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# Impact of cleaning and other interventions on the reduction of hospital-acquired *Clostridium difficile* infections in two hospitals in England assessed using a breakpoint model

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SUMMARY

***Background:*** *Clostridium difficile* infection remains a major challenge for hospitals. Although targeted infection control initiatives have been shown to be effective in reducing the incidence of hospital-acquired *C. difficile* infection, there is little evidence available to assess the effectiveness of specific interventions.

***Aim:*** To use statistical modelling to detect substantial reductions in the incidence of *C. difficile* from time series data from two hospitals in England, and relate these time points to infection control interventions.

***Methods:*** A statistical breakpoints model was fitted to likely hospital-acquired *C. difficile* infection incidence data from a teaching hospital (2002–2009) and a district general hospital (2005–2009) in England. Models with increasing complexity (i.e. increasing the number of breakpoints) were tested for an improved fit to the data. Partitions estimated from breakpoint models were tested for individual stability using statistical process control charts. Major infection control interventions from both hospitals during this time were grouped according to their primary target (antibiotics, cleaning, isolation, other) and mapped to the model-suggested breakpoints.

***Findings:*** For both hospitals, breakpoints coincided with enhancements to cleaning protocols. Statistical models enabled formal assessment of the impact of different interventions, and showed that enhancements to deep cleaning programmes are the interventions that have most likely led to substantial reductions in hospital-acquired *C. difficile* infections at the two hospitals studied.



## Introduction

*Clostridium difficile* infection (CDI) is the most common cause of hospital-acquired diarrhoea in the developed world, and is associated with significant morbidity and mortality.[1] CDI

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was an increasing problem in England until 2007.[2] Since then, mandatory surveillance has shown that there has been a dramatic reduction in cases, particularly those attributed to acute hospital care; in the financial year 2007–2008, there were 33,442 cases of CDI attributed to hospitals in England, and this fell by 61% to 13,195 in the financial year 2009–2010. This represents a decrease in the infection rate from 9.3 to 3.6 cases per 10,000 occupied-bed-days.[3]

Controlling *C. difficile* and reducing infection rates are national health priorities in England.[2] Well-established risk factors for CDI include age >65 years,[4] recent antibiotic use (particularly broad-spectrum antibiotics),[5,6] prolonged and previous hospitalization,[4] and environmental contamination with the spores of the organism.[7] Like other nosocomial infections, *C. difficile* can be spread within hospitals by the hands of healthcare workers inadvertently transmitting bacteria and spores between patients and/or their environment.[8,9] Certainly, poor infection control practices are associated with increased rates of CDI.[10] With the exception of age, major risk factors are modifiable. A range of evidence-based measures have been advocated to help hospitals reduce CDI rates, and these are generally implemented as a 'bundle' which includes antibiotic stewardship, hand hygiene initiatives, rapid isolation of infected patients and environmental cleaning with hypochlorite.[2] Despite this fact, there are no standardized definitions of cleaning in the literature,[11] nor any standardization of the techniques used to assess the effectiveness of cleaning techniques.[12,13]

Active performance management of hospital CDI rates has meant that most hospitals in England have implemented the complete bundle of interventions (as was intended). Whilst each of these interventions has been demonstrated to be effective,[2,14] their relative contribution and transferability across hospitals remains poorly understood. However, now that the incidence of CDI has fallen, it is difficult to determine which interventions had the greatest impact for individual organizations, and which, in times of increasing financial constraint, have the highest priority for continuation. Breakpoint models can detect time points at which significant changes in the stability of time series data are predicted to have occurred,[15] and do not rely on the a-priori specification of change points as required by most segmented regression models.[16] This allows a time series (be it the incidence of an infection, a detectable event of interest or any other measurable occurrence) to be assessed for significant changes in the dynamics of the process without the need to specify when it is likely that change, if any, occurred. Estimation of the time points of structural changes, or breakpoints, within the time series can therefore be performed in an unbiased manner. Through further consideration of factors which may have feasibly contributed towards changes in the time series, it is possible to assess the breakpoints (with associated uncertainty) for coincidence with interventions or modifications which could have contributed to the structural change. Of course, where only a single, major intervention occurs at a known time (e.g. roll-out of a more efficacious vaccine, withdrawal of ineffective treatment), a segmented regression model is appropriate to model and understand the effect of this intervention after consideration of any lag in effectiveness.[16] To the authors' knowledge, breakpoint models have not been applied to assess the impact of infection control interventions on healthcare-associated infections.

The objective of this study was to assess the impact of different infection control interventions used in two hospitals in England on the incidence of hospital-acquired CDI. A combination of statistical breakpoint models[17] and statistical process control charts[18] was applied in order to determine and assess the most likely time points where substantial reductions in the incidence of *C. difficile* occurred.

## Methods

### Setting

Cambridge University Hospitals NHS Foundation Trust (CUH) is a 1100-bed teaching hospital with a wide range of specialties, including transplantation, neurosurgery and infectious diseases, with approximately 183,000 admissions per year. Peterborough & Stamford Hospitals NHS Foundation Trust (PSH) is a 600-bed district general hospital with approximately 75,000 admissions per year.

### *C. difficile* incidence data

Monthly counts of likely hospital-acquired CDI episodes from the two hospitals (CUH and PSH) were used for breakpoint modelling. For CUH, likely hospital-acquired episodes for 2002–2009 were defined using the current UK Department of Health guidelines, which are primarily based on a definition using episodes where the test specimen was taken three or more days after admission (where day zero is the day of admission).[2] For PSH, likely hospital-acquired episodes were defined as those episodes where the specimen was not taken at a general practice, the emergency department or the acute assessment unit. For PSH, CDI episode data for 2005–2009 were used. CDI episodes diagnosed after hospital discharge were not included.

### Infection control interventions

Interventions were introduced at CUH and PSH following the Department of Health guidelines.[2] Evidence of implementation dates was obtained from the minutes of infection control team meetings at both hospitals, and additionally from internal hospital communications (CUH only). Major infection control interventions from both hospitals were grouped according to their primary target: antibiotics, cleaning, isolation or other (Table I).

### Breakpoint modelling

All modelling and statistical testing was implemented in R (http://www.r-project.org). Modelling was performed without any prior knowledge of the intervention data, and does not allow the impact of individual interventions to be assessed. Structural change within each CDI time series was assessed with the recursive estimates test using the *efp* function from the *struchange* library.[17] Breakpoints were estimated using the *breakpoints* function (with a minimum partition size of four months) from the *struchange* library. Structural change was detected from an initial linear regression model where the mean incidence was modelled as stable and then tested for improved fit of multiple regression relationships using an

**Table I**
Major infection control initiatives at two hospitals in England, 2004–2009. Initiatives have been grouped for this study according to their primary target of antibiotics, cleaning, isolation or other

| Year | Month(s) | Hospital | Intervention type | Intervention | Code[a] |
|---|---|---|---|---|---|
| 2004 | Nov | CUH | Cleaning | Enhanced cleaning using hypochlorite | C1 |
| | | | Other | Hand hygiene programme using alcohol gel | C2 |
| 2005 | Mar–May | CUH | Cleaning | Deep clean programme on elderly wards | C3 |
| 2006 | Jan | PSH | Cleaning | Hypochlorite for cleaning of whole bays | P1 |
| 2007 | Jul–Sep | CUH | Cleaning | Deep clean programme expanded and wards decanted | C4 |
| | Nov | CUH | Isolation | First isolation ward opens | C5 |
| 2008 | Jan | PSH | Other | Daily ward rounds by infection control nurse | P2 |
| | Mar | PSH | Other | CDI root cause analysis commenced | P3 |
| | April | PSH | Isolation | Rapid isolation of CDI patients (<2 h) | P4 |
| | | | Cleaning | Deep clean programme commenced | P5 |
| | | | Antibiotics | Restriction, new guidelines and increased education for cephalosporin use | P6 |
| | | | Other | Increased education programme | P7 |
| | May | CUH | Antibiotics | Quinolone use restricted throughout hospital | C6 |
| | | PSH | Antibiotics | New drug chart with dedicated antibiotic section | P8 |
| | Jun | PSH | Antibiotics | Antibiotic audit programme commenced | P9 |
| | | | Other | CDI care bundles introduced | P10 |
| | Jul–Sep | CUH | Cleaning | Deep clean programme formalized with single dedicated decant facility and use of hydrogen peroxide vapour disinfection (Deprox, Hygiene Solutions) | C7 |
| | Sep | PSH | Other | 7-day rapid testing for CDI | P11 |
| | Oct | PSH | Isolation | Opening of new isolation ward | P12 |
| 2009 | Jan | CUH | Isolation | Second improved isolation facility opens for rapid isolation (<2 h) | C8 |
| | | | Other | Daily multi-disciplinary team review of patients with CDI | C9 |

CUH, Cambridge University Hospitals NHS Foundation Trust; PSH, Peterborough & Stamford Hospitals NHS Foundation Trust; CDI, *Clostridium difficile* infection.
[a] Intervention codes have been generated for use in this study.

increasing number of breakpoints, each associated with a shift in regression coefficients.[19] Confidence intervals for breakpoints were estimated using the *confint* function. Both breakpoint modelling and estimation of confidence intervals assume normality in data. Departure from normality for full time series data was tested using the Lilliefors test. In order to test for the most appropriate number of breakpoints, models with increasing complexity (i.e. increasing the number of breakpoints) were tested for their improved fit to the data using the likelihood ratio test from the *LR.sarlm* function. For partitions from breakpoints, Shewhart c-charts with 99% control limits were produced using the *qcc* function from the *qcc* library.[20] Special cause variation was defined as a single data point outside of the 99% control limits or a run of eight or more data points on the same side of the average.[18]

## Results

### *Breakpoint models*

For both hospitals, visually there appear to have been periods of relative stability in monthly CDI counts followed by marked reductions (Figure 1). Furthermore, the recursive estimates test for stability over time indicates that there is significant structural change in the data for both hospitals (Table II). Full time series data for CUH and PSH show no significant departure from normality ($P < 0.05$). Models with three and two breakpoints provide the parsimonious best fit to the data for CUH and PSH, respectively; that is, models with an extra breakpoint (four and three, respectively) did not provide a significantly improved fit to the data (Table II). The point estimates of the suggested breakpoints (Table III) were used to split the datasets into partitions which were assessed for stability using statistical process control chart (SPCC) (Table III and Figure 2). Months with incidence counts above the 99% control limit could represent localized outbreaks/clusters, or – given their occurrence in December–March – may reflect increased incidence associated with winter pressures at the hospitals.

As the definition for a likely hospital-acquired CDI episode differed between the two hospitals, a comparison of counts according to the two definitions was made using CDI data from PSH between April 2007 and December 2009. For this time period, the estimated monthly incidence of hospital-acquired CDI correlated strongly for the two definitions (Spearman's rank correlation coefficient, $r_s = 0.9574$, $P < 0.0001$), and differed by an average of just 1.5 episodes per month (range 0–4).

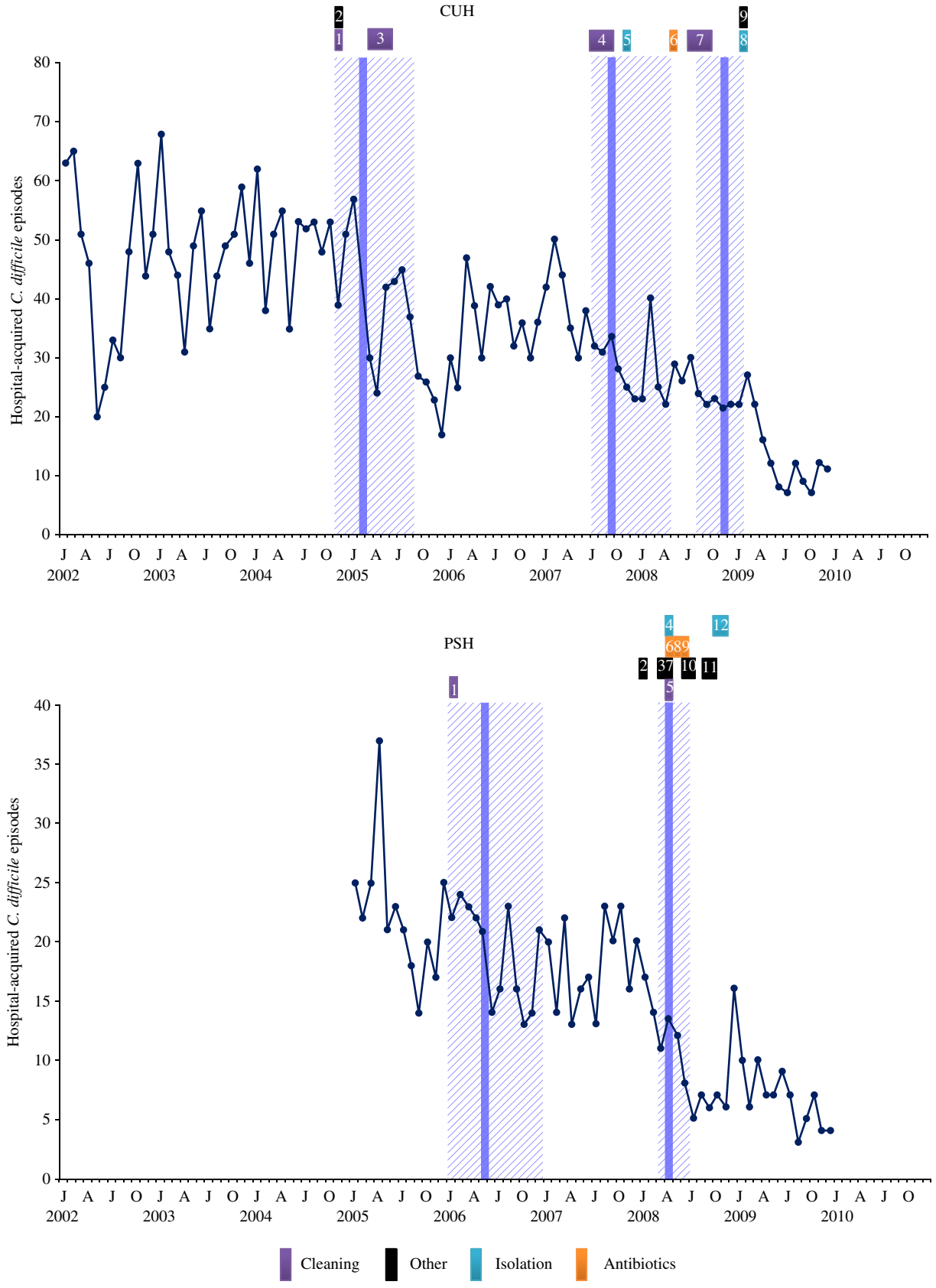


**Figure 1.** Major infection control initiatives and estimated breakpoints in time series of hospital-acquired *Clostridium difficile* infection episodes for two hospitals in England. Point estimates for breakpoints are shown (dark blue) with 95% confidence intervals (light blue). The implementation times for interventions are shown as colour-coded boxes and are numbered according to coding from Table I. CUH, Cambridge University Hospitals NHS Foundation Trust; PSH, Peterborough & Stamford Hospitals NHS Foundation Trust.

**Table II**
Statistical tests for structural change and results of model testing for breakpoints in *Clostridium difficile* incidence data from two hospitals in England

| Hospital | RE test (*P*-value) | Likelihood ratio tests (*P*-value)[a] | | | | Breakpoints[b] |
|---|---|---|---|---|---|---|
| | | 1 vs 0 | 2 vs 1 | 3 vs 2 | 4 vs 3 | |
| CUH | 3.27 (<0.0001) | −60.38 (<0.0001) | −34.34 (<0.0001) | −7.63 (0.0220) | −2.77 (0.2509) | 3 |
| PSH | 2.99 (<0.0001) | −61.56 (<0.0001) | −171.99 (0.0007) | −3.51 (0.1733) | – | 2 |

CUH, Cambridge University Hospitals NHS Foundation Trust; PSH, Peterborough & Stamford Hospitals NHS Foundation Trust; RE, recursive estimates.
[a] Indicates the number of breakpoints in the two models tested. Tests were performed for models with an increasing number of breakpoints until the most parsimonious model was found [i.e. increasing the number of breakpoints did not result in a significantly ($P<0.05$) improved fit to the data].
[b] Represents the number of breakpoints for the selected parsimonious model.

**Table III**
*Clostridium difficile* incidence time series partitions for two hospitals in England estimated using the most parsimonious breakpoint model

| Hospital | Partition | Start month | End month | Duration (months) | Mean *C. difficile* incidence (SD)[a] | Special cause variation[b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | I | II | III | IV |
| CUH | 1 | Jan 2002 | Feb 2005 | 38 | 48 (11.1) | 1 | | 3 | |
| | 2 | Mar 2005 | Sep 2007 | 31 | 35 (7.8) | | | 1 | |
| | 3 | Oct 2007 | Nov 2008 | 14 | 26 (4.9) | | | | |
| | 4 | Dec 2008 | Dec 2009 | 13 | 15 (6.7) | 1 | | | 1 |
| PSH | 1 | Jan 2005 | May 2006 | 17 | 22 (4.8) | 1 | | | |
| | 2 | Jun 2006 | Apr 2008 | 23 | 17 (3.7) | | | | |
| | 3 | May 2008 | Dec 2009 | 20 | 7 (3.0) | 1 | | | |

CUH, Cambridge University Hospitals NHS Foundation Trust; PSH, Peterborough & Stamford Hospitals NHS Foundation Trust; SD, standard deviation.
[a] *C. difficile* incidence represents monthly counts of likely hospital-acquired episodes.
[b] Special cause variation is indicated by deviations from stability for a Shewhart c-chart of each individual partition. The type of special cause variation is indicated: I, the number of data points above the upper 99% control limit; II, the number of runs of eight or more data points above the average; III, the number of data points below the lower 99% control limit; IV, the number of runs of eight or more data points below the average.

### *Interventions*

At least one intervention closely precedes each of the CUH breakpoints, with cleaning initiatives (C1, C4, C7) closely associated with breakpoints (Figure 1). Before the first breakpoint in early 2005, enhanced cleaning with hypochlorite (C1) and major hand hygiene programmes (C2) had been introduced. The expansion of the deep clean programme and designation of a decant ward (C4) coincides with the second breakpoint in 2007, and formalizing the deep clean programme (with a dedicated single decant facility) and use of hydrogen peroxide vapour disinfection (C7) precedes the third breakpoint in late 2008. The marked reduction in incidence following the third breakpoint is somewhat delayed relative to the implementation of C7, and may have resulted from the combined effect of C7 with C8 and C9 (improved isolation facilities and patient review).

The same interventions were typically applied later at PSH than at CUH. The first breakpoint for PSH occurs after the change from just cleaning the patient's bed space to cleaning the whole bay with hypochlorite (P1). The next breakpoint, with a much narrower confidence interval, occurred in early 2008. This followed a number of interventions that were implemented within a short period of time, including commencement of the deep clean programme and restriction of cephalosporin prescribing. The opening of the isolation ward and regular audit of antimicrobial prescribing were introduced shortly after.

## Discussion

Consistent with CDI in England as a whole,[3] the incidence of CDI cases in both hospitals decreased over the time frame of this study. This reduction was ultimately a result of the raised national importance of CDI, primarily as a nosocomial infection which has been targeted at national and local level through a number of effective interventions.[2,14] However, determining the impact of individual interventions on healthcare-associated infections is very difficult, prompting the formal proposal of criteria for such studies.[21] *In situ*, many different interventions are applied, often over a short time period, making even interrupted time series analyses difficult to interpret and subject to limitations.[22] The breakpoint model used in the present study requires no a-priori specification of change points, and can be used to determine the most probable points in a time series where substantial changes in incidence have occurred. This is particularly useful where multiple interventions have been implemented, and where an unbiased approach to assessing impact is required. Given the heterogeneity in the type and timing of interventions in the present study, it has not been possible to take differences in lag times into account to assess the influence of specific interventions. Moreover, different infection control initiatives are likely to have differing lag times before any effectiveness is evident, and the confidence intervals for breakpoint estimates may reflect this fact. In order to account for potential changes in the size/occupancy of each hospital,

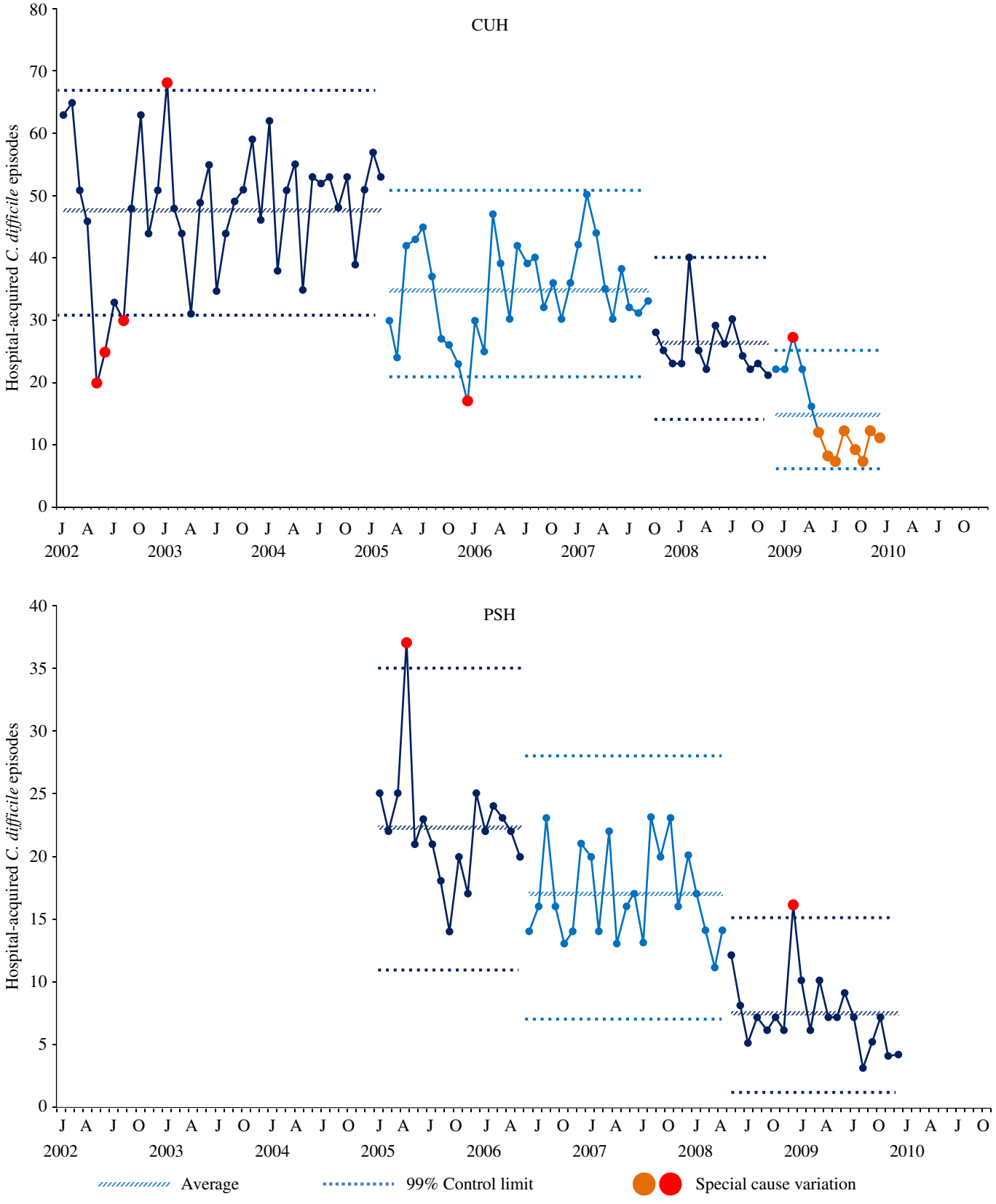


**Figure 2.** Hospital-acquired *Clostridium difficile* infection episodes partitioned into separate statistical process control charts according to breakpoint-model-suggested dates. Details of special cause variation are given in Table III. CUH, Cambridge University Hospitals NHS Foundation Trust; PSH, Peterborough & Stamford Hospitals NHS Foundation Trust.

it may have been more appropriate to use rates instead of counts for this analysis. Counts were used both for their simplicity and the lack of a universally accepted denominator for CDI rates. However, the total numbers of occupied-bed-days for each hospital show no trend, which is suggestive of a reduced number of beds contributing to a reduced incidence of CDI at model-suggested breakpoints.

For CUH, the position of the breakpoints suggests that serial enhancements to cleaning protocols have led to stepwise reductions in the incidence of CDI. The position of the three suggested breakpoints is relatively coincident with cleaning interventions: use of hypochlorite in November 2004, expansion of the cleaning programme (with establishment of a decant ward) in July–September 2007, and formalization of the cleaning programme with additional use of hydrogen peroxide vapour disinfection in July–September 2008, albeit with possible contribution from improved patient isolation and patient review. It seems plausible that patient review, patient isolation and cleaning might act synergistically, in that cleaning is likely to be more effective when all symptomatic patients have been recognized, reviewed and removed from that environment. The first breakpoint for PSH also occurs around the time of an enhanced cleaning intervention (January 2006). The second breakpoint for PSH, which has a very narrow confidence interval, occurred early–mid 2008 and coincides with a period of intense intervention activity targeted against CDI, which included enhancements to cleaning, isolation, antibiotic prescribing and education. The enhanced precision in estimating this breakpoint may be (at least partially) due to the combination of multiple intervention types on CDI transmission.

The finding that deep cleaning was consistently associated with stepwise reductions in CDI incidence rates makes sound biological sense, in that CDI is transmitted through spores which are ubiquitous in the environment and can survive on inanimate objects for prolonged periods.[4] Moreover, routine cleaning measures are not effective in reducing the burden of *C. difficile*,[23] thereby necessitating enhanced or deep cleaning to tackle the burden of environmental contamination that can involve a wide range of sites.[10,24] Enhanced cleaning has also been shown to be effective for other hospital-acquired infections such as meticillin-resistant *Staphylococcus aureus*.[12] Studies have shown that a diverse range of sites can harbour *C. difficile*, and that shedding of *C. difficile* can persist after the resolution of diarrhoea,[25] so decanting patients to a separate ward as part of the infection control process may also be important. The cleaning intervention at CUH that was coincident with the third breakpoint included the use of hydrogen peroxide vapour disinfection. This is supported by the findings that *C. difficile* can be transmitted by the airborne route,[26] and that hydrogen peroxide can be more effective than other cleaning methods at reducing environmental contamination.[27–30]

In addition to the known benefits of efficient and efficacious cleaning programmes, antibiotic prescribing practices can also influence the incidence rates of *C. difficile*.[6,31–33] Broad-spectrum antibiotics are a major trigger for the development of CDI as they disrupt the gastrointestinal bacterial flora, thereby allowing *C. difficile* to grow and produce toxins.[5,6] All antibiotics can result in *C. difficile*-associated disease, but third-generation cephalosporins, penicillins, clindamycin and fluoroquinolones are particularly high risk.[6] CUH restricted the use of cephalosporins in elderly patients in 1997,[34] and restricted fluoroquinolones in May 2008; no immediate impact was demonstrated following the restriction of fluoroquinolone use at CUH (Table IV, Figure 1). Cephalosporins were restricted at PSH in April 2008 at the same time as alterations to cleaning and isolation facilities occurred, whilst fluoroquinolones were not restricted but were discouraged. However, fluoroquinolone usage did not fall in this period (Table IV).

**Table IV**
Daily defined doses of cephalosporins and fluoroquinolones prescribed at two hospitals in England, 2008

| Year | Month | Cephalosporins (DDD) | | Fluoroquinolones (DDD) | |
|---|---|---|---|---|---|
| | | CUH | PSH | CUH | PSH |
| 2008 | Jan | 1192 | 7368 | 4589 | 5401 |
| | Feb | 1153 | 8445 | 3964 | 10051 |
| | Mar | 1119 | 7320 | 3981 | 4745 |
| | Apr | 1020 | 7773 | 4519 | 10330 |
| | May | 1086 | 0 | 4162 | 8250 |
| | Jun | 531 | 123 | 1901 | 6686 |
| | Jul | 583 | 0 | 2128 | 11405 |
| | Aug | 570 | 27 | 1176 | 7838 |
| | Sep | 719 | 0 | 1142 | 8212 |
| | Oct | 856 | 0 | 1535 | 7165 |
| | Nov | 638 | 0 | 1516 | 8435 |
| | Dec | 606 | 6 | 1515 | 9002 |

DDD, daily defined doses; CUH, Cambridge University Hospitals NHS Foundation Trust; PSH, Peterborough & Stamford Hospitals NHS Foundation Trust.

This study describes a useful method for assessing the impact of interventions on time series data. Future developments will include an assessment of the transferability and generalizability of these findings. Of course, no effort has been made to adjust for potential confounding variables, such as the case mix of patients and changing patient to staff ratios, which may have been associated with the number of *C. difficile* cases. Instead, it was assumed that the most likely determinant of structural change for this process would be infection control initiatives. In turn, a modelling method that required no a-priori specification of the dates of breakpoints was selected, as would be required for a segmented regression analysis. The timing of suggested step-wise reductions can be mapped to the implementation of interventions which, in turn, can provide an indication of the effectiveness of interventions for reducing, in this case, CDI incidence in two hospitals in England. While multiple interventions are optimal to reduce the burden of CDI, it is believed that this study demonstrates that, in settings where cephalosporins are not widely used, effective cleaning and rapid isolation are the cornerstones of effective management and prevention of CDI, and have clearly been shown to work in practice. Where decisions regarding the continuation of certain infection control initiatives need to be taken, it may be prudent to consider the effectiveness and impact of cleaning practices in controlling healthcare-associated infections such as *C. difficile*.

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## References

1. Karas JA, Enoch DA, Aliyu SH. A review of mortality due to *Clostridium difficile* infection. *J Infect* 2010;**61**:1—8.
2. Department of Health, Health Protection Agency. *Clostridium difficile infection: how to deal with the problem*. London: Department of Health; 2009.
3. Duerden BI. Contribution of a government target to controlling *Clostridium difficile* in the NHS in England. *Anaerobe* 2011;**17**: 175—179.
4. Viswanathan V, Mallozzi M, Vedantam G. *Clostridium difficile* infection: an overview of the disease and its pathogenesis, epidemiology and interventions. *Gut Microbes* 2010;**1**:234—242.
5. Stoddart B, Wilcox MH. *Clostridium difficile*. *Curr Opin Infect Dis* 2002;**15**:513—518.
6. Owens Jr RC, Donskey CJ, Gaynes RP, Loo VG, Muto CA. Antimicrobial-associated risk factors for *Clostridium difficile* infection. *Clin Infect Dis* 2008;**46**(Suppl. 1):S19—S31.
7. Kaatz GW, Gitlin SD, Schaberg DR, *et al*. Acquisition of *Clostridium difficile* from the hospital environment. *Am J Epidemiol* 1988; **127**:1289—1294.
8. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. *N Engl J Med* 1989;**320**:204—210.
9. Pittet D, Allegranzi B, Sax H, *et al*. Evidence-based model for hand transmission during patient care and the role of improved practices. *Lancet Infect Dis* 2006;**6**:641—652.
10. Dubberke ER, Reske KA, Noble-Wang J, *et al*. Prevalence of *Clostridium difficile* environmental contamination and strain variability in multiple health care facilities. *Am J Infect Control* 2007;**35**:315—318.
11. Dancer SJ. How do we assess hospital cleaning? A proposal for microbiological standards for surface hygiene in hospitals. *J Hosp Infect* 2004;**56**:10—15.
12. Dancer SJ, White LF, Lamb J, Girvan EK, Robertson C. Measuring the effect of enhanced cleaning in a UK hospital: a prospective cross-over study. *BMC Med* 2009;**7**:28.
13. Mulvey D, Redding P, Robertson C, *et al*. Finding a benchmark for monitoring hospital cleanliness. *J Hosp Infect* 2011;**77**:25—30.
14. Hardy KJ, Gossain S, Thomlinson D, Pillay DG, Hawkey PM. Reducing *Clostridium difficile* through early identification of clusters and the use of a standardised set of interventions. *J Hosp Infect* 2010;**75**:277—281.
15. Gran JM, Iversen B, Hungnes O, Aalen OO. Estimating influenza-related excess mortality and reproduction numbers for seasonal influenza in Norway, 1975—2004. *Epidemiol Infect* 2010;**138**:1559—1568.
16. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication using research. *J Clin Pharm Therapeut* 2002;**27**:299—309.
17. Zeileis A, Leisch F, Hornik K, Kleiber C. Strucchange: an R package for testing for structural change in linear regression models. *J Stat Softw* 2002;**7**:1—38.
18. Carey RG. *Improving healthcare with control charts: basic and advanced SPC methods and case studies*. Milwaukee: ASQ Quality Press; 2003.
19. Zeileis A, Kleiber C, Krämer W, Hornik K. Testing and dating of structural changes in practice. *Comput Stat Data Analy* 2003;**44**: 109—123.
20. Scrucca L. qcc: an R package for quality control charting and statistical process control. *R News* 2004;**4**:11—17.
21. Stone SP, Cooper BS, Kibbler CC, *et al*. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *J Antimicrob Chemother* 2007;**59**:833—840.
22. Harris AD, Lautenbach E, Perencevich E. A systematic review of quasi-experimental study designs in the fields of infection control and antibiotic resistance. *Clin Infect Dis* 2005;**41**:77—82.
23. Gerding DN, Muto CA, Owens Jr RC. Measures to control and prevent *Clostridium difficile* infection. *Clin Infect Dis* 2008;**46**:S43—S49.
24. Dumford 3rd DM, Nerandzic MM, Eckstein BC, Donskey CJ. What is on that keyboard? Detecting hidden environmental reservoirs of *Clostridium difficile* during an outbreak associated with North American pulsed-field gel electrophoresis type 1 strains. *Am J Infect Control* 2009;**37**:15—19.
25. 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. *Infect Control Hosp Epidemiol* 2010;**31**:21—27.
26. Best EL, Fawley WN, Parnell P, Wilcox MH. The potential for airborne dispersal of *Clostridium difficile* from symptomatic patients. *Clin Infect Dis* 2010;**50**:1450—1457.
27. Boyce JM, Havill NL, Otter JA, *et al*. Impact of hydrogen peroxide vapor room decontamination on *Clostridium difficile* environmental contamination and transmission in a healthcare setting. *Infect Control Hosp Epidemiol* 2008;**29**:723—729.
28. Shapey S, Machin K, Levi K, Boswell TC. Activity of a dry mist hydrogen peroxide system against environmental *Clostridium difficile* contamination in elderly care wards. *J Hosp Infect* 2008;**70**:136—141.
29. Barbut F, Menuet D, Verachten M, Girou E. Comparison of the efficacy of a hydrogen peroxide dry-mist disinfection system and sodium hypochlorite solution for eradication of *Clostridium difficile* spores. *Infect Control Hosp Epidemiol* 2009;**30**:507—514.
30. Falagas ME, Thomaidis PC, Kotsantis IK, Sgouros K, Samonis G, Karageorgopoulos DE. Airborne hydrogen peroxide for disinfection of the hospital environment and infection control: a systematic review. *J Hosp Infect* 2011;**78**:171—177.
31. Fowler S, Webber A, Cooper BS, *et al*. Successful use of feedback to improve antibiotic prescribing and reduce *Clostridium difficile* infection: a controlled interrupted time series. *J Antimicrob Chemother* 2007;**59**:990—995.
32. Nathwani D, Sneddon J, Malcolm W, *et al*.; Scottish Antimicrobial Prescribing Group. Scottish Antimicrobial Prescribing Group (SAPG): development and impact of the Scottish National Antimicrobial Stewardship Programme. *Int J Antimicrob Agents* 2011;**38**:16—26.
33. Talpaert MJ, Gopal Rao G, Cooper BS, Wade P. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of *Clostridium difficile* infection. *J Antimicrob Chemother* 2011;**66**:2168—2174.
34. Ludlam H, Brown N, Sule O, Redpath C, Coni N, Owen G. An antibiotic policy associated with reduced risk of *Clostridium difficile*-associated diarrhoea. *Age Ageing* 1999;**28**:578—580.