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Association between Antimicrobial Consumption and Resistance in *Escherichia coli*▽

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During a 9-year study period from 1997 through 2005, the association between antimicrobial resistance rates in *Escherichia coli* and outpatient antimicrobial consumption was investigated in 20 hospital districts in Finland. A total of 754,293 *E. coli* isolates, mainly from urine samples, were tested for antimicrobial resistance in 26 clinical microbiology laboratories. The following antimicrobials were studied: ampicillin, amoxicillin-clavulanate, cephalosporins, fluoroquinolones, trimethoprim, trimethoprim-sulfamethoxazole, pivmecillinam, and nitrofurantoin. We applied a protocol used in earlier studies in which the level of antimicrobial consumption over 1 year was compared with the level of resistance in the next year. Statistically significant associations were found for nitrofurantoin use versus nitrofurantoin resistance ($P < 0.0001$), cephalosporin use versus nitrofurantoin resistance ($P = 0.0293$), amoxicillin use versus fluoroquinolone resistance ($P = 0.0031$), and fluoroquinolone use versus ampicillin resistance ($P = 0.0046$). Interestingly, we found only a few associations between resistance and antimicrobial consumption. The majority of the associations studied were not significant, including the association between fluoroquinolone use and fluoroquinolone resistance.

Urinary tract infection (UTI) is one of the most common indications for antimicrobial treatment. The development of antimicrobial resistance in *Escherichia coli* has an influence on the successful treatment of UTIs. The rates of resistance to aminopenicillins and fluoroquinolones among *E. coli* isolates are on the increase, and many isolates already show resistance to two or more classes of antimicrobials (6, 7).

According to current Finnish care recommendations, the first-line antimicrobial agents for the treatment of uncomplicated cystitis are trimethoprim, pivmecillinam, nitrofurantoin, or a fluoroquinolone (28). Cephalexin (cefalexin) or cefadroxil, trimethoprim-sulfamethoxazole, and amoxicillin (amoxicilline) are recommended for use as second-line drugs (28). In Finland, 32% of UTIs are treated with trimethoprim, 18% with pivmecillinam, 16% with nitrofurantoin, and 16% with fluoroquinolones (21).

Studies describing the relationship between antimicrobial consumption and resistance in *E. coli* show that there is no clear evidence of how these two factors are linked to each other (13, 25). Some reports suggest a positive association between antimicrobial consumption and bacterial resistance (19, 26), while others claim that such associations are not evident (1, 4).

The aim of the study described here was to investigate the association between the regional rates of antimicrobial resistance among *E. coli* isolates and antimicrobial consumption in 20 hospital districts in Finland.

MATERIALS AND METHODS

Bacterial isolates and resistance data. A total of 754,293 *E. coli* isolates were tested for antimicrobial resistance in Finland during a 9-year study period from 1997 through 2005. The number of isolates tested in each central hospital district per year varied from 144 to 44,645, with the median being 3,625. Approximately 90% of the isolates were from urine samples. The isolates were from both hospitals and outpatient clinics. With the aid of computerized data management systems, all laboratories reported only one isolate per patient each year.

The susceptibility testing was performed in 27 major microbiological laboratories from 20 of the 21 central hospital districts in Finland (the district of Åland Islands was not included). All Finnish clinical microbiology laboratories in central hospitals and universities as well as major private laboratories were included.

All participating laboratories belong to the Finnish Study Group for Antimicrobial Resistance (the FiRe Network), which is a nationwide network that conducts surveillance for antimicrobial resistance (18). The surveillance data on the antimicrobial agents tested reported from the 20 districts varied slightly by year. All these variations were random and due to the different susceptibility testing methods and data management practices used in the individual laboratories. In 2005, both ampicillin and trimethoprim-sulfamethoxazole were removed from the susceptibility test panel.

Data on susceptibility to the following antimicrobials were included in the study: amoxicillin, amoxicillin-clavulanate, cephalosporins (cephalothin or cephalexin), fluoroquinolones (norfloxacin or ciprofloxacin), trimethoprim, trimethoprim-sulfamethoxazole, amdinocillin (mecillinam), and nitrofurantoin. The number of isolates tested each year with each antimicrobial is presented in Table 1. Susceptibility testing was performed in the laboratories by the disk diffusion method, according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) (17). All laboratories in the FiRe Network are licensed by the government and participate in international and/or national quality control programs.

Antimicrobial consumption. Data on the consumption of antimicrobials were obtained from the National Agency for Medicines. These statistics consist of sales data from wholesalers to pharmacies. The data represent the annual consumption levels from each central hospital district. Data on the consumption of the following antimicrobials were included in the study: cephalosporins, fluoroquinolones (of which levofloxacin, norfloxacin, and ciprofloxacin were also stud-

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TABLE 1. Number of *E. coli* isolates tested annually with each antimicrobial agent[a]

Antimicrobial	No. of *E. coli* isolates tested in:								
	1997	1998	1999	2000	2001	2002	2003	2004	2005
Nitrofurantoin	63,808	48,267	64,581	113,552	78,995	89,643	91,684	100,727	103,036
Fluoroquinolones	28,695	23,122	44,180	106,986	75,472	82,213	86,788	97,716	101,508
Ampicillin	41,900	25,293	31,302	32,573	30,500	19,387	15,291	22,531	0[b]
Amdinocillin	61,033	47,154	59,694	113,564	78,957	88,452	90,267	99,782	101,171
Trimethoprim	63,108	47,660	64,372	108,893	78,254	89,763	91,892	100,895	103,018
Trimethoprim-sulfamethoxazole	21,293	25,900	40,093	89,930	61,532	55,185	63,649	63,815	0[b]
Cefalotin	31,828	59,784	77,062	120,341	82,361	77,518	78,541	80,365	83,788

[a] The numbers from all central hospital districts were added together.
[b] Not included in the annual resistance surveillance report from 2005 onwards.

ied separately), trimethoprim, trimethoprim-sulfamethoxazole, trimethoprim and trimethoprim-sulfamethoxazole added together, pivmecillinam, and nitrofurantoin. Antimicrobial consumption is expressed as defined daily doses (DDD) per 1,000 inhabitants per day.

The antimicrobial consumption data for the different geographical regions varied from 1.58 to 3.28 DDD/1,000 inhabitants/day for amoxicillin, from 0.03 to 1.40 DDD/1,000 inhabitants/day for amoxicillin-clavulanate, from 1.48 to 2.85 DDD/1,000 inhabitants/day for cephalosporins, from 0.24 to 1.26 DDD/1,000 inhabitants/day for fluoroquinolones (levofloxacin, 0 to 0.33 DDD/1,000 inhabitants/day; norfloxacin, 0.01 to 0.23 DDD/1,000 inhabitants/day; ciprofloxacin, 0.13 to 0.23 DDD/1,000 inhabitants/day), from 0.83 to 1.86 DDD/1,000 inhabitants/day for trimethoprim, from 0.32 to 1.38 DDD/1,000 inhabitants/day for trimethoprim-sulfamethoxazole, from 0.21 to 0.90 DDD/1,000 inhabitants/day for pivmecillinam, and from 0.44 to 0.94 DDD/1,000 inhabitants/day for nitrofurantoin.

Statistical analysis. The statistical analysis included the antimicrobial susceptibility results for 754,293 isolates and seven antimicrobial agents from 20 hospital districts from the years 1997 through 2005. Similarly, statistics concerning antimicrobial consumption consisted of data for seven antimicrobial agent groups from the same districts from the time period of 1996 through 2004. The resistance data from each laboratory were added together with the data from other laboratories in the same central hospital district. In this way, the data for each geographical area corresponded to the antimicrobial consumption data provided by the National Agency for Medicines. Table 1 summarizes the number of isolates tested with each antimicrobial.

The levels of regional antimicrobial consumption in 1 year were compared with the levels of regional antimicrobial resistance in the next year. A total of 25 different associations were studied (Table 2). A linear mixed model for repeated measures was used to model the association between the resistance to and the consumption of antimicrobials. (27) The percentage of resistant strains was taken as the dependent variable, while time and the level of antimicrobial consumption in the previous year were the explanatory variables. Thus, the subject in the data was the central hospital district, and all of them had nine consecutive measures.

We used a random coefficients model with random intercept and slope. With this kind of a model, we studied the linear dependency between consumption and resistance while taking into account the fact that the repeated measures were correlated. Handling of the intercept and the slope as random also takes into account the individual levels and changes over time. Mixed models were fitted by using the Proc Mixed procedure in the program SAS (version 9.1) for Windows. There were few extremely large or small resistance values, and those values were most likely erroneous. Those values were excluded from the final calculations.

We could roughly represent the models by the following equation: resistance (in percent) equals approximately intercept + (parameter estimate of drug use × drug use [in DDD per 1,000 inhabitants per day]) + (parameter estimate of time × time).

The most important part of these results is the parameter estimate of drug use and its significance. In addition, the effect of time can be seen in the results. If the parameter estimate of drug use is significant ($P < 0.05$), then the level of drug use is statistically significantly related to the level of resistance. In the study, all of the significant estimates were positive (i.e., greater than 0), meaning that a high level of use is connected to a high level of resistance and a low level of use is connected to a low level of resistance. The parameter estimate of time describes the linear change in the levels of resistance. If the estimate of time is significant and positive, then the level of resistance has increased during the study period. If it is significant and negative, it refers to a significant decrease in the level of resistance. Finally, if the estimate is not significant, then the level of resistance has not changed statistically significantly during the study period.

The statistical analysis was performed in a manner similar to that used in previous studies conducted by our study group of *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (2, 3, 12).

RESULTS

We studied 25 associations between antimicrobial consumption and antimicrobial resistance among *E. coli* isolates in 20

TABLE 2. Links between antimicrobial resistance in *E. coli* and antimicrobial consumption studied

Antibiotic(s) to which resistance was evaluated	Antibiotic consumed
Ampicillin	Amoxicillin
	Amoxicillin + clavulanate
	Fluoroquinolones
Cephalothin or cephalexin	Cephalosporins
	Fluoroquinolones
	Trimethoprim
	Trimethoprim-sulfamethoxazole
	Trimethoprim + trimethoprim-sulfamethoxazole
	Nitrofurantoin
Fluoroquinolones	Amoxicillin
	Amoxicillin + clavulanate
	Cephalosporins
	All fluoroquinolones
	Levofloxacin
	Norfloxacin
	Ciprofloxacin
Trimethoprim	Trimethoprim
	Trimethoprim-sulfamethoxazole
	Trimethoprim + trimethoprim-sulfamethoxazole
Trimethoprim-sulfamethoxazole	Trimethoprim
	Trimethoprim-sulfamethoxazole
	Trimethoprim + trimethoprim-sulfamethoxazole
Amdinocillin	Pivmecillinam
Nitrofurantoin	Cephalosporins
	Nitrofurantoin

central hospital districts. Of these, four associations were statistically significant. The level of nitrofurantoin use was associated with nitrofurantoin resistance ($P < 0.0001$), the level of cephalosporin use was associated with nitrofurantoin resistance ($P = 0.0293$), the level of amoxicillin use was associated with fluoroquinolone resistance ($P = 0.0031$), and the level of total fluoroquinolone use was associated with ampicillin resistance ($P = 0.0046$).

All these associations were positive, indicating that a high level of drug consumption was connected with a high level of antimicrobial resistance and that a low level of drug use was connected with a low level of antimicrobial resistance. No other positive associations were found. In addition, there were no statistically significant negative associations, which means that a low level of consumption was not linked with a high level of resistance and that a high level of consumption was not linked with a low level of resistance for any of the antimicrobial agents studied. The linear change in the rates of resistance over the time period was significant for all antimicrobial agents tested except cephalothin or cephalexin resistance (Table 3). This means that the level of resistance to the antimicrobial agents tested changed significantly during the period of this study.

DISCUSSION

In this study, we found a statistically significant association between nitrofurantoin use and nitrofurantoin resistance, cephalosporin use and nitrofurantoin resistance, amoxicillin use and fluoroquinolone resistance, and, conversely, fluoroquinolone use and ampicillin resistance. Interestingly, there was no association between fluoroquinolone use and fluoroquinolone resistance by evaluation of either the pooled use of all fluoroquinolones or the use of separate agents. No other associations were significant. Thus, the positive associations found between antimicrobial resistance in *E. coli* and antimicrobial use concerned only a few antimicrobial agents.

The results presented in this paper are in line with those presented in several other papers (4, 9, 14). There are a number of reports in which the associations between antimicrobial resistance in *E. coli* and antimicrobial consumption were weak or were not found at all. In a report by Livermore et al., correlations between ampicillin and trimethoprim resistance rates in *E. coli* and prescription of the corresponding antibiotics were weak for isolates from patients with bacteremia (14). In a study by Hay et al., no evidence of a connection between amoxicillin and trimethoprim resistance in *E. coli* isolates recovered from urine samples from asymptomatic patients and exposure to any antibiotic in the previous 12 months was found (9). In a study by Kahlmeter et al., no statistically significant association was found between the resistance of *E. coli* isolates from patients with community-acquired UTIs to amoxicillin-clavulanate, cefadroxil, fosfomycin, amdinocillin, sulfamethoxazole, trimethoprim, and trimethoprim-sulfamethoxazole and the consumption of the same drugs (11). In a work by Colgan et al., no association was found between trimethoprim-sulfamethoxazole resistance and use in patients with acute uncomplicated cystitis (4). In a report from the United Kingdom, despite a decrease in sulfonamide prescriptions, the frequency of sulfonamide resistance in *E. coli* remained high (5). This might be due to the presence of some other selection factors or the fact that the genetic determinants for resistance are incorporated in integrons or plasmids, which can be very stable but which are still efficient vehicles for the spread of resistance determinants (10). Therefore, the removal of the trimethoprim or the trimethoprim-sulfamethoxazole selection pressure will probably not have an immediate impact on the levels of resistance (10).

Livermore et al. noticed that the rates fluoroquinolone resistance among *E. coli* isolates increased, despite the decline in the rates of prescription of fluoroquinolones in the community (13). In contrast, some previous reports showed an association between outpatient fluoroquinolone use and fluoroquinolone resistance (8, 11, 15). A similar finding has been made between community use and resistance in hospitals (19). It may be possible that fluoroquinolone resistance was not directly associated with fluoroquinolone use in this study because the CLSI breakpoints for fluoroquinolone resistance are high. Several mutations in topoisomerase genes or some additional mechanisms are usually required to achieve the breakpoint concentrations. *E. coli* isolates with such high MICs are rare in Finland. One can speculate that the relationship between beta-lactam resistance and fluoroquinolone use may be explained by the fact that the strains have low-level resistance to fluoroquinolones and its mechanism [e.g., a *qnr* gene or an AAC(6′)-Ib-cr variant enzyme-encoding gene] is transferred on the same plasmid as the beta-lactamase gene. This phenomenon has been discussed in recent studies (20, 22). The results of this study suggest that the use of fluoroquinolones for the treatment of UTIs is still sustainable in Finland. Although the levels of resistance are currently not alarmingly high, there was a trend toward a slight increase in the rate of resistance, from 1.8% in 1999 to 3.5% in 2005 (unpublished data). Thus, it may not be reasonable to recommend the use of fluoroquinolones as first-line treatment of UTIs.

The association between nitrofurantoin consumption and resistance is somewhat expected. The literature on this topic is, however, limited. Nevertheless, the use of nitrofurantoin as a first-line drug in Finland can be defended, because the rate of nitrofurantoin resistance in Finland is low, less than 2 to 3%, at present. In addition, nitrofurantoin resistance does not often result in treatment failure (24).

In these kinds of studies, a few factors could have biased the results. First, the prevalence of drug-resistant *E. coli* may be affected by a small circulating clonal group (25). Therefore, recommendations to decrease antibiotic use in a community might not have an impact on the levels of resistance (25). There are also some suggestions that drug-resistant clones of *E. coli* that cause UTIs could be spread by the ingestion of contaminated foods (16). In these cases, intestinal *E. coli* could be a reservoir for resistant strains. Second, increased rates of resistance might also result in the increased rate of use of another antimicrobial (23). From the study results, this kind of phenomenon could be erroneously interpreted as a direct link between drug use and resistance. Third, it is possible that an association between consumption and resistance occurs over a time period shorter than the one used in this study (4, 9). In addition, an association may not be found between consumption and resistance if there is a delay between the reduction in the level of antimicrobial consumption and the subsequent

TABLE 3. Significant associations between antimicrobial resistance and consumption, as well as antimicrobial resistance and time[a]

Antimicrobial	Effect	PE	SE	DF	*t* value	*P* value
Trimethoprim resistance vs:						
Trimethoprim consumption	Intercept	22.7864	2.5613	19	8.90	<0.0001
	Use	1.8562	1.7348	101	1.07	0.2872
	Time	−1.0350	0.1599	18	−6.47	<0.0001
Trimethoprim-sulfamethoxazole consumption	Intercept	23.4825	2.8711	19	8.18	<0.0001
	Use	1.6784	2.6296	101	0.64	0.5248
	Time	−0.9185	0.2281	18	−4.03	0.0008
Trimethoprim + trimethoprim-sulfamethoxazole consumption	Intercept	21.7928	3.2112	19	6.79	<0.0001
	Use	1.4929	1.3003	101	1.15	0.2536
	Time	−0.9414	0.1789	18	−5.26	<0.0001
Trimethoprim-sulfamethoxazole resistance vs trimethoprim consumption	Intercept	14.8609	3.2751	14	4.54	0.0005
	Use	4.0385	2.2581	51	1.79	0.0796
	Time	−0.5120	0.1972	14	−2.60	0.0211
Amdinocillin resistance vs pivemecillinam consumption	Intercept	6.6642	0.8741	19	7.62	<0.0001
	Use	−2.3751	2.0454	99	−1.16	0.2484
	Time	−0.3489	0.1067	18	−3.27	0.0042
Nitrofurantoin resistance vs:						
Cephalosporin consumption	Intercept	1.8621	0.5244	19	3.55	0.0021
	Use	**0.5351**	**0.2420**	**101**	**2.21**	**0.0293**
	Time	−0.1649	0.01780	18	−9.26	<0.0001
Nitrofurantoin consumption	Intercept	1.3163	0.4149	19	3.17	0.0050
	Use	**2.3330**	**0.5706**	**101**	**4.09**	**<0.0001**
	Time	−0.1470	0.01888	18	−7.78	<0.0001
Fluoroquinolone resistance vs:						
Amoxicillin consumption	Intercept	−0.7831	0.9665	18	−0.81	0.4284
	Use	**1.1040**	**0.3602**	**67**	**3.07**	**0.0031**
	Time	0.1340	0.05816	17	2.30	0.0341
Cephalosporin consumption	Intercept	0.4062	1.1655	19	0.35	0.7312
	Use	0.6954	0.5089	84	1.37	0.1754
	Time	0.1348	0.04830	18	2.79	0.0121
Levofloxacin consumption	Intercept	1.4633	0.3140	19	4.66	0.0002
	Use	2.3937	1.4940	70	1.60	0.1136
	Time	0.1553	0.05384	18	2.88	0.0099
Ampicillin resistance vs:						
Fluoroquinolone consumption	Intercept	26.4905	1.4621	10	18.12	<0.0001
	Use	**6.0910**	**2.0193**	**37**	**3.02**	**0.0046**
	Time	−1.0954	0.1987	9	−5.51	0.0004
Amoxicillin consumption	Intercept	27.2247	3.0584	10	8.90	<0.0001
	Use	0.4518	1.1006	37	0.41	0.6838
	Time	−0.6667	0.1602	9	−4.16	0.0024
Amoxicillin-clavulanic acid consumption	Intercept	28.4583	1.0262	10	27.73	<0.0001
	Use	0.7535	1.6045	37	0.47	0.6414
	Time	−0.7592	0.2161	9	−3.51	0.0066

[a] Significant associations between resistance and consumption are highlighted in boldface type. Parameter estimates (PE), standard errors, degrees of freedom (DF), *t* values, and *P* values were obtained by fitting a linear mixed model for repeated measures. The fixed-effects estimates shown here represent the estimated means for the random intercept and slope. See the Materials and Methods section for more detailed information.

decrease in the rate of resistance. In our study, it would have been interesting to investigate also the relationship between resistance and antimicrobial use over time periods shorter than a year, because the emergence of resistance does not necessarily need a long time to develop. However, the consumption rates are currently published on an annual basis in Finland, so we were not able to carry out the investigation with data for a shorter time period. Fourth, different results may be caused by

differences in the age and gender distribution (8, 11). For example, resistance rates and the levels of antimicrobial consumption for elderly people may be higher than those for other age groups. This distribution could not be evaluated with the data available to us. Fifth, these kinds of studies are based on data from either patient-level or population-level resistance and drug consumption data, which often give different results. In addition, the size of the regions selected in the study setting may affect the results (14). For example, in large central hospital districts, an increased rate of use of an antimicrobial could occur in one area of the district but resistance could change in another part of the district.

In this study, we have used a linear mixed model for repeated measures, which takes into account the structure and dependencies of the material. This method is different from the ones used in the studies cited above. In our view, however, the main reason for the possible differences in the results is more likely the different kinds of study materials used in the studies rather than the statistical methods. Factors that give reliability to this study include a very large register of data concerning both bacterial isolates and antimicrobial consumption covering a long, 9-year time span.

In conclusion, we found only a few statistically significant associations between bacterial resistance and antimicrobial use. Only the association between nitrofurantoin use and resistance was as expected. The cross-connection between fluoroquinolone use and ampicillin resistance and vice versa might be of importance and warrants further studies. One way to approach this topic in order to get more evidence on the relationship between drug use and resistance could be to carry out studies at the country or region level but with individual patient data.

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