Non-hospital antimicrobial usage and resistance in community-acquired *Escherichia coli* urinary tract infection

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Objectives: To investigate the correlation between non-hospital antimicrobial consumption and resistance.

Methods: Information on the non-hospital sales of antimicrobials from 14 European countries in 1997 and 2000 was compared with the antimicrobial resistance profiles of *Escherichia coli* isolated from women with community-acquired urinary tract infection in the same countries in 1999/2000.

Results: There was no statistically significant correlation between the consumption of and resistance to co-amoxiclav, cefadroxil, fosfomycin, mecillinam, sulfamethoxazole, trimethoprim or trimethoprim–sulfamethoxazole. On the other hand, there were statistically significant correlations between consumption of broad-spectrum penicillins and quinolones in 1997 and 2000 and resistance to ciprofloxacin (P range 0.0005–0.0045) and nalidixic acid (P range 0.0013–0.0049). Total antimicrobial consumption in 1997 was significantly correlated to ciprofloxacin (P = 0.0009) and nalidixic acid (P = 0.0018) resistance, and there were significant relationships between quinolone consumption in both years and resistance to gentamicin (P range 0.0029–0.0043) and nitrofurantoin (P range 0.0003–0.0007). *E. coli* with multiple antimicrobial resistance were significantly more common in countries with high total antimicrobial consumption.

Conclusions: Owing to the frequent presence of many possible confounding factors, antimicrobial resistance to one drug does not always correlate well to the consumption of the same drug or closely related drugs. This study showed that the degree of antimicrobial consumption was significantly correlated to the incidence of multidrug-resistant *E. coli*.

Keywords: β-lactams, quinolones, multiple resistance, Europe

Introduction

The threat of increasing antimicrobial resistance is of great concern.\(^1\) Resistance to a newly introduced antimicrobial is generally low and increases thereafter as time goes by and usage increases. In the development of strategies against antimicrobial resistance, a better understanding of the relationship between antimicrobial use and resistance is a key factor. The relationship between antimicrobial usage and resistance is complex. Whilst mathematical modelling gives some insight,\(^2\) there is a need for well designed studies to investigate the relationship between antimicrobial consumption and resistance. Several studies have investigated the correlation between prescribing levels and resistance in individual countries or within the regions of a country.\(^3\) Some of these studies have included only routine clinical isolates, and there are few prospective data comparing usage and resistance levels in a specific bacterium across different countries.

We collected information on the non-hospital sales of antimicrobials from 14 European countries in two 1 year periods and compared these data with the resistance profile of *Escherichia coli* isolated from women with community-acquired urinary tract infection in the same countries.\(^7\)\(^8\)

Materials and methods

Isolation of *E. coli*

The isolates were obtained from the ECO SENS project, an international surveillance programme conducted in 1999 and 2000 to determine the susceptibility of the major community-acquired uropathogens.\(^8\)

Details of the study procedures have been published previously,\(^7\)\(^8\) and are therefore only summarized here. Women aged 18–65 years with clinical symptoms of an acute uncomplicated urinary tract infection for <8 days and who gave informed consent were included. Patients with more than three symptomatic episodes in the previous year and those with complicating factors, including an upper urinary tract infection, pregnancy or the presence of urinary tract abnormalities, were excluded.

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Antimicrobial consumption

Non-hospital antimicrobial sales data (1997 and 2000) were purchased from Intercontinental Medical Statistics (IMS Health, London, UK). Data were adjusted to the WHO/Anatomic Therapeutic Classification (ATC) classification system and expressed as a number of defined daily doses (DDD) per 1000 inhabitants per day. In this study, four antimicrobial groups relevant to the treatment of lower urinary tract infection were included: cephalosporins (ATC code J01DA), broad-spectrum penicillins (ATC code J01CA), trimethoprim (ATC code J01EA) and quinolones (ATC code J01M). The data did not allow the separation of the amounts of antimicrobials in combinations. Thus the DDDs for trimethoprim include trimethoprim alone and in combination with sulphonamides.

Resistance in E. coli

The in vitro susceptibility of 2478 E. coli isolates obtained in the ECO SENS study was used. The definition of a positive urine culture was based on the guidelines issued by the Infectious Disease Society of America.9 Susceptibility to a range of antimicrobials was determined by agar disc diffusion according to the recommendations of the Swedish Reference Group for Antibiotics (SRGA).10 The zone diameter breakpoints of the SRGA corresponding to the intermediate/resistant breakpoints: ampicillin >8 mg/L; co-amoxiclav >8 mg/L; cefadroxil >8 mg/L; mecillinam >8 mg/L; trimethoprim–sulfamethoxazole >32 mg/L; ciprofloxacin >1 mg/L; nitrofurantoin >32 mg/L; fosfomycin >32 mg/L; and gentamicin >2 mg/L.
Relationship between antimicrobial usage and resistance

The relationship between antimicrobial consumption and resistance in each country was investigated in two ways. First, the relationship between total consumption and the consumption of the individual antimicrobial groups was determined. Secondly, the relationship between total consumption and the proportions of strains that were resistant to two, and up to nine, antimicrobials was determined. In the latter case analysis was performed on data from all countries, and the analysis was repeated excluding data from Spain and Portugal, which had exceptionally high levels of resistance.

Statistical methods

The correlation between resistance to and consumption of antimicrobial drugs was determined using Pearson’s regression analysis. The Bonferroni correction was used when determining statistical significance.11 When testing for consumption versus resistance to individual antimicrobials, as there were 12 antimicrobials, \( P < 0.0042 \) (i.e. \( P < 0.05/12 \)) indicated significance. When testing for consumption versus the number of multidrug-resistant strains, as there were eight multiple resistance profiles, \( P < 0.00625 \) (i.e. \( P < 0.05/8 \)) indicated significance.

Results

Antimicrobial consumption

Sales of the studied antimicrobials per country within the EU varied between 3.5 and 32.6 DDD/1000 inhabitants/day in 1997 and between 3.6 and 26.8 in 2000 (Figure 1). The consumption of antimicrobials was higher in Southern than in Northern Europe. There were also large differences in the consumption profiles between countries. For example, in 1997 quinolone use varied from 0.3 DDD/1000 inhabitants/day in Portugal to 3.7 DDD/1000 inhabitants/day in Denmark. For comparison, the consumption of and the resistance to specific drugs were recorded for ciprofloxacin, nalidixic acid, gentamicin and nitrofurantoin (Table 2). Furthermore, although not statistically significant, there were strong correlations in 1997 between consumption and the resistance to four or more antimicrobials. Statistically significant correlations for the consumption of and the resistance to specific drugs were recorded for ciprofloxacin, nalidixic acid, gentamicin and nitrofurantoin (Table 2). Furthermore, although not statistically significant, there were strong correlations in 1997 between consumption of broad-spectrum penicillins and ampicillin resistance (correlation coefficient 0.70, \( P = 0.0052 \)) and sulfamethoxazole resistance (correlation coefficient 0.68, \( P = 0.0076 \)), although these were less apparent in 2000 (ampicillin, correlation coefficient 0.66, \( P = 0.01 \); sulfamethoxazole, correlation coefficient 0.66, \( P = 0.0099 \)).

Table 1. Antimicrobial resistance of *E. coli*

<table>
<thead>
<tr>
<th>Country</th>
<th>( n )</th>
<th>AMP</th>
<th>AMC</th>
<th>MEC</th>
<th>CFR</th>
<th>TMP</th>
<th>SUL</th>
<th>SXT</th>
<th>NAL</th>
<th>CIP</th>
<th>NIT</th>
<th>FOV</th>
<th>GEN</th>
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</thead>
<tbody>
<tr>
<td>Austria</td>
<td>126</td>
<td>17.5</td>
<td>2.4</td>
<td>1.6</td>
<td>0.8</td>
<td>9.5</td>
<td>25.4</td>
<td>9.5</td>
<td>2.4</td>
<td>0.8</td>
<td>0.8</td>
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</tr>
<tr>
<td>Belgium</td>
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<td>30.7</td>
<td>2.9</td>
<td>1.5</td>
<td>0.7</td>
<td>13.9</td>
<td>32.8</td>
<td>14.6</td>
<td>6.6</td>
<td>2.9</td>
<td>0.7</td>
<td>0.7</td>
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<tr>
<td>Denmark</td>
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<td>1.2</td>
<td>1.2</td>
<td>10.6</td>
<td>21.2</td>
<td>8.2</td>
<td>3.5</td>
<td>0</td>
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<td>1.2</td>
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<tr>
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<td>182</td>
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<td>4.9</td>
<td>0.5</td>
<td>1.6</td>
<td>5.5</td>
<td>15.4</td>
<td>4.9</td>
<td>1.6</td>
<td>0.5</td>
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<td>1.1</td>
<td></td>
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<tr>
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<td>199</td>
<td>27.6</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0</td>
<td>15.6</td>
<td>31.7</td>
<td>15.1</td>
<td>3.5</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Germany</td>
<td>138</td>
<td>29.0</td>
<td>2.2</td>
<td>2.2</td>
<td>1.4</td>
<td>22.5</td>
<td>34.8</td>
<td>21.0</td>
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<td>2.2</td>
<td>0.7</td>
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<tr>
<td>Greece</td>
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<td>0.8</td>
<td>3.0</td>
<td>13.6</td>
<td>19.7</td>
<td>11.4</td>
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<td>1.5</td>
<td>3.0</td>
<td>1.5</td>
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<tr>
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<td>0.6</td>
<td>22.1</td>
<td>40.3</td>
<td>20.8</td>
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<tr>
<td>Norway</td>
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<td>0</td>
<td>2.4</td>
<td>13.1</td>
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<td>0</td>
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<tr>
<td>Portugal</td>
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<td>45.3</td>
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<td>2.3</td>
<td>26.7</td>
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<td>11.6</td>
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<tr>
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<td>191</td>
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<td>25.1</td>
<td>48.7</td>
<td>25.7</td>
<td>26.7</td>
<td>14.7</td>
<td>4.2</td>
<td>0.5</td>
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</tr>
<tr>
<td>Sweden</td>
<td>193</td>
<td>15.5</td>
<td>5.7</td>
<td>1.6</td>
<td>5.2</td>
<td>8.8</td>
<td>16.6</td>
<td>8.3</td>
<td>2.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>122</td>
<td>27.0</td>
<td>2.5</td>
<td>0</td>
<td>0.8</td>
<td>18.9</td>
<td>31.1</td>
<td>18.9</td>
<td>6.6</td>
<td>2.5</td>
<td>0.8</td>
<td>3.3</td>
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<tr>
<td>UK</td>
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<td>37.2</td>
<td>2.8</td>
<td>1.7</td>
<td>1.7</td>
<td>13.3</td>
<td>31.7</td>
<td>12.2</td>
<td>2.2</td>
<td>0.6</td>
<td>0</td>
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</tr>
<tr>
<td>Total</td>
<td>2093</td>
<td>29.8</td>
<td>3.4</td>
<td>1.2</td>
<td>1.2</td>
<td>21.4</td>
<td>14.8</td>
<td>29.1</td>
<td>14.1</td>
<td>5.4</td>
<td>2.3</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

AMP, ampicillin; AMC, co-amoxiclav; MEC, mecillinam; CFR, cefadroxil; TMP, trimethoprim; SUL, sulfamethoxazole; SXT, trimethoprim–sulfamethoxazole; NAL, nalidixic acid; CIP, ciprofloxacin; NIT, nitrofurantoin; FOV, fosfomycin; GEN, gentamicin; \( n \), number of isolates tested.

Resistance in *E. coli*

Antimicrobial resistance rates as measured in the ECO SENS project are shown in Table 1. Resistance was generally higher in the Mediterranean countries than in Northern Europe. Thus, ampicillin resistance in Spain and Portugal was 54% and 45%, respectively, compared with 16% and 18% in Sweden and Austria. Corresponding figures for trimethoprim were 25% and 27%, and 9% and 10%, respectively. Resistance to co-amoxiclav, mecillinam, cefadroxil, nitrofurantoin, fosfomycin and gentamicin was uncommon. Fluoroquinolone resistance was also uncommon, apart from on the Iberian peninsula. Resistance, as measured with nalidixic acid, was 27% and 12% in Spain and Portugal, respectively, and when measured with ciprofloxacin was 15% and 6%, respectively.

Correlation between consumption and resistance

Total non-hospital antimicrobial consumption correlated to quinolone resistance (Table 2) in 1997, but not in 2000, and to the frequency of multidrug-resistant *E. coli* (Table 3). Figure 2 shows the correlation coefficient for consumption versus the frequency of isolates with resistance to four or more antimicrobials. Statistically significant correlations for the consumption of and the resistance to specific drugs were recorded for ciprofloxacin, nalidixic acid, gentamicin and nitrofurantoin (Table 2). Furthermore, although not statistically significant, there were strong correlations in 1997 between consumption of broad-spectrum penicillins and ampicillin resistance (correlation coefficient 0.70, \( P = 0.0052 \)) and sulfamethoxazole resistance (correlation coefficient 0.68, \( P = 0.0076 \)), although these were less apparent in 2000 (ampicillin, correlation coefficient 0.66, \( P = 0.01 \); sulfamethoxazole, correlation coefficient 0.66, \( P = 0.0099 \)).
The relationship between antimicrobial consumption and antimicrobial resistance is undisputed. It is, however, multifactorial and often confounded by a number of variables that are difficult to control (e.g. co-selection due to cross resistance and associated resistance, the spread of resistant clones by mechanisms not related to consumption, crowding, socioeconomics over time, medicolegalities, etc.). Hillier et al.\textsuperscript{13} conducted a systematic review evaluating published evidence on the relationship between antimicrobial prescribing and antimicrobial resistance of organisms causing community-acquired urinary tract infections. They concluded that the evidence base relating resistance to the community prescribing of antimicrobials is very weak.

Our findings support the notion that although the relationship between resistance and the use and misuse of antimicrobials is undisputed, it is not a simple or direct one. There was no relationship between antimicrobial consumption of and resistance to ampicillin, co-amoxiclav, cefadroxil, mecillinam, sulfamethoxazole, trimethoprim, trimethoprim–sulfamethoxazole and fosfomycin. We did find correlations between the total use of antimicrobials and quinolone resistance and between the use of quinolones and resistance to quinolones, nitrofurantoin and gentamicin, especially in 1997. However, in the Nordic countries, where mecillinam is used and has been used extensively (in 20–30% of all uncomplicated urinary tract infections), there appeared to be no correlation between use over time and resistance development.\textsuperscript{14} A relationship between the use of broad-spectrum penicillins and resistance to ampicillin in \textit{E. coli} may be considered direct and logical, and has been reported by others,\textsuperscript{15,16} but in our study the relationship was not statistically significant.

Total antimicrobial consumption in the community was similar in 1997 and 2000 in most of the 14 countries studied. A significant reduction was seen only in Spain and the UK. Since our resistance frequencies were based on \textit{E. coli} collected between 1999 and 2000 and we did not know whether there may exist a lag phase between consumption and resistance, we obtained consumption figures for a
Antimicrobial usage and resistance in community E. coli

period before (1997) and during (2000) the collection of resistance data. Overall the relationships between resistance frequencies and antimicrobial consumption were stronger in 1997 than in 2000, but the difference was small and we hesitate to conclude that there was a lag phase.

There are dangers with correlational relationships as they do not take into account confounding variables, and certain assumptions have to be made. To avoid the inherent dangers of multiple significance testing on related data, we employed the Bonferroni correction, a recognized procedure for such cases, when defining statistical significance.11

There were strong relationships between consumption of broad-spectrum penicillins, of quinolones and of total antimicrobial consumption and resistance to nalidixic acid and ciprofloxacin, as has been reported by others.3 The relationships between consumption of quinolones and resistance to gentamicin and nitrofurantoin are probably due to the fact that 67% and 79% of gentamicin-resistant E. coli were resistant to ciprofloxacin and nalidixic acid, respectively.17 Similarly, 30% and 67% of nitrofurantoin-resistant E. coli were resistant to ciprofloxacin and nalidixic acid, respectively.17 Thus many of our attempts to correlate resistance and consumption are either foiled or explained by the high degrees of associated resistance seen among the 2478 E. coli from European lower urinary tract infections. Most of this would be explained by plasmid-linked resistances.

Others have been able to show a correlation between trimethoprim consumption and resistance,4,15 as we could not. In our data, the usage of trimethoprim could not be separated from the usage of trimethoprim−sulfamethoxazole, but because of the close association between resistance to trimethoprim and resistance to sulphonamide,17 this should not matter.

There were strong and statistically significant relationships between total antimicrobial consumption and the incidence of multidrug-resistant strains of E. coli, and between total antimicrobial consumption and cumulative antimicrobial resistance rates (adding resistance rates for all 12 antibiotics and correlated to consumption; data not shown). However, when the data from Spain and Portugal were excluded from the analysis, the relationship lost statistical significance. This is not surprising, since most multidrug-resistant isolates were found in Spain and Portugal, both of which were among the countries with the highest consumption figures.

In summary, there were wide variations in European sales of antimicrobials and in the frequency of antimicrobial resistance in E. coli. The highest sales and resistance figures were recorded in the Mediterranean countries. There was no relationship between antimicrobial consumption and resistance to co-amoxiclav, cefadroxil, mecillinam, fosfomycin or trimethoprim, and the suggested correlations between consumption of broad-spectrum penicillins and resistance to ampicillin and sulfamethoxazole were not statistically significant. There were strong and statistically significant relationships in both 1997 and 2000 between, on one hand, resistance to nalidixic acid and ciprofloxacin and, on the other hand, consumption of broad-spectrum penicillins and of quinolones and total antimicrobial consumption. The degree of antimicrobial consumption correlated significantly to the incidence of multidrug-resistant E. coli and to the cumulative resistance rates, but only when data from Spain and Portugal were part of the analysis.

Acknowledgements

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References

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Figure 2. Correlation between total antimicrobial consumption and the proportion of isolates resistant to four or more antimicrobials by country. 1997: Pearson correlation coefficient, $\rho = 0.72$. For $\rho = 0$ under $H_0$, $P = 0.004$. 2000: $\rho = 0.70$. For $\rho = 0$ under $H_0$, $P = 0.005$. 

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