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Improving Quinolone Use in Hospitals by Using a Bundle of Interventions in an Interrupted Time Series Analysis▽

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The objectives of the present study were to determine the effects of multiple targeted interventions on the level of use of quinolones and the observed rates of resistance to quinolones in *Escherichia coli* isolates from hospitalized patients. A bundle consisting of four interventions to improve the use of quinolones was implemented. The outcome was measured from the monthly levels of use of intravenous (i.v.) and oral quinolones and the susceptibility patterns for *E. coli* isolates from hospitalized patients. Statistical analyses were performed using segmented regression analysis and segmented Poisson regression models. Before the bundle was implemented, the annual use of quinolones was 2.7 defined daily doses (DDDs)/100 patient days. After the interventions, in 2007, this was reduced to 1.7 DDDs/100 patient days. The first intervention, a switch from i.v. to oral medication, was associated with a stepwise reduction in i.v. quinolone use of 71 prescribed daily doses (PDDs) per month (95% confidence interval [CI] = 47 to 95 PDDs/month, $P < 0.001$). Intervention 2, introduction of a new antibiotic guideline and education program, was associated with a stepwise reduction in the overall use of quinolones (reduction, 107 PDDs/month [95% CI = 58 to 156 PDDs/month). Before the interventions the quinolone resistance rate was increasing, on average, by 4.6% (95% CI = 2.6 to 6.1%) per year. This increase leveled off, which was associated with intervention 2 and intervention 4, active monitoring of prescriptions and feedback. Trends in resistance to other antimicrobial agents did not change. This study showed that the hospital-wide use of quinolones can be significantly reduced by an active policy consisting of multiple interventions. There was also a stepwise reduction in the rate of quinolone resistance associated with the bundle of interventions.

The use of antimicrobial agents and the rates of antimicrobial resistance vary significantly between countries (8, 9, 16, 27). A substantial proportion of the antimicrobial use is considered inappropriate (30). Apart from the unnecessary costs and potential harm to the patient, inappropriate use can lead to increased selection for and transmission of resistant microorganisms. A recent survey in the Amphia Hospital, Breda, Netherlands, showed that approximately 40% of all antibiotic prescriptions were considered inappropriate (e.g., unnecessary, incorrect choice, or incorrect dosage). The only independent variable associated with inappropriate use was the use of quinolones (30). In many cases the use of quinolones was incorrect because there was no indication for antimicrobial therapy, alternative antimicrobials should have been used (on the basis of hospital, national, and international guidelines), or quinolones were used intravenously (i.v.) where oral forms would suffice. The use of quinolones promotes the spread of antibiotic resistance genes by activating an SOS response, as reported by Beaber et al. (1). This means that the use of quinolones could account for the rapid manner in which resistance genes are disseminating. We therefore performed an intervention study to correct the use of quinolones in hospitalized patients and to determine its effect on the associated costs and the rate of resistance observed in *Escherichia coli*.

MATERIALS AND METHODS

The study was designed as a prospective interrupted time series study consisting of four interventions. The study was performed in the Amphia Hospital, which is a 1,370-bed teaching hospital that includes most medical specialties. The outpatient clinic, the intensive care unit (ICU), and the psychiatry ward were excluded from the interventions. However, these departments were included in the analysis for observed resistance. In 2006, there were 41,712 admissions and 279,403 bed days.

Interventions. During the study period, four interventions involving the use of ciprofloxacin (CIP), the only fluoroquinolone used in the Amphia Hospital were carried out. The interventions were coordinated by a single dedicated project manager. The project manager coordinated all activities of coworkers involved in the project, i.e., consultant microbiologists, pharmacists, pharmacy assistants, and medical specialists.

(i) Intervention 1. Intervention 1 consisted of a switch from i.v. to oral medication (Switch project) (from 1 January 2006 until 31 December 2007). The guideline for an early switch was developed primarily by the hospital antibiotic policy committee and was subsequently approved by the physicians in the hospital. The criteria for a switch from i.v. to oral medication were as follows: first, the patient had to be able to take medication orally (p.o.); second, the patient had to be hemodynamically stable (pulse, <100 beats/min, systolic blood pressure, >100 mmHg); and third, no switch was allowed if the patient was on parenteral nutrition (4, 5, 10, 24). If a switch was performed, the following rules were applied: a dosage of 200 mg twice a day (b.i.d.) i.v. was switched to 500 mg b.i.d. p.o., and one of 400 mg b.i.d. i.v. was switched to 750 mg b.i.d. p.o. The use

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of aluminum- or magnesium-containing antacids, sucralfate, and calcium, bismuth, zinc, and iron salts disturbs the uptake of CIP (18). In those cases, CIP oral medication was administrated more than 2 h before or greater than 4 h after they took another medication(s). From Monday through Friday, all patients with CIP i.v. prescriptions were identified in the pharmacy department information system and checked against the hospital antibiotic policy by a pharmacy assistant. If the patient was considered suitable for a switch, the attending physician was contacted by the pharmacy assistant and a switch was recommended. If the patient was considered potentially suitable but no definite conclusions could be made, the consultant microbiologist was contacted by the pharmacy assistant for advice. If the consultant microbiologist considered the patient suitable for a switch, that individual contacted the attending physician and a switch was recommended. If the patient was considered not suitable for a switch, the i.v. therapy was continued.

(ii) Intervention 2. Intervention 2 consisted of a new antimicrobial guideline for antibiotic use and educational program. On 15 May 2006, a new guideline for antibiotic use was issued in Amphia Hospital. This guideline was developed by the hospital antibiotic policy committee and was subsequently approved by the physicians. The guideline was based on national and international recommendations and adapted to the susceptibility patterns of local pathogens (19). The guideline recommended that empirical use of CIP would be reserved for patients with severe gastroenteritis, prostatitis, or diabetic foot ulcers. In other cases the use of CIP should be based on microbiological diagnostic results. The guideline was sent to all interns, residents, and physicians in a pocket-sized brochure and was made available on the intranet of Amphia Hospital. In June 2006, residents attended group education sessions informing them about the prescription of antimicrobial agents for clinical patients. Restrictive use of CIP was highlighted.

(iii) Intervention 3. Intervention 3 consisted of a restriction note on laboratory reports. In November 2006, a comment on the use of CIP was added to all microbiology results reports: "According to the hospital guideline on antimicrobial treatment, ciprofloxacin is considered a restricted antibiotic which should be prescribed on strict indications only." Furthermore, a letter about the increasing rates of resistance to CIP in Amphia Hospital was sent to all physicians and requested that they follow the local guidelines for antimicrobial therapy.

(iv) Intervention 4. Intervention 4 consisted of active monitoring of prescriptions and feedback. On 1 January 2007, the fourth intervention was initiated. This consisted of active monitoring of CIP prescriptions and the provision of feedback to the prescriber. The hospital's computerized pharmacy records were used to retrieve all orders for CIP prescriptions on a daily basis. Initial screening for the appropriateness of the prescriptions was performed by the project coordinator, according to the local antibiotic prescription guidelines. If the prescriptions did not meet the criteria specified in the guideline, the consultant microbiologist would contact the prescribing intern/resident to discuss the appropriateness of CIP use. The recommendations were registered on a standardized form, and follow-up on the use of the recommendations was checked by the pharmacy assistant.

Outcome measures. The monthly use of CIP i.v. and orally (in grams) was calculated on the basis of the pharmacy department data. Treatment duration was calculated as the difference (in days) between the prescription start and stop dates. If the dosage or method of administration (i.v. or oral) of CIP was changed during therapy, it was assumed that the change had occurred at the beginning of the first day that the patient received the new preparation. The use of CIP (i.v., oral, and total) was translated into prescribed daily doses (PDDs), using 0.8 g as 1 PDD for i.v. CIP and 1.0 g as 1 PDD for oral CIP. The CIP use data were evaluated monthly by a team, including a hospital pharmacist, pharmacy assistant, consultant microbiologist, and the project coordinator. The annual total antibiotic consumption and CIP consumption were translated to PDDs and defined daily doses (DDDs), according to the 2005 Anatomical Therapeutic Chemical Classification System (ATC)/DDD index from the WHO Collaborating Centre for Drug Statistics Methodology (33). Consumption data from the outpatient department were excluded from the analysis.

The susceptibility patterns, including susceptibility to CIP, cefuroxime (CFRX), ceftazidime (CFTZ), trimethoprim-sulfamethoxazole (TMP-SMZ), and tobramycin (TOBR), of the *E. coli* isolates from hospitalized patients, recovered after more than 48 h after admission, were analyzed. The susceptibility patterns were obtained from the laboratory information system from 1 January 2004 to 31 December 2007. Antimicrobial susceptibility testing was performed using an automated system (Vitek bioMérieux). Interpretation of the antimicrobial susceptibility test results was based on guidelines from the Clinical and Laboratory Standards Institute (CLSI) (3). Repeat isolates from a patient after recovery of the initial isolate were excluded from analysis, unless there was a major difference in the susceptibility patterns. A major difference was defined when at least one change from susceptible to resistance was observed. Analyses were performed by considering intermediate susceptibility to be susceptible.

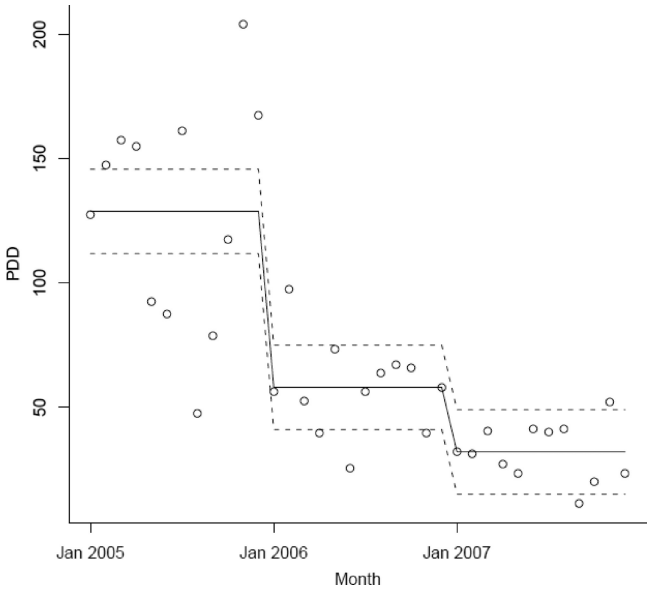

FIG. 1. Monthly use of intravenous ciprofloxacin from 2005 through 2007, in PDDs. Values predicted by the best-segmented regression model are shown by the solid line. Broken lines show the 95% confidence intervals.

Targets and funding. At the initiation of the interventions, the following targets were defined: (i) a 50% reduction of i.v. CIP prescriptions and (ii) a 30% reduction of the absolute amount of CIP use.

On the basis of these assumptions and the anticipated cost savings, the hospital management funded the project by providing financing for a study coordinator (12 h per week) and a pharmacy assistant (18 h per week) during 2006 and 2007.

Data analysis. The privacy of the patients was maintained by coding all data, according to the requirements of the privacy regulation of the Amphia Hospital. Statistical analyses of the CIP use data were performed using segmented regression analysis to allow both stepwise changes and changes in trends, accounting for the combined effects of the interventions on both (20). Bayesian model averaging (BMA) was used to account for model uncertainty by selecting the most likely models (those with the highest posterior probability) and to obtain parameter estimates averaged over the most probable models (by weighting the models by posterior probability) (12). Statistical analyses of the trend in CIP resistance in *E. coli* isolates was performed using segmented Poisson regression models with log-link functions, adjusting for the total number of *E. coli* isolates tested for resistance. The models considered allowed both stepwise changes and log-linear changes in trends, again allowing the cumulative effects of the different interventions and accounting for model uncertainty using BMA (12). In all cases, equal prior probabilities were assigned to possible models and estimated parameters were obtained by averaging over all models that were at least 1/20 as likely as the most likely model (though we report only the three most likely models, in addition to the full model and the model-averaged result). Confidence intervals (CIs) were calculated using at least 100 bootstrap replicates. Analysis was performed in the R (version 2.9) and Stata (release 10) programs (22, 26).

RESULTS

Use of CIP i.v. During the first 12 months, before the interventions were implemented, the monthly use of CIP was stable (mean, 561 PDDs; range, 333 to 634). During the year 2006, 181 patients on CIP i.v. were considered for a switch to oral medication. According to the protocol, 136 (76%) were suitable and a switch was performed for 92 (51%) patients. Directly after the start of the intervention in January 2006, the level of i.v. CIP use was reduced (Fig. 1). In the segmented

TABLE 1. Segmented regression results for the ciprofloxacin intravenous data[a]

Intervention or parameter	Model-averaged coefficient[b] (SD)	Probability of an intervention effect[c]	Full model		Model 1		Model 2		Model 3	
			Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
Intervention 1	−67.9 (17.0)	1	−61.9 (−138.6, 14.9)	0.11	−70.7 (−94.6, −46.7)	<0.001	−68.8 (−94.1, −43.5)	<0.001	−61.4 (−91.7, −31.2)	<0.001
Intervention 2	−1.3 (6.6)	0.07	−30.8 (−115.5, 54.0)	0.46						
Intervention 3	−4.3 (11.5)	0.20	−53.1 (−206.9, 100.7)	0.48			−25.4 (−49.9, −0.98)	0.04		
Intervention 4	−7.0 (14.6)	0.30	−24.2 (−100.5, 52.1)	0.52	−26.0 (−50.0, −2.0)	0.035				
Trend prior to intervention	−0.1 (0.5)	0.09	0.78 (−4.6, 6.2)	0.77						
Change in trend after intervention:										
1	−0.4 (2.0)	0.16	−3.2 (−24.4, 18.1)	0.76					−1.8 (−3.5, −0.03)	0.05
2	−0.02 (1.9)	0.13	11.6 (17.5, 40.6)	0.42						
3	−0.2 (0.9)	0.12	9.4 (−84.8, 103.5)	0.84						
4	−0.2 (0.9)	0.10	−18.8 (−110.8, 73.3)	0.68						

[a] The results of the model-averaged estimates, full model, and three best-fitting models selected by Bayesian model averaging are shown. The posterior model probabilities were <0.01, 0.13, 0.11, and 0.10 for the full model and models 1 to 3, respectively.

[b] Expected value of the coefficient obtained by Bayesian model averaging, combining results from multiple models, weighted according to model probability (see Materials and Methods).

[c] The probability that the coefficient is not zero in the Bayesian model averaging results.

regression analysis of the CIP i.v. data, the most reliable estimate of the combined effects due to the interventions (the model-averaged results) revealed strong evidence that intervention 1 was associated with a large sudden fall in i.v. CIP use, with a probability of 1 of a stepwise change being due to this intervention. In contrast, the full model (incorporating cumulative stepwise changes in levels and changes in trends associated with each intervention) suggested that there was no evidence that any of the four interventions had any impact (Table 1). However, because of multicolinearity, these full model parameter estimates were unstable and therefore unreliable. There was considerable model uncertainty (Table 1, footnote *a*), with the three best-fitting models all having similar posterior probabilities, close to 10%. This model uncertainty is accounted for in the model-averaged results. In the single most likely model (model 1), the level of CIP i.v. use significantly decreased after intervention 4, but accounting for model uncertainty suggested that the true effect was smaller and consistent with chance. Only the effect of intervention 1 was robust to model uncertainty. The annual use of CIP i.v. in the hospital decreased from 1,544 PDDs in 2005 to 696 PDDs in 2006 (a 55% reduction) and 384 PDDs in 2007 (a 75% reduction compared to the level for 2005).

Total use of CIP. The interventions targeted at the overall reduction of the use of CIP (i.v. and oral) started with intervention 2 in May/June 2006. Using segmented regression analysis, 19 models were selected. In this case the full model, the single best model (model 1), and the model-averaged results all agreed and showed strong evidence of a step reduction in CIP use associated with intervention 2 (Fig. 2; Table 2). The best estimate of this (the model-averaged result; Table 2) is a reduction of 131 PDDs/month (95% CI = 34 to 228 PDDs/month). The annual total use of CIP in the hospital, excluding the ICU, decreased from 6,530 PDDs in 2005 to 5,681 PDDs in 2006 (a 13% reduction) and to 3,670 PDDs in 2007 (a 42% reduction compared to the annual use in 2005). The annual hospital use of CIP decreased from 2.7 DDDs/100 patient days in 2005 to 1.7 DDDs/100 patient days in 2007 (Fig. 3). The total antimicrobial use in the hospital increased in the years before the intervention. This increase leveled off in 2006 and 2007, as shown in Fig. 3. No increase in the rates of use of specific groups of antimicrobial agents was observed, and no new antimicrobials were used.

Resistance rates in *E. coli*. Before the start of the interventions, the CIP resistance rate in *E. coli* was increasing by about 5% per year (Fig. 4; Table 3). In the best-fitting Poisson model for the resistance data, a significant stepwise decrease was found to be associated with interventions 2 and 4. However, there was substantial uncertainty in the model choice (the most likely model had a posterior probability of only 0.11), and after accounting for this in the model-averaged results, there was no conclusive evidence in support of any particular intervention.

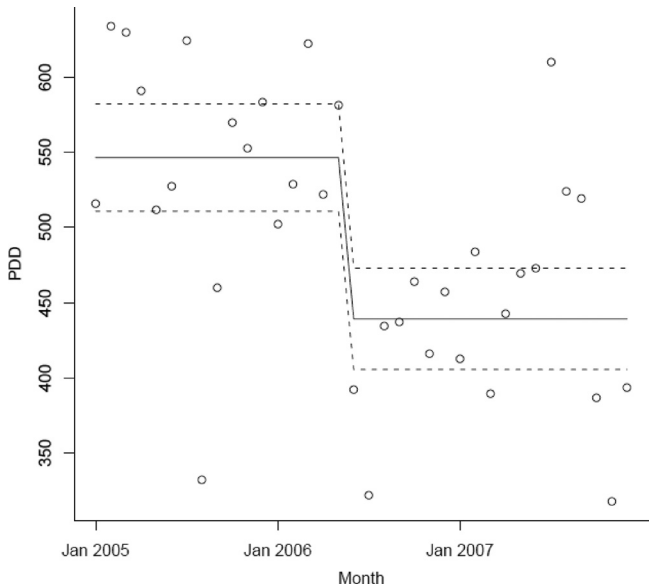

FIG. 2. Monthly use of ciprofloxacin (intravenous and oral) from 2005 through 2007, in PDDs. Values predicted by the best-segmented regression model are shown by the solid line. Broken lines show the 95% confidence intervals.

TABLE 2. Segmented regression results for the total ciprofloxacin data[a]

Intervention or parameter	Model-averaged coefficient[b] (SD)	Probability of an intervention effect[c]	Full model		Model 1		Model 2		Model 3	
			Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
Intervention 1	0.4 (8.7)	0.05	−9.3 (−196.7, 178.1)	0.92						
Intervention 2	−130.8 (49.4)	1	−249.0 (−455.9, −42.2)	0.02	−107.0 (−157.6, −56.4)	<0.001	−136.2 (−204.2, −68.3)	<0.001	−128.7 (184.2, −73.3)	<0.001
Intervention 3	4.9 (19.5)	0.12	−86.8 (−462.2, 288.7)	0.64			39.6 (−30.0, 109.3)	0.26		
Intervention 4	4.7 (19.5)	0.11	18.5 (−167.8, 204.8)	0.84					34.3 (−28.3, 97.0)	0.27
Trend prior to intervention	0.004 (0.9)	0.07	−5.2 (−18.5, 8.0)	0.43						
Change in trend after intervention:										
1	0.8 (3.3)	0.13	20.3 (−31.6, 72.2)	0.43						
2	1.4 (6.3)	0.13	10.7 (−60.2, 81.7)	0.76						
3	−0.5 (8.3)	0.16	15.2 (−214.8, 245.1)	0.89						
4	−1.5 (7.7)	0.16	−44.6 (−269.4, 180.2)	0.69						

[a] The results of the model-averaged estimates, the full model, and three best-fitting models selected by BMA are shown. The posterior model probabilities were <0.01, 0.29, 0.09, and 0.08 for the full model and models 1 to 3, respectively.
[b] The expected value of the coefficient obtained by Bayesian model averaging, combining results from multiple models, weighted according to model probability (see Materials and Methods).
[c] The probability that the coefficient is not zero in the Bayesian model averaging results.

There was, however, evidence that at least one of interventions 2, 3, and 4 was associated with the observed stepwise reduction in resistance; all the best-fitting models included reductions associated with at least one of these. There was little evidence for the efficacy of intervention 1. Very strong evidence was found for an initial increasing trend and little support for models that included a decreasing trend term associated with the interventions. Thus, interventions 2 to 4 may have caused a stepwise reduction in resistance but were unable to reverse the increasing trend.

The rates of resistance to CFRX, CFTZ, TMP-SMZ, and TOBR were studied. There was strong evidence for an increasing trend in the rates of resistance to CRFX and CFTZ. None of the interventions had any effect on these resistance rates. The rates of resistance to TMP-SMZ and TOBR showed no trend up or down, and the interventions did not affect the observed resistance rates.

Costs and savings. Considering only the price of the agent, switching patients from i.v. CIP to oral CIP saved the hospital about €114,000 over 2 years, on the basis of the CIP price in 2005. The overall savings were higher than this, but the additional savings were not calculated because reliable data were not available. The annual cost of the program was approximately €32,000, based on the salaries of the study coordinator and the pharmacy assistant.

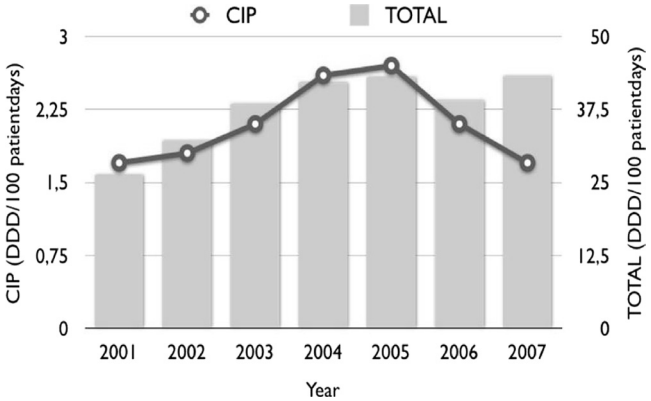

FIG. 3. Annual ciprofloxacin use and overall use.

DISCUSSION

This study shows that implementation of a bundle of interventions targeted at the improved use of CIP was associated with a significant decrease in the level of use of i.v. CIP as well as a decrease in the overall level of use of CIP. The level of i.v. use of CIP decreased immediately after the first intervention (the Switch project). The Switch project improved the quality of care and resulted in important savings, which were sufficient to fund the entire project. The switch from the i.v. to the oral route had several other advantages, which include decreasing

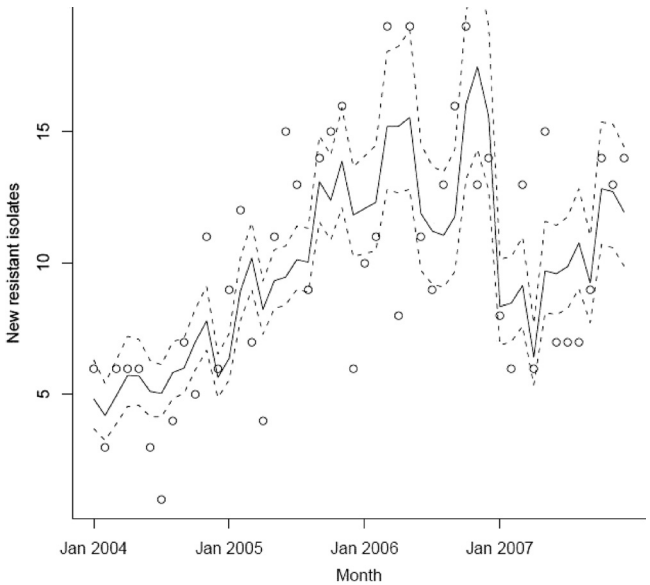

FIG. 4. Observed rates of resistance to ciprofloxacin by *E. coli* isolates from hospitalized patients from 2004 through 2007. Values predicted by the best-segmented regression model are shown by the solid line. Broken lines show the 95% confidence intervals.

TABLE 3. Segmented Poisson regression results for the ciprofloxacin resistance data[a]

Intervention or parameter	Model averaged coefficient[b] (SD)	Probability of an intervention effect[c]	Full model		Model 1		Model 2		Model 3	
			IRR[d] (95% CI)	*P*	IRR (95% CI)	*P*	IRR (95% CI)	*P*	IRR (95% CI)	*P*
Intervention 1	0.98 (0.08)	0.12	0.78 (0.16, 3.82)	0.76						
Intervention 2	0.90 (0.16)	0.34	0.56 (0.22, 1.45)	0.23	0.71 (0.50, 1.00)	<0.05				
Intervention 3	0.77 (0.24)	0.52	0.48 (0.26, 0.89)	0.02					0.67 (0.53, 0.85)	0.001
Intervention 4	0.71 (0.24)	0.61	0.57 (0.20, 1.60)	0.29	0.52 (0.40, 0.68)	<0.001	0.49 (0.38, 0.64)	<0.001	0.67 (0.52, 0.85)	0.001
Trend prior to intervention	1.04 (0.01))	1	1.05 (1.03, 1.07)	<0.001	1.05 (1.03, 1.06)	<0.001	1.04 (1.03, 1.05)	<0.001	1.04 (1.03, 1.05)	<0.001
Change in trend after intervention:										
1	0.99 (0.02)	0.19	1.04 (0.68, 1.58)	0.85						
2	1.00 (0.02)	0.13	1.05 (0.69, 1.60)	0.82						
3	0.99 (0.07)	0.15	1.10 (0.53, 2.31)	0.80						
4	1.02 (0.07)	0.15	0.83 (0.41, 1.67)	0.60						

[a] The results of the model-averaged estimates, full model, and three best-fitting models selected by BMA are shown. Confidence intervals are calculated by bootstrapping. The posterior model probabilities were <0.01, 0.11, 0.09, and 0.07 for the full model and models 1 to 3, respectively.
[b] Expected value of coefficient obtained by Bayesian model averaging, combining results from multiple models, weighted according to model probability (see Materials and Methods).
[c] The probability that the coefficient is not zero in the Bayesian model averaging results.
[d] IRR, incidence rate ratio.

the risk of complications from i.v. catheters, increasing the patient's comfort and mobility, and discharging the patient from the hospital earlier because the patient no longer had an i.v. catheter (5, 17).

The overall level of use of CIP was reduced, which was most likely caused by intervention 2, which comprised the introduction of a new guideline and an educational program. We did not detect an additional effect of interventions 3 and 4, but we cannot determine if these interventions influenced the sustainability of the effect. Therefore, we conclude that the combination of interventions reduced the overall level of use of CIP and that intervention 2 was an essential part of the bundle. Intervention 2 was relatively simple and required limited resources. Van Hees et al. described a similar significant reduction due to educational interventions targeted at CIP use in a hospital with a low level of CIP use (5.7 DDDs/100 patient days in 2004) (29). However, those CIP use data were difficult to compare with our findings because the antimicrobial use was expressed in the number of prescriptions per 1,000 admissions and only a limited number of wards was included in the intervention program. These studies show the effect of having antimicrobial guidelines and implementing them locally by using educational sessions on use of the antimicrobial.

To put these findings into perspective, it is important to understand that the current study was performed in a setting with a relatively low level of quinolone use compared with that at most Dutch hospitals (27). The average level of Dutch hospital use of quinolones in 2005 was 7.4 DDDs/100 patient days (6). This is nearly three times higher than the level in our hospital in 2005 (Fig. 3). During the study period, the use of CIP declined further to 1.7 DDDs/100 patient days in 2007. At the same time, the use in other Dutch hospitals further increased (6).

Although it is generally agreed upon that more antimicrobial use results in an increase in the rate of resistance, it is unclear if the opposite is also true. We measured the susceptibility of *E. coli*, since this organism is an important target for quinolones and is the most frequently encountered clinically relevant species of the *Enterobacteriaceae* family. Before the start of the interventions, the observed rate of resistance to CIP increased 4.6% annually (Fig. 4). This increase was interrupted by a stepwise decrease in the rate of resistance, and this was most likely associated with interventions 2 and 4. The data showed that at least one intervention was associated with a reduction in the rate of resistance, but there was no conclusive evidence to determine which intervention.

There are several difficulties in determining the association of the interventions with the observed resistance. The relationship between the amount of antimicrobial use and the development of resistance has been clearly established both in the community setting (9, 15, 23, 25) and in the hospital setting (11, 31). However, the extent to which a trend toward increasing rates of resistance can be reversed by changes in prescribing practices is less clear. For example, the complete cessation of sulfonamide use in the United Kingdom did not lead to a decrease in the rate of resistance in *E. coli* during the 1990s (7). A likely explanation is that plasmids containing sulfonamide resistance determinants also contained genes encoding resistance to other antibiotics and that continued use of these agents during the study period maintained the selective pressure for the multiresistance plasmids (7, 13). Lipsitch concluded that interventions to control antimicrobial use could decrease the rate of resistance, but expectations for their success should be moderate, as the relations are indirect and nonlinear (13). He postulated that in the most successful cases in the community, 5 years or more is required to observe a substantial decline in the rate of resistance (13). Van Eldere et al. also reported that changes in the observed rates of resistance among *Streptococcus pneumoniae* isolates was delayed after the level of use of broad-spectrum penicillins decreased (28). Of note, that study described a reservoir of resistance in the community which was probably different from that in the hospital setting. In our hospital-based study, the change in the resistance rate occurred approximately 6 months after the level of CIP use was reduced. In contrast to the community, changes in antimicrobial prescribing practices in hospitals could have a much more rapid effect, because of the dilution effect of the newly admitted patients (14). This hypothesis is based on the

assumption that cross infection with resistant strains is minimal and that resistance rates among outpatients are lower than those among hospitalized patients. Recent studies in our hospital found a low rate of nosocomial transmission of highly resistant Gram-negative bacteria. The number of infections due to a strain and acquired by nosocomial transmission divided by the number of infections due to strains of the same species and not acquired by nosocomial transmission was 0.05 (32). The resistance rate for CIP in the community in the Netherlands is also relatively low. A recent study reported 3% CIP resistance among bacterial pathogens isolated from patients on admission to the hospital (2). Moreover, we previously demonstrated that the rate of CIP resistance on individual medical wards correlated with the amount of use on the individual wards (31). These data suggest that the volume of antimicrobial use in the hospital is an important determinant for the observed resistance. Our study design prevents us from making strong statements about what caused the decrease in the CIP resistance rate. We can conclude that it is at least plausible that the decreased incidence of CIP-resistant *E. coli* isolates cultured from clinical patients in our hospital resulted from changes in the levels of quinolone use.

There are some limitations of this study. First, we used a quasiexperimental interrupted time series design, which has well-known limitations (21). We were able to overcome some of these through use of a segmented regression analysis, the most appropriate method for assessing the effects of our interventions on reducing the levels of use of CIP and other antimicrobial agents. However, it is less clear how we should analyze and interpret the subsequent effects on the observed resistance, given the uncertainties about the mechanisms selected for the resistant organisms (13, 14). Second, the ICU was excluded from the study. We did not include that unit because the consultant microbiologists involved in the study visited the ICU on a daily basis to advise physicians about antimicrobial treatment. Therefore, we assumed that we would not be able to improve antimicrobial use in that unit. Third, the follow-up period was relatively short, which prevented us from determining the long-term effect of this intervention on antimicrobial resistance.

The observed effect on the CIP resistance rates could also be biased by the occurrence of outbreaks or by changes in the infection control policy that were not part of the bundle of interventions. As mentioned before, we measured the occurrence of the horizontal spread of resistant microorganisms in the hospital during the study period and found a very low rate of transmission, and no major outbreaks were observed (32). The infection control policy regarding the prevention of transmission of resistant microorganisms was implemented before 2005, and no changes have been made since then. Therefore, it is unlikely that the observed resistance rates were influenced by these factors.

The cost analysis was limited to the cost of the change from i.v. to oral CIP use. This was a very clear intervention with no hidden costs or substitution effects. The effects of the reduced total level of use of CIP were not included in the cost analysis. Although there are likely cost savings associated with this as well, these are much more difficult to quantify. The total amount of antibiotic use did not increase, and no new, more expensive agents were used during the study period. Therefore, the savings calculated for this report are a minimal estimate. Still, this minimal estimate was sufficient to pay for the costs of this project.

In conclusion, multiple targeted interventions improved the use of CIP in our hospital. A Switch project from i.v. to oral therapy was successful and saved money. Subsequent interventions, including the introduction of a new guideline and an educational program, reduced the overall level of CIP use by 30%. An increasing trend in the rates of resistance observed among the *E. coli* isolates was reversed in association with the decrease in the level of CIP use. These findings show that a bundle of interventions can reduce the levels of use of antimicrobial agents in a hospital and could reverse the increase in the rate of antimicrobial resistance.

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