Chapter 14

Antibiotic Policy—Slovenian Experiences

Milan Čižman and Bojana Beović
Department of Infectious Diseases, University Medical Centre Ljubljana, Japljeva 2, 1525 Ljubljana, Slovenia

1. INTRODUCTION

Antibiotic resistance is increasing worldwide. Infections with resistant organisms have been associated with treatment failures, higher morbidity and mortality, and increased cost. In Slovenia, antibiotic resistance has become a serious healthcare issue both in hospitals and in the community. *Streptococcus pneumoniae* is becoming increasingly resistant to penicillin (20% in 2001) and erythromycin (13% in 2001). The resistance of *Streptococcus pyogenes* to erythromycin (7% in 2001) is increasing year by year. High resistance rates to fluoroquinolones have been observed recently in *Escherichia coli* and *Campylobacter* sp. isolates (10–15% and 45%, respectively in 2001). The problem of methicillin resistant *Staphylococcus aureus* in hospitals appears to be moderate and is stable or decreasing (20% in 2001). In 2001, the resistance of *Pseudomonas aeruginosa* to fluoroquinolones and to carbapenems was 30% and 10%, respectively (Mueller-Premru *et al*., 2002). Antibiotic utilization patterns and the impact of antibiotic policy measures in the community and in hospitals in Slovenia are presented and discussed.

2. COUNTRY AND REIMBURSEMENT

Slovenia is a small central European country with 1,992,035 million inhabitants according to the census in 30 June 2001. Almost all inhabitants (>99%)

Antibiotic Policies: Theory and Practice. Edited by Gould and van der Meer
Kluwer Academic / Plenum Publishers, New York, 2005

have compulsory insurance. Over 1 million people have additional insurance. Medicinal products are grouped in three categories: the so-called positive list, the intermediary (semi-reimbursed) list, and the negative list. Generally, compulsory insurance covers 75% of the price of a medicinal product from the positive list and 25% of the price of a product from the intermediary list. Compulsory insurance also covers the full cost of medicinal products from the positive list for children, young people up to 18 years of age, students, handicapped individuals, and persons suffering from contagious diseases, as well as the full cost of drugs and other medicinal products from the intermediary list for children, young people, students, and handicapped individuals. Additional insurance covers the difference to 100% of the price for medicinal products from the positive and intermediary lists for other citizens. Most antibiotics are on the positive list.

3. NATIONAL ANTIBIOTIC POLICY

Slovenia does not have a national expert committee on antibiotic policies, in contrast with some other Eastern European countries (Krcmery *et al*., 2000). A prescription is needed for every antibiotic purchase, and in human medicine, antibiotics may only be prescribed by physicians. Since there is no national expert committee, the existing guidelines, both for hospitals and primary care, have been developed by hospital committees and/or individuals (Čižman and Beović, 2002; Čižman and Marolt, 1998).

3.1. Ambulatory care

The consumption of antibiotics in ambulatory care has been monitored in Slovenia since 1974. All pharmacies in the country are involved in the monitoring process. Data on the number of packages and the cost of antibiotics purchased, the age and gender of the patients, and the identity numbers of the physicians and healthcare institutions prescribing antibiotics are collected and analysed (Oražem and Milovanovič, 1996).

In the 1980s, the number of prescriptions for all antimicrobial agents for systemic use, including antibacterials, antifungals, antivirals, and antiparasitic drugs, was between 770 and 860 per 1,000 inhabitants per year. Antibacterial drugs represented 95% of all antimicrobial products. Antimicrobial agents in turn accounted for 12.2–14.5% of all prescriptions and were the second most commonly prescribed group of medicinal products. Extended-spectrum penicillins were the most commonly prescribed class of antibiotics (36–39%), followed by narrow-spectrum penicillins (18–24%), trimethoprim/sulfamethoxasol

(TMP/SMX) and sulfonamides (13–19%), and tetracyclines (9–12%). Over the decade, a decline in the use of narrow-spectrum penicillins, tetracyclines, and TMP/SMX was observed, accompanied by an increase in the use of extended-spectrum penicillins, cephalosporins, and at the end of the decade, macrolides (roxithromycin, azithromycin) (Marolt-Gomišček and Čižman, 1992).

In the first half of the 1990s, the proportion of antimicrobial prescriptions increased to 16% (Oražem and Milovanovič, 1996). The consumption of macrolides, quinolones, cephalosporins, and extended-spectrum penicillins increased steadily, while the number of prescriptions for sulfonamides (including combinations), narrow-spectrum penicillins and tetracyclines declined (Oražem and Milovanovič, 1996). Amoxicillin (20%) was the most commonly prescribed antibacterial agent, followed by amoxicillin/clavulanic acid (16.5%), narrow-spectrum penicillins (16.2%), TMP/SMX (11.7%), and azithromycin (7.2%). Cefaclor (2.7% of all antibacterials) was the most commonly prescribed cephalosporin and ciprofloxacin the most common fluoroquinolone (1.0%).

From 1996 to 1999, the total consumption of antibacterials in Slovenia increased by 39%, attaining 19.8 DDD/1,000 inhabitants/day in 1999 (Čižman *et al*., 2003). The consumption of tetracyclines, narrow-spectrum penicillins, TMP/SMX, cephalosporins, lincosamides, and extended-spectrum penicillins decreased, but the consumption of combinations of penicillins with β-lactamase inhibitors (amoxicillin/clavulanic acid), macrolides, and fluoroquinolones increased significantly. The increased use of macrolides and fluoroquinolones was associated with the emergence of resistance in *S. pyogenes, S. pneumoniae*, and *E. coli* (Čižman *et al*., 1999; Čižman *et al*., 2000; Čižman *et al*., 2001a, b; Čižman *et al*., 2002).

In 1990, the Health Insurance Company in collaboration with infectious diseases (ID) specialists decided to restrict the use of amoxicillin/clavulanic acid and cephalosporins to cases where penicillin or TMP/SMX had proved ineffective or the prescription was based on susceptibility testing (Fürst, 2001). Fluoroquinolones were to be used only as sequential therapy in patients after discharge from hospital. Because of a steady increase in the consumption of amoxicillin/clavulanic acid and fluoroquinolones, the health insurance company imposed further restrictions on the use of these two antibacterial classes in 1999. Amoxicillin/clavulanate could no longer be prescribed for patients with *S. pyogenes* infections, and fluoroquinolones could only be given as an alternative treatment for acute respiratory and urinary tract infections (after clinical failure of other antibiotics), or on the basis of susceptibility tests showing sensitivity to quinolones and resistance to other antibiotics.

In 2001, the total outpatient consumption of antibiotics declined to 17.4 DDD/1,000 inhabitants/day, but still remained 36% higher than in Denmark and 21% higher than in Sweden over the same period (ESAC, 2003). The pattern of use of antibiotics in Slovenia in 2001 is shown in Table 1. The decline in

Table 1. The pattern of antimicrobial use in Slovenia in 2001

Antibiotic group	Ambulatory care %	Hospital care %
Tetracyclines	4.42	1.13
Chloramphenicols	0.00	0.01
Penicillins	58.79	43.24
Cephalosporins	2.98	18.55
Macrolides	18.16	6.57
Lincosamides	0.63	2.90
TMP/SMX	6.89	3.42
Aminoglycosides	0.00	4.68
Quinolones	7.58	13.65
Others	0.00	5.18
Total use in DDD/1,000 inhabitants/day	17.4	1.80

consumption may be attributed to the measures imposed by the health insurance company as well as to the educational efforts of ID physicians aiming to raise the awareness of general practitioners about appropriate prescribing of antibiotic drugs.

3.2. Hospital antibotic policy

In 2001, a total of 335,557 patients were admitted to 27 hospitals (1 tertiary care centre with 4 hospitals, 11 general hospitals and 12 special hospitals including psychiatric hospitals and rehabilitation centres). The mean length of hospital stay was 8.3 days and the total number of bed-days was 2,773,164 (Institute of Public Health of the Republic of Slovenia, 2002).

Almost every hospital in Slovenia has a therapeutic committee (TC). Antibiotic committees, composed of ID physicians and other specialists, have been founded in all larger hospitals over the past 20 years. The multidisciplinary composition of antibiotic committees ensures that the antibiotic policy is influenced and accepted by the different specialities in the institution. In hospitals, all antibiotics registered in the country are usually available. Unregistered antibiotics can only be purchased by request to the TC of the University Medical Centre Ljubljana (UMC), which is the only tertiary care centre in the country. In 1998, the antibiotic committee of the UMC published guidelines, which were later adopted by many other hospitals in Slovenia (Čižman and Marolt, 1998). They include recommendations on empiric therapy, documented therapy, and prophylaxis of common community- and hospital-acquired infections. The dosage, length of treatment, and cost are included as well.

Since 1998, lists of so-called restricted antibiotics have been drawn up in several hospitals. In General Hospital Celje, antimicrobial agents are divided into four groups with different levels of restriction (Šibanc *et al*., 2002).

At the University Medical Centre Ljubljana, a list of restricted antimicrobials has been maintained since 1999. At the beginning it included 12 antimicrobial agents: ceftazidime, cefoperazone, cefpirome, imipenem, meropenem, aztreonam, vancomycin, teicoplanin, amikacin, tobramycin, chloramphenicol, and lipid forms of amphotericin B. In all hospital departments except intensive care, hemato-oncology, and surgical infection units, the use of any drug from the list is subject to authorization by an ID specialist. Piperacillin-tazobactam and cefepime were added to the list after being registered in 2001 and 2002. Several other hospitals follow the pattern of restriction applied in Ljubljana.

Slovenia participates in the ESAC (European Surveillance of Antimicrobial Consumption) project. Table 2 shows the consumption of antibacterials in Slovenian hospitals from 1985 to 2001, including the data collected for the ESAC project (Čižman *et al*., 2003).

The data presented in Table 2 show an increase in the total use of antibacterials and specifically an increase in the use of combinations of penicillins and β-lactamase inhibitors (especially amoxicillin/clavulanic acid), cephalosporins, carbapenems, macrolides, lincosamides, fluoroquinolones, and some other antibacterials including glycopeptides. On the other hand, the consumption of narrow-spectrum penicillins, tetracyclines, amphenicols, and TMP/SMX decreased as in ambulatory care. Excluding all psychiatric hospitals and rehabilitation centres, the total consumption of antibacterials in Slovenia in the years 1998–2001 was between 48.28 and 50.60 DDD/100 bed-days (data covering annually 89–100% of bed-days).

A trend towards an increased use of systemic antibacterials has been observed in many countries. The consumption per 100 bed-days in the Netherlands increased from 37.2 DDD in 1991 to 42.5 DDD in 1996 (Janknegt, *et al*., 2000), and in Denmark from 39.24 in 1997 to 42.8 DDD in 1999 (Danmap, 2000). In the Netherlands, the data covered over 70% of all hospital bed-days and in Denmark 95% of all bed-days (excluding psychiatric hospitals, private hospitals, and one rehabilitation centre).

In Slovenian hospitals, the consumption of antibacterials for systemic use in 2001 was 20% higher than in Denmark and Sweden (Sørensen and Monnet, 2002; Strama, 2001). The total consumption per 100 bed-days varied considerably between hospitals: in maternity hospitals it was between 23 and 29 DDD, in general hospitals between 38 and 69 DDD, in the tertiary care centre around 65 DDD, in special hospitals (orthopaedic surgery, oncology, pulmonology) it ranged from 20 to 100 DDD, in psychiatric hospitals from 3 to 13 DDD, and in rehabilitation centres from 5 to 13 DDD. In general hospitals, the utilization of

Table 2. Use of antibacterials in Slovenian hospitals (in DDD/100[a] bed-days)

ATC group	Therapeutic group	1985	1990	1995	2000	2001
J01AA	Tetracyclines	3.972	2.139	1.073	0.5853	0.5384
J01B	Amphenicols				0.0075	0.0057
J01C	Penicillins	25.138	21.801	22.844	20.9451	20.5057
J01CA	Penicillins with extended spectrum	13.374	0.076	3.386	1.6420	1.5414
J01CE	β-lactamase sensitive penicillins	10.500	8.529	6.443	2.4295	2.6498
J01CF	β-lactamase resistant penicillins	1.264	0.916	0.512	1.3941	1.5416
J01CR	Combinations of penicillins, including β-lactamase inhibitors	0.000	3.280	12.500	15.4795	14.7729
J01DA	Cephalosporins	4.672	6.546	8.576	9.5900	8.7981
J01DF	Monobactams	0.000	0.000	0.002	0.0003	0.0004
J01DH	Carbapenems	0.000	0.071	0.189	0.2495	0.2931
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	3.572	2.738	2.051	2.0204	1.6251
J01FA	Macrolides	1.195	1.959	2.981	3.5181	3.1178
J01FF	Lincosamides	0.355	0.440	0.913	1.2902	1.3753
J01GB	Aminoglycosides	2.841	2.318	2.718	2.2910	2.2192
J01MA	Fluoroquinolones	0.000	2.597	3.537	5.8517	6.4751
	Others	0.128	0.0509	1.246	2.3520	2.4579
J01	Total antibacterials for systemic use	42.148	41.326	46.345	48.4123	47.4119

[a]ATC/DDD classification, WHO version, 2001.

individual antibiotic classes varied significantly from one hospital to another. As it seems unlikely that these big differences between hospitals only reflect differences in morbidity from bacterial infections, other explanations must be sought.

In Slovenia, penicillins are the most commonly prescribed class of antibiotics (43%), followed by cephalosporins (18.5%), fluoroquinolones (13.6%), macrolides (6.5%), and other drugs, mainly metronidazole (1.8 DDD/100 bed-days), and glycopeptides (0.6 DDD/100 bed-days) (Table 2). In the Netherlands and Denmark, penicillins are prescribed more widely than in Slovenia (57%), followed by cephalosporins (8–12%), fluoroquinolones (5–8%), and aminoglycosides (4–5%). The situation in the United Kingdom is similar to that in the Netherlands and Denmark (Standing Medical Advisory Committee, 1998). In Sweden, after penicillins, the most widely used group of antibiotics

in 2001 were cephalosporins with 0.24 DDD/1,000 inhabitants per day (17%), followed by fluoroquinolones with 0.19 DDD/1,000 inhabitants per day (14.6%) (Strama, 2002).

4. ANTIBIOTIC POLICY IN THE TERTIARY CARE CENTRE

The University Medical Centre Ljubljana (UMC) is the only tertiary care centre in Slovenia. In 2001 the UMC had 2,455 beds and admitted 82,594 patients, who stayed in hospital for a total of 582,745 bed-days, the average length of stay being 7.0 days. An open drug formulary is used for all drugs in the centre.

In the period from 1995 to 1997, the consumption of antibacterial drugs in the UMC (including psychiatric units which accounted for approximately 25% of bed-days) increased by 5.9%, attaining 43.68 DDD/100 bed-days in 1997 (Vižintin and Čižman, 1998). β-lactam agents were the most commonly used antimicrobials (53%), followed by macrolide and lincosamide antibiotics (13%), and quinolones (12%) (Vižintin and Čižman, 1998). In most units, a trend towards increasing use of macrolides, lincosamides, and quinolones was associated with a marked decline in the use of tetracyclines and amphenicols.

The utilization of some problem antibiotics in the UMC has been regulated since 1998. The original list of so-called restricted agents, drawn up by the antibiotic committee, included 11 antibacterials and 1 antifungal drug (lipid associated forms of amphotericin B). Any drug from the list may be prescribed only on approval of ID or a few members of the antibiotic committee. A special order form, including data on the patient, type of infection or prophylaxis, and dosage is used for these drugs. Exceptionally, the use of an antibiotic from the list may be approved by telephone on the basis of previous consultation. The utilization of these antibiotics in individual hospital departments is monitored by a team of two ID doctors. Several departments may be covered by one team. Other common measures such as stop orders, systematic education of physicians, auditing, computer guided prescription, or rotation of antibiotics (Gould, 1999, 2002; Keuleyan and Gould, 2001; Struelens *et al*., 1999; van der Meer and Gyssens, 2001; Wilton *et al*., 2002) have not been used in the UMC. Unfortunately, the hospital management shows inadequate understanding of problems of antibiotic consumption and bacterial resistance and so most of the work in this field is done on a voluntary basis by a handful of enthusiasts. The consumption of antibacterials in the UMC from 1998 to 2002 is presented in Figure 1.

The data in Figure 1 show a 9% increase in the total consumption of antibacterials (from 58.91 to 64.31 DDD/100 bed-days) in the period from 1998 to 2002. The highest increase was observed in fluoroquinolones (64%),

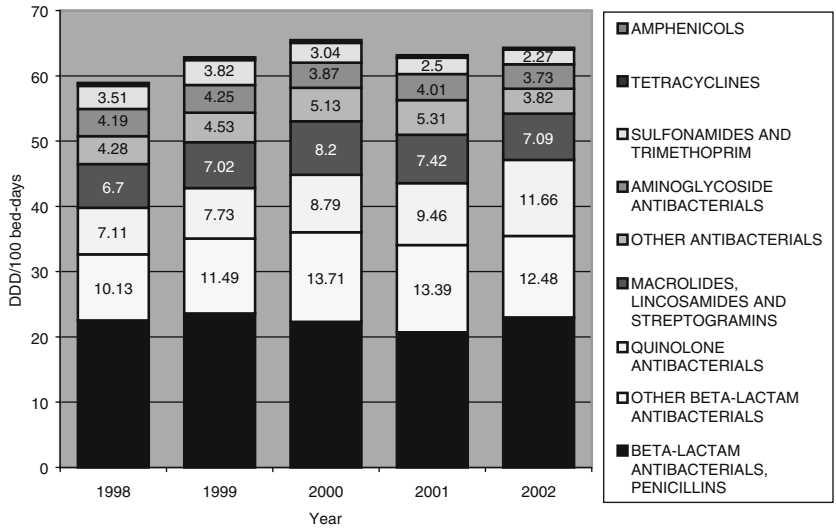

Figure 1. Consumption of antibiotics in the UMC Ljubljana (DDD/100 bed-days)

followed by macrolides and lincosamides (9%), and other β-lactam antibacterials (33%). The consumption of penicillins was stable, whereas the consumption of other antibacterials, aminoglycosides, TMP/SMX, tetracyclines, and amphenicols decreased. The consumption of restricted antibiotics varied from 2.93 DDD/100 bed-days in 1998 to 2.77 DDD/100 bed-days in 1999, 3.76 DDD/100 bed-days in 2001, and 3.39 DDD/100 bed-days in 2002. In the same period, the average length of hospital stay declined from 7.9 days in 1998 to 7.3 days in 2002. Since restricted antibacterials accounted for only 5% of all antibiotic consumption in the centre, the institution of restrictive measures for this group of antibiotics could not influence significantly the total consumption of antibitiotics in the hospital. Consequently, a decrease in the total use of antibiotics was observed only in a few departments where ID specialists were responsible for the treatment of all bacterial infections (Beović *et al*., 2003). On the other hand, restricted antimicrobials represent approximately a third of the total cost of antimicrobial agents in the centre. Therefore the restrictions may be expected to have a significant financial impact, besides helping to reduce the development of resistant organisms (White *et al*., 1997).

5. CONCLUSION

The consumption of antibiotics in Slovenia is moderate. At the national level, antibiotic consumption has decreased over the past 2 years both in outpatient and

inpatient settings. The resistance rates in some common community pathogens are moderate but show a tendency to increase. The problem of methicillin resistant *S. aureus* is stable and decreasing. The restrictive measures imposed by the health insurance company, along with the educational efforts of ID specialists have had a major role in reducing the consumption in outpatient settings. In hospitals, effective collaboration of ID specialists with microbiologists, hospital pharmacists, and departmental staff is often impossible due to inadequate awareness of the problem on the part of the management team.

REFERENCES

Beović, B., Matos, B., Bošnjak, R., Seme, K., Mueller-Premru, M., Hergouth-Križan, V. *et al*., 2003, Prevention of nosocomial lower respiratory tract infections in patients after intracranial artery aneurysm surgery with a short course of antimicrobials. *Int. J. Antimicrob. Agents*, **21**.

Černelč, V., 2002, Utilization review of systemic antimicrobials in Slovene hospitals. *Med. Razgl.*, **41**(Suppl.), 43–42.

Čižman, M. and Beovič, B., 2002, Priročnik za ambulantno predpisovanje protimikrobnih zdravil. Arkadia.

Čižman, M. and Marolt, M., 1998, Priporočila za uporabo protimikrobnih zdravil KC 1998. Komisija za antibiotike v KC, Klinični center, Sekcija za kemoterapijo SZD.

Čižman, M., Oražem, A., Križan-Hergouth, V., and Kolman, J., 2001a, Correlation between increased consumption of fluoroquinolones in outpatients and resistance of *Escherichia coli* from urinary tract infections. *J. Antimicrob. Chemother.*, **47**, 502.

Čižman, M., Pečar-Čad, S., Stefancic, M., Elseviers, M., Ferech, M., Van der Stichele, R. *et al*. 2003, Consumption of antibiotics in Slovenia, first results of the ESAC retrospective data collection. ESCMID Meeting, Glasgow.

Čižman, M., Pokorn, M., Paragi, M., and the Slovenian Meningitis Study Group, 2002, Antimicrobial resistance of *invasive Streptococcus pneumoniae* in Slovenia from 1997 to 2000. *J. Antimicrob. Chemother.*, **49**, 582–584.

Čižman, M., Pokorn, M., Seme, K., and Oražem, A., 2001b, The relationship between trends in macrolide use and resistance to macrolides of common respiratory pathogens. *J. Antimicrob. Chemother.*, **47**, 475–477.

Čižman, M., Pokorn, M., Seme, K., Paragi, M., and Oražem, A., 1999, Influence of increased macrolide consumption on macrolide resistance of common respiratory pathogens. *Eur. J. Clin. Microbiol. Infect. Dis.*, **18**, 522–524.

Danmap, Danmap 2000-Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. ISSN 1600-2032.

ESAC—European Surveillance of Antimicrobial Consumption, 2002, Interim report, November 2001–2, 51–76.

Fürst, J., 2001, Primerjava uporabe zdravil v otroški dobi v Sloveniji in Skandinaviji. In C. Kržišnik and T. Battelino (eds.), *Izbrana poglavja iz pediatrije*. Medicinska fakulteta Univerze v Ljubljani, Katedra za pediatrijo, pp. 71–76.

Gould, I. M., 1999, Stewardship of antibiotic use and resistance surveillance: the international scene. *J. Hosp. Infect.*, **43**(Suppl.), 253–260.

Gould, I. M., 2002, Antibiotic policies and control of resistance. *Curr. Opin. Infect. Dis.*, **15**, 395–400.

Institute of Public Health of the Republic of Slovenia. Health Statistical Year Book, 2002, Hospital treatment of diseases.

Janknegt, R., Lashof, A. O., Gould, I. M., and van der Meer, J. W. M., 2000, Antibiotic use in Dutch hospitals 1991–1996. *J. Antimicrob. Chemother.*, **45**, 251–256.

Keuleyan, E. and Gould, I. M., 2001, Key issues in developing antibiotic policies: From an institutional level to Europe-wide, European Study Group on Antibiotic Policy (ESGAP), Subgroup III. *Clin. Microbiol. Infect.*, **7**, 16–21.

Krcmery, V., Jeljaszewicz, J., Grzesiowski, P., Hryniewicz, W, Metodiev, K., Stratchounski, L. *et al*., 2000, National and local antibiotic policies in central and eastern Europe. *J. Chemother.*, **12**, 471–474.

Marolt-Gomišček, M. and Čižman, M., 1992, The usage of antibiotics for outpatients and recommendations for the treatment of bacterial infections. *Zdrav. Vestn.*, **61**, 403–406.

Mueller-Premru, M., Seme, K., Križan-Hergouth, V., Andlovic, A., Kolman, J., and Gubina, M., 2002, Trends of bacterial resistance at the University Medical Center in Ljubljana. *Med. Razgl.*, **41**(Suppl. 2), 25–34.

Oražem, A. and Milovanovič, M., 1996, Out-patient prescribing of antibacterials for systemic use in Slovenia. *Med. Razgl.*, **35**(Suppl. 1), 1–11.

Sørenson, L. T., and Monnet, D., 2002, Control of antibiotic use in the community: The Danish experience. *Infect. Control Hosp. Epidemiol.*, **21**, 387–389.

Standing Medical Advisory Committee, 1998, Subgroup on Antimicrobial Resistance, the path of least resistance. Department of Health http://www.doh.gov.uk/smac.thm

Struelens, M. J., Byl, B., and Vincent, J. L., 1999, Antibiotic policy: A tool for controlling resistance of hospital pathogens. *Clin. Microbiol. Infect.*, **5**(Suppl.), 19–24.

Šibanc, B., Lešničar, G., and Tratar, F., 2002, Results of controlled antimicrobial treatment at the Celje general hospital between 1995–2000. *Med. Razgl.*, **41**(Suppl.), 53–60.

The Swedish Strategic Programme for the rational use of antimicrobial agents (Strama), 2001, O. Cars K. Ekdahl (eds.) Swedres 2001, A report on Swedish antibiotic utilisation and resistance in human medicine. The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA) and the Swedish Institute for Infectious Disease Control, 23–26.

Van der Meer, J. W. M. and Gyssens, I. C., 2001, Quality of antimicrobial drug prescription in hospital. *Clin. Microbiol. Infect.*, **7**(Suppl. 6), 12–15.

Vižintin, T. and Čižman, M., 1998, Antimicrobial usage and trends in the University Medical Centre in Ljubljana from 1995 to 1997. *Zdrav. Vestn.*, **67**, 721–725.

White, A. C. Jr., Atmar, R. L., Wilson, J., Cate, T. R., Stager, C. E., and Greenberg, S. B., 1997, Effects of requiring prior authorization for selected antimicrobials: Expenditures, susceptibilities, and clinical outcomes. *Clin. Infect. Dis.*, **25**, 230–239.

WHO Collaborating Centre for Drug Statistics Methodology, 2001, Guidelines for ATC classification and DDD assignment. Oslo.

Wilton, P., Smith, R., Coast, J., and Millar, M., 2002, Strategies to contain the emergence of antimicrobial resistance: A systematic review of effectiveness and cost-effectiveness. *J. Health Serv. Res. Policy*, **7**, 111–117.