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Modelling the impact of antibiotic use on antibiotic-resistant *Escherichia coli* using population-based data from a large hospital and its surrounding community

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Objectives: To determine the temporal relationship between antibiotic use and incidence of antibiotic-resistant *Escherichia coli* in both the inpatient and outpatient setting of a large urban area.

Methods: A retrospective observational time-series analysis was performed to evaluate the incidence of non-duplicate clinical isolates of *E. coli* resistant to ciprofloxacin, trimethoprim/sulfamethoxazole and cefepime from January 2000 through December 2007, combined with a transfer function model of aggregated data on antibiotic use in both settings obtained from the hospital's pharmacy and outpatient billing offices.

Results: Ciprofloxacin resistance increased from 6.0% (2000) to 15.4% (2007; $P < 0.0001$) and cefepime resistance from 0.9% (2002) to 3.2% (2007; $P = 0.01$). Trimethoprim/sulfamethoxazole resistance remained stable (23.7%–25.8%). Total antibiotic use increased in both settings, while fluoroquinolone use increased significantly only among outpatients. A temporal effect between fluoroquinolone resistance in community *E. coli* isolates and outpatient use of ciprofloxacin (immediate effect and time lag 1 month) and moxifloxacin (time lag 4 months) was observed, explaining 51% of the variance over time. The incidence of cefepime resistance in *E. coli* was correlated with ciprofloxacin use in the inpatient (lag 1 month) and outpatient (lag 4 months) settings and with the use of ceftriaxone (lag 0 month), piperacillin/tazobactam (3 months) and cefepime (3 months) in the hospital ($R^2 = 51\%$).

Conclusions: These results support efforts to reduce prescribing of fluoroquinolones for control of resistant *E. coli* including extended-spectrum β-lactamase producers and show the added value of time-series analysis to better understand the interaction between community and hospital antibiotic prescribing and its spill-over effect on antibiotic resistance.

Keywords: antibiotic resistance, *E. coli*, fluoroquinolone resistance, extended-spectrum β-lactamase-producing bacteria, transfer function model, health policy making, time-series analysis

Introduction

Switzerland is known as a country with a low level of antibiotic use in the outpatient setting.[1,2] Nevertheless, there seems to be a relative overuse of fluoroquinolones, compared with other European countries.[1] According to the Swiss resistance surveillance network, fluoroquinolone resistance in clinical isolates of *Escherichia coli* was 15.9% in 2008, which is similar to countries like Belgium and France that have much higher overall antibiotic use.[3,4] This finding is not surprising since a link between fluoroquinolone use and resistance to this antimicrobial class has been described in *E. coli* isolates from the inpatient as well as the outpatient setting on both an ecological and an individual patient level.[5–8] Similar evidence has been reported for the link between use of certain antibiotics and the rate of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.[8,9]

Hitherto, most studies linking antibiotic use to antibiotic resistance have focused on either the outpatient or the inpatient setting as if these were completely separate entities. This separation is, however, artificial since antibiotic resistance is imported from

the community into the hospital and vice versa. Thus, antibiotic use in one setting is likely to impact antibiotic resistance in the other.[10] The particular healthcare structure in the Swiss canton of Geneva offers a unique opportunity to analyse in parallel the association between antibiotic use and resistance in *E. coli* using data from both the community and the only major public hospital. The objective of this study was to determine the time-varying effect of antibiotic use on the incidence of antibiotic-resistant *E. coli* in both the inpatient and outpatient setting of this large urban area in Switzerland.

Methods

Setting

In the Swiss canton of Geneva with a population of ~450 000 inhabitants there is only one major public hospital, providing both primary and tertiary care. The University of Geneva Hospitals (HUG) is a 2200 bed healthcare centre with ~45 000 admissions and >850 000 outpatient visits each year. Outpatient prescriptions in the canton are systematically recorded by the major invoicing office of the Swiss pharmacists' organization (OFAC, Geneva, Switzerland). Figure 1 summarizes important information about the study population, definitions and policies implemented during the study period.

Antibiotic use

During the study period, no institutional policy regarding antibiotic use at HUG was implemented. Some recommendations regarding costly antibiotics were provided; restriction was, however, rare. Moreover, at the pharmacy level, refusal to dispense a drug was uncommon and physicians could prescribe any antimicrobial agent available at HUG.[11] In the outpatient setting there was equally no restriction.

Data collection

Antimicrobial consumption in the hospital

Monthly aggregated data of all antimicrobial drugs delivered within HUG were provided by the pharmacy department from January 2000 to December 2007. Long-term care units and the psychiatry department were excluded, due to their low antibiotic use and high number of patient-days, which would have diluted antibiotic usage data. In addition, paediatric wards were excluded since antibiotic use cannot be measured appropriately in defined daily doses (DDDs) in this setting.[12] Following the WHO's recommended metric, the DDD, i.e. the assumed average maintenance dose per day for a drug used for its main indication in an adult, antibiotic usage was expressed as monthly aggregated DDDs according to the 2007 ATC classification and normalized per 1000 patient-days (antibiotic use density).[13]

Antimicrobial consumption in the community

The outpatient database used in this study was constructed from prescription files of the OFAC, which serves as an administrative intermediary between Swiss pharmacists and health insurance companies. OFAC prescriptions cover 92% of all prescriptions filled and 80% of the insured population in the canton of Geneva. All protected patient information was removed to create anonymous datasets in accordance with Swiss data protection regulations. Antibiotic use was expressed as monthly aggregated DDDs, normalized per 1000 inhabitants.

Bacterial isolates

The microbiology laboratory of HUG provided monthly aggregated data from January 2000 to December 2007 on the number of incident clinical *E. coli* isolates. All isolates are routinely tested for resistance to ciprofloxacin, trimethoprim/sulfamethoxazole and cefepime using the disc diffusion method. Results are interpreted according to CLSI criteria.[14]

Geneva surrounding community setting: population of 453 000 inhabitants. Outpatient prescriptions are systematically recorded by OFAC, covering 92% of all prescriptions filled and 80% of the insured population in the canton of Geneva.
HUG setting: primary and tertiary care teaching hospital in Switzerland with 2200 beds. Long-term care units and paediatric and psychiatry departments were excluded from this analysis. Infection control programme with one director, three associate hospital epidemiologists and nine full-time infection control nurses. **Population characteristics**: mean hospitalization days, 51 524 per month (range 48 102–55 128); 850 000 outpatient visits each year.
Infection control campaigns during the study: HUG launched two hospital-wide promotion campaigns; Vigigerme® in spring 2003 and 'Clean care is safer care' in autumn 2005 (including hand hygiene observation of healthcare personnel).
Antibiotic use: during the study period there was no institutional antibiotic policy; physicians could prescribe any antimicrobial agent available at HUG. Beginning in March 2006, HUG experienced a shortage of cefepime leading to an increase in piperacillin/tazobactam use.
ESBL screening and isolation policy: systematic on-admission screening of specific patient groups at high risk of ESBL carriage, i.e. patients formerly known to be ESBL carriers or patients coming from regions with endemic rates. ESBL carriers underwent contact precautions routinely and were isolated in single rooms whenever possible.
Definition of ESBL: number of incident clinical *E. coli* isolates resistant to cefepime.
Study period: January 2000 to December 2007.

Figure 1. Population, setting, definitions, antibiotic policy, promotion campaigns, infection control interventions and study period.

The incidence of cefepime resistance in *E. coli* was considered as a surrogate marker for production of ESBL since confirmatory tests for ESBL production were introduced only in 2004.[15]

Isolates resistant to ciprofloxacin, cefepime and trimethoprim/sulfamethoxazole obtained <48 h after admission were defined as community associated (CA) and those obtained ≥48 h after admission were classified as hospital associated (HA). Due to the limited number of cefepime-resistant isolates no distinction was made between CA and HA isolates. Incidence density of resistant isolates was expressed as the number of cultures per 1000 patient-days with the elimination of duplicates by including only the first *E. coli* isolate.[16] All non-susceptible isolates (i.e. resistant and intermediate) were considered resistant.

Statistical analysis

Since temporally sequenced observations on antibiotic use and resistance are not independent, applying simple regression analysis would be inappropriate.[17] Therefore, as suggested by the ORION statement,[18] we used time-series analysis with autoregressive integrated moving average (ARIMA) models using the Box–Jenkins method integrating the stochastic dependence of consecutive data over time.[19] We developed five different models to analyse the association between antibiotic use and resistance in CA and HA isolates of *E. coli*, focusing on the link with ciprofloxacin, cefepime and trimethoprim/sulfamethoxazole usage. A linear transfer function modelling method proposed by Lopez-Lozano was used to quantify the dynamic relationship between antibiotic use and the incidence of resistant isolates, taking into account possible time delays (lag times) of up to 5 months.[17,19,20]

To meet the stationarity requirement (constant mean, variance and autocorrelation through time), ciprofloxacin resistance in *E. coli* isolates and other explanatory variables were logarithmically transformed, while ESBL data and associated explanatory variables were transformed by first-order differentiation. Trimethoprim/sulfamethoxazole resistance in *E. coli* did not need any transformation.

For each individual series, we fitted an ARIMA model according to Box–Jenkins methodology and performed the following steps.[19] We first checked whether the series needed to be differentiated [i.e. whether the parameter 'd' equals 0, 1 or 2 in the ARIMA (p,d,q) model] with the augmented Dickey–Fuller test. We then created the model by determining the values of the remaining parameters 'p' and 'q' of the ARIMA (p,d,q) model with the autocorrelation (ACF) and partial autocorrelation (PACF); subsequently, we estimated model parameters by an unconditional least squares method; and finally checked the adequacy of the model, i.e. the residuals to be 'white noise' (Ljung–Box statistic), and statistical significance of the parameters at a P value of <0.05.

After obtaining the univariate ARIMA models, we identified the transfer function model from the cross-correlation function estimating the correlations between the antibiotic use series at different time lags and the incidence of resistant CA and HA isolates. We then estimated the transfer function model. Significance tests for parameter estimates at a P value of <0.05 were used to eliminate the unnecessary terms. Among different models we chose the most parsimonious one, i.e. the model with the fewest parameters and highest biological plausibility. All final model residuals passed a 'white noise' test (based on Ljung–Box statistics). For each model, the R^2 coefficient was calculated as goodness-of-fit measure, expressing the fraction of the variance of the dependent variable explained by the dynamic regression model. All statistical analyses were performed with EViews 6 software (QMS, Irvine, CA, USA).

Results

Antibiotic use in both settings

Monthly rates of antimicrobial use in the canton of Geneva and at HUG from January 2000 to December 2007 are detailed in Table 1. In the outpatient setting average antimicrobial use over the study period was 14.2 DDDs/1000 inhabitants with a positive upward trend ($P = 0.0061$). Penicillins were the most widely used antibiotic class (34%; pooled rate, 4.87 DDDs/1000 inhabitants), followed by fluoroquinolones, macrolides, cephalosporins and trimethoprim/sulfamethoxazole.

At HUG, average antimicrobial use over the study period was 550 DDDs/1000 patient-days with a positive upward trend ($P = 0.0114$). In this setting, penicillins were also the most widely used antibiotic class (161 DDDs/1000 patient-days), followed by cephalosporins and carbapenems (151 DDDs/1000 patient-days) and fluoroquinolones (76 DDDs/1000 patient-days).

Incidence and dynamic regression of ciprofloxacin resistance in E. coli

A significant increase in the incidence of CA ciprofloxacin-resistant *E. coli* isolates (4.8% in 2000 to 14.6% in 2007; $P < 0.0001$) and HA ciprofloxacin-resistant *E. coli* isolates (7% in 2000 to 16.7% in 2007; $P < 0.0001$; $R^2 = 0.20$) was observed (Table 2 and Figure 2). The average monthly incidence was 0.31 (range 0–0.91) for CA ciprofloxacin resistance and 0.44 (range 0.15–0.84) for HA ciprofloxacin resistance in clinical isolates per 1000 patient-days. For the CA ciprofloxacin-resistant isolates, we identified an ARIMA model with one significant autoregressive term of order 1 and one significant moving average term order 1 ($R^2 = 0.31$); the HA ciprofloxacin resistance model had one significant autoregressive term of order 1 ($R^2 = 0.14$).

The transfer function model of CA ciprofloxacin resistance explained 51% of the variation in incidence (Table 3). In this model, two statistically significant explanatory variables were identified, outpatient ciprofloxacin and moxifloxacin usage, whereas outpatient norfloxacin, levofloxacin and ofloxacin use was not statistically significant. For example, an increase of 1% in ciprofloxacin use would generate an immediate increase of 1.28% in the number of CA ciprofloxacin-resistant isolates and an additional 0.97% 1 month later.

The transfer function model of HA ciprofloxacin resistance explained only 18% of the incidence of HA resistance (Table 3). Outpatient ciprofloxacin use was identified as the only statistically significant explanatory variable. According to this model an increase of 1% in community ciprofloxacin use would be followed by an increase 1 month later of 0.74% in HA ciprofloxacin-resistant *E. coli* isolates.

Incidence and dynamic regression of cefepime resistance in E. coli

The monthly average incidence of resistance to cefepime in *E. coli* was 0.15 (range 0–0.41) clinical isolates per 1000 patient-days. Regarding the incidence of cefepime resistance, we identified an ARIMA model (1,1,0) after first-order differentiation with an autoregressive term of order 1 ($R^2 = 0.15$). The transfer function model ($R^2 = 0.51$), yielded statistically significant effects of inpatient use of ceftriaxone, ciprofloxacin, cefepime and piperacillin/tazobactam, as well as outpatient use of ciprofloxacin, on the incidence of cefepime-resistant *E. coli* isolates (Table 4). An increased hospital usage of 1 DDD of the following antibiotics would time-dependently raise the cefepime resistance rate to different extents (Table 4). For instance, the

Table 1. Quantity and trends of antibiotic use in the canton of Geneva and at HUG, January 2000 to December 2007

		Surrounding community				HUG			
WHO classification	Antimicrobial use	average monthly use (min–max)[a]	% of J01 use	trend	*P*	average monthly use (min–max)[b]	% of J01 use	trend	*P*
J01	total antibiotic use	14.22 (8.6–19.77)	100	upward	0.0061	550 (456–622)	100	upward	0.0114
J01C	amoxicillin/clavulanate	3.32 (1.86–5.14)	23	upward	<0.001	94 (63–141)	17	downward	0.04
	amoxicillin	1.55 (0.85–2.39)	11	upward	<0.001	62 (39–96)	11	no	0.1214
	piperacillin/tazobactam	0	0			4.6 (0–18.3)	1	upward	<0.001
J01D	cefazolin	0	0			8.4 (3.3–17.2)	2	downward	<0.001
	second-generation cephalosporins	1.3 (0.56–2.9)	9	downward	<0.001	40 (26.3–61.2)	7	upward	<0.001
	third-generation cephalosporins	0.61 (0.23–1.09)	4	upward	<0.001	52.1 (29.2–72.8)	10	upward	<0.001
	cefepime	0	0			25.1 (0–41.3)	5	downward	<0.001
	carbapenems	0	0			25.5 (16.2–45)	5	upward	0.0029
J01M	fluoroquinolones	2.6 (1.77–3.25)	18	upward	<0.001	76.4 (49.3–100.4)	14	no	0.5057
	ofloxacin	0.1 (0.06–0.16)	1	no	0.5776	3.3 (0.3–7.7)	1	no	0.05071
	ciprofloxacin	1.24 (0.87–1.73)	9	upward	<0.001	47.7 (30.8–66.8)	9	upward	0.0254
	norfloxacin	0.7 (0.53–0.86)	5	upward	<0.001	13.6 (6.2–23.5)	3	downward	<0.001
	levofloxacin	0.26 (0.11–0.54)	2	downward	<0.001	20.3 (1.5–21.9)	2	no	0.1032
	moxifloxacin	0.28 (0–0.54)	2	upward	<0.001	1.5 (0–6.5)	0	upward	<0.001
J01FA	macrolides	2.13 (1.02–3.95)	15	no	0.5004	38.6 (18.7–80)	7	no	0.2035
J01EE01	trimethoprim/sulfamethoxazole	0.4 (0.28–0.55)	3	downward	<0.001	16.6 (6.7–24.8)	3	upward	0.0103
J01XA	glycopeptides	0	0			16.1 (7.3–25.6)	3	no	0.6961

[a]Quantities of antimicrobials expressed in DDDs per 1000 inhabitants.
[b]Quantities of antimicrobials expressed in DDDs per 1000 patient-days.

Table 2. Percentages of non-duplicate clinical isolates of *E. coli* resistant to ciprofloxacin, trimethoprim/sulfamethoxazole and cefepime (*n*); data from the Microbiology Laboratory, HUG, January 2000 to December 2007

Antibiotic resistance to	Total	2000	2001	2002	2003	2004	2005	2006	2007	*P* for trend
Ciprofloxacin total	10.9 (2097)	6.0 (134)	7.9 (191)	9.4 (241)	11.9 (315)	10.4 (245)	12.8 (271)	13.6 (332)	15.4 (368)	<0.0001
Ciprofloxacin (CA)	9.4 (970)	4.8 (50)	6.1 (46)	6.8 (102)	9.3 (135)	8.8 (121)	10.4 (135)	11.3 (171)	14.6 (215)	<0.0001
Ciprofloxacin (HA)	12.8 (1123)	7.0 (84)	8.7 (145)	12.9 (140)	15.2 (180)	12.8 (124)	16.4 (136)	17.2 (161)	16.7 (153)	<0.0001
Trimethoprim/sulfamethoxazole total	23.9 (4780)	23.7 (549)	24.5 (611)	21 (554)	23.3 (639)	23.8 (576)	24.4 (593)	24.5 (610)	25.8 (648)	0.2753
Trimethoprim/sulfamethoxazole (CA)	21.5 (2484)	21.3 (265)	20.7 (247)	19.4 (302)	21.5 (336)	22.2 (317)	21.7 (321)	22.3 (340)	23.2 (356)	0.2198
Trimethoprim/sulfamethoxazole (HA)	27 (2296)	26.5 (284)	28 (364)	23.3 (252)	25.9 (303)	26.1 (259)	28.6 (272)	28 (270)	29.8 (292)	0.3674
Cefepime total	1.9 (289)	1.39 (3)	1.37 (4)	0.92 (24)	1.44 (38)	1.34 (32)	2.11 (50)	2.51 (60)	3.22 (78)	0.0098

Total = aggregated data for CA and HA resistant isolates.

resistance rate would increase immediately by 0.0041 after increased ceftriaxone usage, and by 0.0043 1 month after increased in-hospital usage of ciprofloxacin and an additional 0.0045 after 5 months.

Incidence and dynamic regression of resistance in E. coli to trimethoprim/sulfamethoxazole

No significant trends in the incidence of trimethoprim/sulfamethoxazole-resistant CA and HA *E. coli* isolates were observed (Table 2 and Figure 2). The average monthly incidence of CA trimethoprim/sulfamethoxazole resistance was 1.05 isolates per 1000 patient-days (range 0.43–2.08) and 0.97 isolates per 1000 patient-days (range 0.28–1.60) for HA isolates.

No model could sufficiently explain the rate of resistance in the community. For HA trimethoprim/sulfamethoxazole resistance, the model yielded a very low R^2 (0.14). Only outpatient use of trimethoprim/sulfamethoxazole was identified as a statistically significant variable in this model (lag 4 months; $P = 0.0085$).

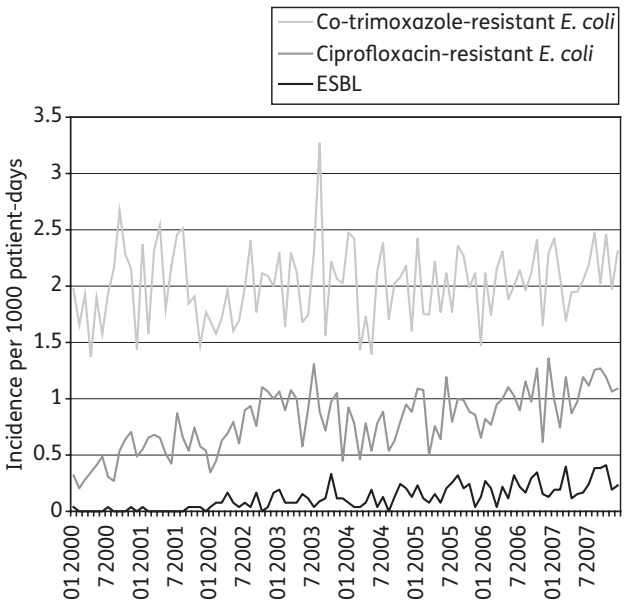

Figure 2. Monthly incidence of non-duplicate clinical isolates of ciprofloxacin-, trimethoprim/sulfamethoxazole (co-trimoxazole)- and cefepime-resistant *E. coli* isolates per 1000 patient-days. HUG, January 2000 to December 2007. ESBL, ESBL-producing *E. coli*.

Discussion

During this study, we observed an increase in fluoroquinolone resistance among CA and HA isolates of *E. coli*, with slightly higher rates in the latter group. This is in line with data from most other European countries, where a general increase in fluoroquinolone-resistant *E. coli* has been observed.[7] It is noteworthy that the rate of ciprofloxacin resistance in *E. coli* is approaching the resistance rate of trimethoprim/sulfamethoxazole, an antibiotic that has mostly been abandoned as empirical therapy for upper urinary tract infections due to the high resistance rate.

We also observed a notable increase in cefepime-resistant *E. coli* over the study period, which probably reflects the epidemiology of ESBL-producing Enterobacteriaceae in our region, as in the rest of Europe.[21] Rates of trimethoprim/sulfamethoxazole resistance were, however, stable over the study period in both settings despite a significant decrease in trimethoprim/sulfamethoxazole use in the community. This phenomenon has also been observed in other countries and is possibly related to co-selection of trimethoprim/sulfamethoxazole resistance by other antibiotics.[22–24] Factors influencing the reversibility of antibiotic resistance in the absence of antibiotic pressure are still incompletely understood.[25] Two recent papers also failed to show a significant association between trimethoprim/sulfamethoxazole use and resistance on an individual patient level.[26,27]

Our findings confirm the relatively high outpatient antimicrobial use (14.2 DDDs/1000 inhabitants) in the canton of Geneva compared with German-speaking Switzerland.[1] The exact causes of the variation in antibiotic use within Switzerland are

Table 3. Multivariate transfer function model of fluoroquinolone use in both settings and temporal relationship with the incidence of non-duplicate clinical isolates of *E. coli* resistant to ciprofloxacin per 1000 patient-days; HUG, January 2000 to December 2007

	CA ciprofloxacin resistance, $R^2=0.51$				HA ciprofloxacin resistance, $R^2=0.18$			
Variable	lag[a] (months)	parameter[b] (SE)	*t* statistic	*P* value	lag[a] (months)	parameter[b] (SE)	*t* statistic	*P* value
Constant		−1.16 (0.24)	−4.94	<0.0001		−0.94 (0.08)	−12.31	<0.0001
Ciprofloxacin[c]	0	1.28 (0.49)	2.62	0.0104				
Ciprofloxacin[c]	1	0.97 (0.48)	2.00	0.0485	1	0.74 (0.28)	2.65	0.0095
Moxifloxacin[c]	4	0.43 (0.16)	2.69	0.0088				
Autoregressive term[d]	1	0.30 (0.11)	2.78	0.0068	2	0.27 (0.10)	2.76	0.0069
Moving average term[e]	8	0.35 (0.11)	3.22	0.0019				

[a]Delay necessary to observe the effect.
[b]Size and direction of the effect, with variables expressed in logarithms.
[c]Outpatient use.
[d]The autoregressive term represents the past value of the resistance.
[e]The moving average term represents disturbances or abrupt changes of resistance.

Table 4. Multivariate transfer function model of antibiotic use in both settings and temporal relationship with the incidence of non-duplicate clinical isolates of *E. coli* resistant to cefepime per 1000 patient-days; HUG, January 2002 to December 2007; $R^2 = 0.51$

Variable	Lag[a] (months)	Parameter[b] (SE)	*t* statistic	*P* value
Ceftriaxone[c]	0	0.0041 (0.0017)	2.4047	0.0195
Ciprofloxacin[c]	1	0.0043 (0.0013)	3.2126	0.0022
Ciprofloxacin[c]	5	0.0045 (0.0014)	3.2045	0.0022
Cefepime[c]	3	0.0034 (0.0016)	2.1502	0.0358
Piperacillin/ tazobactam[c]	3	0.0099 (0.0042)	2.3073	0.0247
Ciprofloxacin[d]	4	0.247 (0.0080)	3.0809	0.0032
Autoregressive term[e]	1	−0.5877 (0.0108)	−5.4236	<0.0001

[a]Delay necessary to observe the effect.
[b]Size and direction of the effect.
[c]Hospital use.
[d]Outpatient use.
[e]The autoregressive term represents the past value of the resistance.

unclear, but socioeconomic and cultural factors most likely play a role.[1] Overall antibiotic use is slightly lower than that described by Filippini *et al.*[1] (15.6 DDDs/1000 inhabitants in 2002), possibly reflecting the different data sources and classification methods. As in other European countries, fluoroquinolone use has increased over the past few years and represented 18% of total outpatient antibiotic use.[7] According to antibiotic prescribing quality indicators established by the European Surveillance of Antimicrobial Consumption, this represents excess fluoroquinolone use.[28] Unlike antibiotic use in the community, overall antibiotic use at HUG is comparable to that of other Swiss tertiary care centres.[29] Fluoroquinolone use remained relatively stable, constituting ∼14% of overall antibiotic use. This also represents a relatively high use compared with other European countries, but is much lower than the USA, where fluoroquinolones represent the most frequently prescribed antibiotic class.[30,31]

We found a correlation between outpatient fluoroquinolone use and ciprofloxacin resistance, in both CA and HA isolates. This finding confirms previous data that have shown that regions with higher fluoroquinolone use have higher rates of fluoroquinolone-resistant *E. coli*.[7] One of the few studies correlating community antibiotic use to rates of antibiotic-resistant microorganisms in hospitals serving these communities also observed a significant correlation between community fluoroquinolone use and fluoroquinolone-resistant *E. coli* in 17 hospitals in the USA.[32] Importantly, unlike other studies we did not find a correlation between fluoroquinolone use in the hospital and the rate of ciprofloxacin resistance in HA isolates.[6,33] This finding might be explained by the fact that most *E. coli* detected in clinical isolates during the hospital stay are part of the endogenous patient flora and therefore probably of community origin. Relatively stable fluoroquinolone use in the hospital during the study period might also have contributed to this finding. A recently published study has investigated the relationship between outpatient fluoroquinolone consumption in a region in south-western France and the incidence of fluoroquinolone-resistant *E. coli* between 2004 and 2007 in the only tertiary-care academic centre in the region.[34] Using similar methods, the researchers found a significant effect of levofloxacin use in the community with resistant HA *E. coli*, albeit with a very long time lag (12 months). In contrast to this investigation, the strength of our study was that a more complete dataset over a longer time period with better population coverage was analysed in a smaller, but more homogeneous, region, yielding biologically plausible findings.

Importantly, we found an association between the incidence of cefepime resistance in *E. coli* (indicating ESBL production in most isolates) and the use of several antibiotic classes in the hospital (notably ceftriaxone, ciprofloxacin, cefepime and piperacillin/tazobactam) and fluoroquinolone use in the community. The short time lags for hospital use of ciprofloxacin (lags 1 and 5 months) and ceftriaxone (lag 0) are noteworthy since—as opposed to time lags of >6 months—they are also biologically plausible.[35] This finding confirms a recent study from Germany that showed an association between the use of third-generation cephalosporins and fluoroquinolones and the incidence of nosocomial ESBL-producing bacteria, however, after a longer time lag (up to 3 months).[20] In addition, several other studies have observed an association between previous use of cephalosporins and fluoroquinolones, and infection with ESBL producers in the outpatient and inpatient settings.[8,36] The frequent cross-resistance observed in ESBL-carrying organisms, which is often mediated by genes carried in the same mobile genetic elements as ESBLs, is thought to be responsible for the effect of fluoroquinolone use on ESBL incidence. Outpatient fluoroquinolone use might be of particular importance with regard to possible interventions to contain the current epidemic of CTX-M-15-producing *E. coli*, a frequent cause of CA urinary tract infection in Europe.[37]

Our study has several limitations. This study is a single-centre, retrospective, observational, ecological study using aggregate data. This design bears the risk of ecological bias, since the use of individual patient data might give different results.[38] DDDs may not represent true prescription data and may not appropriately reflect antibiotic use in adults with renal impairment and other co-morbidities.[39] DDDs remain, however, the most commonly applied unit for measuring antibiotic use, since it allows internal and external benchmarking. Since our main goal was to analyse the impact of antibiotic use on resistance, we did not adjust antibiotic use in the community for the incidence of flu-like illness as done by other groups, which might be important when analysing trends over several years.[40,41] Although we could eliminate prescriptions for children from the hospital antibiotic use data, we were not able to do this for the community data. Fluoroquinolones are, however, rarely used in children and outpatient fluoroquinolone data should mostly reflect use in adults. A further limitation is the fact that we only had access to microbiological data from the laboratory at HUG and thus only patients consulting at that hospital were included. Even though HUG serves also as the major primary care hospital in the region, the patient population might be slightly different from the population seen by general practitioners in Geneva.[15] Nevertheless, yearly susceptibility data provided by the largest external microbiology laboratory in Geneva confirm the resistance data observed in CA isolates at our hospital (data not

shown). We included only clinical isolates of *E. coli* in our analysis and did not include surveillance cultures. We therefore probably underestimated the incidence of resistance, notably with regard to ESBL carriage. We used cefepime resistance as surrogate marker for ESBL production since we did not have reliable data about confirmatory test results for the entire study period. This definition might have overestimated ESBL rates. We know, however, that in our setting cefepime resistance in *E. coli* is nearly universally associated with ESBL production. A further limitation is that we did not type isolates or assess mechanisms of fluoroquinolone resistance, which might change over time and thus modify the impact of fluoroquinolones on resistance selection.[42,43]

Despite these limitations, we believe that this study is valuable since it combines longitudinal data over several years from a distinct metropolitan area and the only major public hospital in the same area. By using appropriate statistical methods, our study provides further evidence that antibiotic use in the community influences resistance rates in hospital (spill-over effect). We were also able to confirm the influence of inpatient and outpatient antibiotic use, notably fluoroquinolones and third-generation cephalosporins, on ESBL-producing *E. coli*.

Controlling antibiotic resistance has proved to be far more difficult than its creation and selection. Nevertheless there is some evidence that antibiotic resistance can be controlled by reducing unnecessary antibiotic use.[44] A recently published retrospective study from Israel showed that reduction in ciprofloxacin use in the community in the context of a restriction policy was associated with a concomitant increase in susceptibility to ciprofloxacin in *E. coli* from urinary isolates.[45] Our results are in line with previous studies and confirm the impact of fluoroquinolone use in the inpatient and outpatient setting on resistant *E. coli*. Efforts to substitute fluoroquinolones for certain indications with antibiotics with less ecological impact such as nitrofurantoin or fosfomycin for urinary tract infections should continue.

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Transparency declarations

No conflicts of interest to declare.

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