Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired *Clostridium difficile*, extended-spectrum β-lactamase-producing coliforms and meticillin-resistant *Staphylococcus aureus*

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ARTICLE INFO

ABSTRACT

A restrictive antibiotic policy banning routine use of ceftriaxone and ciprofloxacin was implemented in a 450-bed district general hospital following an educational campaign. Monthly consumption of nine antibiotics was monitored in defined daily doses (DDDs) per 1000 patient-occupied bed-days (1000 pt-bds) 9 months before until 16 months after policy introduction. Hospital-acquired *Clostridium difficile*, meticillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β-lactamase (ESBL)-producing coliform cases per month/1000 pt-bds were identified and reviewed throughout the hospital. Between the first and final 6 months of the study, average monthly consumption of ceftriaxone reduced by 95% (from 46.213 to 2.129 DDDs/1000 pt-bds) and that for ciprofloxacin by 72.5% (109.804 to 30.205 DDDs/1000 pt-bds). Over the same periods, hospital-acquisition rates for *C. difficile* reduced by 77% (2.398 to 0.549 cases/1000 pt-bds), for MRSA by 25% (1.187 to 0.894 cases/1000 pt-bds) and for ESBL-producing coliforms by 17% (1.480 to 1.224 cases/1000 pt-bds). Time-lag modelling confirmed significant associations between ceftriaxone and *C. difficile* cases at 1 month (correlation 0.83; $P < 0.005$), and between ciprofloxacin and ESBL-producing coliform cases at 2 months (correlation 0.649; $P = 0.002$). An audit performed 3 years after the policy showed sustained reduction in *C. difficile* rates (0.259 cases/1000 pt-bds), with additional decreases for MRSA (0.409 cases/1000 pt-bds) and ESBL-producing coliforms (0.809 cases/1000 pt-bds). In conclusion, banning two antibiotics resulted in an immediate and profound reduction in hospital-acquired *C. difficile*, with possible longer-term effects on MRSA and ESBL-producing coliform rates. Antibiotic stewardship is fundamental in the control of major hospital pathogens.

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1. Introduction

There are continuing concerns over hospital-acquired infections (HAIs) caused by *Clostridium difficile*, meticillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β-lactamase (ESBL)-producing coliforms [1]. It is already known that these pathogens are associated with antibiotic consumption, with some classes encouraging certain organisms more than others [1–3]. Intensive use of cephalosporins or quinolones, for example, has been linked with increasing rates of *C. difficile*, MRSA and/or ESBL-producing coliforms, whilst reduced consumption has facilitated

decreased rates of one or more of these pathogens [1–5]. As a response to high rates of HAIs, it was decided to impose a restrictive antibiotic policy banning the routine use of third-generation cephalosporins, specifically ceftriaxone, and quinolones throughout the hospital. Prospective surveillance programmes were set up to monitor rates of hospital-acquired *C. difficile*, MRSA and ESBL-producing coliforms. Previous studies have not necessarily monitored the effect of such a policy for a whole hospital, nor have they included surveillance of all three pathogens simultaneously. The aim of stewardship was primarily to reduce the number of *C. difficile* cases, although it was hoped that the policy would also impact on MRSA and ESBL-producing coliforms. This article describes how prescribing practices were changed and what happened after two key antibiotics were removed from first-line prescribing on a hospital-wide basis.

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2. Materials and methods

2.1. Antimicrobial policy implementation

Hairmyres Hospital is a 450-bed district general hospital in a rural area just outside Glasgow, UK. The hospital admits adult patients only, specialising in care of the elderly, respiratory, endocrinology and cardiology, with most surgical specialties represented, including orthopaedics, vascular, ear, nose and throat (ENT), and ophthalmology. There is an Accident & Emergency (A&E) department, a high dependency unit and an 8-bed Intensive Care Unit (ICU). Antimicrobial prescribing policies for empirical treatment of various infections and surgical prophylaxis are overseen by a Healthboard Infection Committee; day-to-day advice on antimicrobial prescribing is provided by one consultant microbiologist, who also authorises microbiological results. The microbiologist is supported by an on-site Clinical Pathology Accreditation (CPA)-accredited laboratory, out-of-hours cross cover by colleagues at neighbouring hospitals and two infection control nurses.

Specific concern over *C. difficile* was raised following increasing cases among hospital in-patients during January 2008. Surveillance figures published later that year confirmed the high rate of *C. difficile* compared with other Scottish hospitals [6]. It was decided to initiate an educational programme encouraging prescribers to reduce consumption of cephalosporins and quinolones on a voluntary basis. This was done by providing a series of lectures to all medical staff starting in January 2008 as well as weekly teaching for small groups of junior doctors. A letter summarising the problem and requirement for prescribing change was sent to all senior staff, including doctors, pharmacists and managers. Daily microbiological authorisation suppressed release of cephalosporins and quinolones on ward reports unless no other agents were available. Ad hoc discussion took place when ward doctors phoned for advice on individual patients, with restricted agents either stopped or changed to alternative therapy.

From January 2008, the infection control team initiated prospective surveillance of all cases of *C. difficile*, MRSA and ESBL-producing coliforms on a ward-by-ward basis using national guidelines and definitions. Monthly consumption of antibiotics was collected and recorded in defined daily doses (DDDs) per 1000 patient-occupied bed-days (pt-bds) (http://www.whocc.no/atc_ddd_index/). Macrolides (erythromycin and clarithromycin), ceftriaxone, amoxicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, gentamicin, ciprofloxacin and meropenem were monitored. Information Management provided monthly bed occupancy figures for the hospital using the hospital TrakCare® system.

Following a small outbreak of *C. difficile* on the gastroenterology ward in May 2008, formal restriction of cephalosporins and quinolones was proposed. This began during August 2008, to coincide with hospital-wide changeover of junior doctors. The antimicrobial policy was contained within an induction programme for all new doctors. Empirical prescription of ceftriaxone for systemic sepsis and surgical prophylaxis was changed to amoxicillin, gentamicin and metronidazole. The most notable intervention was complete removal of ceftriaxone and ciprofloxacin from all wards except for A&E and the ICU. The educational programme then continued for prescribers on a regular basis, with feedback on HAI rates sent to clinicians and managers from late 2008. The antibiotic policy continued after the study finished in December 2009.

Preliminary data from this study were presented at the 20th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 10–13 April 2010, Vienna, Austria. One year later, 2011 rates of *C. difficile*, MRSA and ESBL-producing coliforms were audited using the same definitions in order to gauge long-term effects of the restrictive policy. HAI and bed occupancy data were subsequently collected on a monthly basis throughout 2011.

2.2. Surveillance definitions

Specimens were sent to the laboratory when clinically indicated. Hospital-acquired *C. difficile* was defined as onset of symptoms >48 h after admission (or with onset of symptoms in the community following hospital admission within the previous 4 weeks) along with a positive *C. difficile* toxin test. Hospital-acquired MRSA was confirmed if MRSA was isolated from any specimen >48 h after hospital admission, with no previous record of MRSA carriage or infection. Similarly, ESBL-producing coliform isolated from any specimen >48 h after admission was defined as hospital-acquired, with no previous record of ESBL-producing coliform carriage or infection. Whilst screening for these organisms was not routinely performed during 2007–2009, patients awaiting elective surgery were offered MRSA screening (nose, perineum and wounds) and urinalysis.

Determination of new acquisitions was performed systematically for all patients following laboratory confirmation. After excluding duplicate specimens, each new acquisition alert was subjected to rigorous investigation, including inspection of patient notes, details on previous hospital admission(s), antimicrobial therapy and review of microbiological history using the laboratory database. Whilst new acquisitions of *C. difficile* were generally conclusive, investigation of potential new acquisitions of MRSA and ESBL-producing coliforms often revealed prior acquisition months or even years before the current admission and these patients were excluded. There were no genotyping data to confirm persistent carriage of specific strains, but the database held details of previously isolated organisms with full antibiogram. This helped evaluate long-term carriage of specific phenotypes of MRSA and ESBL-producing coliforms. Microbiological results for individual patients moving between hospital and the community could be tracked for a decade or more.

Patients lacking historical microbiological data and/or history of recent (within 1 year) hospital admission and/or transfers from another hospital or healthcare institution were excluded, as well as frequent hospital attendees due to chronic disease. Patient notes were tagged for future reference following confirmation of acquisition. Enhanced investigation of all potential acquisitions was maintained throughout the study owing to the fact that patients were not routinely screened for study organisms. Universal screening for MRSA was introduced as national policy in 2010.

Healthboard policies were applied throughout the whole hospital by the same infection control team. Other than sporadic ward closures due to norovirus, there were no outbreaks caused by any of the three organisms under surveillance, apart from the cluster of *C. difficile* cases previously mentioned, and there were no additional infection control interventions over the study period.

2.3. Laboratory methods

Isolation and identification of *C. difficile*, MRSA and ESBL-producing coliforms from patient specimens were subject to standard operating procedures in an accredited NHS microbiology laboratory. Briefly, *C. difficile* in liquid stool was confirmed by enzyme immunoassay assay (*C. difficile* Tox A/B II; TechLab Inc.), with a proportion of cultured isolates sent to a reference facility for further characterisation. Selection of isolates for typing adhered to reference laboratory recommendations, e.g. investigation of case clusters, fatal outcome and multiple occurrences.

Specimens from all sites were cultured on Oxoid Brilliance Chromogenic MRSA agar overnight and suspect colonies were checked

Table 1

Monthly rates of hospital-acquired meticillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* and extended-spectrum β-lactamase (ESBL)-producing coliforms and consumption of key antibiotics following introduction of a restrictive antibiotic policy for 2 years.

Date	Rate (/1000 pt-bds)			Consumption (DDDs/1000 pt-bds)							
	MRSA	*C. difficile*	ESBL-producing coliforms	CFX	GEN	TZP	AMX	AMC	Macro	CIP	MER
Nov. 2007	n/c	n/c	1.220	58.713	19.068	12.210	144.579	274.5	35.64	51.68	13.834
Dec. 2007	n/c	1.883	1.130	83.254	24.800	21.705	223.582	363.147	39.27	96.571	8.005
Jan. 2008	2.078	3.03	1.212	70.515	27.991	12.690	131.861	272.06	43.74	87.654	4.545
Feb. 2008	0.735	1.837	1.377	44.219	21.122	11.601	160.139	336.909	30.83	96.905	8.265
Mar. 2008	1.081	2.972	1.171	54.535	26.867	14.533	138.363	265.243	36.90	52.526	7.881
Apr. 2008	1.130	1.977	1.695	41.612	44.879	15.191	141.310	146.921	33.48	142.045	12.945
May 2008	1.433	2.580	1.147	34.595	40.300	25.281	134.27	247.343	37.20	128.937	8.123
June 2008	0.664	1.993	2.278	31.800	34.333	18.428	122.662	264.233	35.64	150.755	9.255
July 2008	0.751	0.751	1.408	27.509	41.780	19.405	162.473	215.995	32.13	146.747	7.746
Aug. 2008	0.497	0.795	1.889	5.668	20.384	18.505	167.023	177.468	29.26	118.345	4.474
Sept. 2008	0.932	1.553	2.795	4.347	39.675	12.21	257.711	180.944	43.50	82.124	3.364
Oct. 2008	0.870	0.580	1.644	1.692	39.476	12.99	259.62	153.476	44.93	57.411	2.66
Nov. 2008	1.403	1.309	0.842	2.619	60.799	10.773	260.499	172.145	42.46	73.931	4.911
Dec. 2008	1.082	0.541	1.442	2.884	88.33	16.139	505.858	266.805	70.03	68.265	5.858
Jan. 2009	0.802	0.356	0.713	1.912	80.23	12.55	271.684	140.649	47.13	105.17	4.903
Feb. 2009	0.728	0.312	1.04	2.496	64.832	14.376	312.981	182.016	42.59	64.76	3.640
Mar. 2009	0.738	0.277	1.845	1.015	63.653	18.295	254.336	157.300	40.27	50.387	4.612
Apr. 2009	1.375	0.458	0.825	2.933	56.365	18.412	193.52	118.733	43.4	10.503	5.957
May 2009	0.534	0.802	0.98	2.316	70.372	19.126	284.874	117.967	44.81	27.632	6.235
June 2009	1.359	0.291	0.874	1.310	82.343	18.533	248.932	159.02	41.62	30.072	2.184
July 2009	0.559	0.559	1.676	4.376	80.382	25.012	364.97	141.676	29.19	28.305	7.682
Aug. 2009	0.933	1.027	1.587	1.166	71.236	18.029	216.239	165.273	30.19	36.211	9.800
Sept. 2009	0.865	0.288	0.865	0.576	72.220	14.920	281.013	135.62	36.27	27.308	6.966
Oct. 2009	0.765	0.510	1.020	3.188	76.670	14.922	345.761	102.57	37.81	26.87	2.551
Nov. 2009	0.882	0.617	1.323	2.161	93.066	20.67	324.32	125.803	45.85	32.463	2.426

pt-bds, patient-occupied bed-days; DDDs, defined daily doses; CFX, ceftriaxone; GEN, gentamicin; TZP, piperacillin/tazobactam; AMX, amoxicillin; AMC, amoxicillin/clavulanic acid; Macro, macrolides (erythromycin and clarithromycin); CIP, ciprofloxacin; MER, meropenem; n/c, not collected.
The educational component of restrictive antibiotic policy began in December 2007; formal component of policy was introduced in July 2008.

for coagulase production using Staph Xtra Latex (Pro-Lab Diagnostics) followed by tube coagulase. Presumed MRSA were tested for penicillin-binding protein using Latex PBP2I (Oxoid Ltd.) and VITEK 2 analyses for confirmation and antibiogram. Sporadic isolates were sent to a reference facility according to national protocol.

ESBL-producing coliforms were also identified using the VITEK 2 analyser, accompanied by standard cephalosporin and clavulanic acid disk testing (Mast Diagnostics). The definition of 'coliforms' used was lactose-fermenting Gram-negative non-spore-forming bacilli capable of producing acid and gas when incubated at 35–37 °C. The following genera and species were identified and included: *Escherichia coli*; *Klebsiella* spp. (mostly *Klebsiella pneumoniae*); *Enterobacter* spp. (mostly *Enterobacter cloacae*); *Serratia* spp. (mostly *Serratia marcescens*); *Hafnia alvei*; and *Citrobacter koseri*. Over 95% of the ESBL-producing Gram-negative bacilli identified were *E. coli* and *K. pneumoniae*. Any unidentifiable isolates and/or those showing resistance to carbapenem agents were sent to a reference laboratory for verification.

2.4. Statistics

A Poisson regression model (adjusted for overdispersion) was used with log occupied bed-days as an offset. Linear trend terms were used to assess temporal changes. The main hypothesis was to see whether the trend in HAI rates following antimicrobial restriction was the same as the trend before the intervention. If that hypothesis was not rejected, then there was a further test of the effect of the restrictions in shifting the level of HAI cases. Variable selection was based upon Akaike information criterion (AIC), and residual analysis was used to assess model fit and serial correlation.

Correlations between cases of ESBL-producing coliforms and ciprofloxacin or ceftriaxone (adjusted for patient-occupied bed-days) were calculated at time lags of 0–5 months. Poisson regression was again used to assess which of the antibiotics was the better predictor of ESBL-producing coliform cases.

3. Results

Average monthly consumption of ceftriaxone reduced from 46.213 DDDs/1000 pt-bds for January–June 2008 to 2.129 DDDs/1000 pt-bds for June–November 2009 (95% reduction). Over the same periods, ciprofloxacin consumption decreased from 109.804 to 30.205 DDDs/1000 pt-bds (72.5% reduction). The pre-intervention hospital-acquisition MRSA rate during the initial 6 months was 1.187 cases/1000 pt-bds, decreasing to 0.894 cases/1000 pt-bds (25% reduction) for the final 6 months of the study; for *C. difficile* it was 2.398 cases/1000 pt-bds, decreasing to 0.549 cases/1000 pt-bds (77% reduction); and for ESBL-producing coliforms it was 1.480 cases/1000 pt-bds, decreasing to 1.224 cases/1000 pt-bds (17% reduction).

Prior to formal introduction of the policy in August 2008, the rate of *C. difficile* cases was already decreasing at a rate of 6.59% per month [95% confidence interval (CI), –2.52%, 15.02%; P = 0.169] (Table 1; Fig. 1). This was attributed to the educational component of the intervention, which could explain the lack of policy effect on the changing trend of *C. difficile* infections (P = 0.69). Adjusting for the decreasing trend, the policy was associated with a 45.22% reduction (95% CI, –4.79%, 72.05%; P = 0.09) in the rate of *C. difficile* infections. If the trend is ignored, which is reasonable for the data from December 2007 to June 2008, then the policy was associated with a 70.20% (95% CI, 57.12%, 79.53%) reduction in the rate of *C. difficile*.

For MRSA, there was no evidence of any effect of the restrictive policy on the trend (P = 0.78) nor on the rates of MRSA acquisition following introduction of the policy (P = 0.62). The total MRSA acquisition rate was constant over the study period. The MRSA bacteraemia rate in this hospital was initially low (0.4 cases/1000 acute occupied bed-days) and did not change during the study. For ESBL-producing coliforms, there was borderline evidence of an effect of the policy on the trend (P = 0.075), which gave an 8.21% (95% CI, –0.39%, 16.15%) reduction.
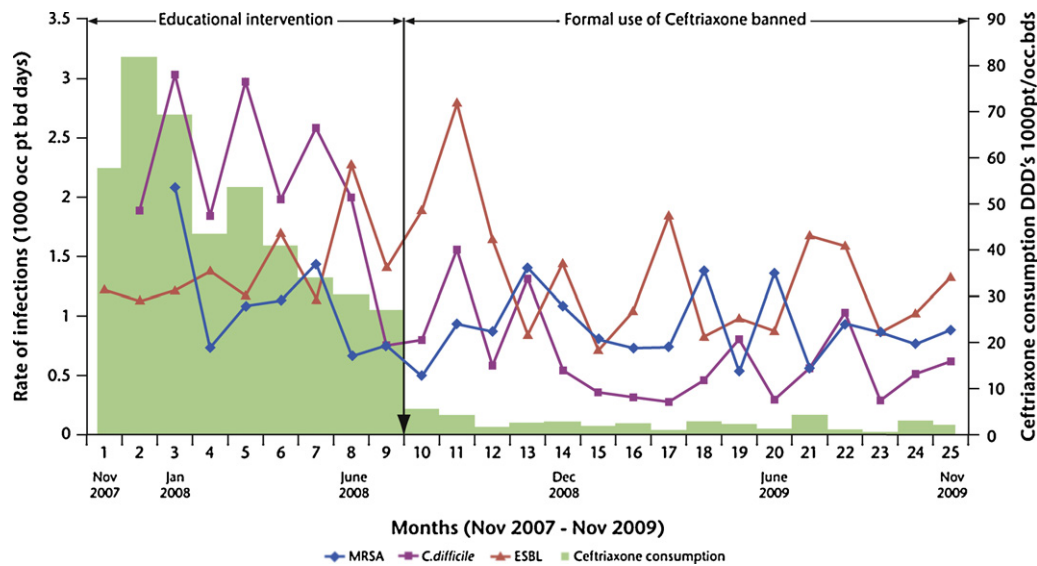
Fig. 1. Hospital-acquired meticillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* and extended-spectrum β-lactamase (ESBL)-producing coliform rates following a restrictive antibiotic policy in a district general hospital over 2 years. pt/occ.bds, patient-occupied bed-days; DDDs, defined daily doses.

Based upon AIC, backward selection within the Poisson regression model using an overdispersed distribution showed that the antibiotics most associated with the temporal changes of *C. difficile* were ceftriaxone (rates decrease as ceftriaxone consumption decreases) and amoxicillin (rates decrease as amoxicillin consumption increases) (Table 2). Time-lag modelling showed a 1-month association between ceftriaxone and *C. difficile* cases (correlation 0.83; $P < 0.005$).

Time-lagged investigation (0–5 months) was used to examine possible associations between ciprofloxacin consumption and ESBL-producing coliform infections (correlation 0.36: $P = 0.08$) (Table 2; Fig. 2). Adjusting for any association between ceftriaxone and ESBL-producing coliform rates, ciprofloxacin consumption and ESBL-producing coliform rates were associated at lags 0, 1 and 2 months (Fig. 3). The strongest association occurred at a lag of 2 months (correlation 0.649; $P = 0.002$), whilst associations at lags 0 and 1 month are borderline ($P = 0.047$ and $P = 0.044$, respectively). ESBL-producing coliform rates increased as monthly ciprofloxacin consumption increased for all three lags. Adjusting for the association between ciprofloxacin and ESBL-producing coliform rates, there was no association between ESBL-producing coliforms and ceftriaxone consumption at any lag between 0 and 5 months.

This study finished at the end of 2009, but restrictions on ciprofloxacin and ceftriaxone have continued. Low rates of *C. difficile* have been maintained, as during 2011 monthly rates varied between 0.2 and 0.6 cases/1000 pt-bds, with an average rate of 0.259 cases/1000 pt-bds (data not shown). We also found decreased numbers of patients acquiring MRSA and ESBL-producing coliforms. In 2011, the average monthly hospital-acquired rate for ESBL-producing coliforms was 0.809 cases/1000 pt-bds and for MRSA it was 0.409 cases/1000 pt-bds, with an MRSA bacteraemia rate of 0.2 cases/1000 acute occupied bed-days. These rates represent further reductions for all three pathogens.

4. Discussion

Introducing and reinforcing a restrictive antimicrobial policy in this hospital had a rapid and profound effect on the rate of hospital-acquired *C. difficile*. The relationship between consumption of broad-spectrum antibiotics and *C. difficile* rates has already been established, with the highest risk for *C. difficile* infection within the first month following antibiotic use [1–3,7]. Whilst the most significant association occurred between *C. difficile* rate and ceftriaxone consumption, it is possible that reduction of cases could be attributed to other antibiotic trends. *Clostridium difficile* isolates were typed and whilst ribotype 0127 was not identified, we were aware of others that were uniformly resistant to quinolone antibiotics. Targeting both ceftriaxone and ciprofloxacin may have ultimately been the most important factor in decreasing *C. difficile* rates.

At the time of this study, there were no national data on antimicrobial consumption for individual hospitals. This was one of the reasons that we decided to examine our infection rates against consumption of key antibiotics. Furthermore, there were no national

Table 2
Correlation between antibiotic consumption and acquisition rate of target pathogens per 1000 patient-occupied bed-days over 2 years in a district general hospital.

Antibiotic or antibiotic class	*Clostridium difficile*		MRSA		ESBL-producing coliforms	
	Correlation	*P*-value	Correlation	*P*-value	Correlation	*P*-value
Ceftriaxone	0.83	<0.005	0.13	0.58	−0.02	0.92
Gentamicin	−0.70	<0.005	0.07	0.77	−0.30	0.14
Piperacillin/tazobactam	−0.06	0.77	−0.05	0.81	0.04	0.84
Amoxicillin	−0.65	<0.005	−0.13	0.56	−0.12	0.58
Amoxicillin/clavulanic acid	0.65	<0.005	0.06	0.78	0.11	0.61
Macrolides	−0.21	0.34	0.27	0.22	−0.17	0.43
Ciprofloxacin	0.48	0.02	−0.06	0.78	0.36	0.08
Meropenem	0.46	0.03	0.04	0.86	0.09	0.68

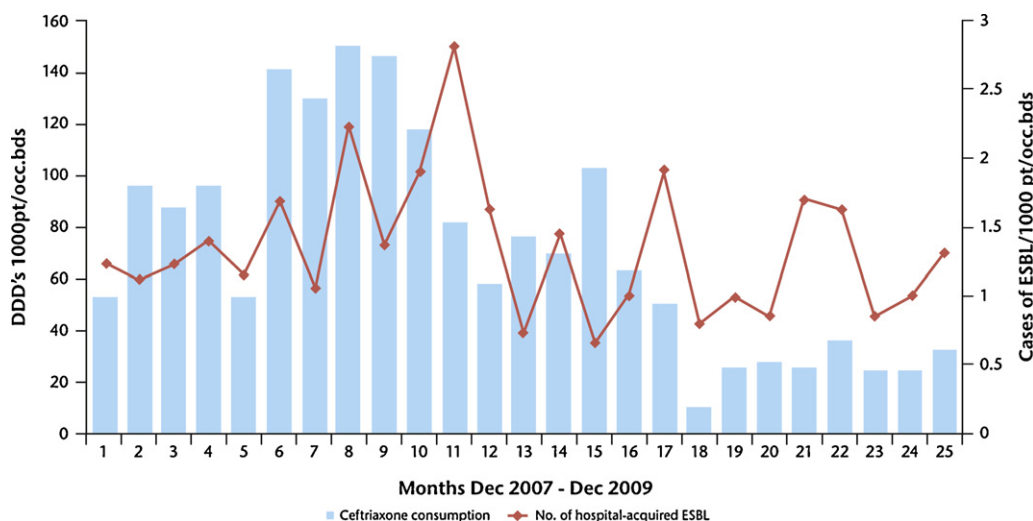MRSA, meticillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum β-lactamase.

Fig. 2. Ciprofloxacin consumption and number of cases of hospital-acquired extended-spectrum β-lactamase (ESBL)-producing coliforms. DDDs, defined daily doses; pt/occ.bds, patient-occupied bed-days.

data on ESBL-producing coliform rates, although we knew that the MRSA bacteraemia rate was comparable with other Scottish hospitals of similar size.

Spatiotemporal modelling suggests that reducing patient susceptibility to *C. difficile* infection is more effective for control than trying to stop transmission once a patient is infected [8]. This is supported by our experience and contrasts with the finding that there was little or no effect on initial rates of MRSA or ESBL-producing coliforms [9]. Infection control procedures for *C. difficile* may be more effective for preventing *C. difficile* transmission than those implemented for patients with either MRSA or ESBL-producing coliforms. Patients with diarrhoea were prioritised for isolation, whereas those colonised with MRSA or ESBL-producing coliforms were not. Whilst some ESBL-producing coliform strains can be maintained in humans without any identifiable selective pressure,

Fig. 3. Time-lag modelling of ciprofloxacin consumption against extended-spectrum β-lactamase (ESBL)-producing coliform acquisition rates. Adjusting for any association between ceftriaxone and ESBL-producing coliform rates, there is an association between ciprofloxacin usage and ESBL-producing coliforms at lags 0, 1 and 2 months. The strongest association is at a lag of 2 months ($P = 0.002$); associations at lags 0 and 1 month are borderline ($P = 0.047$ and $P = 0.044$, respectively).

we found a time–lag relationship between ciprofloxacin consumption and the incidence of ESBL-producing coliforms [1]. It is possible that ciprofloxacin use is driving rates of ESBL-producing coliforms on a hospital-wide basis. This is supported by two studies showing that fluoroquinolone use correlates with increased ESBL-producing coliforms in ICU patients, and another linking quinolone use with ESBL-producing coliforms in hospital and the community. The latter found a 1-month lag effect between quinolone consumption and ESBL-producing coliform rates rather than the 2 months reported here [10–12].

Gaining support for restricting antibiotics among prescribing colleagues in the hospital initially proved difficult. The educational component was almost exclusively provided by the on-site microbiologist and helped reinforce knowledge on prescribing practices and the longer-term consequences of antibiotic consumption [2,13]. The effect of the initial education programme is clearly seen in Fig. 1, whereby consumption of ceftriaxone decreased even before the restrictive policy was formally implemented. Advice on prescribing often conflicted with published guidelines on the management of a specific condition, however, which recommended one or both of the targeted antibiotics. Thus, gastroenterologists initially refused to curtail ciprofloxacin prescribing for spontaneous bacterial peritonitis (SBP) [14]. Restrictions were eventually accepted after the outbreak in May 2008, following which independent audit was performed on the microbiological aetiology of SBP in order to improve prescribing practices. By far the best method of restricting use of a particular drug was physical removal from ward stores by the pharmacists [15]. This meant that doctors did not have easy access to banned agents out-of-hours, although pharmacy would supply it on an individual named-patient basis following clinical discussion. Routine surveillance confirmed that unrestricted antibiotic prescribing did not encourage ICU-acquired infection caused by MRSA, ESBL-producing coliforms or *C. difficile*, but it is possible that daily ward rounds by the on-site microbiologist helped control consumption of banned agents.

This type of study suffers from the fact that cause-and-effect between HAI rates and changes in antibiotic consumption are notoriously difficult to prove [1]. Antimicrobial policy changes are confounded by infection control practices on the wards, including urinary and vascular catheter use [16,17]. In addition, there was occasional use of related drugs such as moxifloxacin, levofloxacin and cefuroxime, albeit at a low level, which could have influenced the effect of the policy. Meropenem consumption decreased
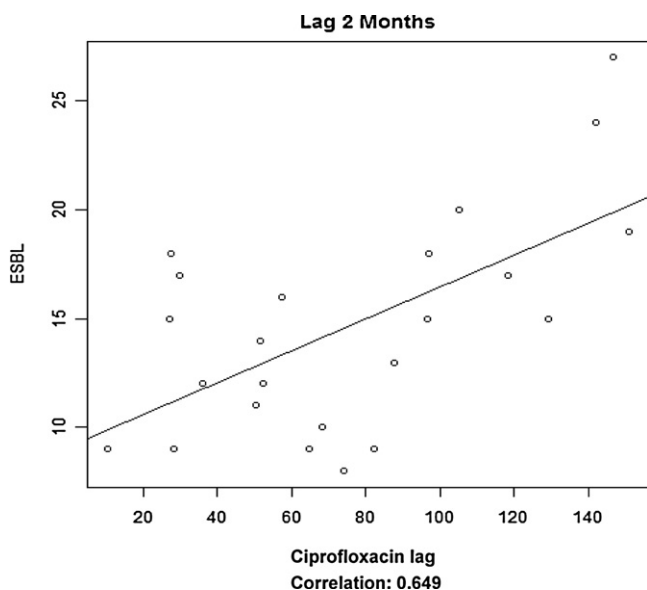
throughout the study and could have had an impact on *C. difficile* rates, although there was no statistical correlation. We believe that this was because overall use of meropenem was low and, furthermore, it was generally only used for patients in intensive care.

Consumption of empirical amoxicillin and gentamicin escalated throughout the study and could also have confounded the overall effect. Given the surge in gentamicin prescribing, we were forced to monitor the management of dosage and levels, with auditing of incidents regarding gentamicin. After initial turbulence, gentamicin is now generally well managed, although resistance is increasing among hospital isolates (data not included). Amoxicillin resistance also increased among hospital *E. coli* isolates, although this has only recently been detected. Ecological studies are limited compared with individual-level analysis because is not possible to evaluate time as an important exposure variable related to the emergence of resistance. The ecological 'bias' or analysis of aggregated data may be compromised by the failure of level-effect estimates to reflect the biological effect at the individual patient level [18].

Whilst low rates of *C. difficile* have been maintained to date, it is possible that continued restrictions have influenced MRSA and ESBL-producing coliform acquisition longer term, subject to the confounders already described. Three years after initiating the antibiotic policy, the 2011 rate of hospital-acquired *C. difficile* was 0.259 cases/1000 pt-bds, for MRSA it was 0.409 cases/1000 pt-bds and for ESBL-producing coliforms it was 0.809 cases/1000 pt-bds. These rates are among the lowest achieved since the study began and reflect observed lower rates of surgical site infection.

Retrospective search of the database for carbapenem resistance among hospital-acquired ESBL-producing coliforms using appropriate clinical definitions identified five cases in 2008, one in 2009, three in 2010, one in 2011 and none so far during 2012. These numbers are too small to draw any conclusions, but it is possible that the restrictive policy has had some impact on extreme drug resistance in this hospital. Three of the cases in 2008 were fatal [19]. Whilst there have not been any specific interventions to control ESBL-producing coliforms during the last 4 years, universal screening for MRSA began in 2010 and continued throughout 2011. This may have contributed towards reduced hospital-acquired MRSA in 2011, since there was only an insignificant reduction in MRSA acquisition from 2007 to 2009 [5].

In conclusion, banning ceftriaxone and ciprofloxacin from first-line prescribing resulted in a rapid reduction in hospital-acquired *C. difficile*, with smaller reductions in ESBL-producing coliforms and MRSA over an initial 2-year period. Quinolone consumption appears to be driving ESBL-producing coliform acquisition in this hospital. Continued restrictions on antibiotic prescribing have helped maintain low rates of *C. difficile* to date. Infection control interventions aside, it is possible that the policy has also impacted upon ESBL-producing coliform and MRSA acquisition long term. Antimicrobial stewardship is fundamental for controlling HAIs and we should strive to reduce antibiotic use at all costs [20].

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