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Associated antimicrobial resistance in *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*

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ABSTRACT

Associated resistance to four to six related and unrelated antimicrobial agents was investigated in consecutive non-duplicate isolates of *Escherichia coli* (n = 39 425), *Pseudomonas aeruginosa* (n = 1070), *Staphylococcus aureus* (n = 7489), *Streptococcus pneumoniae* (n = 1604) and *Streptococcus pyogenes* (n = 2531). In all species, high proportions (76.5–88.9%) of isolates were susceptible to all the drugs investigated. Irrespective of species, isolates resistant to one drug were more likely to be resistant to any of the other drugs than were susceptible isolates. Thus, trimethoprim resistance in *E. coli* was 38.4% among ampicillin-resistant vs. 3.9% among ampicillin-susceptible isolates, and erythromycin resistance in *Strep. pneumoniae* was 41% among doxycycline-resistant vs. 1% among doxycycline-susceptible isolates. In all five species investigated, there was also significant associated resistance among unrelated drugs, highlighting the fact that resistance development occurs primarily among bacteria already resistant to one or more antimicrobial agents. For the clinician, pronounced resistance associations mean that when empirical therapy fails because of resistance, there is a reduced chance of choosing an alternative successful empirical agent. For the epidemiologist, who uses routine clinical susceptibility data to describe resistance development, resistance associations mean that if the dataset contains results for isolates selected on the basis of their susceptibility to another drug, structurally related or not, a bias of false resistance is introduced.

Keywords Antimicrobial resistance, associated resistance, development, empirical therapy, resistance, susceptibility

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INTRODUCTION

Resistance to antimicrobial drugs is increasing rapidly worldwide in almost all bacterial genera and to almost all drug classes. The use, misuse and abuse of antibiotics are held to be responsible for this development [1,2]. Clonal outbreaks affect antimicrobial resistance development, as exemplified by *Streptococcus pyogenes* and macrolide resistance [3], *Neisseria meningitidis* and sulphonamide resistance [4], *Staphylococcus aureus* and fusidic acid resistance [5], and *Streptococcus pneumoniae* and penicillin and trimethoprim–sulphamethoxazole resistance [6]. Cross-resistance, i.e., resistance to two or more drugs, often mediated by a single resistance mechanism, is well-documented and important for resistance to many classes of antimicrobial agents, e.g., β-lactams, fluoroquinolones and macrolides [7]. Associated resistance, i.e., increased resistance to one drug in the presence of resistance to another unrelated drug, is only rarely investigated systematically, although concomitant resistance to many different drugs is a well-known phenomenon among isolates of methicillin-resistant *Staph. aureus* and penicillin-resistant *Strep. pneumoniae* [8]. Only one previous study has systematically investigated associated resistance in various pathogens to several classes of drugs. Fluit *et al.* [9] investigated ten common bacterial pathogens and described the rates of resistance to a series of

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antimicrobial agents in isolates resistant to the primary drug. However, this study did not give or compare resistance rates in bacteria that are resistant or susceptible to the primary drug.

The objective of the present study was, therefore, to determine the degree of associated resistance in five unrelated bacterial species. To exclude the possibility that the findings were associated randomly with a certain period, isolates of *Escherichia coli* were studied over a period of 12 years.

MATERIALS AND METHODS

Study design

The study was performed in the clinical microbiology laboratory for the county of Kronoberg, Sweden, which has a population of 179 000 inhabitants and two small towns, each with a general hospital. All clinical samples from the area have been handled by the above-mentioned laboratory since 1985. Non-duplicate routine quantitative susceptibility test data for five pathogens (*E. coli*, *Pseudomonas aeruginosa*, *Staph. aureus*, *Strep. pneumoniae* and *Strep. pyogenes*) were analysed retrospectively. With few exceptions (see below), all isolates of the five pathogens from hospitalised and community patients during the periods specified below were included in the study. *E. coli* isolates were from 1993–2004 and isolates of the other species were from 2001–2004. For *E. coli*, only urinary tract isolates were included and a longer period was studied in order to exclude the possibility that the findings were influenced by a randomly chosen period. *E. coli* was chosen for the temporal analysis as: (i) there were enough isolates to permit the analysis; (ii) it is one of the most common species isolated in all laboratories; and (iii) the same six antimicrobial agents were tested throughout the 12-year period. Bacteria isolated as part of screening programmes for multidrug-resistant bacteria were not included. All isolates were categorised systematically for susceptibility to four to six defined antibiotics each. Only antibiotics forming part of the primary test panel were included, and any isolate without data for all defined antibiotics was excluded. All data were derived from the ADBakt database (http://www.autonik.se) used at the laboratory.

The Swedish Reference Group for Antibiotics (SRGA) classification system (http://www.srga.org) does not have a susceptible (S) category for *E. coli* and ampicillin, or for *E. coli* and cefadroxil. In these cases, the intermediate (I) category is considered to represent isolates without any mechanisms of resistance to the respective drugs, and the I and S categories were merged. For species–antibiotic combinations where the I categorisation represented low-level resistance, the results in susceptibility categories I and resistant (R) were merged.

Antimicrobial susceptibility testing

Breakpoints and susceptibility testing procedures were used as recommended by the SRGA. All tests were performed on IsoSensitest agar either without (*E. coli*, *P. aeruginosa*, *Staph. aureus*) or with (*Strep. pneumoniae*, *Strep. pyogenes*) defibrinated horse blood and β-nicotinamide adenine dinucleotide. Reference strains *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *Staph. aureus* ATCC 29213, *Strep. pneumoniae* ATCC 49619 and *Strep. pyogenes* CCUG 25571 were tested 5 days a week using the same procedure as for the routine isolates. Routine susceptibility test results were only accepted if the inhibition zone diameters for the control strains were within the acceptable performance range.

There were no changes in the SRGA methodology that affected the studied species and antibiotics during the study period, except for fluoroquinolones. For the fluoroquinolones, norfloxacin was used in 1993–1998, ciprofloxacin in 1999–2000, and nalidixic acid in 2001–2004. Since nalidixic acid provides a more sensitive resistance detection system for fluoroquinolones, the breakpoints for norfloxacin and ciprofloxacin were adapted retrospectively to allow the detection of low-level fluoroquinolone resistance.

Data presentation

For each of the species, antimicrobial resistance to one drug was calculated in the presence and absence of resistance to each of the other drugs investigated. This technique was used previously in an analysis of all *E. coli* isolates in the ECO·SENS project, performed in 16 European countries and Canada [10]; thus, the principal results of the ECO·SENS project could be compared with those of the present study. The ECO·SENS study addressed only *E. coli* isolates and had a geographical, but not a temporal, aspect.

Statistics

The data were analysed using Microsoft Excel pivot tables. Statistical analysis calculating the relative risk (p values and 95% CIs) of an isolate being resistant to a second antibiotic when already resistant to a first antibiotic was calculated for all combinations. Small sample correction was performed in all the analyses.

RESULTS

In all species, the majority (76.5–88.9%) of isolates were fully susceptible to all the drugs investigated (Table 1). For *E. coli*, this proportion was 78.6% in 1993 and 76.3% in 2004 ($p > 0.05$). The proportion of isolates resistant to more than one of the drugs tested was 12.9% for *E. coli*, 2.7% for *P. aeruginosa*, 2.9% for *Staph. aureus*, 3.6% for *Strep. pneumoniae*, and 1.5% for *Strep. pyogenes*. All results concerning associated resistance in these five species are presented in Tables 2–6, with the overall resistance rate presented on the bottom line. Associated resistance, i.e., resistance to one drug in the presence of resistance to any of the other drugs, was pronounced in all five pathogens.

For *E. coli* (Table 2), six antibiotics were evaluable for a total of 39 425 urinary tract isolates. Trimethoprim resistance was almost ten-fold

Table 1. Bacterial species and antimicrobial agents analysed

Species[a]	No. of isolates analysed	Antimicrobial agents	Isolates without resistance to any of the antimicrobial agents analysed (%)
Escherichia coli	39 425	FQ, TMP, AMP[b], CFR[b], MEC, NIT	76.8
Pseudomonas aeruginosa	1 070	PIP, CAZ, IPM, GEN, CIP	85.1
Staphylococcus aureus	7 489	MET, CLI, ERY, SXT, FUS	83.4
Streptococcus pneumoniae	1 604	PEN, CLI, ERY, DOX, SXT	88.9
Streptococcus pyogenes	2 531	PEN, CLI, ERY, DOX	84.1

FQ, fluoroquinolone; TMP, trimethoprim; AMP, ampicillin; CFR, cefadroxil; MEC, mecillinam; NIT, nitrofurantoin; PIP, piperacillin; CAZ, ceftazidime; IPM, imipenem; GEN, gentamicin; CIP, ciprofloxacin; MET, methicillin; CLI, clindamycin; ERY, erythromycin; SXT, trimethoprim–sulphamethoxazole; FUS, fusidic acid; PEN, penicillin; DOX, doxycycline.
[a]Consecutive isolates between 2000 and 2004, except for *E. coli* (1993–2004).
[b]Antibiotics for which the intermediate (I) and susceptible (S) categories were merged (see Materials and methods).

higher (38.4% vs. 3.9%) in ampicillin-resistant than in ampicillin-susceptible isolates of *E. coli*. The same pattern was found for all investigated antimicrobial agents, irrespective of chemical relatedness, although it was more pronounced between chemically related drugs such as ampicillin and mecillinam, or ampicillin and cefadroxil (Table 2). With the exception of fluoroquinolones, antimicrobial resistance rates changed only marginally over the 12-year observation period. Although magnitudes differed, the tendency of associated resistance was the same in both periods and for all drugs (Table 2).

For *P. aeruginosa*, resistance to three related drugs (piperacillin, ceftazidime and imipenem) and two unrelated drugs (gentamicin and ciprofloxacin) was studied in 1070 consecutive isolates (Table 3). The same pattern observed for *E. coli* was obtained, and all risk ratios were statistically significant, irrespective of whether the drugs were related or not. As an example, ciprofloxacin resistance was five- to ten-fold more common, and gentamicin resistance was five- to 30-fold more common, in isolates resistant to any of the other drugs than in sensitive isolates.

For *Staph. aureus*, five drugs could be investigated, two of which (erythromycin and clindamycin) were related. Not surprisingly, erythromycin resistance was very high (97.2%) in clindamycin-resistant isolates, and clindamycin resistance was very high (58.3%) in erythromycin-resistant isolates, but resistance to erythromycin or clindamycin was almost non-existent among isolates sensitive to the counterpart drug (Table 4). However, fusidic acid resistance was also significantly higher in isolates resistant to clindamycin (34.5%) or erythromycin (33.2%) than in sensitive isolates (13.1% and 12.8%, respectively).

Table 2. Associated resistance in *Escherichia coli* isolates (comparison between 1993 and 2004)

Agent and no. of isolates susceptible (S) and resistant (R)			Antimicrobial resistance (%) in the absence and presence of resistance to another drug and the relative risk (RR[a]) of resistance in susceptible vs. resistant organisms																			
			FQ				TMP				AMP				CFR				MEC				NIT			
			1993		2004		1993		2004		1993		2004		1993		2004		1993		2004		1993		2004	
	n (1993)	*n* (2004)	%	RR	%	RR	%	RR	%	RR	%	RR	%	RR	%	RR	%	RR	%	RR	%	RR	%	RR	%	RR
FQ																										
S	2901	3315	0	NA	0	NA	7.1	***4.7***	8.6	***5.6***	16.9	1.3	16.9	***3.0***	0.7	***8.3***	0.4	***3.7***	10.5	1.7	5.8	***3.5***	0.3	***29.9***	0.5	***8.7***
R	25	154	100		100		32.0		48.1		20.0		50.6		4.0		1.3		16.0		20.1		8.0		4.5	
TRI																										
S	2711	3111	0.6	***6.1***	2.6	***8.0***	0	NA	0	NA	13.1	***5.0***	12.1	***6.0***	0.6	***4.2***	0.4	***3.1***	8.0	***5.5***	4.2	***6.3***	0.2	***10.6***	0.5	***4.2***
R	215	358	3.7		20.7		100		100		65.1		73.2		2.3		1.1		43.7		26.3		2.3		2.2	
AMP																										
S	2431	2830	0.8	1.3	2.7	***4.5***	3.1	***9.1***	3.4	***12.0***	0	NA	0	NA	0.2	***19.1***	0.1	***17.1***	1.6	***34.7***	0.6	***55.9***	0.3	**2.9**	0.6	**2.1**
R	495	639	1.0		12.2		28.3		41.0		100		100		3.4		2.0		54.9		32.6		0.8		1.3	
CFR																										
S	2905	3453	0.8	**8.3**	4.4	**3.4**	7.2	***3.5***	10.3	**2.7**	16.5	***4.9***	18.1	***4.5***	0	NA	0	NA	10.5	***2.9***	6.3	***6.2***	0.2	***31.1***	0.7	4.1
R	21	16	4.8		12.5		23.8		25.0		81.0		81.3		100		100		28.6		37.5		4.8		0.0	
MEC																										
S	2616	3245	0.8	1.8	3.8	***3.7***	4.6	***6.6***	8.1	***5.2***	8.5	***10.3***	13.3	***7.0***	0.6	***3.5***	0.3	***8.9***	0	NA	0	NA	0.3	**5.1**	0.6	**3.0**
R	310	224	1.3		13.8		30.3		42.0		87.7		92.9		1.9		2.7		100		100		1.3		1.8	
NIT																										
S	2915	3444	0.8	***27.0***	4.3	***6.9***	7.2	***6.6***	10.2	***3.3***	16.8	**2.3**	18.3	**1.8**	0.7	***28.4***	0.5	4.1	10.5	***3.7***	6.4	**2.8**	0	NA	0	NA
R	11	25	18.2		28.0		45.5		32.0		36.4		32.0		14.3		0.0		36.4		16.0		100		100	

FQ, fluoroquinolone; TMP, trimethoprim; AMP, ampicillin; CFR, cefadroxil; MEC, mecillinam; NIT, nitrofurantoin; NA, not applicable.
[a]Statistical significance for all RRs is shown in bold for $p < 0.05$, and in bold and italics for $p < 0.001$.

Table 3. Associated resistance in *Pseudomonas aeruginosa* isolates (2000–2004)

Agent and no. of isolates susceptible (S) and resistant (R)	Antimicrobial resistance in the absence and presence of resistance to another drug and the relative risk (RR[a]) of resistance in susceptible vs. resistant organisms									
	Piperacillin		Ceftazidime		Imipenem		Gentamicin		Ciprofloxacin	
	%	RR	%	RR	%	RR	%	RR	%	RR
Piperacillin										
S (n = 1039)	0	NA	0.6	***27.9***	5.0	***3.5***	0.3	***33.0***	7.8	***4.7***
R (n = 31)	100		16.1		16.1		9.7		35.5	
Ceftazidime										
S (n = 1059)	2.5	***19.1***	0	NA	5.1	***5.9***	0.6	**7.1**	8.3	***4.7***
R (n = 11)	45.5		100		27.3		0.0		36.4	
Imipenem										
S (n = 1013)	2.6	***3.7***	0.8	***7.3***	0	NA	0.5	**4.8**	7.7	***3.3***
R (n = 57)	8.8		5.3		100		1.8		24.6	
Gentamicin										
S (n = 1064)	2.6	***20.1***	1.0	**7.1**	5.3	**4.3**	0	NA	8.3	***8.3***
R (n = 6)	50.0		0.0		16.7		100		66.7	
Ciprofloxacin										
S (n = 978)	2.0	***5.9***	0.7	***6.3***	4.4	***3.5***	0.2	***19.0***	0	NA
R (n = 92)	12.0		4.3		15.2		4.3		100	
Overall resistance rate (n = 1070)	2.9		1.0		5.3		0.6		8.6	

NA, not applicable.
[a]Statistical significance for all RRs is shown in bold for p <0.05, and in bold and italic for p <0.001.

Table 4. Associated resistance in *Staphylococcus aureus* isolates (2000–2004)

Agent and no. of isolates susceptible (S) and resistant (R) to respective agent	Antimicrobial resistance in the absence and presence of resistance to another drug and the relative risk (RR[a]) of resistance in susceptible vs. resistant organisms									
	Methicillin		Clindamycin		Erythromycin		Trimetho-prim–sulpha-methoxazole		Fusidic acid	
	%	RR	%	RR	%	RR	%	RR	%	RR
Methicillin										
S (n = 7480)	0	NA	2.4	***6.7***	3.9	***6.7***	0.3	**16.1**	13.6	0.4
R (n = 9)	100		11.1		22.2		0.0		0.0	
Clindamycin										
S (n = 7312)	0.1	**7.3**	0	NA	1.7	***57.5***	0.3	***6.7***	13.1	***2.6***
R (n = 177)	0.6		100		97.2		1.7		34.5	
Erythromycin										
S (n = 7194)	0.1	**8.1**	0.1	***763.6***	0	NA	0.3	**2.7**	12.8	***2.6***
R (n = 295)	0.7		58.3		100		0.7		33.2	
Trimethoprim–sulphamethoxazole										
S (n = 7465)	0.1	**16.0**	2.3	***6.1***	3.9	**2.6**	0	NA	13.6	1.1
R (n = 24)	0.0		12.5		8.3		100		12.5	
Fusidic acid										
S (n = 6471)	0.1	0.3	1.8	***3.4***	3.0	***3.2***	0.3	1.0	0	NA
R (n = 1018)	0.0		6.0		9.6		0.3		100	
Overall resistance rate (n = 7489)	0.1		2.4		3.9		0.3		13.6	

NA, not applicable.
[a]Statistical significance for all RRs is shown in bold for p <0.05, and in bold and italic for p <0.001.

Strep. pneumoniae (Table 5) and *Strep. pyogenes* (Table 6) exhibited an identical pattern to *Staph. aureus*, except that fusidic acid was not investigated. All risk ratios were statistically significant, irrespective of whether the drugs were related. Resistance to other antibiotics was much higher in penicillin-non-susceptible than in penicillin-susceptible *Strep. pneumoniae*. Clindamycin resistance was 8.9% vs. 0.6%, erythromycin resistance was 17.8% vs. 1.5%, doxycycline resistance was 24.4% vs. 2%, and trimethoprim–sulphamethoxazole resistance was 80% vs. 6.5%, respectively.

DISCUSSION

Associated resistance was analysed in five unrelated species: *E. coli*, *P. aeruginosa*, *Staph. aureus*, *Strep. pneumoniae* and *Strep. pyogenes*. As expected, cross-resistance, i.e., resistance to a drug in the presence of resistance to another structurally related drug, was common. Surprisingly, associated resistance between structurally unrelated drugs was also pronounced for almost all drugs in all five species. Interestingly, the few instances in which this was not statistically significant were at the beginning of the period

Table 5. Associated resistance in *Streptococcus pneumoniae* isolates (2000–2004)

Agent and no. of isolates susceptible (S) and resistant (R) to respective agent	Antimicrobial resistance in the absence and presence of resistance to another drug and the relative risk (RR[a]) of resistance in susceptible vs. resistant organisms									
	Penicillin		Clindamycin		Erythromycin		Doxycycline		Trimetho-prim–sulpha-methoxazole	
	%	RR	%	RR	%	RR	%	RR	%	RR
Penicillin										
S (n = 1559)	0	NA	0.6	***16.2***	1.5	***12.4***	2.0	***12.5***	6.5	***12.2***
R (n = 45)	100		8.9		17.8		24.4		80.0	
Clindamycin										
S (n = 1591)	2.6	***12.8***	0	NA	1.1	***86.0***	1.9	***43.0***	8.2	***7.7***
R (n = 13)	30.8		100		100.0		84.6		61.5	
Erythromycin										
S (n = 1573)	2.4	***11.3***	0.0	***1348.7***	0	NA	1.6	***34.3***	7.9	***5.4***
R (n = 31)	25.8		41.9		100		54.8		41.9	
Doxycycline										
S (n = 1562)	2.2	***12.3***	0.1	***169.1***	0.9	***44.4***	0	NA	7.6	***6.0***
R (n = 42)	26.2		26.2		40.5		100		45.2	
Trimethoprim–sulphamethoxazole										
S (n = 1466)	0.6	***40.7***	0.3	***16.4***	1.2	***7.7***	1.6	***8.8***	0	NA
R (n = 138)	26.1		5.8		9.4		13.8		100	
Overall resistance rate (n = 1604)	2.8		0.8		1.9		2.6		8.6	

NA, not applicable.
[a]Statistical significance for all RRs is shown in bold for p <0.05, and in bold and italic for p <0.001.

Table 6. Associated resistance in *Streptococcus pyogenes* isolates (2000–2004)

Agent and no. of isolates susceptible (S) and resistant (R) to respective agent	Antimicrobial resistance in the absence and presence of resistance to another drug and the relative risk (RR[a]) of resistance in susceptible vs. resistant organisms[b]					
	Clindamycin		Erythromycin		Doxycycline	
	%	RR	%	RR	%	RR
Clindamycin						
S (n = 2503)	0	NA	1.4	***59.0***	14.0	***6.4***
R (n = 28)	100		85.7		89.3	
Erythromycin						
S (n = 2471)	0.2	***222.4***	0	NA	13.8	***4.1***
R (n = 60)	40.0		100		56.7	
Doxycycline						
S (n = 2156)	0.1	***41.8***	1.2	***7.5***	0	NA
R (n = 375)	6.7		9.1		100	
Overall resistance rate (n = 2531)	1.1		2.4		14.8	

NA, not applicable.
[a]Statistical significance for all RRs is shown in bold for p <0.05, and in bold and italic for p <0.001.
[b]Penicillin resistance rates are not shown, since all isolates were susceptible to penicillin.

studied, and involved fluoroquinolones, i.e., drugs against which resistance was rare in the beginning and an increasing problem at the end of the study period.

The finding of associated resistance underlines the importance of not using subsets of clinical susceptibility test data for calculating resistance rates for epidemiological purposes. If susceptibility to ciprofloxacin is determined only in nalidixic acid-resistant *E. coli*, this leads to an obvious bias that most microbiologists would instantly recognise. However, the data clearly show that the same tendency exists for unrelated drugs. For example, if trimethoprim susceptibility is determined in *E. coli* isolates resistant to fluoroquinolones (or ampicillin or nitrofurantoin), the same bias ensues. This pattern was seen with all five pathogens for all structurally related and almost all unrelated drugs, and in both older and recent data for *E. coli*. Many laboratories extend testing to include more active drugs or drugs for intravenous use 'if the isolate exhibits resistance to three or more of the routinely tested first-line antimicrobial agents' (or according to another similar algorithm). The present data clearly show that, although this may be a perfectly sensible and satisfactory procedure for clinical susceptibility testing, it obviates the use of the same data for surveillance and epidemiological purposes. Resistance rates derived from such laboratory practices become misleading. Although all the *E. coli* data concerned isolates from urinary tract infections, the data for *Strep. pneumoniae* were from upper respiratory tract infections, for *Staph. aureus* from skin and soft-tissue infections, and for *Strep. pyogenes* from throat swabs and soft-tissue infections. Taken together, there are no data to suggest that this is not a general phenomenon.

Although several previous reports have revealed that *E. coli* isolates resistant to one antimicrobial agent are likely to be resistant to other antimicrobial agents [10–15], a systematic analysis of associated resistance in unrelated pathogens has not been published previously. In

2003, the ECO·SENS project addressed associated resistance in a more systematic fashion and revealed that resistance in *E. coli* to any agent, not only agents within the same or related classes of drugs, was associated with a marked increase in resistance to all other agents tested, with fosfomycin being a possible exception [10]. This was true for all 17 countries investigated, and, together with the present results generated over longer periods for other species, indicates that this is a general phenomenon.

In 2005, Kresken *et al.* [16] reported that four species of Enterobacteriaceae with resistance to nalidixic acid frequently exhibited resistance to non-quinolone agents. Zhanel *et al.* [11] demonstrated associations among ampicillin, trimethoprim–sulphamethoxazole and ciprofloxacin resistance in 1681 isolates of *E. coli* from Canada. Sahm *et al.* [12] reported similar results from an analysis in which only 31% of the isolates included in the study were analysed for resistance to all antibiotics. Karlowsky *et al.* [13] confirmed these results and suggested a connection between nitrofurantoin and ciprofloxacin resistance, and subsequently concluded from additional data that ciprofloxacin-resistant *E. coli* isolates were often multiresistant [14]. In the present study, the results clearly indicated that associated resistance is a general phenomenon that is not confined to particular drug combinations in certain species.

Overall, the present study indicates that, irrespective of species, most antimicrobial resistance development occurs among bacteria that are already resistant to one or more antimicrobial agents. The results of the ECO·SENS study revealed that *c.* 70% of *E. coli* isolates from the Nordic countries were devoid of resistance to any of the 12 antimicrobial agents tested, compared with 76.8% to the six antimicrobial agents tested in the present study. This is a piece of good news that is not often recognised. However, the corresponding figures for Spain and Portugal were only 30–40% in the ECO·SENS project [15].

Strategies to counteract resistance often involve reducing selection pressure by limiting the use of certain antimicrobial agents or classes of antimicrobial agents. This strategy pre-supposes that the fitness cost of resistance will reduce resistance over time. The present results indicate that this strategy will often be foiled by co-selection by almost any drug, whether or not structurally related. Thus, pronounced associated resistance would seem to obviate a successful intervention based on a reduction in use of a single class of drug. The presence of multidrug efflux pumps and the linkage of resistance genes in integrons make the dynamics of resistance development more complex than was thought originally. Enne *et al.* [17] reported the same frequencies of sulphonamide resistance among *E. coli* isolates from 1991 and 1999, despite a huge decrease in prescriptions of sulphonamides in 1995 and thereafter. The failure to observe a decrease in sulphonamide resistance was ascribed to associated resistance between sulphonamides and other antibiotics.

For the clinician, these results mean that should empirical antimicrobial therapy for a patient fail because of antimicrobial resistance, the statistical chance of making an effective second empirical choice is small. This emphasises the importance of performing diagnostic culture and susceptibility testing, not with the aim of indicating empirical first-line therapy, but with the aim of enabling the clinician to choose the correct antimicrobial agent should the primary empirical therapy fail.

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