An evaluation of the impact of antibiotic stewardship on reducing the use of high-risk antibiotics and its effect on the incidence of *Clostridium difficile* infection in hospital settings

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Objectives: To evaluate the impact of a high-risk antibiotic stewardship programme on reducing antibiotic use and on hospital *Clostridium difficile* infection (CDI) incidence rates. A secondary objective was to present the possible utility of time-series analysis as an antibiotic risk classification tool.

Methods: This was an interventional, retrospective, ecological investigation in a medium-sized hospital over 6.5 years (January 2004 to June 2010). The intervention was the restriction of high-risk antibiotics (second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones and clindamycin). Amoxicillin/clavulanic acid and macrolides were classified as medium-risk antibiotics based on time-series analysis findings and their use was monitored. The intervention was evaluated by segmented regression analysis of interrupted time series.

Results: The intervention was associated with a significant change in level of use of high-risk antibiotics (coefficient −17.3, $P < 0.0001$) and with a borderline significant trend change in their use being reduced by 0.156 defined daily doses/100 bed-days per month ($P = 0.0597$). The reduction in the use of high-risk antibiotics was associated with a significant change in the incidence trend of CDI ($P = 0.0081$), i.e. the CDI incidence rate decreased by 0.0047/100 bed-days per month. Analysis showed that variations in the incidence of CDI were affected by the age-adjusted comorbidity index with a lag of 1 month (coefficient 0.137051, $P = 0.0182$). Significant decreases in slope (coefficient −0.414, $P = 0.0309$) post-intervention were also observed for the monitored medium-risk antibiotics.

Conclusions: The restriction of the high-risk antibiotics contributed to both a reduction in their use and a reduction in the incidence of CDI in the study site hospital. Time-series analysis can be utilized as a risk classification tool with utility in antibiotic stewardship design and quality improvement programmes.

Keywords: time-series analysis, *C. difficile* infection, risk classification, quality improvement

Introduction

Although the introduction of antibiotics is considered to be one of the key medical interventions in relation to reducing human morbidity and mortality, their intensive use has contributed to the spread of pathogen resistance, which greatly reduces therapeutic options.[1,2] Antibiotic resistance is a multifactorial problem that requires a multifaceted solution, including strategies to optimize the use of current antibiotics, improved diagnostics to identify the aetiology of infections, the development of new antibiotics and vaccines, infection control measures to prevent transmission of resistant species, and educational activities for both public and healthcare professionals.[3] In recognition of the size of the problem, antimicrobial stewardship approaches have been developed with the ultimate goal of maximizing clinical

cure while limiting the unintended consequences, such as the emergence and spread of resistance.[4] The role of antibiotic stewardship as a modality to improve patient care and healthcare outcomes has been well documented, and as such is considered a central component in any multifaceted approach.[4–8]

A key driver for informing the development of an efficient antibiotic policy should be the identification of the specific antibiotics that contribute most to the spread of local pathogen resistance and then to reduce their use. Following a major *Clostridium difficile* infection (CDI) outbreak in the Northern Health and Social Care Trust (NHSCT) in Northern Ireland in January 2008,[9] and in the light of reports of association of high-risk antibiotics (such as fluoroquinolones and cephalosporins) with the spread of CDI,[10] a revised antibiotic policy was created and implemented across the NHSCT. This policy included the restriction of high-risk antibiotics (second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones and clindamycin; January 2008). In September 2008, the remaining antibiotics were classified and grouped as medium or low risk. The medium-risk antibiotic classification (i.e. amoxicillin/clavulanic acid and macrolides) was based on the identified size effect of each class, utilizing a robust time-series analysis.[11] The purpose of this classification was to monitor the use of antibiotic risk groups. This analysis is considered the appropriate technique to evaluate temporally sequenced observations on resistant pathogens and antibiotic use since it takes into account the autocorrelation existing between consecutive observations.[12–15]

The aim of the present investigation was to evaluate the impact of restricting high-risk antibiotics (which commenced in January 2008) on reducing their use and on CDI incidence rates. A secondary objective was to evaluate the possible utility of time-series analysis as an antibiotic risk classification tool and examine how it can inform the design of efficient, specifically tailored strategies aimed at optimizing antibiotic therapy in healthcare settings.

Methods

Setting and study period

The Northern Health and Social Care Trust (NHSCT) consists of four acute hospitals: Antrim Area Hospital, Mid-Ulster Hospital, Whiteabbey Hospital and Causeway Hospital, serving a population of ∼420000 inhabitants. The present study took place in one hospital within the Trust (Causeway; 233 beds), since this hospital was not affected by a CDI outbreak which occurred in 2008.[9] The study involved an ecological time-series analysis with a defined intervention period. The intervention took place in January 2008, and its impact on reducing the use of high-risk antibiotics was assessed through evaluation of antibiotic usage for the period January 2004 to June 2010. However, its specific impact on the incidence of CDI was evaluated for the period from April 2006 to June 2010, since age-adjusted comorbidity index data were only available for this period (see below). An overview of the study characteristics and definitions is provided in Figure 1.

Microbiology and pharmacy data

The number of CDI cases was obtained from the clinical microbiology information system on a monthly basis and expressed per 100 bed-days. The presence of *C. difficile* was identified via the detection of toxins A and B directly from the faeces of patients with suspected CDI. The

microbiology laboratory utilized the Premier™ Toxin A and B kit, an ELISA technique. A CDI case was defined as a toxin-positive test plus diarrhoea [an increased number (two or more) of watery/liquid stools, i.e. type 5, 6 and 7 according to the Bristol Stool Scale,[16] that is greater than normal for the patient, over a period of 24 h].

Antibiotic use data were obtained from the pharmacy information system at monthly intervals and were converted into defined daily doses (DDDs; ATC/DDD version 2010),[17] and expressed as number of DDDs per 100 bed-days. The age-adjusted comorbidity index was calculated using the Charlson index[18] and necessary data for calculations were obtained from the Hospital Episode Statistics (HES) database. Data in relation to age-adjusted comorbidity index were available from April 2006.

Hospital antibiotic policy

The NHSCT devised an antibiotic policy to minimize the use of high-risk antibiotics (January 2008; Tables S1 and S2, available as Supplementary data at *JAC* Online). In September 2008, the NHSCT classified other antibiotics as medium-risk (amoxicillin/clavulanic acid and macrolides) or low-risk antibiotics (Table S3, available as Supplementary data at *JAC* Online) based on the findings of a previously published time-series analysis study.[11] For example, previous analysis showed that treatment of 14 and 8 patients with second- and third-generation cephalosporins, respectively, would result in the occurrence of one CDI case, whilst treatment of 94 and 78 patients with amoxicillin/clavulanic acid and macrolides would result in the development of one CDI case.[11] The latter estimation of size effects confirmed the classification of the second- and third-generation cephalosporins (and in a similar way the fluoroquinolones) as high-risk antibiotics, while assisting in classifying amoxicillin/clavulanic acid and macrolides as medium-risk antibiotics. The revised antibiotic policy is shown in Tables S2 and S3, available as Supplementary data at *JAC* Online.

The revised policy was in place in January 2008, and adherence to the policy was improved and maintained as described elsewhere (i.e. using audit and feedback and preauthorization requirements).[19] Clinical staff were encouraged to adhere to the hospital policy and their compliance with the hospital policy was observed and recorded using a standardized procedure form.[19] The use of antimicrobials not included in the policy was monitored through exemption forms which required authorization by a consultant microbiologist. The exemption forms were assessed by the Antimicrobial Management Team (AMT) as appropriate or inappropriate with a written explanation. Results of the audits (including exemption form audits) were directly shared with the prescribing physicians.

Statistical analysis

The impact of restricting the use of high-risk antibiotics on their actual use and on CDI incidence rates was evaluated utilizing the segmented regression analysis of interrupted time series, as described elsewhere.[20] This analysis allowed estimation of changes between pre-intervention (January 2004 to December 2007) and intervention (January 2008 to June 2010) phases, while accounting for both sudden changes and the change trends of the outcome of interest. Monthly cases of CDI were modelled as incidence rate and the monthly mean age-adjusted comorbidity indices were also modelled in the analysis. All modelled CDI and antibiotic variables were stationary at the 5% level according to the augmented Dickey–Fuller test. The high-risk antibiotic series was tested for stationarity before and after the intervention. Analysis of the residuals of the fitted models showed that residuals were normally distributed (using the Jarque–Bera test), and there was no evidence of serial correlation (according to the Breusch–Godfrey test). In addition, analysis of the residuals of the fitted models showed no evidence of

| Setting: Causeway Hospital (233 beds), provides a range of acute hospital services (e.g. general medicine, cardiology, general surgery, gynaecology, intensive care etc.), with one full-time microbiology consultant and one full-time Infection Prevention and Control Nurse (IPCN). | Dates: (i) 1 January 2004 to 30 June 2010, for the evaluation of the intervention effect on the use of high-risk antibiotics; and (ii) 1 April 2006 to 30 June 2010, for the evaluation of the intervention effect on the incidence of CDI. | Population characteristics: All adult inpatients admitted to Causeway, including medical, cardiology, surgical, gynaecology and intensive care patients. Annual average of 13556 admissions was documented. |

Major infection control changes during the study period: Restriction of high-risk antibiotic group: second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones and lincosamides (clindamycin).

	Antibiotic policy	CDI screening policy	Cleaning policy
Phase 1: 48 months (1 January 2004 to 31 December 2007)	There were no formal antibiotic guidelines for the year 2004; however, antibiotics were grouped as described in Table S1, and represented guidance similar to an antibiotic policy. Antibiotic guidelines were in place for the years 2005-2010. Fluoroquinolones and cephalosporins were used for the period prior to January 2008 (see Table S2).	The testing of faeces from all patients 65 years of age and older with diarrhoea was the routine practice. The testing of faeces for patients at least 2 years of age and younger than 65 years of age was done at physician request; toxin assays were done twice per day.	Detergent and water were used for general ward cleaning, on a daily basis. Detergent followed by 1000 ppm hypochlorite solution was used for cleaning the bed space on transfer and the isolation rooms on discharge or transfer of the CDI patient.
Phase 2: 30 months (1 January 2008 to 30 June 2010)	An antibiotic risk group was implemented as follows. (i) High-risk group (January 2008): second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones and clindamycin. (ii) Medium-risk group (September 2008): amoxicillin/clavulanic acid and macrolides. (iii) Low-risk group (September 2008): the remaining used antibiotics (see Table S3). Revised guidelines (see Table S2) were in place across the hospital.	Diarrhoeal stool from all patients 12 years of age and older was tested. Toxin assays were done twice per day and when requested by the physician.	Chlorine dioxide (Tristel®) was used for general ward cleaning on a daily basis from January 2008 to October 2009. This was changed to chlorine releasing agent (Actichlor®) from November 2009 to June 2010. Detergent followed by 1000 ppm hypochlorite solution was used for cleaning the bed space on transfer and isolation rooms on a daily basis and on discharge or transfer of the patient.

Isolation policy (for both phases): All CDI cases isolated in single rooms. Aprons and gloves worn as for contact precautions. Hand hygiene with soap and water before and after all contact with CDI patients, as alcohol rub is not sporicidal. Each single room had a sink-and wall-mounted soap dispenser.

Definition of *Clostridium difficile* infection (CDI): a toxin-positive test plus diarrhoea [an increased number (two or more) of watery/liquid stools (i.e. type 5, 6 and 7 according to the Bristol Stool Scale) that is greater than normal for the patient, over a period of 24 h]. Duplication was removed from these data such that more than one positive *C. difficile* test from the same patient (≤28 days apart) was considered as a single case.

Figure 1. Overview of setting, population, antibiotic policy and infection control interventions, isolation policy and definitions.

heteroscedasticity (using the Breusch–Pagan–Godfrey test) with the exception of high- and low-risk antibiotic models; heteroscedasticity-adjusted standard errors were used for the latter series. Significance tests for parameter estimates were used to eliminate the unnecessary terms in the CDI models in order to generate the most parsimonious model. A *P* value of <0.05 was considered to be statistically significant, and the most parsimonious CDI model was selected. Analyses were performed using EViews 6 software (QMS, Irvine, CA, USA).

Results

A total of 320 CDI cases were identified in the study site hospital over the six and a half year study period (January 2004 to June 2010). The average observed monthly hospital CDI incidence was 0.08/100 bed-days (range, 0–0.27). In the pre-intervention period (January 2004 to December 2007), there was a significant increase over time in the use of all antibiotic risk groups (Table 1). The monthly average age-adjusted comorbidity index for the period April 2006 to June 2010 was 2.54 (range, 2.26–2.81). An increased trend in age-adjusted comorbidity index (*P*<0.0001) was observed over this period (Figure 2).

The results showed that the introduction of the revised antibiotic policy was associated with a significant change in level of use of high-risk antibiotics (coefficient −17.3, *P*<0.0001) and total antibiotic use (coefficient −14.2, *P*=0.0074), but

there was no significant change in level of use for medium- and low-risk antibiotics (Table 1). There was a borderline significant change in high-risk antibiotic use trend after the intervention, with their use being reduced by 0.156 DDD/100 bed-days per month (*P*=0.0597). Significant decreases in the slope (coefficient −0.414, *P*=0.0309) and a trend towards significance (coefficient −0.455, *P*=0.0823) post-intervention were also observed for medium-risk antibiotics and total antibiotic use, respectively (Table 1). Graphs for monthly CDI incidence rates versus use of antibiotic risk groups are presented in Figure 3.

Before the introduction of the antibiotic policy intervention, results obtained with model a showed that there was no significant trend change in the CDI incidence rate (*P*=0.2086; Table 2). After the intervention, there was no significant change in the level (*P*=0.3093); however, a significant change in trend was observed (*P*=0.0081), with the CDI incidence rate being reduced by 0.0047/100 bed-days per month. In addition, analysis showed that variations in the incidence of CDI were affected by the age-adjusted comorbidity index with a lag of 1 month (coefficient 0.137051, *P*=0.0182; Table 2). The determination coefficient (R^2) of the final model was 0.32, i.e. 32% of the variation in the incidence of CDI in the study site hospital was explained by the identified model for the entire study period. After eliminating the non-significant terms in model a, both slope change and the mean age-adjusted comorbidity index

Table 1. Changes in antibiotic use after the intervention using segmented regression analysis, Causeway Hospital, January 2004 to June 2010

Antibiotics	Intercept (SE)	Trend (SE)	P value	Level change after the intervention (SE)	P value	Trend change after the intervention (SE)	P value	R^2
High-risk	16.33913 (0.858485)	0.127907 (0.042300)	0.0034	−17.32837 (1.889594)	<0.0001	−0.156308 (0.081729)	0.0597	0.85
Medium-risk	29.51124 (2.343088)	0.409639 (0.083249)	<0.0001	1.681502 (3.756344)	0.6557	−0.413556 (0.187981)	0.0309	0.45
Low-risk	27.26129 (1.306487)	0.130833 (0.044098)	0.0040	1.433148 (1.802152)	0.4290	0.115238 (0.120102)	0.3404	0.50
Total	73.11165 (3.217255)	0.668378 (0.114308)	<0.0001	−14.21372 (5.157773)	0.0074	−0.454626 (0.258113)	0.0823	0.34

SE, standard error.
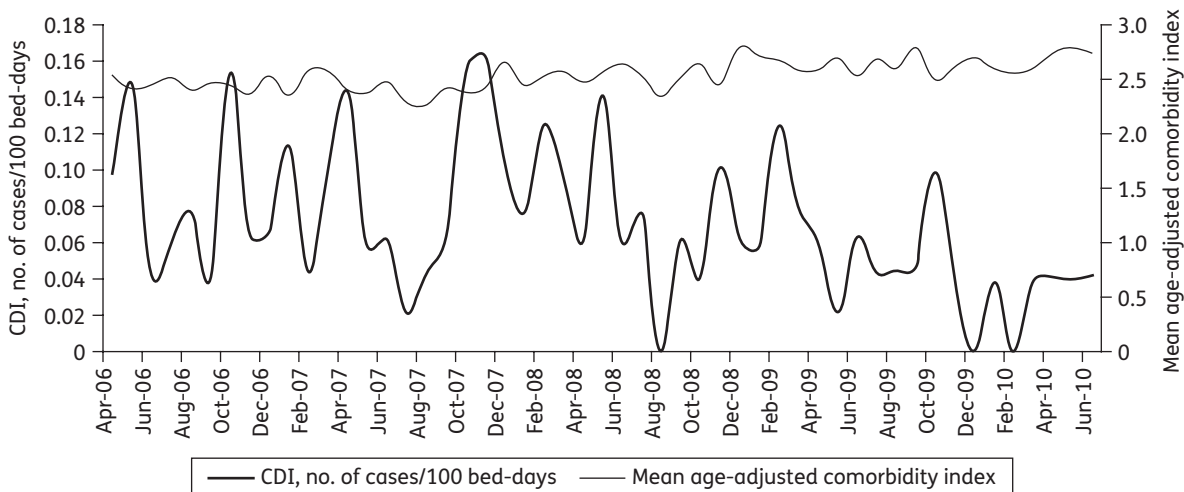
Figure 2. Monthly CDI incidence versus monthly mean age-adjusted comorbidity index, April 2006 to June 2010, Causeway Hospital.
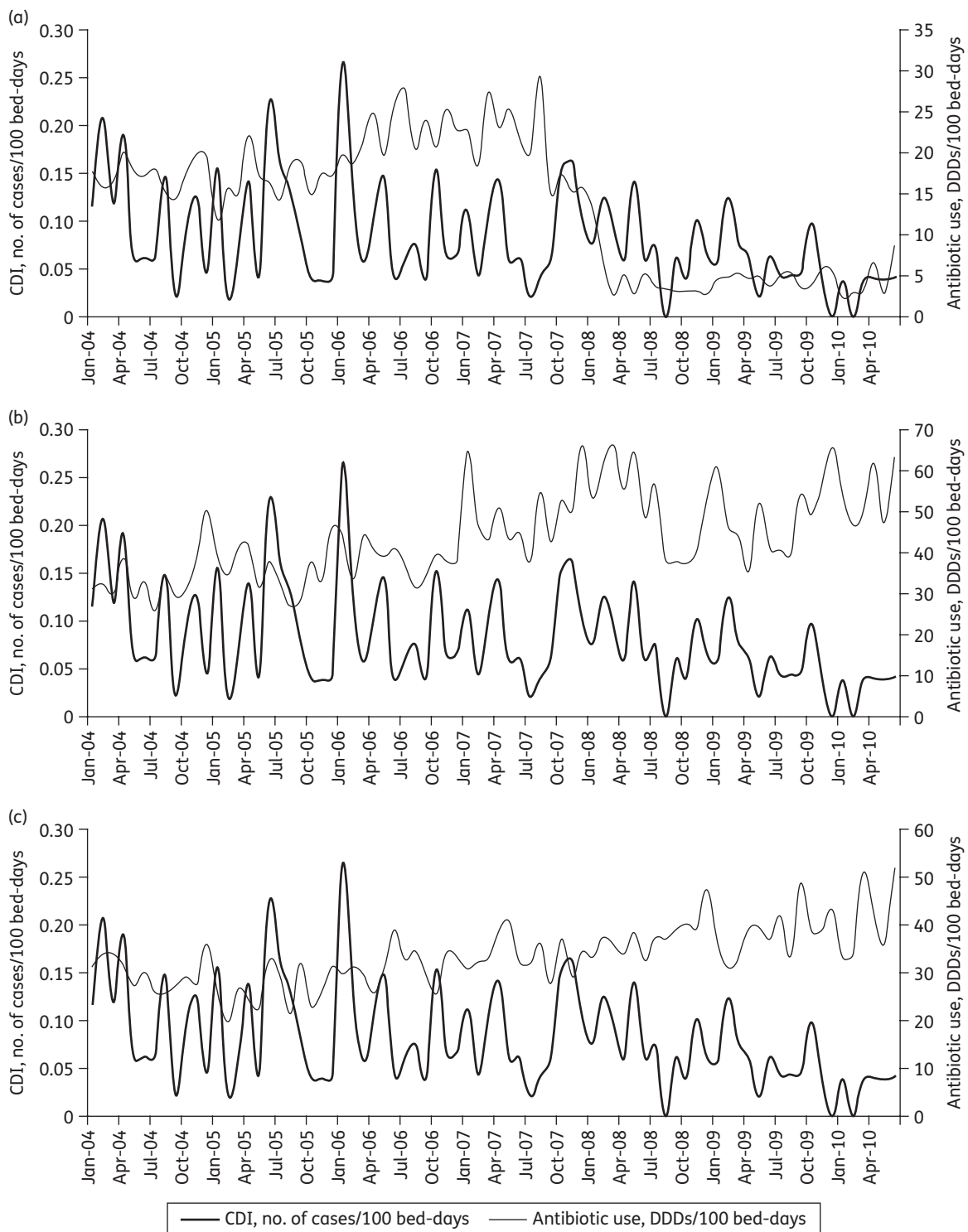
Figure 3. Monthly CDI incidence versus use of antibiotic risk groups, January 2004 to June 2010: (a) high-risk antibiotic group; (b) medium-risk antibiotic group; and (c) low-risk antibiotic group.

variables remained significant in the most parsimonious model (model b; Table 2). Plots for the monthly CDI incidence versus use of high- and medium-risk antibiotic groups are presented in Figures 4 and 5. In order to give a better visual representation of these plots, data were plotted using a 5 month moving average transformation, i.e. the value plotted for a specific month is the average of the value observed that month, the previous 2 months and the following 2 months.

Table 2. Parameter estimates from the full and most parsimonious segmented regression models assessing changes in *C. difficile* incidence rates after the intervention, Causeway Hospital, April 2006 to June 2010

Term	Coefficient (SE)[a]	T ratio	P value
a. Full segmented regression model ($R^2=0.32$)			
intercept	−0.317859 (0.157838)	−2.013837	0.0500
trend	0.001819 (0.001426)	1.275851	0.2086
level change after the intervention	−0.02262 (0.021995)	−1.028396	0.3093
trend change after the intervention	−0.004703 (0.001698)	−2.770124	0.0081
mean age-adjusted comorbidity index[b]	0.137051 (0.055915)	2.451039	0.0182
b. Most parsimonious segmented regression model ($R^2=0.29$)			
intercept	−0.200868 (0.127628)	−1.573862	0.1222
change in trend after the intervention	−0.002908 (0.000670)	−4.339937	0.0001
mean age-adjusted comorbidity index[b]	0.117378 (0.051837)	2.264382	0.0282

[a]Indicates the size and direction of the effect; SE, standard error.
[b]Lag time, 1 month; represents the delay necessary to observe the effect.

Discussion

AMTs face a constant challenge in designing their local antibiotic stewardship programme efficiently in the face of high and increasing resistance, a patient population with multiple comorbidities, and the limited number of new antibiotics being available. The findings of this study showed that the introduction of the antibiotic policy was associated with a significant reduction in the use of high-risk antibiotics. Although there was no significant change in the use of the medium-risk antibiotics, it is interesting to note that monitoring their use resulted in halting an increased use trend (pre-intervention) and reversing it into a significant decreased trend (post-intervention; Table 1). There were no significant changes in either the level or the trend in low-risk antibiotics.

Given the previous points, together with the reduction in medium-risk antibiotics being relatively small, and the fact that the data showed that the incidence of CDI was significantly decreased, it is reasonable to assume that the reduction in the use of high-risk antibiotics was likely to be the predominant factor in driving the observed decrease in CDI incidence rates. The present findings are in line with the evidence of the involvement of the identified antibiotic agents in increasing CDI incidence rates in hospitals, and provide further evidence for the cause–effect relationship between antibiotic use and resistance proposed by McGowan.[10,11,15,21–29] In addition, the analysis included an adjustment for patient case mix characteristics (i.e. the Charlson comorbidity index). The age-adjusted comorbidity index is considered an essential criterion in determining the disease burden, thus providing risk-adjustment criteria for case-mix purposes.[18,30]

The involvement of the AMT in optimizing adherence to the antibiotic policy was a key step in the successful implementation of the policy and thus the observed decrease in CDI incidence rates. There are two proactive core strategies that provide the foundation for an antimicrobial stewardship programme: (i) prospective audit of antimicrobial use with direct interaction and feedback to the prescriber; and (ii) formulary restriction and pre-authorization requirements, which were linked to immediate and significant reductions in antimicrobial use and costs. Prospective audit and prescriber feedback is undoubtedly effective in improving antibiotic prescribing, although maintaining such practice is challenging. The long-term beneficial impact of formulary restriction on controlling antimicrobial resistance was less clear.[4] The results of this dual approach, however, were satisfactory and this approach could be implemented in hospitals as routine practice for maintaining desired levels of adherence to hospital antibiotic policy.[19]

While much effort has been dedicated to improved antibiotic stewardship, there is a lack of robust methodological tools to guide informed decisions on optimizing antibiotic prescribing (e.g. determining antibiotic classes to be restricted). A practical method for modelling time series by the use of autoregressive integrated moving average (ARIMA) models was provided by Box and Jenkins,[14] and its application to the assessment of relationships between antibiotic use and resistance has been presented in several studies.[11,15,30–35] In addition, a possible way forward for estimating the number of patients needed to be treated with specific antibiotics in order to cause the incidence of a pathogen case, within a specific time-frame, has been provided.[11,15] The latter assisted in the design of efficient antibiotic stewardship along the lines presented in the present paper (which was demonstrated through reversing the increased use of the monitored medium-risk antibiotics), and, as such, time-series analysis may have the potential to be used as a risk classification tool.

The study has some limitations. First, the impacts of restricting high-risk antibiotic use on CDI incidence rates could have been improved if other possible predictors (e.g. infection control activity) had been available. Such variables are likely to be involved in the variance that was not explained by the model presented. Second, it was not possible to obtain data on the distribution of severe CDI cases (and related mortality) before and after the intervention. Nevertheless, no cases of CDI ribotype 027, which is normally associated with severe cases, were identified in Causeway hospital. Third, the evaluation of the impact of the intervention on specific patient clinical outcomes (e.g. length of hospital stay, mortality) was not feasible since this level of data was not available.
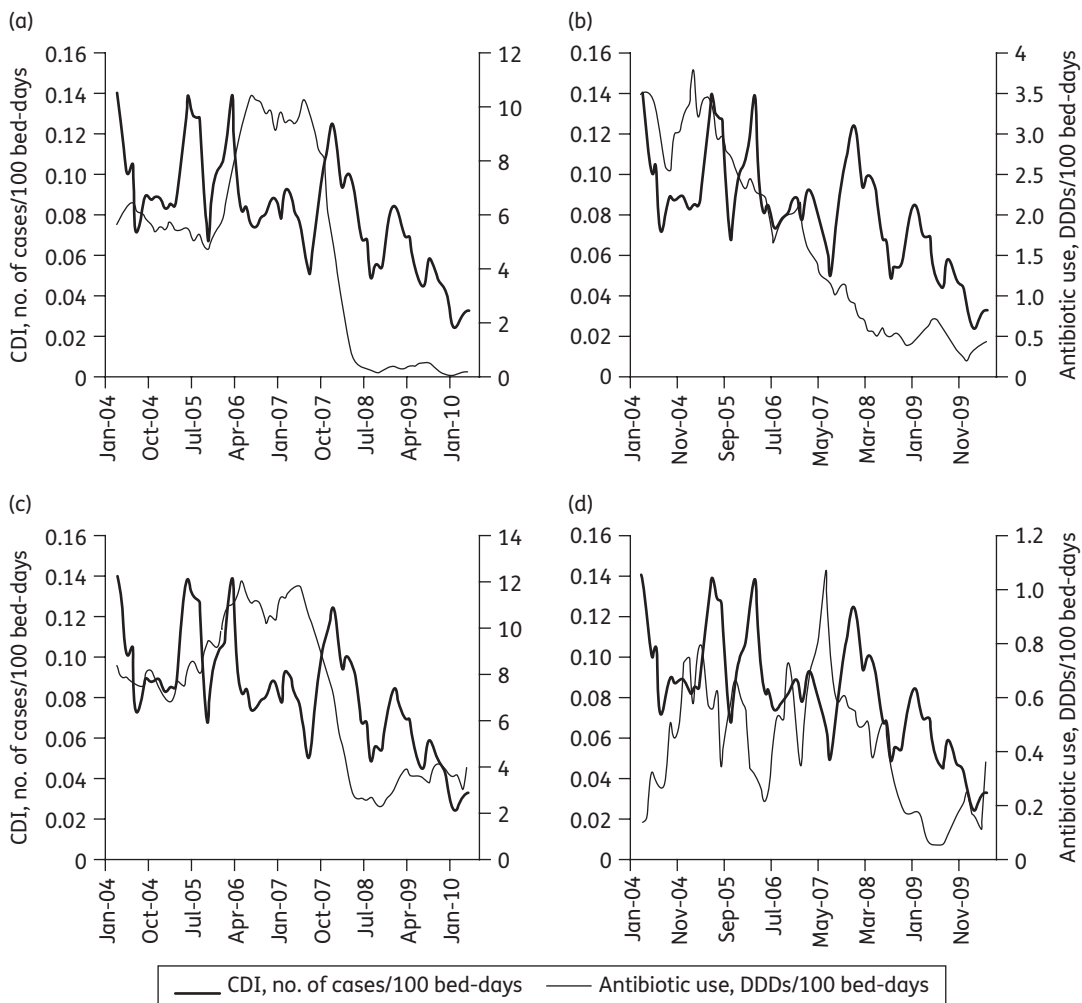
Figure 4. Monthly CDI incidence versus use of high-risk antibiotic group elements (5 month moving average), January 2004 to June 2010: (a) second-generation cephalosporins; (b) third-generation cephalosporins; (c) fluoroquinolones (mainly ciprofloxacin); and (d) lincosamides (clindamycin).
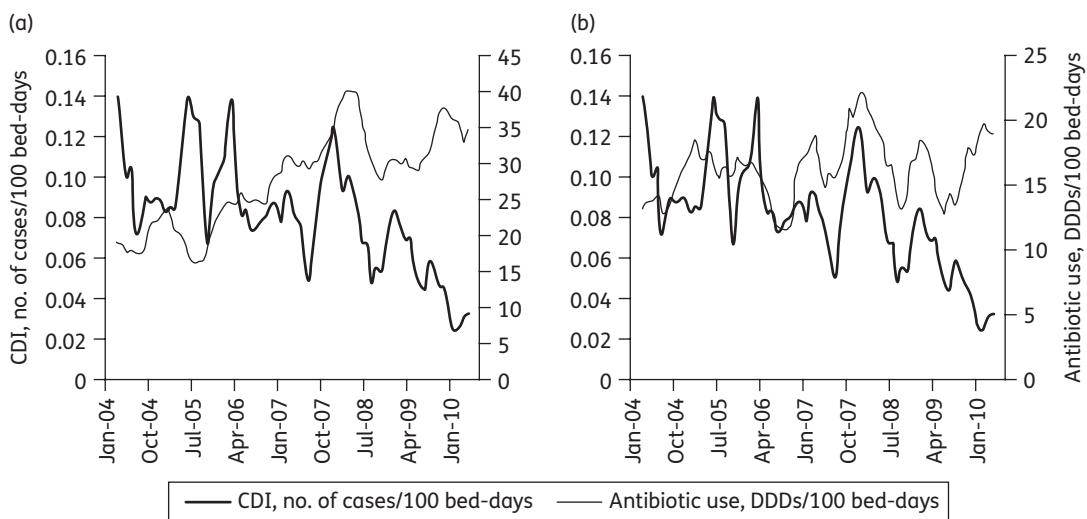
Figure 5. Monthly CDI incidence versus use of medium-risk antibiotic group elements (5 month moving average), January 2004 to June 2010: (a) amoxicillin/clavulanic acid; and (b) macrolides.

In conclusion, the presented research assessed the impact of a revised antibiotic policy on CDI incidence rates in hospitalized patients. This antibiotic policy contributed to both a reduction in the use of high-risk antibiotics and the incidence of CDI in the study site hospital. Time-series analysis can be utilized as a valuable risk classification tool with utility in antibiotic stewardship design and quality improvement programmes.

Supplementary data

Tables S1, S2 and S3 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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