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Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of *Clostridium difficile* infection

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Objectives: To evaluate the impact of an 'intervention' consisting of revised antibiotic guidelines for empirical treatment of common infections and enhanced stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of *Clostridium difficile* infection (CDI).

Methods: This was a retrospective, quasi-experimental study using interrupted time series (ITS) over 12 months before and after the intervention. The setting was adult medical and surgical wards in University Hospital Lewisham, an acute general hospital in London. The intervention was introduced in April 2006. Revised guidelines avoided broad-spectrum antibiotics, e.g. fluoroquinolones, cephalosporins, clindamycin, amoxicillin and co-amoxiclav, as they were considered to be 'high risk' for CDI. Instead, 'low risk' antibiotics such as penicillin, clarithromycin, doxycycline, gentamicin, vancomycin, trimethoprim and nitrofurantoin were recommended. Changes in antibiotic usage and incidence of CDI before and after the intervention were compared using segmented regression analysis. The negative binomial model was used to analyse the time series to estimate the CDI incidence rate ratio (IRR) following the intervention.

Results: The intervention was associated with a significant reduction in the use of fluoroquinolones by 105.33 defined daily doses (DDDs)/1000 occupied bed-days (OBDs) per month [95% confidence interval (CI) 34.18–176.48, $P<0.001$] and cephalosporins by 45.93 DDDs/1000 OBDs/month (95% CI 24.11–67.74, $P<0.0001$). There was no significant change in total antibiotic, clindamycin, amoxicillin or co-amoxiclav use. There was a significant decrease in CDI following the intervention [IRR 0.34 (0.20–0.58), $P<0.0001$].

Conclusions: Revised antibiotic guidelines and enhanced stewardship was associated with a significant stepwise reduction in the use of cephalosporins and fluoroquinolones and a significant decrease in the incidence of CDI.

Keywords: antibiotics, fluoroquinolones, cephalosporins, interrupted time series, CDI

Introduction

Clostridium difficile infection (CDI) is the most common healthcare-associated infection (HCAI) in England with a total number of 51829 cases reported in 2005–06.[1] This incidence rose by 7% in 2006–07, when 55620 cases were recorded.[2]

CDI is endemic in University Hospital Lewisham, an acute general hospital in South London. Between April 2005 and March 2006, 349 cases of CDI were recorded. At that time our guidelines recommended levofloxacin for treatment of mild to moderate community-acquired pneumonia and norfloxacin for lower urinary tract infection. Cefuroxime was recommended for severe community-acquired pneumonia and pyelonephritis. Ceftazidime and co-amoxiclav were advised when treating hospital-acquired pneumonia and aspiration pneumonia, respectively. In light of the high incidence of CDI at University Hospital Lewisham and reports of association of CDI with widespread use of agents such as fluoroquinolones and

cephalosporins,[3–7] we reviewed our antibiotic guidelines for the management of common medical infections.

After a consultation process, revised guidelines recommending reduced use of broad-spectrum antibiotics considered to be 'high risk' for development of CDI were implemented in April 2006. At the same time an enhanced antibiotic stewardship programme was instituted to promote compliance with the revised antibiotic guidelines.

The aim of this study was to evaluate the impact of the antibiotic guidelines and stewardship in reducing broad-spectrum antibiotic usage and its effect on incidence of CDI.

Methods

Setting

The study was conducted at University Hospital Lewisham, an acute general hospital in South London. Table S1 (available as Supplementary data at *JAC* Online) provides details of the setting, population, infection control policies and CDI definition throughout the study.

Study design

A retrospective, quasi-experimental study was performed to assess the effect of revised antibiotic guidelines introduced in April 2006 by comparing antibiotic use and CDI for a period of 12 months before and after implementation of the revised antibiotic guidelines.

Revised antibiotic guidelines—development, implementation and antibiotic stewardship

Senior clinicians were consulted and local antimicrobial resistance patterns were considered when developing the revised guidelines. These antibiotic guidelines (Table S2, available as Supplementary data at *JAC* Online) recommended avoiding antibiotics considered as 'high risk' for CDI, such as fluoroquinolones, cephalosporins, clindamycin, and broad-spectrum penicillins, such as co-amoxiclav.[3–9] Furthermore, these high-risk antibiotics were removed from ward stocks in order to reduce their availability. Instead, antibiotics considered as 'low risk' for CDI, such as penicillin, clarithromycin, doxycycline, gentamicin, vancomycin, trimethoprim and nitrofurantoin, were promoted.[8]

Antibiotic stewardship was facilitated through the formation of an antibiotic management team (AMT) comprising a consultant microbiologist and an antibiotic pharmacist. Any high-risk antibiotic prescribed by clinicians or supplied by the Pharmacy Department was brought to the attention of the AMT. The AMT performed regular ward rounds five times a week (compared with irregular thrice weekly rounds before October 2006) to optimize adherence to revised antibiotic guidelines and control the use of high-risk antibiotics. In addition, the guidelines were promoted in a variety of ways, including teaching sessions, face-to-face discussions and provision of laminated pocket-size guideline cards to clinicians and ward pharmacists. Larger laminated versions of the guidelines were also displayed on every ward. An electronic version was also accessible via the hospital intranet.

Data collection

Information regarding hospital bed occupancy, antibiotic usage and CDI was obtained from the hospital's patient administration system (PAS), pharmacy computer system (Ascribe) and infection control database, respectively.

Antibiotic usage

The impact of the intervention on antibiotic usage was analysed, comparing 12 months before (April 2005–March 2006) and after (April 2006–March 2007) introduction of the revised antibiotic guidelines.

Monthly antibiotic usage data were obtained for both periods. Data for antibiotic packs issued to adult inpatients only, either as ward stock or dispensed to individual patients, were included. Discharge and outpatient supplies were excluded, but pre-labelled discharge packs supplied as ward stock were included, as they could have been started during the hospital stay.

To compare antibiotic usage in a consistent manner, the defined daily doses (DDDs) were used.[10] Monthly antibiotic pack usage was converted into monthly DDDs for each of the two periods. Inpatient usage was expressed per 1000 occupied bed-days (OBDs) to account for variation in activity. OBDs were obtained from the hospital's patient information management system.

CDI

Throughout the study, the microbiology laboratory used a standard operational procedure for handling stool specimens, which remained unchanged. Patients' diarrhoeal specimens received in the laboratory were tested for Premier™ *C. difficile* toxin A and B using a commercially available test (Meridian Diagnostics Inc., Cincinnati, OH, USA). Patients were regarded as having CDI if they had diarrhoea and a stool sample was found to be positive for toxin A or B. All cases reported are distinct patient episodes and include all patients >2 years of age. Samples sent from general practitioners (GPs) were excluded.

A record of the cases was maintained by the infection control nurses, and the numbers of distinct patient episodes were gathered from this record.

As a part of the national *C. difficile* ribotype surveillance, a limited number (10) of *C. difficile*-positive stools were cultured and the isolates were sent for ribotyping to the Anaerobe Reference Laboratory, Cardiff, Wales.

Outcomes

The primary outcome was a change in the levels of antibiotic consumption immediately after introduction of the revised guidelines and any differences between pre-intervention and post-intervention trends. The secondary outcome was the impact of the revised guidelines on the monthly count of CDI adjusted for numbers of OBDs.

Statistical analysis

Segmented regression analysis of interrupted time series (ITS) data was used to determine the differences in levels and trends over time due to the revised antibiotic guidelines. This approach allows for assessment of the immediate and longer-term effects of an intervention by measuring both the associated sudden change and the change in trend of the outcome of interest.[11–13]

Analysis of the residuals of the fitted models showed no evidence of autocorrelation, but evidence of heteroscedasticity was found with 4 of the 16 antibiotics or classes of antibiotics. We therefore used the Huber–White sandwich estimator to obtain robust variance estimates.

CDI data showed evidence of overdispersion, and we therefore used a negative binomial model with robust standard errors to analyse these data, adjusting for changing bed occupancy (OBDs). The model used allowed for pre- and post-intervention trends and accounted for autocorrelation adjusted for the number of CDI cases in the previous month.

Statistical analysis was performed using Stata 8 (StataCorp, College Station, TX, USA), and two-sided P values ≤ 0.05 were considered to be

significant. Correlation between DDDs/bed occupancy and DDDs/number of admissions was determined using Pearson's statistical test. Pearson's correlation coefficient was always >0.9. Given that a correlation coefficient in the range 0.8–1 is considered as a very strong correlation, it was decided to present the data per bed occupancy only.

Ethical considerations

In keeping with our hospital's Ethics Committee policy, no formal ethical approval was considered necessary, as it was an audit study using anonymized routinely collected data.

Results

Antibiotic use

Broad-spectrum and high-risk antibiotics

Table 1 shows that before introduction of the revised antibiotic guidelines, baseline level of use was higher for fluoroquinolones than for cephalosporins, and neither had significant trends. The introduction of revised antibiotic guidelines was associated with a significant sudden reduction in the levels of use of fluoroquinolones and cephalosporins. These changes in levels correspond to a 58.5% and 45.8% drop in fluoroquinolone and cephalosporin use, respectively. These lower levels of use were maintained over the study period: no significant change in trend for fluoroquinolones or cephalosporins was observed after introduction of the revised antibiotic guidelines. Although there was no significant change in the level of co-amoxiclav, the marked trend for increased use of co-amoxiclav before the revised guidelines were introduced was reversed following introduction of the guidelines. There was no significant change in trend or level for clindamycin or amoxicillin.

Figure 1 shows the monthly use for restricted antibiotics and fitted values from the segmented regressions.

Low-risk antibiotics (as recommended in the revised antibiotic guidelines)

Table 2 shows that in the group of antibiotics targeted for increased use, there was a significant increase in the levels for penicillin, macrolides, gentamicin, nitrofurantoin and trimethoprim after introduction of the revised guidelines, but there was no significant change in trend except for macrolides, for which a significant decreasing trend in overall use was observed following the initial post-intervention increase.

For doxycycline and vancomycin, there was no evidence of a change in either level or trend.

Figure 1 shows the monthly use for low-risk antibiotics and fitted values from the segmented regressions.

Untargeted antibiotics

Table 2 also shows that, after introduction of the revised guidelines, the trends and levels of carbapenems, piperacillin/tazobactam and teicoplanin use did not change significantly, although there was a marked trend for decreased use of carbapenems before introduction of the revised guidelines.

Table 1. Changes in total antibiotic use and antibiotics targeted for decreased use after the intervention assessed using a statistical model allowing for both linear trend and level of change after the introduction of revised antibiotic guidelines

Antibiotic	Baseline level (95% CI)	Initial trend (95% CI)	*P* value	Change in level after the intervention (95% CI)	*P* value	Change in trend after the intervention (95% CI)	*P* value
Total antibiotic use	1068.40 (928.07, 1208.72)	33.75 (9.76, 57.73)	0.008[a]	42.04 (−178.34, 262.42)	0.695	−33.22 (−65.94, −0.50)	0.047[a]
Antibiotics targeted for decreased use (high-risk antibiotics)							
fluoroquinolones	180.75 (143.23, 218.28)	−0.02 (−8.46, 8.42)	0.996	−105.33 (−176.48, −34.18)	0.006[a]	2.32 (−6.62, 11.26)	0.594
cephalosporins	100.18 (84.01, 116.34)	0.72 (−1.73, 3.16)	0.547	−45.93 (−67.74, −24.11)	<0.0001[a]	0.65 (−2.35, 3.65)	0.657
clindamycin	3.88 (0.34, 7.43)	0.07 (−0.32, 0.45)	0.721	−0.63 (−3.45, 2.19)	0.646	−0.20 (−0.65, 0.25)	0.368
co-amoxiclav	72.64 (38.88, 106.40)	5.66 (0.39, 10.92)	0.037[a]	−34.31 (−72.13, 3.52)	0.073	−8.91 (−14.83, −2.99)	0.005[a]
amoxicillin	219.00 (136.77, 301.24)	6.57 (−3.74, 16.88)	0.199	−75.76 (−171.09, 19.56)	0.113	−4.63 (−19.09, 9.82)	0.511

Baseline levels (and changes in these) are expressed as DDDs/1000 OBDs.
Trend terms represent monthly changes in DDDs/1000 OBDs.
[a]Statistically significant ($P \leq 0.05$).

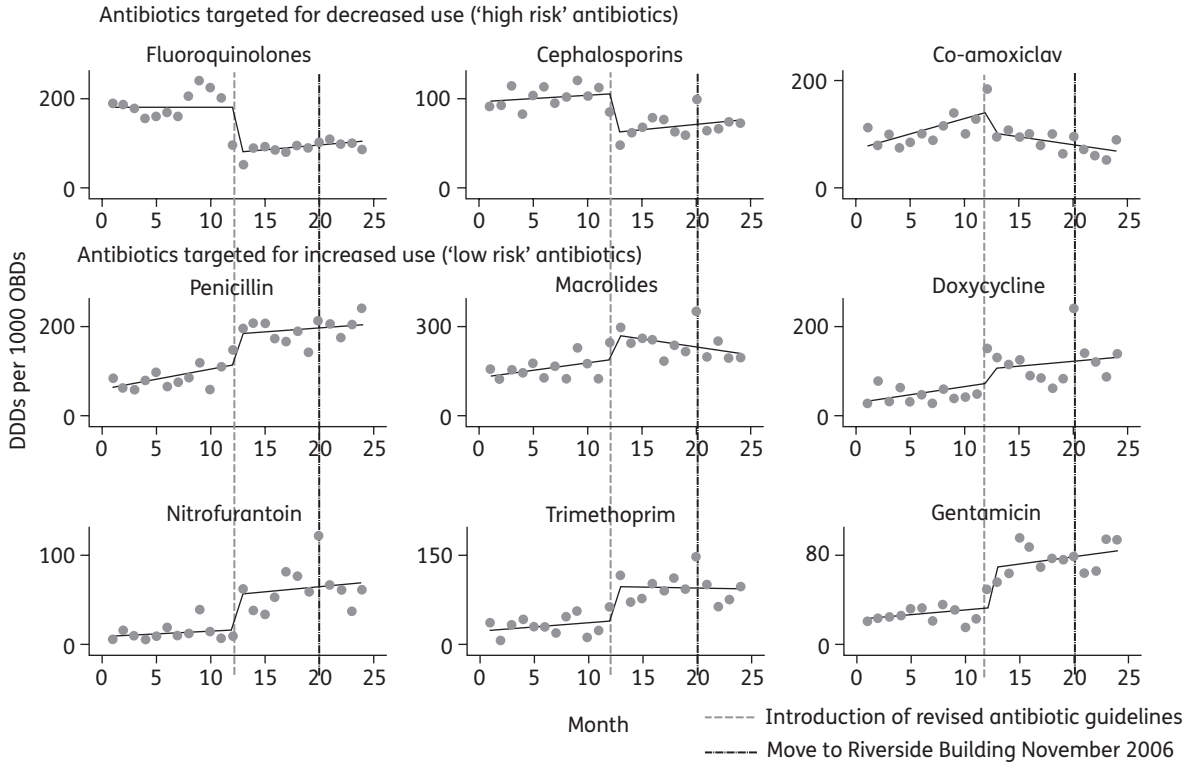

Figure 1. Monthly use of antibiotics before and after the introduction of revised antibiotic guidelines.

Total antibiotic use

As shown in Table 1, there was no significant change in the level of total antibiotic use. Before introduction of the revised guidelines, there was a marked trend of increased use of total antibiotics. However, after introduction of the revised guidelines, the trend of total antibiotic use decreased significantly. It is interesting to note that the introduction of revised antibiotic guidelines completely removed the increasing trend in total antibiotic consumption, i.e. the reduction in the trend was almost exactly the same as the initial trend.

Antibiotic stewardship interventions

The AMT made several interventions that resulted in changes in antibiotic prescribing. The nature and number of the interventions made are shown in Table 3.

CDI

The negative binomial model showed a significant decrease in CDI associated with the intervention [incidence rate ratio (IRR) 0.34; 95% confidence interval (CI) 0.20–0.58, $P<0.0001$]. There was a significant decrease in trend in CDI following the intervention [IRR 0.93 (0.88–0.99), $P=0.015$], but no trend before the intervention [IRR 1.00 (0.94–1.06), $P=0.94$] (Figure 2).

C. difficile ribotypes

In the year 2006, three isolates were ribotype 106, two were 015 and one was 027. In 2007, all four isolates were ribotype 027.

Discussion

This is a robust retrospective quasi-experimental 2 year study using an ITS design to determine the impact of a hospital-wide intervention on all antibiotic usage. A particular strength of this study is the relatively long time series used, which allows both pre- and post-intervention trends to be clearly identified. Furthermore, to ensure transparency of reporting we followed the ORION (Outbreak Reports and Intervention studies Of Nosocomial infection) statement 'designed especially for quasi-experimental (i.e. non-randomized) study designs commonly used in hospital epidemiology: interrupted time series with and without control groups, and outbreak reports'.[14] Similar studies have been undertaken in a hospital in Northern Ireland and in care of the elderly wards in a London teaching hospital with similar results.[11,15] Our study, together with these studies, re-emphasizes the key role that broad-spectrum antibiotics play in CDI.

Although ITS is a relatively strong quasi-experimental design, potential threats to the validity of the conclusions must be considered. A major threat to validity could have been the move in November 2006 of adult medical and care of the elderly wards to a new building with an extra 13 side rooms available. However, before and after the intervention, all cases of CDI could be isolated either in side rooms or in four-bed bays holding only patients with CDI. Furthermore, no major change in CDI rates was observed following this move: we recorded similar monthly numbers of CDI 5 months before and after the move to the new building, as shown in Figure 2. We therefore believe the decrease in CDI after introduction of the revised antibiotic guidelines was most likely caused by the decrease in usage of high-risk antibiotics.[3–5]

Table 2. Changes in use of antibiotics targeted for increased use and untargeted antibiotics after the intervention assessed using a statistical model allowing for both linear trend and level of change after the introduction of revised antibiotic guidelines

Antibiotic	Baseline level (95% CI)	Initial trend (95% CI)	*P* value	Change in level after the intervention (95% CI)	*P* value	Change in trend after the intervention (95% CI)	*P* value
Antibiotics targeted for increased use (low-risk antibiotics)							
penicillin (benzylpenicillin and phenoxymethylpenicillin)	62.40 (35.99, 88.81)	4.85 (−0.03, 9.74)	0.051	74.00 (26.31, 121.68)	0.004[a]	−2.80 (−9.46, 3.86)	0.391
macrolides	107.48 (77.72, 137.23)	4.18 (−1.91, 10.26)	0.168	70.96 (13.73, 128.18)	0.018[a]	−8.50 (−16.02, −0.98)	0.029[a]
gentamicin	17.33 (10.79, 23.87)	0.76 (−0.76, 2.28)	0.308	29.27 (9.14, 49.40)	0.007[a]	0.39 (−2.18, 2.96)	0.755
nitrofurantoin	8.03 (1.44, 14.62)	0.53 (−0.79, 1.86)	0.412	37.01 (12.34, 61.69)	0.005[a]	0.64 (−2.91, 4.19)	0.711
doxycycline	24.66 (−11.75, 61.08)	3.35 (−3.32, 10.02)	0.308	27.08 (−28.16, 82.32185)	0.319	−1.64 (−9.55, 6.27)	0.670
trimethoprim	17.76 (1.48, 34.04)	1.17 (−1.57, 3.91)	0.384	48.28 (18.70, 77.87)	0.003[a]	−1.51 (−5.66, 2.64)	0.456
vancomycin iv	6.39 (4.63, 8.14)	0.19 (−0.02, 0.40)	0.071	0.68 (−2.26, 3.61)	0.636	−0.17 (−0.72, 0.37)	0.514
Untargeted antibiotics							
carbapenems	20.01 (16.17, 23.86)	−0.99 (−1.50, −0.47)	0.001[a]	4.02 (−1.79, 9.84)	0.165	0.59 (−0.20, 1.39)	0.133
piperacillin/tazobactam	6.17 (2.55, 9.79)	−0.15 (−0.73, 0.42)	0.590	5.04 (−0.27, 10.35)	0.062	0.02 (−0.70, 0.75)	0.945
teicoplanin	8.99 (5.53, 12.43)	0.04 (−0.42, 0.49)	0.869	−0.99 (−4.82, 2.84)	0.597	−0.15 (−0.66, 0.36)	0.543

iv, intravenous.
Baseline levels (and changes in these) are expressed as DDDs/1000 OBDs.
Trend terms represent monthly changes in DDDs/1000 OBDs.
[a]Statistically significant ($P \leq 0.05$).

Clindamycin was considered the highest-risk agent for CDI in the 1970s.[9,16] Since early reports highlighting an association between clindamycin and CDI, clindamycin has been rarely prescribed in the UK. As a result of being rarely prescribed, clindamycin is infrequently implicated in CDI in the UK. Our study showed that there was no change in trend nor level for clindamycin usage and the monthly clindamycin consumption was very low both before and after introduction of revised antibiotic guidelines. Thus, in our study, the decrease in CDI cannot be associated with clindamycin usage.

Cephalosporins have been incriminated as an important predisposing cause of CDI since the 1980s.[3–5] Throughout the 1990s and early 2000s, cephalosporins were more frequently used in UK hospitals. Prior to the revised guidelines, in keeping with the British Thoracic Society guidelines, we recommended cephalosporins for the treatment of severe community-acquired lower respiratory tract infections.[17,18] In our study we demonstrated that a reduction in cephalosporin use following introduction of the revised guidelines was accompanied by a decrease in CDI rates.

Prior to 2005, fluoroquinolones were acknowledged to be uncommonly associated with CDI.[8,19,20] At the time of the increased incidence of CDI in our hospital, and in the period thereafter, many reports and studies recorded a strong association between fluoroquinolones and CDI.[6,7,21]

Our study showed that the revised antibiotic guidelines predominantly promoting the restriction of fluoroquinolones and cephalosporins prompted a significant and sudden decrease in both fluoroquinolone and cephalosporin use, which was followed by a significant decrease in CDI rates. Given the widespread use of fluoroquinolones in our hospital prior to introduction of the guidelines, it is conceivable that restriction of these antibiotics played a major role in the decrease in CDI rates.

Overall, antibiotic use in our hospital was in line with that seen in other hospitals in the UK.[22] Total antibiotic use in DDDs/1000 OBDs was approximately equal before and after introduction of the revised antibiotic guidelines, with no significant change in level but a slight decrease in trend. Despite the absence of a significant change in total antibiotic use, CDI cases decreased

Table 3. AMT interventions during October 2006–March 2007

AMT interventions[a]	Number
Total number of patients reviewed	386
Advice or change accepted by medical/surgical teams	381
Advice or change rejected by medical/surgical teams	1
Unknown if advice or change accepted by medical/surgical teams	4
Number of diagnosis reviewed/changed by the AMT	75
Total number of antibiotics stopped	429
Total number of antibiotics started	294
Dose of antibiotic changed	64
Frequency of antibiotic changed	35
iv to po switch	85

iv, intravenous; po, oral.
[a]Please note that the AMT frequently made multiple interventions during patient review.

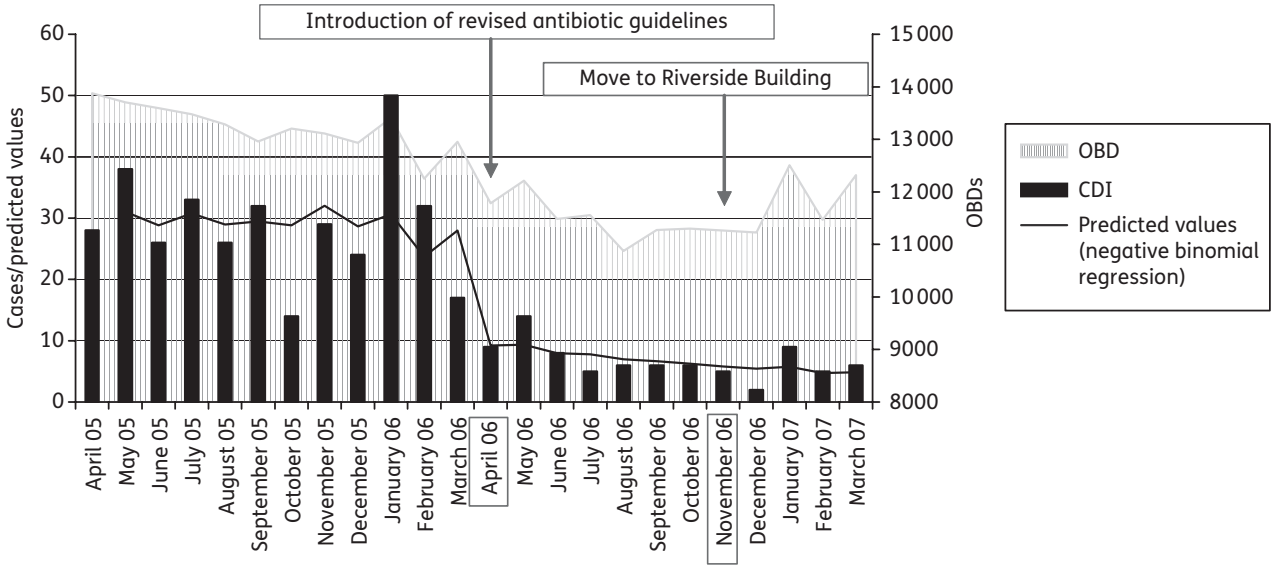

Figure 2. Monthly count data for new cases of CDI and the number of OBDs before and after the introduction of revised antibiotic guidelines.

significantly, demonstrating that reduction in the use of certain classes of antibiotics, i.e. high-risk antibiotics, was likely to be a predominant factor in the decrease in the number of cases of CDI.

It is interesting to note that further analysis showed that a decrease in fluoroquinolone and cephalosporin use did not result in a significant increase in alternative costly broad-spectrum antibiotics such as carbapenems, piperacillin/tazobactam or teicoplanin. This was possibly because of the regular ward rounds and the clinical advice given by the AMT.

As shown in Table 3, interventions made by the AMT resulted in a substantial number of changes in antibiotic prescriptions. Of particular note is that on 75 occasions the diagnosis of infection was changed. This highlights that, in addition to monitoring compliance with antibiotic guidelines, antibiotic stewardship involves reviewing the clinical diagnosis. That the advice of the AMT was rejected on only one occasion demonstrates that is feasible to implement antibiotic stewardship without conflicts with clinicians.

To assess the clinical impact of the revised guidelines on clinical outcome, our clinical colleagues undertook a limited review of elderly patients treated for urinary tract and lower respiratory tract infections for a period of 80 days before (group A, 380 patients) and after (group B, 247 patients) introduction of the revised guidelines. We demonstrated that there were no significant differences in length of stay and readmission rate between the two groups. However, there was a significant decrease in mortality following introduction of the guidelines [19 patients died in group A; 9 in group B (odds ratio 0.49, $P=0.004$)].[23]

In the absence of 'in-house' ribotyping facilities, we had only limited information on the prevalent ribotypes for a part of the study period. The limited information available indicates the emergence of the 027 ribotype during 2007.

There were a number of limitations to this study. The data used in this study were essentially retrospective. CDI rates were derived from the laboratory data and were therefore dependent on the submission of specimens in suspected cases of CDI and the accuracy of the testing methods. As we did not type all the strains of *C. difficile*, we are unable to comment on any changes in the strains, which may have affected the number of CDI cases.

No distinction between community and hospital-acquired CDI could be made during the period studied.

Data were not collected on staffing levels, agency rates, admissions from nursing homes, adult age group or severity of infection. While these must be considered potential confounders, to our knowledge there were no changes in any of these that could plausibly explain changes in the outcome measures.

We have only limited information on clinical outcomes and we did not systematically collect information regarding toxicity of the recommended antibiotics. However, during our ward rounds as part of antibiotic stewardship we were not made aware of any increased incidence of toxicity or side effects.

In conclusion, our study showed that a reduction in the use of broad-spectrum antibiotics and antibiotic stewardship played key roles in reducing the incidence of cases of CDI. Such a reduction in broad-spectrum and high-risk antibiotics was achieved without an increase in adverse clinical outcomes.

Funding

This study was carried out as part of our routine work.

Transparency declarations

Pharmaceutical companies have paid lecture fees and provided sponsorship to attend conferences unrelated to this study to G. G. R. All other authors: none to declare.

Supplementary data

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

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