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Temporal effects of antibiotic use and *Clostridium difficile* infections

Nathalie Vernaz[1], Kirsteen Hill[2], Stephanie Leggeat[3], Dilip Nathwani[2], Gabby Philips[3], Pascal Bonnabry[1] and Peter Davey[4]*

[1]Department of Pharmacy, Hopitaux Universitaires de Geneva, Rue Michel du Crest 24, CH 12211 Geneva 14, Switzerland; [2]Infection Unit, East Block, Ninewells Hospital, Dundee DD1 9SY, Scotland, UK; [3]Medical Microbiology and Infection Control, Ninewells Hospital, Dundee DD1 9SY, Scotland, UK; [4]Division of Community and Population Sciences and Education, University of Dundee, Mackenzie Building, Kirsty Semple Way, Dundee DD2 4BF, Scotland, UK

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***Objectives*: We tested a previously published model for the analysis of the temporal relationship between antibiotic use and the incidence of *Clostridium difficile* infection in a hospital with stable incidence of infection at >1 case per 1000 admissions per month.**

***Methods*: The study period was from April 2004 to June 2008 and used data from Infection Control and Hospital Pharmacy. We first described the monthly variation in *C. difficile* infection and then constructed a multivariate transfer function model that included lag time (cases of *C. difficile* infection in previous months and delays between changes in antibiotic use and changes in *C. difficile* infection).**

***Results*: The average incidence of *C. difficile* infection was 1.5 cases per 1000 patients per month with no significant increase over 3 years. The number of cases of *C. difficile* infection in 1 month was dependent on the average number of cases of *C. difficile* infection in the previous 2 months. The models with data from the whole hospital showed a statistically significant relationship between the number of both hospital-acquired *C. difficile* infections and total *C. difficile* infections and consumption of piperacillin/tazobactam, ciprofloxacin and cefuroxime. The association between *C. difficile* infection and consumption of co-amoxiclav was only significant for hospital-acquired *C. difficile* infection. The model for hospital-acquired *C. difficile* infections explained 61% of the variance in *C. difficile* infections.**

***Conclusions*: These results provide support for antibiotic policies that minimize the use of broad-spectrum penicillins (co-amoxiclav and piperacillin/tazobactam), cephalosporins and fluoroquinolones.**

Keywords: time series analysis, hospital-acquired infections, piperacillin/tazobactam, cephalosporins, fluoroquinolones, co-amoxiclav

Introduction

The aim of this study was to apply a model for time series analysis of the temporal relationship between antibiotic use and the incidence of *Clostridium difficile* infection in a hospital with stable incidence of infection at >1 case per 1000 admissions per month. The model was developed and tested in Geneva, where the average incidence of infections over 6 years was <0.27 cases per 1000 admissions per month, ranging from 0.04 to 0.54 cases per 1000 admissions per month.[1] In Geneva, a transfer function model that included all antibiotic use and alcohol-based hand rubs only explained 17% of variation in *C. difficile* infections, and the use of broad-spectrum cephalosporins was the only statistically significant explanatory variable.[1] Our hypothesis was that stronger relationships between *C. difficile* infection and antibiotic use would be present in a hospital with a higher incidence of *C. difficile* infection.

A common error in the statistical analysis of time series is to assume that one observation in a data set is independent from the other observations. This is often not true in a time series, especially when the observations are cases of infection. It is very likely that the number of cases of *C. difficile* in a ward in 1 month is influenced by the number of cases in previous months, so these observations are dependent on one another.

*Corresponding author. Tel: +44-1382-420000; Fax: +44-1382-420001; E-mail: p.g.davey@cpse.dundee.ac.uk

One of the key steps in the statistical analysis of a time series will therefore be to extract this structure and transform the initial time series into a series of independent values.

Methods

Data collection

Ninewells Hospital is a University Hospital with 879 beds; there were 51498 inpatient admissions and 16412 day cases in 2004.[2] The hospital has full specialist services with the exception of cardiothoracic surgery and organ transplantation. The data about *C. difficile* infections were provided from the Infection Control database in the Department of Medical Microbiology at Ninewells Hospital and the data about antibiotic use were provided by the Pharmacy Department, extracted with Business Objects from the Ascribe database. The study period was from April 2004 to June 2008. For statistical analysis, we first described the monthly variation in *C. difficile* infection and then constructed a multivariate transfer function model that included lag time (cases of *C. difficile* infection in previous months and delays between changes in antibiotic use and changes in *C. difficile* infection). The model has been described in detail previously.[1] Monthly antibiotic use was expressed in the WHO's recommended metric, the defined daily dose.[3] A P value of <0.05 was considered to be statistically significant.

Ethics approval was not required because we only used routine data aggregated by hospital wards.

Modelling

The main analysis used only *C. difficile* infections that presented in the hospital (onset of symptoms >48 h after admission to hospital), labelled HA_CDIFF. We also repeated all analyses with total cases of *C. difficile* (TOT_CDIFF), which includes *C. difficile* infection presenting from the community. Data from the Infection Control team showed that of the 43 *C. difficile* infections presenting from the community between February and June 2008, 30 (70%) occurred in people who had been inpatients within the previous 12 weeks. It is therefore plausible that hospital antibiotic use has some influence on the number of *C. difficile* infections that present in the community.

Previous point prevalence surveys of antibiotic use at Ninewells Hospital showed that cefuroxime is mainly used for the treatment of surgical infections, whereas in medical wards there is very little use of cefuroxime because co-amoxiclav is the main therapeutic antibiotic.[4] In contrast, in surgical wards most of the co-amoxiclav use is due to single dose, pre-operative antibiotic prophylaxis. Fluoroquinolone use was also substantially different between the Medicine and Cardiovascular wards, where levofloxacin and moxifloxacin were used to treat respiratory infections, whereas ciprofloxacin was the only fluoroquinolone that was used significantly in other wards. We therefore applied the same models restricted to data from wards in the Medicine and Cardiovascular group (HA_CDIFF M&C and TOT_CDIFF M&C) to test the hypothesis that there would be a stronger association between *C. difficile* infections and co-amoxiclav use or fluoroquinolone use in medical wards than we had seen in the whole hospital.

Statistical methods

Since temporally sequenced observations on antibiotic use and resistance are not independent, applying simple regression analysis would be inappropriate.[5] We chose an autoregressive integrated moving average (ARIMA) model with the Box–Jenkins method, which allows for the stochastic dependence of consecutive data over time.[5] This method estimates the dependence between observations over time and relaxes the assumption of independent observations, which lessens a common threat to valid inferences.[6] The major limitation regarding the use of this approach is that it has large data requirements.[6] The recommended minimum is 50 timepoints. We used 51 monthly timepoints from April 2004 to June 2008.

We used linear transfer function modelling to quantify the dynamic relationship between the use of several antibiotics and the incidence of *C. difficile* infections, taking into account delays of up to 5 months in effect.[1,7] For each individual series, we identified and fitted an ARIMA model according to the Box–Jenkins method.[5] First, we checked if the series were stationary with the augmented Dickey–Fuller test; we accepted changes of <10% in mean and variance as stationary. Second, we determined the ARIMA model orders with the autocorrelation and partial autocorrelation functions. Third, we estimated model parameters by the unconditional least squares method. Finally, we checked the adequacy of the model and eliminated irrelevant variables with the Ljung–Box statistic at a P value of <0.05. The generated coefficient R^2 measures the overall fit of the regression line, expressing how close the points are to the estimated regression line in the scatter plot. In other terms, R^2 is the fraction of the variance of the dependent variable explained by the regression.

All statistical analyses were performed with EViews 6 software (QMS, Irvine, CA, USA).

Results

C. difficile infections

There were between 10 and 36 cases of *C. difficile* infection per month over the 3 year study period with an average incidence of 1.5 cases per 1000 patients per month (Figure 1). There was a non-significant upward trend in HA_CDIFF ($P=0.0932$), a significant upward trend in TOT_CDIFF ($P=0.0309$) and a non-significant upward trend in HA_CDIFF M&C ($P=0.9054$) and TOT_CDIFF M&C ($P=0.5336$).

All the time series analyses have a moving average order of 2, meaning that the number of cases of *C. difficile* infection in 1 month is dependent on the average number of cases of

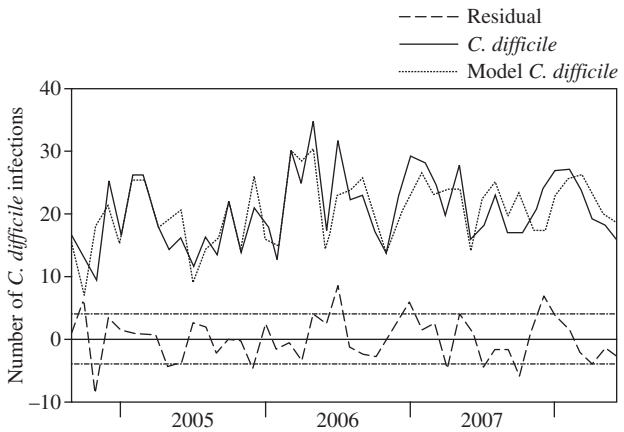

Figure 1. Transfer function model for *C. difficile* infections; Ninewells Hospital April 2004 to June 2008.

C. difficile infection in the previous 2 months. By including this moving average in the model, we transformed the original time series of *C. difficile* infections into independent values that can be analysed with standard statistical tests.

Modelling

In the models with data from the whole hospital, we found a statistically significant relationship between the number of both hospital-acquired *C. difficile* infections and total *C. difficile* infections and consumption of piperacillin/tazobactam, ciprofloxacin and cefuroxime (Table 1). The association between *C. difficile* infection and consumption of co-amoxiclav was only significant for hospital-acquired *C. difficile* infections (Table 1). The model for hospital-acquired *C. difficile* infections explained 61% of the variance in *C. difficile* infections over time, whereas the model for total *C. difficile* infections only explained 49% of the variance (Table 1).

In the models with data from the Medicine and Cardiovascular wards, we found a statistically significant relationship between the number of both hospital-acquired *C. difficile* infections and total *C. difficile* infections and consumption of piperacillin/tazobactam, co-amoxiclav and fluoroquinolones (Table 1). The association between *C. difficile* infection and consumption of ceftriaxone was only significant for total *C. difficile* infection (Table 1). The model for hospital-acquired *C. difficile* infections explained 53% of the variance in *C. difficile* infections over time and the model for total *C. difficile* infections explained 56% of the variance (Table 1).

Graphical presentation shows a close relationship between the observed number of monthly *C. difficile* infections and the number predicted by the transfer function model. The residual was <10 *C. difficile* infections in any month (Figure 1). Supplementary data regarding the modelling results with additional charts are available at *JAC* Online (http://jac.oxfordjournals.org).

Discussion

Our analysis shows a strong relationship between variation in antibiotic use and variation in *C. difficile* infections (Table 1). A weakness of our data is that we did not have data about individual patient exposure to antibiotics and our analysis is therefore subject to ecological bias. However, in general, ecological bias weakens the association between exposure and outcome.[8]

Overall, these results provide support for antibiotic policies that minimize the use of broad-spectrum penicillins (co-amoxiclav and piperacillin/tazobactam), cephalosporins and fluoroquinolones. The differences between the results for the whole hospital versus the Medicine and Cardiovascular wards were expected because of the recommendations of the Hospital Antibiotic Policy at the time and the results of previous point prevalence surveys (see the Modelling sub-section in the Methods section). We also expected minor differences between the results of analyses that used only HA_CDIFF versus TOT_CDIFF because we have found that most cases of *C. difficile* infection presenting from the community had been hospitalized within the previous 12 weeks, as has been reported from other hospitals.[9,10] A substantial proportion of the ceftriaxone use by Medicine and Cardiovascular wards is for outpatient or home parenteral therapy.[11] This probably explains why ceftriaxone use in these wards was associated with total

Table 1. Transfer function model for *C. difficile* infections; Ninewells Hospital April 2004 to June 2008

	Lag time (months)	Ninewells HA_CDIFF	Ninewells TOT_CDIFF	Medicine and Cardiovascular ward level HA_CDIFF M&C	Medicine and Cardiovascular ward level TOT_CDIFF M&C
Piperacillin/tazobactam	4			0.05014*	
	5	0.091559*	0.092976*		0.054005**
Co-amoxiclav	0	0.002732*		0.005096**	0.010654*
Ciprofloxacin	0		0.007828*		
	5	0.003976*			
Fluoroquinolones[a]	4			0.011412*	0.007004**
Cefuroxime	2	0.005655**			
	3	0.005535*	0.003399**		
	4	0.006130*			
Ceftriaxone	2				0.014068**
	3				0.023926*
Moving average order 2		0.963635*	0.953730*	1.2379*	0.957879*
Overall fitting		61.35%	48.66%	53.45%	55.65%

[a]Ciprofloxacin, levofloxacin and moxifloxacin.
*Statistically significant at *P* value <1%.
**Statistically significant at *P* value <5%.

rather than hospital-acquired *C. difficile* infections. There are several plausible explanations for a lag in the association between antibiotic use and *C. difficile* infections. First, there is a delay between drug supply to the wards and consumption by patients. Second, the link between antibiotic consumption and *C. difficile* infection has several steps (environmental contamination, colonization of patients, exposure to antibiotics, symptomatic infection and diagnosis), each of which can add further delay.

We expected that *C. difficile* infection would be associated with the use of cephalosporins, fluoroquinolones and co-amoxiclav.[12] In a meta-analysis, co-amoxiclav had the third highest pooled odds ratio for increased risk of *C. difficile* infection after cefotaxime and ceftazidime.[12] However, we were surprised that variation in piperacillin/tazobactam was so strongly associated with *C. difficile* infections in our model because replacement of third-generation cephalosporin use by piperacillin/tazobactam has been associated with sustained reduction in *C. difficile* infections.[13] It has been proposed that piperacillin/tazobactam is less likely to be associated with *C. difficile* infections because it inhibits growth of *C. difficile* and because it stimulates less toxin production than cefotaxime.[12,14] However, β-lactam plus β-lactamase inhibitor combinations have been associated with *C. difficile* infections, even in studies of single dose use for surgical prophylaxis.[15]

These data were critical in supporting the Antimicrobial Management Team at Ninewells Hospital with the implementation of a new antibiotic policy that limits the use of cephalosporins, co-amoxiclav and fluoroquinolones. These recommendations are part of the national Scottish Antimicrobial Prescribing guidelines on antimicrobial measures to reduce *C. difficile*-associated disease.[16] Use of piperacillin/tazobactam was already restricted by an Alert Antibiotic Policy but the results of the model have reminded clinicians that it is plausible that use of any broad-spectrum antibiotic will increase the risk of *C. difficile* infection.[12] Modelling drug use by performing a time series analysis is a useful tool for decision-makers and complements traditional surveillance and epidemiological analyses.

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Supplementary data

Supplementary data are available at *JAC* Online (http://jac.oxfordjournals.org/).

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