**8.** Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial Clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ : Canadian Medical Association journal* 2005;173:1037-1042.

**9.** Campbell RR, Beere D, Wilcock GK, Brown EM. Clostridium difficile in acute and long-stay elderly patients. *Age and ageing* 1988;17:333-336.

**10.** Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. *Archives of internal medicine* 2010;170:784-790.

**11.** Dubberke ER, Reske KA, Olsen MA, et al. Evaluation of Clostridium difficile-associated disease pressure as a risk factor for C difficile-associated disease. *Archives of internal medicine* 2007;167:1092-1097.

**12.** Miller AC, Polgreen LA, Cavanaugh JE, Polgreen PM. Hospital Clostridium difficile infection (CDI) incidence as a risk factor for hospital-associated CDI. *American journal of infection control* 2016;44:825-829.

**13.** Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J, Jr. Clostridium difficile-associated diarrhea and colitis. *Infection control and hospital epidemiology* 1995;16:459-477.

**14.** Kim KH, Fekety R, Batts DH, et al. Isolation of Clostridium difficile from the environment and contacts of patients with antibiotic-associated colitis. *The Journal of infectious diseases* 1981;143:42-50.

**15.** Bobulsky GS, Al-Nassir WN, Riggs MM, Sethi AK, Donskey CJ. Clostridium difficile skin contamination in patients with C. difficile-associated disease. *Clinical infectious diseases* 2008;46:447-450.

**16.** Sethi AK, Al-Nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ. Persistence of skin contamination and environmental shedding of Clostridium difficile during and after treatment of C. difficile infection. *Infection control and hospital epidemiology* 2010;31:21-27.

**17.** Landelle C, Verachten M, Legrand P, Girou E, Barbut F, Brun-Buisson C. Contamination of healthcare workers' hands with Clostridium difficile spores after caring for patients with C. difficile infection. *Infection control and hospital epidemiology* 2014;35:10-15.

**18.** Shrestha SK, Sunkesula VC, Kundrapu S, Tomas ME, Nerandzic MM, Donskey CJ. Acquisition of Clostridium difficile on Hands of Healthcare Personnel Caring for Patients with Resolved C. difficile Infection. *Infection control and hospital epidemiology* 2016;37:475-477.

**19.** Shaughnessy MK, Micielli RL, DePestel DD, et al. Evaluation of hospital room assignment and acquisition of Clostridium difficile infection. *Infection control and hospital epidemiology* 2011;32:201-206.

**20.** McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clinical infectious diseases* 2018;66:e1-e48.

**21.** Eyre DW, Cule ML, Wilson DJ, et al. Diverse sources of C. difficile infection identified on whole-genome sequencing. *The New England journal of medicine* 2013;369:1195-1205.

**22.** Tschudin-Sutter S, Carroll KC, Tamma PD, et al. Impact of Toxigenic Clostridium difficile Colonization on the Risk of Subsequent C. difficile Infection in Intensive Care Unit Patients. *Infection control and hospital epidemiology* 2015;36:1324-1329.

**23.** Bruminhent J, Wang ZX, Hu C, et al. Clostridium difficile colonization and disease in patients undergoing hematopoietic stem cell transplantation. *Biology of blood and marrow transplantation* 2014;20:1329-1334.

**24.** Smith CM, Le Comber SC, Fry H, Bull M, Leach S, Hayward AC. Spatial methods for infectious disease outbreak investigations: systematic literature review. *Euro surveillance : European communicable disease bulletin* 2015;20.

**25.** Curtis DE, Hlady CS, Kanade G, Pemmaraju SV, Polgreen PM, Segre AM. Healthcare worker contact networks and the prevention of hospital-acquired infections. *PloS one* 2013;8:e79906.

**26.** Knox G. The detection of space-time interactions. *Applied Statistics* 1964;13:25-29.

**27.** Takaguchi T, Masuda N, Holme P. Bursty communication patterns facilitate spreading in a threshold-based epidemic dynamics. *PloS one* 2013;8:e68629.

**28.** Akbarpour M, Jackson MO. Diffusion in networks and the virtue of burstiness. *Proceedings of the National Academy of Sciences of the United States of America* 2018;115:E6996-e7004.

**29.** Cao J. Th size of the connected components of excursion sets of $X^2$, t and F fields. *Advances in Applied Probability* 1999;31:579-595.

**30.** Mantel N. The detection of disease clustering and a generalized regression approach. *Cancer Research* 1967;27:209-220.

**31.** Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia: when should they be treated and what is optimal therapy. *Infectious disease clinics of North America* 2013;27:149-155.

**32.** Ottosen J, Evans H. Pneumonia: challenges in the definition, diagnosis, and management of disease. *The Surgical clinics of North America* 2014;94:1305-1317.

**33.** Bowerman TJ, Zhang J, Waite LM. Antibacterial treatment of aspiration pneumonia in older people: a systematic review. *Clinical interventions in aging* 2018;13:2201-2213.

**34.** Polgreen PM, Yang M, Bohnett LC, Cavanaugh JE. A time-series analysis of clostridium difficile and its seasonal association with influenza. *Infection control and hospital epidemiology* 2010;31:382-387.

**35.** Stiller A, Salm F, Bischoff P, Gastmeier P. Relationship between hospital ward design and healthcare-associated infection rates: a systematic review and meta-analysis. *Antimicrobial resistance and infection control* 2016;5:51.

**36.** Dettenkofer M, Seegers S, Antes G, Motschall E, Schumacher M, Daschner FD. Does the architecture of hospital facilities influence nosocomial infection rates? A systematic review. *Infection control and hospital epidemiology* 2004;25:21-25.

**37.** Rexach CE, Tang-Feldman YJ, Cohen SH. Spatial and temporal analysis of Clostridium difficile infection in patients at a pediatric hospital in California. *Infection control and hospital epidemiology* 2005;26:691-696.

**38.** Hornbeck T, Naylor D, Segre AM, Thomas G, Herman T, Polgreen PM. Using sensor networks to study the effect of peripatetic healthcare workers on the spread of hospital-associated infections. *The Journal of infectious diseases* 2012;206:1549-1557.