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Impact of antibiotic restriction on resistance levels of *Escherichia coli*: a controlled interrupted time series study of a hospital-wide antibiotic stewardship programme

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Objectives: We evaluated the effect of an antibiotic stewardship programme (ASP) on the use of antibiotics and resistance levels of *Escherichia coli* using a method that allowed direct comparison between an intervention hospital and a control hospital.

Methods: The study was conducted as a retrospective controlled interrupted time series (ITS) at two university teaching hospitals, intervention and control, with 736 and 552 beds, respectively. The study period was between January 2008 and September 2014. We used ITS analysis to determine significant changes in antibiotic use and resistance levels of *E. coli*. Results were directly compared with data from the control hospital utilizing a subtracted time series (STS).

Results: Direct comparison with the control hospital showed that the ASP was associated with a significant change in the level of use of cephalosporins [−151 DDDs/1000 bed-days (95% CI −177, −126)] and fluoroquinolones [−44.5 DDDs/1000 bed-days (95% CI −58.9, −30.1)]. Resistance of *E. coli* showed a significant change in slope for cefuroxime [−0.13 percentage points/month (95% CI −0.21, −0.057)] and ciprofloxacin [−0.15 percentage points/month (95% CI −0.26, −0.038)].

Conclusions: The ASP significantly reduced the use of cephalosporins and fluoroquinolones, with concomitant decreasing levels of *E. coli* resistance to cefuroxime and ciprofloxacin. The same development was not observed at the control hospital.

Introduction

Clinically relevant outcome measures of the effects of antibiotic stewardship programmes (ASPs) are needed for use as quality indicators. Professionals, administrators and authorities request such outcome measures[1] and they are of utmost importance to ensure sustainable effects of ASPs,[2] as well as for the general acceptance of such programmes. However, evaluating and reporting the effect of ASPs is not without challenges and there are several pitfalls, including a lack of control groups.[3]

We implemented an ASP to curb increasing problems with MDR organisms. The ASP focused on reducing the use of cephalosporins and fluoroquinolones. A nearby comparable hospital that was not part of the programme served as a control hospital.

This study evaluates the outcomes of the ASP by investigating its impact on the resistance of *E. coli* to cefuroxime and ciprofloxacin. We used a method that allowed direct comparison between the intervention hospital and the control hospital in an interrupted time series (ITS) analysis.

Materials and methods

Design and setting

This study was conducted as a retrospective ITS analysis in accordance with the ORION guidelines,[4] with a pre-implementation phase from January 2008 to December 2010, an implementation phase from January to December 2011 and a post-implementation phase from January 2012 to September 2014. It took place in the Capital Region of Denmark at Herlev Hospital (intervention) and Hvidovre Hospital (control). For further details of the hospitals see Table S1 (available as Supplementary data at *JAC* Online). The study was approved by the Danish Data Protection Agency

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Intervention

The ASP was implemented during January–December 2011 and consisted of multiple parts, but it primarily provided new antibiotic guidelines for empirical treatment replacing cephalosporins and fluoroquinolones with narrow-spectrum penicillins and gentamicin.[5] For further details see Table S2.

Laboratory procedures

Identification of microorganisms was performed using standard methods[6] and susceptibility testing was performed by disc diffusion methods according to EUCAST recommendations.[7] We included *E. coli* isolates from all types of specimens, but excluded isolates from primary care. When multiple identical isolates from the same patient occurred within a 30 day window, only the first isolate was used. From March 2012 to June 2013, the intervention hospital temporarily changed susceptibility testing of ciprofloxacin. To adjust for this change, we re-tested all blood cultures of *E. coli* from this period. Therefore, during this period we calculated the level of resistance to ciprofloxacin at the intervention hospital using only results from the re-tested blood cultures.

Outcomes

Our primary outcomes were change in use of cephalosporins and fluoroquinolones and resistance of *E. coli* to cefuroxime and ciprofloxacin. We determined antibiotic use by adjusting the monthly use of antibiotics (sales data) for changes in the number of occupied bed-days and expressed it as DDDs per 1000 occupied bed-days. DDDs were defined according to ATC/DDD index 2014.[8] We expressed resistance as the percentage of resistant isolates out of the total number of isolates that were tested for the specific resistance.

Statistical methods

We discarded observations from the implementation phase from the analysis, according to the method described by Cochrane Effective Practice and Organisation of Care.[9] To estimate how the hospitals differed before and after the implementation, we performed an ITS analysis of the difference in outcomes at the two hospitals by subtracting data points of the control hospital from data points of the intervention hospital for each month, yielding a subtracted time series (STS). An analysis excluding the Department of Haematology and the ICU was performed (Table S3). We used the proc autoreg function in SAS 9.4 to test (using Durbin–Watson statistics) and adjust for autocorrelation in order to estimate to the final model parameters. To control for seasonality, we used stepwise autoregression with the NLAG option set to 13.[10]

Results

Implementing the ASP was associated with a significant decrease in the use of cephalosporins at the intervention hospital [−150 (95% CI −172, −128) DDDs/1000 bed-days], but not at the control hospital (Table 1 and Figure 1). After the ASP's implementation, the slope changed significantly at the control hospital, resulting in a decrease in the use of cephalosporins, but not at

Table 1. ITS analysis of antibiotic use and resistance of *E. coli* at Herlev Hospital (intervention) and Hvidovre Hospital (control), with a direct comparison of the two hospitals in the STS

		Pre-implementation slope	Change in level (implementation period)	Change in slope
		Monthly change in DDDs/1000 bed-days (95% CI)	Change in DDDs/1000 bed-days (95% CI)	Monthly change in DDDs/1000 bed-days (95% CI)
Cephalosporins	intervention	0.44 (−0.24, 1.12)	−150 (−172, −128)**	−0.57 (−1.52, 0.38)
	control	1.15 (0.42, 1.87)*	1.14 (−21.2, 23.5)	−3.19 (−4.28, −2.10)**
	STS	−0.82 (−1.63, −0.006)*	−151 (−177, −126)**	2.77 (1.58, 3.96)**
Fluoroquinolones	intervention	−0.10 (−0.56, 0.36)	−38.5 (−52.9, −24.1)**	0.15 (−0.52, 0.83)
	control	0.060 (−0.44, 0.56)	8.61 (−4.33, 21.5)	−0.41 (−1.22, 0.39)
	STS	−0.27 (−0.73, 0.18)	−44.5 (−58.9, −30.1)**	0.67 (−0.011, 1.33)
Penicillins/BLIs	intervention	0.58 (−0.31, 1.48)	109 (82.6, 136)**	−0.91 (−2.27, 0.44)
	control	0.51 (0.086, 0.93)*	−4.39 (−17.8, 8.99)	0.80 (0.19, 1.40)*
	STS	0.10 (−0.70, 0.91)	112 (88.0, 136)**	−1.70 (−2.92, −0.48)*
		Monthly change in resistance in percentage points (95% CI)	Change in resistance in percentage points (95% CI)	Monthly change in resistance in percentage points (95% CI)
E. coli resistance, cefuroxime	intervention	0.068 (0.021, 0.12)*	0.25 (−1.17, 1.66)	−0.11 (−0.18, −0.041)*
	control	0.031 (−0.019, 0.080)	1.17 (−0.32, 2.66)	0.016 (−0.59, 0.091)
	STS	0.054 (0.0008, 0.11)*	−1.47 (−3.14, 0.19)	−0.13 (−0.21, −0.057)*
E. coli resistance, ciprofloxacin	intervention	0.13 (0.055, 0.21)*	5.43 (3.06, 7.80)**	−0.25 (−0.36, −0.15)**
	control	0.13 (0.087, 0.17)**	2.18 (0.86, 3.50)*	−0.10 (−0.16, −0.041)*
	STS	0.0070 (−0.069, 0.083)	2.90 (0.50, 5.29)*	−0.15 (−0.26, −0.038)*

*$P < 0.05$; **$P < 0.0001$.

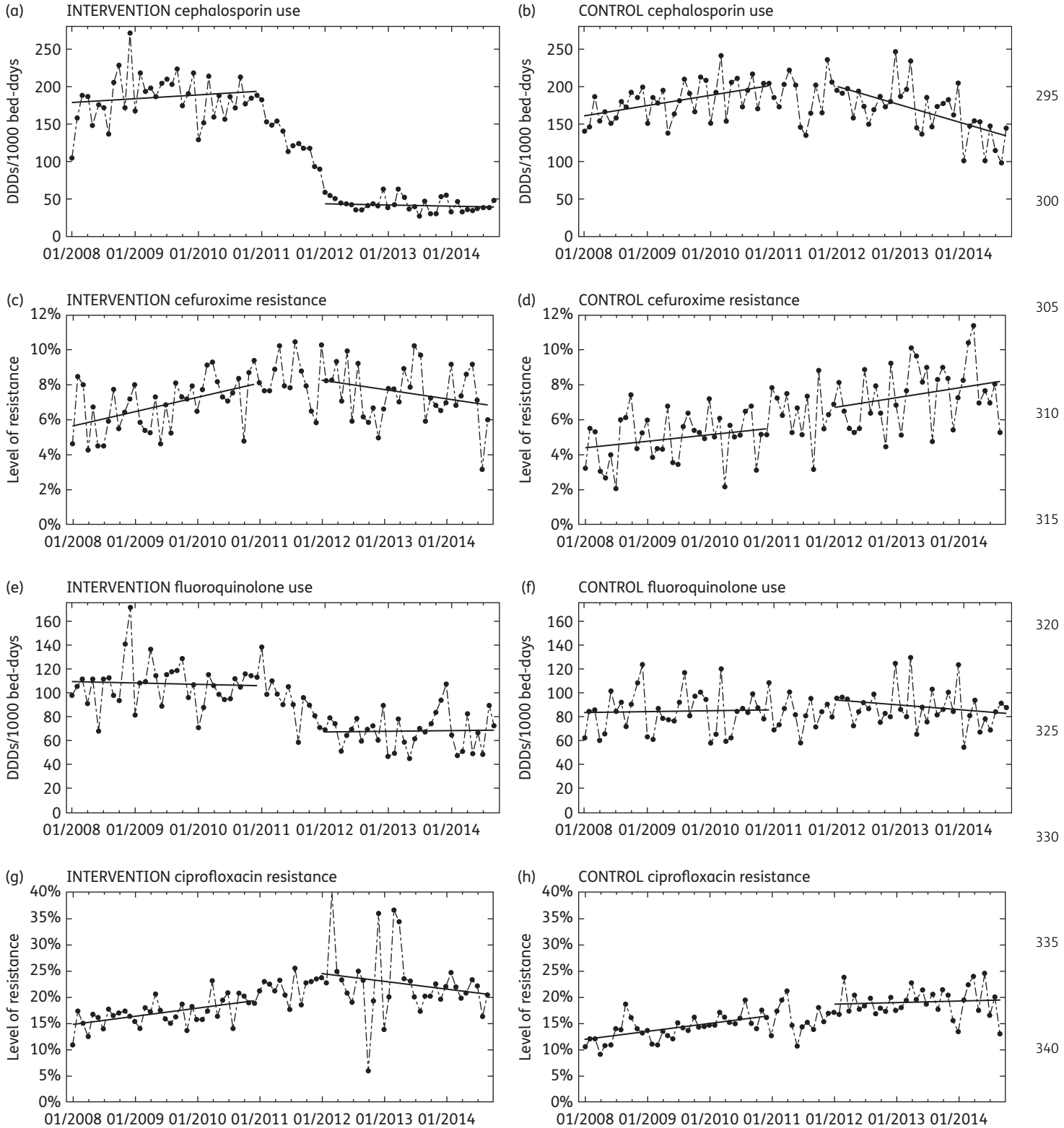

Figure 1. Use of cephalosporins and fluoroquinolones compared with resistance of *E. coli* to cefuroxime and ciprofloxacin. Use of cephalosporins at (a) the intervention hospital and (b) the control hospital. Resistance of *E. coli* to cefuroxime at (c) the intervention hospital and (d) the intervention hospital. Use of fluoroquinolones at (e) the intervention hospital and (f) the control hospital. Resistance of *E. coli* to ciprofloxacin at (g) the intervention hospital and (h) the control hospital.

the intervention hospital, resulting in a difference of 2.77 (95% CI 1.58, 3.96) DDDs/1000 bed-days in the direct comparison.

Resistance to cefuroxime was increasing at both hospitals prior to 2011. The STS indicated that the increase was significantly higher at the intervention hospital [0.054 (95% CI 0.0008, 0.11) percentage points]. We observed no change at either hospital during the implementation. After the implementation, the slope changed significantly at the intervention hospital [−0.11 (95% CI −0.18, −0.041) percentage points], but not at the control hospital, resulting in a decrease in resistance at the intervention hospital, but a continuous increase at the control hospital.

For fluoroquinolones, the ASP resulted in a significant reduction in use at the intervention hospital [−38.5 (95% CI −52.9, −24.1) DDDs/1000 bed-days], but no significant change at the control hospital. No changes were observed after implementation.

The resistance levels of *E. coli* increased significantly at both hospitals prior to 2011. During the implementation, we observed significant increases in resistance level at both hospitals. After the implementation, the slope changed significantly at both hospitals, resulting in a decreasing trend in resistance at the intervention hospital and a reduction in slope at the control hospital. The STS supported this by indicating a significant decrease in the difference between the two hospitals [−0.15 (95% CI −0.26, −0.038) percentage points for ciprofloxacin].

During implementation we observed an unintended increase in the use of penicillins in combination with β-lactamase inhibitors [penicillins/β-lactamase inhibitors (BLIs)] at the intervention hospital of 112 (95% CI 88.0, 136) DDDs/1000 bed-days when compared with the control. For ITS analysis of other antibiotics, see Table S4.

Discussion

The purpose of this study was to evaluate the effect of an ASP on the use of antibiotics and resistance levels of *E. coli*. We observed a significant and sustained reduction in the use of cephalosporins and fluoroquinolones when compared with the control. After the ASP's implementation, resistance to both antibiotics decreased significantly when directly compared with the control hospital. However, during implementation, we also observed an unexpected increase in the use of penicillins/BLIs, which could be a risk factor of *Clostridium difficile* infections (CDIs).[11]

A previous study has shown similar results regarding antibiotic use and the development of resistance in *E. coli*, but did not use a control for direct comparison.[12] Another study has shown similar results with regard to cefuroxime use, but not with *E. coli*, which may be explained by the focus in that study on ESBL only.[13] Only a few other studies have used resistance in *E. coli* as an outcome, but have not reported any positive effect on resistance.[14,15]

We chose *E. coli* because it is prevalent and causes clinically relevant infections. The disadvantage of *E. coli* was the small difference in resistance levels between primary and secondary care in our setting,[16] giving a small margin of improvement, assuming that resistance levels will not fall below those in primary care. During the study period, the use of cephalosporins and fluoroquinolones remained constant in primary care.[16]

The impact of ASPs at hospital level is difficult to document, since contemporary hospital systems are constantly changing and ASPs are often implemented to curb abrupt changes in antimicrobial resistance.[3] Since hospital use of antibiotics in general only accounts for a small proportion of their total use, ASPs have only limited effect on resistance in primary care, and the impact of the ASP must be considered relative to the resistance level in the community.[16] To overcome these obstacles, we used STS to determine whether the ASP caused significant differences between the hospitals, thereby adjusting for changes in primary care. This method has previously been described in other contexts, but, to our knowledge, has not previously been used for the evaluation of ASPs.[17–19]

Our study has strengths and weaknesses. We used STS, which enabled direct comparison between the two hospitals. We had a long study period and we included the entire hospital in the analysis. However, we did not distinguish between nosocomial and community-acquired infections, as this would be adjusted for by comparing the two hospitals assuming they have similar distribution between nosocomial and community-acquired infections. Higher ciprofloxacin resistance may have occurred because only re-tested blood cultures were used from March 2012 to June 2013, since *E. coli* isolates from blood cultures in Denmark have a higher resistance than those from urine.[16] We do not believe that the spill-over effect of cephalosporin use affected the antibiotic use of the control hospital, since the change happened late in the study period and after the ASP's implementation. Changes in infection control to curb an increase in CDIs were implemented at both hospitals in 2011–12. These changes focused on controlling CDIs, and we do not believe that they influenced the spread of antimicrobial-resistant *E. coli*. The study was conducted in a setting with low levels of antibiotic resistance and may not be generalizable to settings with higher resistance.

In conclusion, the introduction of an ASP was associated with a significantly reduced use of cephalosporins and fluoroquinolones, with concomitant decreasing resistance of *E. coli* to cefuroxime and ciprofloxacin. The same development was not observed at the control hospital.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 to S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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