Impact of an intervention to control *Clostridium difficile* infection on hospital- and community-onset disease; an interrupted time series analysis

J. Price[1], E. Cheek[2], S. Lippett[1], M. Cubbon[1], D. N. Gerding[3], S. P. Sambol[3], D. M. Citron[4] and M. Llewelyn[1,5]

1) *Department of Microbiology and Infection, Brighton and Sussex University Hospitals NHS Trust,* 2) *Department of Statistics, University of Brighton, Brighton, UK,* 3) *Hines VA Hospital, Hines Illinois, and Loyola University Chicago Stritch School of Medicine, Maywood, IL* 4) *RM Alden Laboratory, Culver City, CA, USA and* 5) *Brighton and Sussex Medical School, Falmer, Brighton, UK*

Abstract

Strategies to reduce rates of *Clostridium difficile* infection (CDI) generally recommend isolation or cohorting of active cases and the reduced use of cephalosporin and quinolone antibiotics. Data supporting these recommendations come predominantly from the setting of epidemic disease caused by ribotype 027 strains. We introduced an initiative involving a restrictive antibiotic policy and a CDI-cohort ward at an acute, 820-bed teaching hospital where ribotype 027 strains account for only one quarter of all CDI cases. Antibiotic use and monthly CDI cases in the 12 months before and the 15 months after the initiative were compared using an interrupted time series analysis and segmented regression analysis. The initiative resulted in a reduced level of cephalosporin and quinolone use (22.0% and 38.7%, respectively, both $p < 0.001$) and changes in the trends of antibiotic use such that cephalosporin use decreased by an additional 62.1 defined daily doses (DDD) per month ($p < 0.001$) and antipseudomonal penicillin use increased by 20.7 DDD per month ($p = 0.011$). There were no significant changes in doxycycline or carbapenem use. Although the number of CDI cases each month was falling before the intervention, there was a significant increase in the rate of reduction after the intervention from 3% to 8% per month (0.92, 95% CI 0.86–0.99, $p = 0.03$). During the study period, there was no change in the proportion of cases having their onset in the community, nor in the proportion of ribotype 027 cases. CDI cohorting and restriction of cephalosporin and quinolone use are effective in reducing CDI cases in a setting where ribotype 027 is endemic.

Keywords: Antibiotic policy, *clostridium difficile*, Infection control
Original Submission: 28 July 2009; **Revised Submission:** 5 October 2009; **Accepted:** 5 October 2009
Editor: M. Paul
Article published online: 14 October 2009
Clin Microbiol Infect 2010; **16**: 1297–1302
10.1111/j.1469-0691.2009.03077.x

Corresponding author and reprint requests: M. Llewelyn, Infectious Diseases & Therapeutics, Brighton and Sussex Medical School, Medical Research Building, University of Sussex, Falmer, Brighton BN1 9PS, UK
E-mail: m.j.llewelyn@bsms.ac.uk

Introduction

Clostridium difficile has emerged as a major nosocomial pathogen. Numerous reports from North America and Europe have described increases in incidence and severity of *C. difficile* infection (CDI) over the last 10 years [1–3]. There were over 290 000 hospitalizations related to CDI in the USA in 2005 and the UK Health protection agency recorded over 40 000 CDI cases in 2008 [4]. CDI severity appears to have increased as new strains, in particular those of restriction endonuclease (REA) type BI/ribotype 027, have emerged [5,6]. Several features have been implicated in the emergence and virulence of BI/027 strains, including the presence of a binary toxin gene, a deletion in the regulatory *tcdC* gene, resistance to quinolone antibiotics and hypersporulation [7].

The most important modifiable risk factors for developing CDI are antibiotic exposure, particularly to cephalosporin and quinolone antibiotics, and contact with patients with CDI or their caregivers and environment [8].

Consequently, recommendations for the control of CDI frequently involve antibiotic policies restricting the use of these antibiotic classes and enhanced efforts to isolate or cohort patients with active CDI [9,10]. In January 2008, we introduced an initiative in our hospital involving a new antibi-

otic policy restricting cephalosporin and quinolone use and the opening of a ward specifically for the cohorting of patients with CDI. In the present study, we report the impact of this on antibiotic use and the frequency of CDI.

Materials and Methods

Setting

Brighton and Sussex University Hospitals NHS Trust (BSUHT) is an 820-bed teaching hospital providing acute secondary care services to 500 000 people in Brighton, Hove and Mid-Sussex and tertiary services (cardiothoracic, oncology and renal) to a population of approximately two million.

Rationale

We launched the initiative in response to recommendations made by the UK Department of Health Healthcare Commission after an inspection of our hospital in October 2007.

Population and case definitions

Table 1 gives details of the population and case definitions throughout the study. All patients testing positive for *C. difficile* toxins A or B were included in the study. The laboratory does not test repeat samples from the same patient within 30 days of a previous positive sample.

Intervention

The initiative introduced had two main components: (i) the opening of an 11-bed cohort ward for patients with CDI and (ii) a new antibiotic policy restricting the use of cephalosporins and quinolones. Although these measures were introduced simultaneously, efforts to improve compliance with good infection control practice and surveillance were ongoing throughout the study period. Throughout the study, alcohol gels were used as the primary agent for hand hygiene with hand-washing advised after contact with CDI cases.

The cohorting ward was specifically for patients with CDI. Patients testing positive for CDI who still had on-going diarrhoea were transferred to the cohort ward on the same day. The ward had its own nursing staff and all patients admitted to the ward were transferred to the care of the infectious diseases team. All staff working on the ward wore scrubs and put on a new apron and gloves between each patient contact. A small minority of CDI patients had health needs, most usually surgical or high-dependency, which prevented transfer to the ward; however, all patients eligible for transfer to the ward were accommodated there.

The new antibiotic policy replaced cephalosporin and quinolone antibiotics with aminopenicillin or antipseudomonal penicillins. Examples of how this was achieved are given in Table 1. The policy was widely publicised in the hospital but no specific measures were put in place to enforce compliance.

Assessment of impact

A retrospective interrupted time series (ITS) analysis looking at antibiotic use and number of CDI cases was conducted, with the pre-intervention phase being January to December 2007 and the post-intervention phase being January 2008 to March 2009. Data were gathered from information routinely recorded by the infection control and pharmacy departments. Bed occupancy data were obtained from the hospital's clinical information unit.

Outcomes

The primary outcomes were: (i) change in use of targeted antibiotics and (ii) the reduction in number of CDI cases. To determine changes in use of untargeted antibiotics we also gathered data on use of aminopenicillins, antipseudomonal

TABLE 1. Population, clinical setting, nature and timing of interventions

Setting: 820–bed acute teaching hospital with a rate of CDI close to the UK average	Dates: 1 January 2007 to 31 March 2009	Population characteristics: all in-patients from whom a diarrhoeal stool tested positive for *Clostridium difficile* toxin >72 h after admission. Total bed days during the study period
Intervention: A package of measures to combat CDI, specifically a cephalosporin- and quinolone-restrictive antibiotic policy and a cohort ward for CDI patients		
	Antibiotic policy	Isolation policy
Phase 1: 12 months (1 January 2007 to 31 December 2007)	Nonrestrictive antibiotic guidelines	All patients with diarrhoea to go into side-rooms, with standard isolation
Phase 2: 15 months (1 January 2008 to 31 March 2009)	Cephalosporin and quinolone restrictive	All eligible patients to go to CDI cohort ward within 24 h of CDI diagnosis until discharge
Nonrestrictive antibiotic guidelines (phase 1): community-acquired pneumonia; cefuroxime + clarithromycin, cellulitis; ceftriaxone, hospital-acquired pneumonia; ciprofloxacin		
Restrictive antibiotic guidelines (phase 2): e.g. community-acquired pneumonia; amoxicillin + clarithromycin, cellulitis; benzylpenicillin and flucloxacillin, hospital-acquired pneumonia; piperacillin-tazobatam.		
Case definition of CDI (both phases): a patient from whom a liquid stool tested positive for *C. difficile* toxin A or B Case definition of hospital-associated CDI (both phases) : onset more than 72 h after admission to hospital or within 72 h after discharge.		
Detail of the cohorting intervention. The cohorting ward was only for CDI patients and had dedicated nursing staff. All patients were looked after by one medical team. All staff wore scrubs and changed gloves and aprons between all patient contacts. All patients eligible for cohorting on the ward were admitted there during the study period.		

CDI, *Clostridium difficile* infection.

penicillins and carbapenems. For controls, we gathered data on use of doxycycline (an antibiotic unlikely to be affected by the intervention), monthly admissions and bed occupancy.

Potential confounders

Data were obtained on number of admissions and bed days each month but not on compliance with infection control practices such as hand cleaning. There were no major changes in policies related to environmental cleaning (chlorine dioxide solution used for decontamination) or infection control education or monitoring during the study period. There were no changes in laboratory methods for handling samples during the study time, although the laboratory switched from working 5–7 days per week in July 2008.

Microbiological analysis

Throughout the study, hospital policy was that patients with diarrhoea should have stool sent for microbiological analysis and that all liquid stool samples received by the microbiology laboratory were tested for *C. difficile* toxins A and B using Premier toxin A and B ELISA (Meridian Bioscience, Cincinnati, OH, USA). Runs were performed once each day. Formed stools were not tested. In each phase of the study, stool samples from a subset of patients (consecutive patients between June and November 2007 and March to August 2008) who were involved in a separate study of the relationship between ribotype and outcome were frozen at −80°C and subsequently cultured for *C. difficile* (R.M. Alden Research Laboratory, Culver City, CA, USA). *C. difficile* isolates underwent REA in the laboratory of D. Gerding (Hines Veterans Affairs Hospital, Hines, IL, USA).

Statistical analysis

The effect of the intervention on antibiotic usage was analysed using segmented regression analysis to compare the pre- and post-intervention phases in terms of level both and linear trend. The ordinary least squares segmented regression model is given by the equation:

$$Y_t = \beta_0 + \beta_1 \times \text{month}_t + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{month after intervention}_t + \varepsilon_t$$

where Y_t is the outcome in month t, month_t is the number of months from the start of the study period, intervention_t = 0 before the intervention and 1 after the intervention, month after intervention_t is the number of months after the intervention and is equal to zero before the intervention, β_0 is the baseline level of the outcome at the start of the study period, β_1 is the pre-intervention trend, β_2 is the change in post intervention level, β_3 is the change in post intervention trend and ϵ_t is the error. The errors are assumed to be independent. This assumption was tested using the Durbin–Watson statistic. If autocorrelation in the errors was detected, this was adjusted for by including an autoregressive term in the regression model.

A Poisson segmented regression model was used for the number of CDI cases which was assumed to follow a Poisson distribution with mean number of cases in month t, μ_t, given by:

$$\ln(\mu_t) = \beta_0 + \beta_1 \times \text{month}_t + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{month after intervention}$$

Again, the residuals were tested for autocorrelation. Data were analysed using SPSS 15.0.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA).

Ethical considerations

Data on antibiotic use and CDI cases were collected as part of the infection control team's routine clinical governance activity. All data used in the study were anonymized, routinely collected data. In keeping with our institution's policy on governance activity, the study was not subjected to formal ethical review.

Results

Antibiotic use

The impact of the intervention on antibiotic use is described in Fig. 1 and Table 2. There was evidence of first-order autocorrelation in the residuals from the regression on cephalosporins, and therefore a term for the lagged residuals was included in the model. There was no significant residual autocorrelation for the other antibiotics.

Before the intervention, the only significant trend in antibiotic use was a gradual increase in carbapenem use, which continued after the intervention. After the intervention, there were significant decreases in the level of use of cephalosporins (22.0%) and quinolones (38.7%) (both $p < 0.001$). There were also significant changes in the trends for cephalosporins and antipseudomonal penicillins so that use of cephalosporins decreased by an additional 62.1 defined daily doses (DDD) per month ($p < 0.001$) and antipseudomonal penicillins increased by 20.7 DDD per month ($p = 0.011$). The level of aminopenicillin use also appeared to increase after the intervention, although this did not reach statistical significance. There were no significant changes in level or trend for doxycycline use.

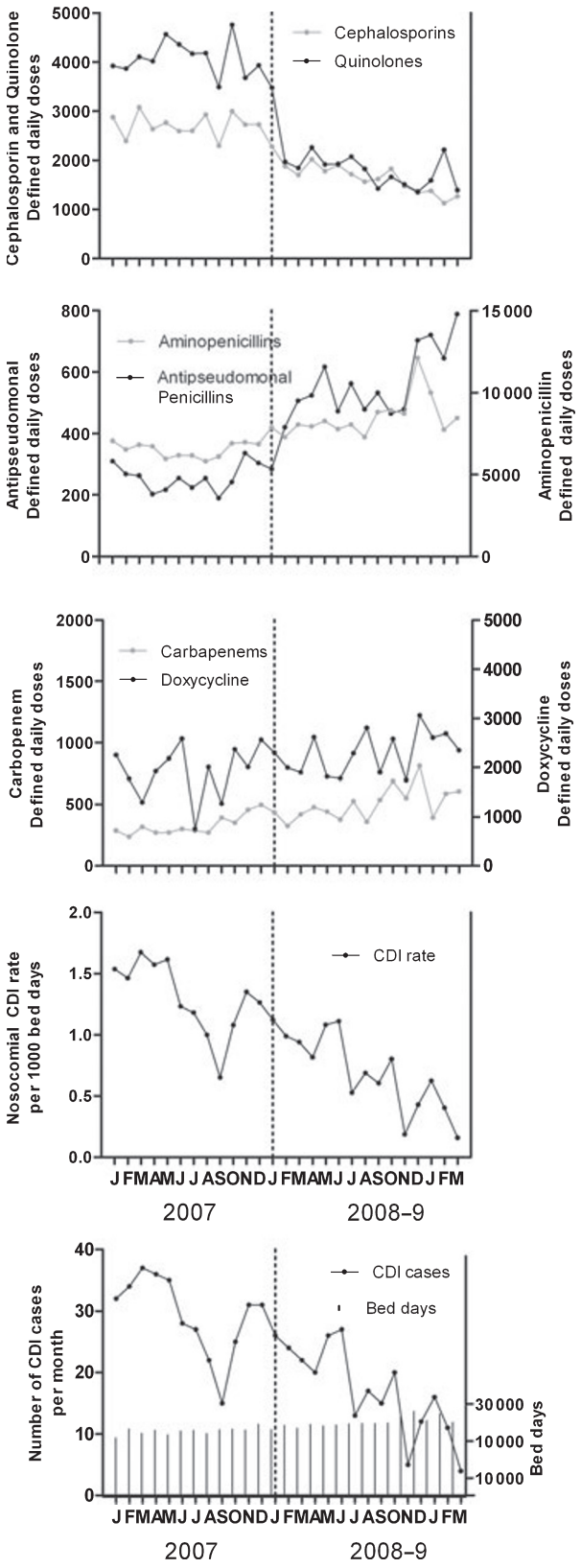

FIG. 1. Monthly antibiotic use (defined daily doses), *Clostridium difficile* infection (CDI) rate for nosocomial cases, total number of CDI cases and bed days between January 2007 and March 2009.

CDI cases

In the pre-intervention phase, there were 353 CDI cases and 82 887 admissions to the hospital compared to 258 CDI cases and 117 358 admissions in the post-intervention phase. The CDI rate was 1.30 cases/1000 bed days in the pre-intervention period and 0.69 cases/1000 bed days in the post-intervention period. In the segmented Poisson regression analysis of the total number of CDI cases, the residuals showed no evidence of autocorrelation and no adjustment was made. Prior to the intervention, there was a significant downward trend, with the number of cases decreasing by 3% per month [multiplicative factor of exp(−0.032) = 0.97 per month (p 0.04, 95% CI 0.94–1.00)]. After the intervention, there was a significant change, with the number of cases decreasing by 8% per month (multiplicative decrease per month was exp(−0.032) × exp(−0.047) = 0.92 (p 0.03, 95% CI 0.86–0.99). The goodness of fit of the model was adequate (χ^2 = 31.5, p 0.11).

The proportion of CDI cases each month with an onset in the community varied between 0.29 and 0.73. There was no significant change in the proportion of community cases before and after the intervention.

Microbiological analysis

C. difficile was cultured from 68 and 59 cases in phases 1 and 2 of the study, respectively. The proportion of cases caused by different REA types is shown in Table 3. Ribotypes are inferred from Killgore *et al.* [11]. In both phases, REA type/ribotype strains DH/106 and BI/027 predominated. There was no significant difference in the frequency of different strain types between the study phases (p 0.17).

Discussion

We have reported the impact of an initiative to combat CDI that was associated with a sustained reduction in the number of CDI cases at our hospital. We have described the intervention and analysis in line with the ORION statement on reporting intervention studies in nosocomial infection [12]. We have chosen to analyse the impact of the intervention on the total number of CDI cases per month rather than correcting for number of admissions or bed occupancy because our CDI patients are almost exclusively very elderly and have extensive health care contact, even if their CDI symptoms had an onset outside hospital. Consequently, it does not appear to be appropriate to either exclude the community-onset cases from analysis or to correct the total case number for our hospital activity. Nevertheless, because the burden of CDI is more commonly presented as rate per

TABLE 2 Antibiotic use before and after the intervention. The effect of the intervention on antibiotic usage (expressed as defined daily doses) was analysed using segmented regression analysis to compare the pre- and post-intervention phases in terms of level both and linear trend

	Pre-intervention			Post-intervention change			
Antibiotic	**Level**	**Trend**	**p-value**	**Level**	**p-value**	**Trend**	**p-value**
Cephalosporins	2703 (2553, 2852)[a]	2.072 (−18.44, 22.58)[a]	0.836	−594.2 (−786.3, −402.1)[a]	<0.001	−62.14 (−86.73, −37.55)[a]	<0.001
Quinolones	4105 (3592, 4618)	−3.43 (−73.18, 66.32)	0.920	−1588 (−2229, −947.2)	<0.001	−69.33 (−155.1, 16.40)	0.108
Aminopenicillins	6527 (5401, 7652)	−3.64 (−156.6, 149.3)	0.961	922.2 (−482.7, 2327)	0.188	138.5 (−49.51, 326.4)	0.141
Antipseudomonal Penicillins	246.1 (154.1, 338.1)	1.45 (−11.05, 13.95)	0.813	106.2 (−8.626, 221.1)	0.068	20.67 (5.300, 36.03)	0.011
Doxycycline	1744 (1128, 2360)	25.78 (−57.95, 109.5)	0.531	−74.22 (−843.3, 694.9)	0.844	13.04 (−89.87, 116.0)	0.796
Carbapenems	212.2 (97.9, 326.5)	17.86 (2.33, 33.39)	0.026	−64.70 (−207.4, 77.95)	0.36	−0.279 (−19.37, 18.81)	0.976

95% confidence intervals are given in parentheses.
[a]Adjusted for first-order autocorrelation.

TABLE 3. Frequency of *Clostridium difficile* strain types

	Phase 1	Phase 2
DH/106	25 (36.8)	26 (44.1)
BI/027	19 (27.9)	15 (25.4)
G/002	6 (8.8)	1 (1.7)
J/001	5 (7.4)	1 (1.7)
Other	13 (19.1)	16 (27.1)
Total	68 (100)	59 (100)

Ribotypes are inferred from restriction endonuclease type according to Killgore *et al.* [11]. Number and (%) of each type are shown. No significant differences exist in the proportion of cases caused by each strain type in each phase of the study ($p = 0.17$).

10000 bed days for hospital-onset disease, we also provide these data in Fig. 1.

A major challenge for any study which, like ours, attempts to assess the impact of a healthcare-associated infection intervention is to be certain that any changes observed are truly accounted for by the intervention. When we introduced the initiative in January 2008, we were already making considerable efforts to improve infection control practice and this is the likely explanation for the downward trend in CDI cases before the intervention. Recent guidelines in the UK and elsewhere describe wide-ranging measures to combat CDI but, arguably, the two measures most likely to change practice are enhanced isolation and restriction of cephalosporin and quinolone use; precisely the measures we introduced [9].

These measures were introduced simultaneously in our hospital and no other significant changes in practice likely to impact on *C. difficile* transmission were made at this time. Our demonstration of a statistically robust change in CDI rates after the intervention supports the efficacy of enhanced isolation and antibiotic restriction in reducing CDI. Because the two elements of our intervention were introduced together, our data do not allow us to distinguish the relative impact of each. A further limitation of the present study is that we have not been able to assess the potential for changes in antibiotic policy to cause harm in terms of either changing patterns of resistance or adverse clinical outcomes. Neither have we assessed the costs of the intervention. However, given the relative paucity of data supporting the efficacy of cohort wards and antibiotic restriction in controlling CDI, we feel that real-life clinical data such as ours are important.

Several previous studies have assessed the impact of infection control strategies on CDI. Two recent North American studies conducted in the setting of epidemic spread of BI/027 strains demonstrated a reduction in CDI incidence associated with restriction of high-risk antibiotics, both alone and as part of a 'bundle' of measures [13,14]. Similarly, Debast *et al.* [15] demonstrated the efficacy of a 'bundle' approach in a Dutch hospital, also in the context of an epidemic of BI/027 disease.

In the UK, the epidemiology of *C. difficile* has involved the progressive replacement of J/001 strains by DH/106 and BI/027 strains rather than the epidemic emergence of BI/027 that has been seen elsewhere [16]. Our data are therefore very typical of the UK, demonstrating the co-existence of BI/027 and DH/106 strains in our patient population. Our data demonstrate no increase in ribotype 027 over the time period of this study. Although our sample size is small, the data obtained do not suggest that our intervention has affected BI/027 strains differentially. This may be because DH/106 strains, which are uncommon outside the UK, are, similar to BI/027 strains, usually resistant to quinolone antibiotics [16]. Fowler *et al.* [17] reported that the control of broad-spectrum antibiotic use was effective in reducing CDI in another UK acute hospital. That study did not contain any strain analysis and was conduced before BI/027 strains became established in the UK.

The present study also differs from previous studies in that we have observed a reduction in both hospital- and

community-onset CDI. It is possible that this is explained by changes in infection control or antibiotic prescribing in primary care at the same time as our intervention. This is unlikely because no specific infection control interventions were made in the community during the study period. It is more likely that, in an endemic setting where CDI affects, almost exclusively, very elderly patients with extensive health care contact, infection control interventions in secondary care impact on CDI presenting in both primary and secondary care. This further suggests that interventions in primary care, particularly targeting antibiotic prescribing, should impact on both hospital and community onset CDI.

Acknowledgements

We are grateful to J. Cohen for his comments on the manuscript.

Transparency Declaration

The costs of *C. difficile* culture and typing of isolates in this study was supported by Optimer Pharmaceuticals (San Diego California) and the US Department of Veterans Affairs Research Service through a grant to D.N.G.. D.N.G. holds patents for the prevention and treatment of *C. difficile*-associated disease licensed to ViroPharma, has research funding from Massachusetts Biological Laboratories, ViroPharma, GOJO, Cepheid, Optimer and Merck, is a consultant for Optimer, Salix, GOJO, Schering-Plough, Cepheid, BD GeneOhm and ViroPharma. The other authors are not aware of any conflicts of interest.

References

1. Loo VG, Poirier L, Miller MA *et al.* A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005; 353: 2442–2449.
2. Pepin J, Valiquette L, Alary ME *et al. Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ* 2004; 171: 466–472.
3. Kuijper EJ, van Dissel JT, Wilcox MH. *Clostridium difficile*: changing epidemiology and new treatment options. *Curr Opin Infect Dis* 2007; 20: 376–383.
4. Zilberberg MD, Shorr AF, Kollef MH. Increase in adult *Clostridium difficile*-related hospitalizations and case-fatality rate, United States, 2000–2005. *Emerg Infect Dis* 2008; 14: 929–931.
5. McDonald LC, Killgore GE, Thompson A *et al.* An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med* 2005; 353: 2433–2441.
6. Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. *Infect Control Hosp Epidemiol* 2002; 23: 653–659.
7. Razavi B, Apisarnthanarak A, Mundy LM. *Clostridium difficile*: emergence of hypervirulence and fluoroquinolone resistance. *Infection* 2007; 35: 300–307.
8. Dubberke ER, Reske KA, Yan Y, Olsen MA, McDonald LC, Fraser VJ. *Clostridium difficile* – associated disease in a setting of endemicity: identification of novel risk factors. *Clin Infect Dis* 2007; 45: 1543–1549.
9. Department of Health. http://doh.gov.uk. *Clostridium difficile* infection: how to deal with the problem. 2009. [cited 2009 July 24] Health Protection Agency. Available at: http://hpa.org.uk.
10. Dubberke ER, Gerding DN, Classen D *et al.* Strategies to prevent *clostridium difficile* infections in acute care hospitals. *Infect Control Hosp Epidemiol* 2008; 29 (suppl 1): S81–S92.
11. Killgore G, Thompson A, Johnson S *et al.* Comparison of seven techniques for typing International epidemic strains of *Clostridium difficile*: restriction endonuclease analysis, pulsed-field gel electrophoresis, PCR-ribotyping, multilocus sequence typing, multilocus variable-number tandem-repeat analysis, amplified fragment length polymorphism, and surface layer protein A gene sequence typing. *J Clin Microbiol* 2008; 46: 431–437.
12. Stone SP, Cooper BS, Kibbler CC *et al.* The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *Lancet Infect Dis* 2007; 7: 282–288.
13. Muto CA, Blank MK, Marsh JW *et al.* Control of an outbreak of infection with the hypervirulent *Clostridium difficile* BI strain in a university hospital using a comprehensive "bundle" approach. *Clin Infect Dis* 2007; 10: 1266–1273.
14. Valiquette L, Cossette B, Garant MP, Diab H, Pepin J. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin Infect Dis* 2007; 2: S112–S121.
15. Debast SB, Vaessen N, Choudry A, Wiegers-Ligtvoet EA, van den Berg RJ, Kuijper EJ. Successful combat of an outbreak due to *Clostridium difficile* PCR ribotype 027 and recognition of specific risk factors. *Clin Microbiol Infect* 2009; 15: 427–434.
16. Brazier JS, Raybould R, Patel B *et al.* Distribution and antimicrobial susceptibility patterns of *Clostridium difficile* PCR ribotypes in English hospitals, 2007-08. *Euro Surveill* 2008; 9: 13.
17. 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.