Analysis of the causes and consequences of decreased antibiotic consumption over the last 5 years in Slovenia

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Objectives: Compared with European countries, the use of antibiotics in Slovenia is moderate. In the period 1999–2002 an 18.67% decrease in outpatient antibiotic consumption was noted. The aim of the present study was to analyse this decrease and its consequences.

Methods: The data on outpatient antibiotic consumption were obtained from the Institute of Public Health and Health Insurance Institute of Slovenia and expressed in defined daily doses (DDD)/1000 inhabitant-days. The number of media publications on ‘antibiotic drugs’ and ‘bacterial resistance’ during the study period was obtained. In 2000, the prescription of co-amoxiclav and fluoroquinolones was restricted because of a constant increase in the consumption of these drugs. The data on incidence of acute mastoiditis and penicillin resistance among invasive pneumococci were obtained.

Results: The total outpatient consumption of antibacterials increased from 15.21 DDD/1000 inhabitant-days in 1996 to 20.08 in 1999, and decreased to 16.97 in 2003. The consumption of restricted antibiotics decreased from 7.29 in 1999 to 5.25 DDD/1000 inhabitant-days in 2003. There was a positive correlation between antibiotic consumption and the number of newspaper articles ($r = 0.92$), and a negative correlation between the number of diagnostic tests and antibiotic consumption ($r = -0.73$ for the C-reactive protein test and $-0.68$ for the streptococcal antigen detection test). Reduced antibiotic consumption was paralleled by a decrease in penicillin resistance among invasive pneumococci. No increase in mastoiditis cases was observed in spite of reduced antibiotic consumption.

Conclusion: Restriction of antibiotic prescription proved to be effective in reducing outpatient antibiotic consumption. The effect was prolonged and affected restricted antibiotics as well as non-restricted drugs.

Keywords: antibiotic prescribing, bacterial resistance, interventions

Introduction

In human medicine, 80–90% of antimicrobial drugs are used in outpatients and the rest in hospitalized patients.¹ It is estimated that 20–50% of antibiotic use is questionable.² The consequences of antibiotic overuse and misuse include the risk of adverse side effects, higher cost and higher rate of antimicrobial resistance of community pathogens. It is irrefutable that antibiotic use promotes resistance development.³ Countries with the highest per capita antibiotic consumption have the highest resistance.⁴ Compared with other European countries a moderate use of antibiotics is observed in Slovenia.⁵ In the period 1999–2002, an 18.67% decrease in the consumption of antibacterials was noted.⁶

The aim of the present study was to analyse this decrease and its consequences.

Materials and methods

Population and antibiotic consumption data

Slovenia is a small Central European country with 1 996 773 inhabitants according to the census of 30 June 2003.⁷ Almost all inhabitants (>99%) have compulsory health insurance. A prescription is needed for every antibiotic purchase, and in human medicine antibiotics are prescribed by physicians only. The consumption of antibiotics in outpatient care has been monitored since 1974. Data on the number of packages, the cost of antibiotics, the age and gender
of the patients, the identity numbers of the physicians and healthcare institutions prescribing antibiotics are collected every 3 months and published annually.1

For the period 1996–2003 the data on outpatient antibiotic consumption were collected using the anatomical therapeutic classification (ATC)/defined daily doses (DDD) (WHO version 2004) and the results expressed in DDD per 1000 inhabitant-days.7 The number of packages of antibiotics was provided by Institute of Public Health of the Republic of Slovenia for the period 1997–2003 and by the Health Insurance Institute of Slovenia for 1996.

Restrictive intervention

In June 2000, the Health Insurance Institute of Slovenia introduced restrictive measures for the prescription of co-amoxiclav and fluoroquinolones because of a constant increase in the consumption of these drugs. The restriction was suggested by infectious disease specialists. Co-amoxiclav could no longer be prescribed for patients with Streptococcus pyogenes infections diagnosed clinically or documented microbiologically. Fluoroquinolones could only be given as an alternative treatment for acute respiratory and urinary tract infections after clinical failure of first-choice antibiotics, or on the basis of susceptibility tests showing sensitivity to fluoroquinolones and resistance to first-choice antibiotics.

Educational interventions

Focused campaigns directed at public and healthcare professionals were not organized. Published papers containing the key words ‘antibiotic drugs’ and ‘bacterial resistance’ in the proceedings of annual national scientific meetings for general practitioners, infectious disease physicians, specialists of internal medicine and paediatricians were collected. The same keyword search for published papers was performed in Slovenian medical journals (Slovenian Medical Journal, Medicinski razgledi, Zdravstveno varstvo and KRKA v medicini in farmaciji), in six national newspapers and magazines (newspaper: Delo, circulation 86 000; weekly magazine: Jana, circulation 39 000; monthly magazines: Zdravje, circulation 17 000, Moj malček, circulation 9 200, Viva, circulation 22 000 and Otrok in družina, circulation 8 800) and a commercial TV station (POP TV, average media rating of news programs in 2003, 12.9%, i.e., 229 000 viewers), and the Slovenian internet search engine www.najdi.si from 1996–2003. The number of diagnostic tests such as C-reactive protein (CRP) and rapid streptococcal antigen detection tests sold in Slovenia were analysed as well.

The impact/consequence of reduced antibiotic use

The annual number of mastoidectomies was used as an indicator of possible adverse consequences of reduced antibiotic use. The data on the number of mastoidectomies in children <15 years of age were obtained from the Department of Otorhinolaryngology at the Ljubljana University Medical Centre, which has a catchment area of 835 000 inhabitants. The incidence rates of acute mastoiditis were calculated for a 3 year pre-intervention period and a 3 year post-restriction period.

The penicillin resistance rate of invasive Streptococcus pneumoniae in Slovenia during 1996–2003 was used as another measure of consequence of reduced antibiotic use. For the first 3 years, previously published data were used and for the last 4 years, European Antibiotic Resistance Surveillance Study (EARSS) data were used.10,11

Statistical methods

For the restrictive intervention, the trend of antibiotic consumption was calculated using the least squares method for the period before the intervention. A P value of <0.05 was considered statistically significant. For the post-intervention period, the difference between the observed antibiotic use and the predicted pre-intervention trend was calculated. The correlation between the number of educational interventions and antibiotic consumption was calculated using the Pearson coefficient.

Results

The consumption of antibacterials and the number of published papers and communications are shown in Table 1. The total outpatient consumption of antibacterials increased from 15.21 DDD/1000 inhabitant-days in 1996 to 20.08 DDD/1000 inhabitant-days in 1999, falling to 16.33 DDD/1000 inhabitant-days in 2002 and again increasing to 16.97 DDD/1000 inhabitant-days in 2003. The consumption of non-restricted antibiotics increased from 10.87 DDD/1000 inhabitant-days in 1996 to 12.78 DDD/1000 inhabitant-days in 1999, falling to 10.75 DDD/1000 inhabitant-days in 2002 and increasing to 11.72 DDD inhabitant-days in 2003. The consumption of restricted antibiotics has been decreasing steadily from 7.29 DDD/1000 inhabitant-days in 1999 to 5.25 DDD/1000 inhabitant-days in 2003. The consumption of co-amoxiclav decreased from 5.78 DDD/1000 inhabitant-days in 1999 to 4.10 DDD/1000 inhabitant-days in 2003 and the consumption of fluoroquinolones from 1.50 DDD/1000 inhabitant-days to 1.14/1000 inhabitant-days, with a transient increase of 0.6 DDD/1000 inhabitant-days in 2002 compared with 2001. Levofoxacin and moxifloxacin were launched in Slovenia in 2001 and 2002, respectively. The consumption of these two drugs was 0.13 DDD/1000 inhabitant-days in 2002 and in 2003 (Table 1).

The number of published papers including the keywords ‘antibiotic drugs’ and ‘bacterial resistance’ at national scientific meetings during 1996–2003 was 50. There were 27 articles published in four national medical journals during 1996–2003. In six national newspapers and magazines, 74 published papers included the aforementioned keywords. There was a strong positive correlation between antibiotic consumption and the number of papers published in lay media (r = 0.92).

Using the search criteria, 35 TV communications (Table 1) and 1866 websites were found. In Table 1, the numbers of Quick Read CRP tests and rapid streptococcal antigen detection tests are shown. During 1997–2003 a constant increase in the use of CRP tests (from 36 240–27 890) and streptococcal antigen detection tests (from 9600–27 890) was observed. According to 2003 data, ~90% of CRP tests were used in primary care. There was considerable negative correlation between the number of diagnostic tests and antibiotic consumption (r = −0.73 for the CRP and −0.68 for the streptococcal antigen detection test).

In Figure 1, the consumption of co-amoxiclav is shown. If there had been no restrictions in June 2000 and the pre-restriction trend continued, the post-restriction cumulative consumption of this drug by the end of 2003 would have been higher by 11.58 DDD/1000 inhabitant-days. In Figure 2, the data for fluoroquinolones is shown. The cumulative decrease in fluoroquinolone consumption from mid-2000 to the end of 2003 was 1.59 DDD/1000 inhabitant-days.
In Table 2, the costs of restricted and non-restricted antibiotics during 1999–2003 are shown. During 1999–2003, a 22% decrease in co-amoxiclav outpatient costs was observed. The total outpatient antibiotic cost decreased by 8%. The decrease in outpatient antibiotic consumption was paralleled by a decrease in penicillin resistance in invasive S. pneumoniae isolates, with a lag time of 1 year as shown in Figure 3. A positive correlation between aminopenicillin consumption and pneumococcal non-susceptibility to penicillin was observed with a 1 year lag ($r = 0.59$).

In a 3 year pre-restriction period (1997–1999), there were nine cases of mastoiditis in children <15 years of age with an incidence rate of 2.35 cases per 100 000 patient-years. In the period 2001–2003, there were eight cases of mastoiditis, giving an incidence of 2.09 cases per 100 000. Thus, no increase in mastoiditis cases was observed in spite of reduced antibiotic consumption.

In Table 1, educational interventions, total antibiotic consumption and the use of rapid diagnostic tests in outpatients in Slovenia, 1996–2003.

<table>
<thead>
<tr>
<th>Year</th>
<th>AMOX/CA</th>
<th>FQ</th>
<th>LEV+MOX</th>
<th>non-R</th>
<th>PEN</th>
<th>AMP</th>
<th>MAC</th>
<th>Professional communications</th>
<th>lay articles</th>
<th>TV</th>
<th>CRP test</th>
<th>Streptococcal antigen test</th>
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<td>15.21</td>
<td>3.25</td>
<td>1.08</td>
<td>–</td>
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<td>2.79</td>
<td>6.07</td>
<td>2.14</td>
<td>11</td>
<td></td>
<td></td>
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</tr>
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<td>1997</td>
<td>17.99</td>
<td>3.55</td>
<td>1.29</td>
<td>–</td>
<td>13.15</td>
<td>3.00</td>
<td>7.02</td>
<td>2.84</td>
<td>11</td>
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<tr>
<td>1998</td>
<td>19.66</td>
<td>4.92</td>
<td>1.53</td>
<td>–</td>
<td>13.21</td>
<td>3.03</td>
<td>8.18</td>
<td>3.52</td>
<td>11</td>
<td></td>
<td></td>
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<tr>
<td>1999</td>
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<td>5.78</td>
<td>1.51</td>
<td>–</td>
<td>12.79</td>
<td>2.67</td>
<td>8.88</td>
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<td></td>
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<td>2000</td>
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<td>2.47</td>
<td>7.74</td>
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<tr>
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<td>1.26</td>
<td>0.0781</td>
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<td>7.41</td>
<td>3.16</td>
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<td></td>
<td></td>
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<tr>
<td>2002</td>
<td>16.33</td>
<td>4.27</td>
<td>1.315</td>
<td>0.1315</td>
<td>10.75</td>
<td>2.35</td>
<td>7.02</td>
<td>2.81</td>
<td>6</td>
<td></td>
<td></td>
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<td>2003</td>
<td>16.98</td>
<td>4.11</td>
<td>1.15</td>
<td>0.1318</td>
<td>11.72</td>
<td>2.59</td>
<td>7.32</td>
<td>2.98</td>
<td>10</td>
<td></td>
<td></td>
<td>184 450</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.30</td>
<td>7</td>
<td></td>
<td></td>
<td>92</td>
</tr>
</tbody>
</table>

AMOX/CA, co-amoxiclav; FQ, fluoroquinolones; LEV, levofloxacin; MOX, moxifloxacin; non-R, non-restricted antibiotics; PEN, narrow spectrum penicillin; AMP, aminopenicillins; MAC, macrolides; NA, not available; R, correlation with total antibiotic consumption.

### Discussion

In Table 2, the costs of restricted and non-restricted antibiotics during 1999–2003 are shown. During 1999–2003, a 22% decrease in co-amoxiclav outpatient costs was observed. The total outpatient antibiotic cost decreased by 8%. The decrease in outpatient antibiotic consumption was paralleled by a decrease in penicillin resistance in invasive S. pneumoniae isolates, with a lag time of 1 year as shown in Figure 3. A positive correlation between aminopenicillin consumption and pneumococcal non-susceptibility to penicillin was observed with a 1 year lag ($r = 0.59$).

In a 3 year pre-restriction period (1997–1999), there were nine cases of mastoiditis in children <15 years of age with an incidence rate of 2.35 cases per 100 000 patient-years. In the period 2001–2003, there were eight cases of mastoiditis, giving an incidence of 2.09 cases per 100 000. Thus, no increase in mastoiditis cases was observed in spite of reduced antibiotic consumption.
1999–2003, the reduction in consumption was higher for restricted antibiotics (27.9%) than for non-restricted antibiotics (8.4%) (Table 1). The post-restriction decrease for co-amoxiclav was 28.9 and 23.9% for fluoroquinolones. During 1999–2003, total antibiotic consumption decreased by 3.10 DDD/1000 inhabitant-days—one DDD for restricted and 1.07 DDD for non-restricted antibiotics. Thus a combination of educational and restrictive interventions seems to be more efficient than a single intervention. Based on interventions in hospitals, restrictive interventions are consistently more effective than educational ones. Educational interventions are of limited efficacy and the effects are temporary unless constantly reinforced. National strategic programmes for the control of resistance to antimicrobials have been initiated in various countries in Europe, Australia, Canada and the USA. These programmes include surveillance of antibiotic usage and resistance rates, optimizing antibiotic use including diagnostic tests and treatment guidelines, education of professionals and the public, and infection prevention (infection control and immunization). The data on efficacy of interventions designed to control outpatient antibiotic consumption are limited.

In Belgium, antibiotic sales decreased by 17 and 9% following two successive 3 month national public campaigns in 2000–01 and 2001–02, but the effect was transient, of 1 month duration. The Swedish strategic programme for the rational use of antimicrobial agents and surveillance of resistance (STRAMA), including many educational activities, reduced total antibiotic use by 0.5 DDD/1000 inhabitant-days between 2000 and 2003. Antibiotic sales (excluding methenamine) in the period 2000–03 were 13.7, 13.8, 13.3 and 13.0 DDD/1000/day, respectively. The important issue in the national programme is funding, which increased to €800 000 in 2003.

The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) was established in 1995 and coordinates national surveillance and research programmes in bacteria from animals, food and humans. The consumption of antibacterials in Denmark is low and stable. The total consumption of antibacterials increased from 12.24 DDD/1000 inhabitant-days in 1997 to 13.72 in 2003. The interventions used to maintain low consumption of antibiotics include auditing, the reimbursement of the use of rapid diagnostic tests such as group A streptococcal antigen test, lectures arranged by clinical microbiology laboratories and not by pharmaceutical companies, and the system of reimbursement.

No reduction in the prescription of antibiotics was seen in the study of the use of the CRP test at a primary level. The CRP test was cost effective mainly on the basis of a reduction in the use of hospital laboratory services by general practitioners. A recent retrospective study showed excessive use of CRP in patients with respiratory tract infections in Swedish primary healthcare. Higher CRP values were associated with a higher frequency of antibiotic prescribing. Antibiotics were prescribed in 21% of patients when the CRP value was <25 mg/mL and in 80% of cases when the CRP was >100 mg/L. Antibiotics were prescribed for 84% of lower respiratory tract infections with a CRP value >50 mg/L and in 43% of cases with a CRP value <50 mg/L. CRP has a diagnostic value in conjunction with other tests and physical findings and for monitoring response to therapy. If the implementation is followed by education and clinical guidelines, opportunities exist for a more appropriate use of antibiotics.

Antigen testing for group A streptococci is commonly used in Scandinavian countries. It may also add to the reduction of antimicrobial use. In a group of patients in whom a rapid streptococcal test was performed, 66.1% were prescribed an antibiotic compared with 83% of the group where no test was performed. In Finland, only 44% of patients with throat infection received

### Table 2. Costs (in million EUR) of total, non-restricted, restricted and individually for co-amoxiclav and fluoroquinolones in outpatients in Slovenia, 1999–2003

<table>
<thead>
<tr>
<th>Year</th>
<th>Total antibiotics</th>
<th>Non-restricted</th>
<th>Restricted</th>
<th>Co-amoxiclav</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>24 532 854</td>
<td>13 040 714</td>
<td>11 492 140</td>
<td>8 857 740</td>
<td>2 634 400</td>
</tr>
<tr>
<td>2000</td>
<td>23 402 267</td>
<td>13 104 159</td>
<td>10 298 108</td>
<td>7 733 471</td>
<td>2 564 637</td>
</tr>
<tr>
<td>2001</td>
<td>23 119 291</td>
<td>13 247 993</td>
<td>10 871 298</td>
<td>7 047 287</td>
<td>2 824 011</td>
</tr>
<tr>
<td>2002</td>
<td>22 157 156</td>
<td>12 092 338</td>
<td>10 064 818</td>
<td>7 066 059</td>
<td>2 998 759</td>
</tr>
<tr>
<td>2003</td>
<td>22 459 488</td>
<td>12 906 657</td>
<td>9 552 831</td>
<td>6 910 173</td>
<td>2 642 658</td>
</tr>
</tbody>
</table>

### Figure 3. Total outpatient of antibiotic use, penicillin resistance rates in invasive S. pneumoniae isolates and the annual number of mastoidectomies in children <15 years of age in the Ljubljana region (population 835 000).
antimicrobial treatment. In contrast, in Slovenia 74.8% of patients with throat infections are treated with antibiotics. In 2000, there were 346,899 episodes of acute tonsillopharyngitis in Slovenia, thus in only 3.5% of episodes was a streptococcal antigen test used. The influence of streptococcal antibiotic testing on antibiotic use is therefore marginal. There was a negative correlation between the number of streptococcal antigen tests and the consumption of narrow spectrum penicillins ($r = -0.60$), macrolides ($r = -0.47$) and aminopenicillins ($r = -0.36$).

Attempts to restrict or reduce the use of a single antibiotic or a whole class of antibiotics are more common in hospitals than in the community. In a recent study, an interventional policy for appropriate use of certain antibiotics was associated with a significant decrease in total use and cost of antibiotics, the reduction in costs far exceeding the costs of the programme itself. In contrast to developed countries, restrictive measures to decrease the outpatient use of antimicrobials are common practice in Central and Eastern Europe (CEE). In a recent review of antibiotic policies in CEE, restriction of antibiotic use was present in six of 16 countries. Restricted outpatient antibiotics are usually ‘expensive’ antibiotics such as the new fluoroquinolones, linezolid and others. The effects of outpatient antibiotic use restriction have not been evaluated yet. These effects can be cost effective, but because of relatively low consumption of restricted class(es) the reduction of total consumption is low. In our country, the reduction of co-amoxiclav was 1.66 DDD and the reduction of fluoroquinolones was 0.36 DDD/1000 inhabitant-days.

The data on mastoidectomies performed showed no difference in the two observation periods, indicating that the reduction of outpatient antibiotic consumption was not accompanied by an increase in the incidence of acute mastoiditis. In a comparative study across several European countries, Canada, Australia and the USA the incidence rate of acute mastoiditis was higher in the Netherlands (3.8/100,000 patient-years in children aged 14 years and younger) with low antibiotic prescription rate for acute otitis media compared with other countries with a higher antibiotic prescription rate (e.g. between 1.2–2.0/100,000 patient-years for the UK, Canada, Australia and the USA). On the other hand it should be noted that in the year 1999 the Hib vaccination programme was introduced in Slovenia, probably compensating for the decreased use of antibiotics.

The present retrospective study showed that short-term restrictive measures could be effective in reducing the consumption of antibiotics in the community. It is not clear how much the increased use of diagnostic tests and educational measures add to the reduction. The most effective approach for improving antimicrobial use is probably a combination of many interventions, which should be supported by government and regulatory institutions.

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