

## Benchmarking antimicrobial drug use at university hospitals in five European countries

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### ABSTRACT

A point-prevalence survey of five European university hospitals was performed to benchmark antimicrobial drug use in order to identify potential problem areas in prescribing practice and to aid in establishing appropriate and attainable goals. All inpatients at the university hospitals of Rijeka (Croatia), Tartu (Estonia), Riga (Latvia), Vilnius (Lithuania) and Karolinska-Huddinge (Sweden) were surveyed for antimicrobial drug use during a single day. The frequency of antimicrobial drug use was 24% in Rijeka, 30% in Tartu, 26% in Riga, 14% in Vilnius and 32% in Huddinge. Surgical patients were treated with antimicrobial agents more often than medical patients in Riga (53% vs. 31%), Tartu (39% vs. 26%) and Vilnius (54% vs. 25%). Two-thirds of patients in Rijeka, Tartu, Riga and Vilnius, and fewer than half of the patients in Huddinge, received antimicrobial agents intravenously. Broad-spectrum antimicrobial agents were used most commonly in Rijeka. The prevalence of nosocomial infections treated with antibiotics was 9% at Huddinge, and 3–5% at the other centres. Benchmarking antimicrobial drug use at five university hospitals identified differences and problem areas. The high rates of intravenous administration, poor compliance with guidelines, and prolonged surgical prophylaxis were general problems that deserved specific attention at all centres. A change in prescription practices may reduce unnecessary drug use and decrease antimicrobial resistance.

**Keywords** Antimicrobial agents, benchmarking, European hospitals, nosocomial infections, point-prevalence survey, prescribing habits

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### INTRODUCTION

It has been estimated that 30–50% of hospitalised patients receive antimicrobial agents, and that up

to 50% of prescribed antimicrobial agents are not prescribed optimally [1–4]. It has been recognised generally that bacterial resistance is an unavoidable consequence of antimicrobial drug use, and that it correlates with the overall use of antimicrobial drugs in a defined setting [5–8]. Factors that promote the emergence of resistance include frequent use of broad-spectrum antimicrobial agents, prolonged use of antimicrobial agents,

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more frequent use of invasive devices and procedures, large numbers of patients with complex medical problems in small areas within a hospital, and the presence of patients who require prolonged hospitalisation and often harbour antibiotic-resistant bacteria [9]. The aim of the present study was to benchmark the pattern of antimicrobial drug use at five European university hospitals.

## MATERIALS AND METHODS

### Setting

The study was carried out at five European university hospitals of similar size in Croatia, Estonia, Latvia, Lithuania and Sweden during the year 2003 (Table 1). The University Hospital Rijeka (Croatia) comprises departments covering all major specialties. Renal transplantation is performed in the surgical department, but bone marrow, heart and liver transplantations are not performed. The Tartu University Hospital (Estonia) includes all major medical and surgical specialties, including transplantations (kidney, liver and bone marrow). The Stradins University Hospital in Riga (Latvia) is the only referral hospital in Latvia for cardiac surgery and renal transplantation. The Vilnius University Hospital (Lithuania) includes all major specialties, except neurosurgery, orthopaedic surgery and traumatology, infectious diseases and obstetrics. Bone marrow, renal and heart transplantations are performed at this hospital. Tuberculosis patients are not generally treated in this hospital. The Karolinska University Hospital, Huddinge (Sweden) includes all major specialties, except neurosurgery, and has a transplantation centre.

### Guidelines for antimicrobial drug use/infection control programmes

In Rijeka, restricted release of antimicrobial agents has been implemented as a method to improve antimicrobial drug use. Amikacin, carbapenems, third- and fourth-generation cephalosporins, amoxicillin-clavulanic acid (co-amoxiclav), glycopeptides, linezolid and piperacillin-tazobactam can be dispensed by the hospital pharmacy only on receipt of an order form signed by a chief physician. Recommendations for surgical prophylaxis are provided, with cefazolin being the main agent. While a Drug and Therapeutics Committee (DTC) releases guidelines and recommendations for anti-

microbial drug use, there is no formal infection control programme. Occasional lectures are given concerning rational antimicrobial drug use as part of continuing medical education.

In Tartu, the restricted release antimicrobial agents include cefazolin and cefoxitin, which may be used only for surgical prophylaxis. The antibiotic formulary is approved by the DTC. An infection control department is responsible for guidelines concerning rational antimicrobial drug use. Lectures on the rational use of antimicrobial agents are given by the infection control doctors.

In Stradins, Riga, a restricted release list of antimicrobial agents includes amikacin, ampicillin-sulbactam, cefepime, ceftazidime, chloramphenicol, intravenous clindamycin, imipenem, linezolid, meropenem, piperacillin-tazobactam, rifampicin, intravenous trimethoprim-sulphamethoxazole and vancomycin. These agents may be prescribed only by an infectious disease consultant or following approval by the medical director. In the intensive care unit, any antimicrobial agent can be prescribed without restrictions. Guidelines for surgical prophylaxis have been developed with the assistance of an infectious disease consultant. The antibiotic formulary is reviewed by the DTC at the beginning of each year. There is no specific educational programme concerning rational antimicrobial drug use.

In Vilnius, a restricted release list of antimicrobial agents includes amikacin, carbapenems, third- and fourth-generation cephalosporins, linezolid, piperacillin-tazobactam and vancomycin. These agents may only be prescribed after consultation with a clinical pharmacologist or following approval by the medical director. Some surgical departments have their own guidelines for surgical prophylaxis, which were developed in collaboration with a microbiologist and a clinical pharmacologist. The hospital pharmacy supplies departments with any drug from the recommended list. Occasional lectures on rational antimicrobial drug use are given in some departments.

At the Karolinska-Huddinge hospital, the DTC has formulated a list of recommended antimicrobial agents for hospital use. In addition, many clinics have their own guidelines for treatment and prophylaxis, many of which were developed in collaboration with a consultant in infectious diseases. There are no restrictions on the prescription of antimicrobial agents. Educational activities in rational antimicrobial drug use take place within an infection control programme that began in the year 2000 [10].

### Study methodology

A modified point-prevalence study design was used; all wards in each centre were surveyed once during one day in May 2003. The charts of all hospitalised patients who received an antimicrobial agent (ATC codes J01 and J04, classified according to WHO ATC/DDD Index 2003) [11] were reviewed, and the clinical data were recorded anonymously in a patient-specific protocol [10]. The data were collected in Rijeka by physicians during their internship, supervised by a specialist in clinical pharmacology, in Tartu by two specialists in infectious diseases, in Riga by an infectious disease consultant and an infection control nurse, in Vilnius by a clinical pharmacologist and an infection control specialist, and in Huddinge by an infectious disease consultant/hospital epidemiologist and an infectious diseases nurse [12].

**Table 1.** Demographical data for the participating hospitals

	No. of beds	No. of patients	Occupancy rate (%)	Primary catchment area (population)
University Hospital, Rijeka	1191	938	78.8	340 000
Tartu University Hospital	929	745	80.2	400 000
Stradins University Hospital, Riga	1037	927	89.4	900 000
Vilnius University Hospital	1000	876	87.6	1 500 000
Karolinska University Hospital, Huddinge	761	652	85.7	300 000

The main purpose of antimicrobial drug use was classified as treatment, medical or surgical prophylaxis, or unclear (with insufficient data in the medical record).

Departments were grouped as 'medical' (cardiology, endocrinology, gastroenterology, haematology, infectious diseases, medical admission, neonatology, nephrology, neurology, paediatrics, pulmonology and rheumatology), 'surgical' (abdominal surgery, cardiac surgery with intensive care unit, gynaecology, neurosurgery with intensive care unit, orthopaedics, paediatric surgery, plastic surgery, stomatological surgery, surgical admission, endocrinology surgery, thoracic surgery, transplantation, urology and vascular surgery) or 'other' (dermatovenerology, general intensive care, paediatric intensive care, geriatrics, obstetrics, oncology, ophthalmology, otorhinolaryngology and rehabilitation). Tuberculosis was treated at the department of pulmonology in Rijeka, at a specialised department, classified as 'other', in Tartu, and at medical and surgical departments in Huddinge. Tuberculosis patients are not generally treated at Stradins hospital, Riga, or Vilnius hospital, Lithuania.

In order to focus on the bulk (90%) of the prescriptions, the pattern of antimicrobial drug use was presented as drug utilisation 90% (DU90%) profiles [13,14]. The number of days of hospitalisation before use of antimicrobial agents were compared at admission, 1–2 days after admission, and >2 days after admission. For patients who received treatment, the frequency of consultation with infectious disease specialists was determined at each centre, as well as whether the indication for an antimicrobial drug was documented in the medical record, and whether the choice of antimicrobial agent was based on susceptibility testing. The source of infection was categorised as hospital- or community-acquired. A hospital-acquired infection was defined as an infection that appeared  $\geq 48$  h after admission, and a community-acquired infection

was defined as an infection that appeared within 48 h of hospital admission [15]. The type of infection was classified according to the main organ systems affected. Neither the necessity nor appropriateness of antimicrobial drug use, nor the correctness of the diagnoses, was evaluated in this study. Statistical evaluation of data was performed using Statistica v.6.0 software (StatSoft Inc., Tulsa, OK, USA). The comparisons were made using appropriate statistical tests with a significance level of  $p < 0.05$ . The study assembled anonymous structured data from antibiotic utilisation and infection control programmes as part of hospital quality assessments, and did not require ethical approval.

## RESULTS

There was no significant difference in the gender distribution of patients among the different hospitals (Pearson chi-square test,  $p$  0.145), or in the age (K-W ANOVA,  $p$  0.143). Overall, 1025 of 4138 patients admitted received antimicrobial agents, with frequencies of 24.2% in Rijeka, 30.3% in Tartu, 25.9% in Riga, 14.4% in Vilnius and 31.6% in Huddinge. The percentage of patients receiving antimicrobial agents was higher in medical departments in Rijeka and Huddinge, but higher in surgical departments in Tartu, Riga and Vilnius (Fig. 1). More than one antimicrobial agent was prescribed to 21% of patients in Rijeka, 35% in Tartu, 24% in Riga, 17% in Vilnius, and 24% in Huddinge. The number of antimicrobial agents

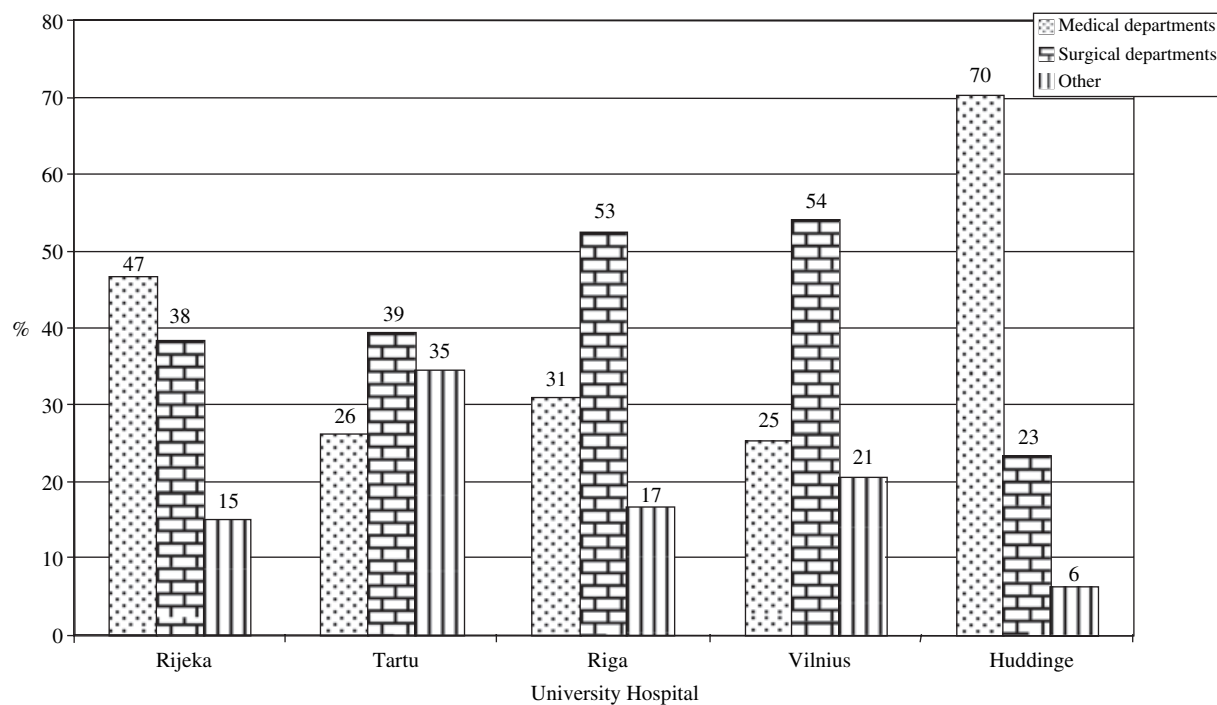


Fig. 1. The percentage of patients who received antimicrobial agents in different departments of five university hospitals.

**Table 2.** Reasons for administration of antimicrobial agents to 1025 patients in five university hospitals

	Rijeka n (%)	Tartu n (%)	Riga n (%)	Vilnius n (%)	Huddinge n (%)
Treatment	151 (67)	162 (72)	118 (49)	76 (60)	142 (69)
Surgical	54 (24)	32 (14)	44 (18)	25 (20)	37 (18)
prophylaxis					
Medical	18 (8)	0 (0)	8 (3)	15 (12)	27 (13)
prophylaxis					
Unclear	4 (2)	32 (14)	70 (29)	10 (8)	0 (0)
Total	227	226	240	126	206

prescribed per patient in the centres studied did not differ significantly (1.2–1.6 courses/patient). The route of administration was intravenous for 60.5% patients in Rijeka, 64.5% in Tartu, 72% in Riga, 60.5% in Vilnius, and 49% in Huddinge. In all five centres, the majority of the patients received antimicrobial agents for therapeutic purposes. The proportion of patients with an unclear indication for antibiotic treatment ranged from 0% in Huddinge to 29% in Riga (Table 2). Of the prescribed agents, 90% (the DU90% profile) were accounted for by 20 antimicrobial agents (of 29 available) in Rijeka, 20 (of 27) in Huddinge, 15 (of 22) in Vilnius, 12 (of 21) in Riga, and 19 (of 31) in Tartu (Table 3). The variations among centres, in terms of the time between admission and commencing antibiotic treatment, are summarised in Table 4.

Consultation with an infectious disease specialist concerning antimicrobial treatment occurred

**Table 4.** Intervals between admission and commencement of antimicrobial treatment (AB) for 1025 patients at five centres

Start of AB	Hospital				
	Rijeka (%)	Tartu (%)	Riga (%)	Vilnius (%)	Huddinge (%)
On admission	113 (49.8)	70 (31.0)	87 (36.2)	37 (29.4)	55 (26.7)
1–2 days	24 (10.6)	63 (27.9)	65 (27.1)	23 (18.2)	91 (44.2)
>2 days	90 (39.6)	93 (41.1)	88 (36.7)	66 (52.4)	60 (29.1)
Total	227	226	240	126	206

significantly more frequently in Huddinge, and least frequently in Tartu (Pearson chi-square test,  $p < 0.000001$ ). Similarly, the indication for antimicrobial administration was documented significantly more often in the medical records in Huddinge than in the other centres (Pearson chi-square test,  $p = 0.000009$ ). Susceptibility testing and culture were also performed significantly more often in Huddinge than in the other hospitals (Pearson chi-square test,  $p < 0.001$ ) (Table 5).

Among community-acquired infections, lower respiratory tract infection predominated in all centres (Rijeka 32%, Tartu 38%, Riga 23%, Vilnius 30%, Huddinge 27%), followed by intra-abdominal infections in Rijeka (21%) and Riga (23%), infections of skin and sub-mucosae in Tartu (14%) and Vilnius (24%), and urinary tract infections in Huddinge (20%). The frequency of patients with nosocomial infections was 4.8% in

**Table 3.** Distribution of prescribed antimicrobial agents (AB) accounting for 90% of all treatment courses (the DU90% profile) in five selected hospitals

Rijeka			Tartu			Riga			Vilnius			Huddinge		
AB	n	%	AB	n	%	AB	n	%	AB	n	%	AB	n	%
Cefuroxime	41	14.0	Gentamicin	39	13.5	Cefazolin	80	26.4	Ciprofloxacin	18	11.8	Cefuroxime	33	12.8
Gentamicin	27	9.2	Ampicillin	29	10.1	Ciprofloxacin	52	17.2	Amoxicillin	16	10.5	Metronidazole	26	10.1
Metronidazole	25	8.5	Cefuroxime	28	9.7	Metronidazole	33	10.9	Cefazolin	15	9.9	Ciprofloxacin	22	8.5
Co-amoxycylav	22	7.5	Cefazolin	27	9.4	Ampicillin	25	8.3	Co-trimoxazole	15	9.9	Cloxacillin	16	6.2
Anti-tuberculosis agents	20	6.8	Anti-tuberculosis agents	24	8.3	Gentamicin	18	5.9	Cefuroxime	13	8.6	Co-trimoxazole	16	6.2
Ciprofloxacin	17	5.8	Ciprofloxacin	22	7.6	Cefuroxime	15	5.0	Metronidazole	11	7.2	Imipenem	14	5.4
Ceftriaxone	15	5.1	Metronidazole	17	5.9	Ceftriaxone	14	4.6	Ampicillin	11	7.2	Norfloxacin	14	5.4
Cefepime	14	4.8	Oxacillin	17	5.9	Amoxicillin	11	3.6	Penicillin G	9	5.9	Cefotaxime	12	4.7
Cefazolin	12	4.1	Penicillin G	8	2.8	Ofloxacin	10	3.3	Gentamicin	8	5.3	Clindamycin	12	4.7
Amoxicillin	9	3.1	Amoxicillin	7	2.4	Doxycycline	7	2.3	Vancomycin	5	3.3	Penicillin V	9	3.5
Cephalexin	8	2.7	Co-trimoxazole	7	2.4	Co-trimoxazole	6	2.0	Ceftriaxone	4	2.6	Vancomycin	8	3.1
Vancomycin	8	2.7	Cefotaxime	6	2.1	Ceftazidime	5	1.7	Cefepime	4	2.6	Penicillin G	8	3.1
Doxycycline	8	2.7	Erythromycin	6	2.1	DU90% 1–12	276	91.2	Roxithromycin	3	2.0	Amoxicillin	7	2.7
Rifampicin	8	2.7	Amikacin	5	1.7	13–21		8.8	Oxacillin	3	2.0	Flucloxacillin	7	2.7
Cefotaxime	7	2.4	Piperacillin-tazobactam	5	1.7				Ceftazidime	2	1.3	Gentamicin	7	2.7
Meropenem	7	2.4	Cefoxitin	5	1.7				DU90% 1–15	137	90.1	Ceftazidime	6	2.3
Ceftazidime	5	1.7	Ceftazidime	4	1.4				16–22		9.9	Pivmecillinam	5	1.9
Pefloxacin	5	1.7	Imipenem	3	1.0							Meropenem	4	1.6
Penicillin G	5	1.7	Co-amoxycylav	3	1.0							Ampicillin	4	1.6
Clarithromycin	5	1.7	DU90% 1–19	262	90.7							Azithromycin	3	1.2
DU90% 1–20	268	91.3	20–31		9.3							DU90% 1–20	233	90.5
21–29		8.7										21–27		9.5

**Table 5.** Factors associated with the prescription of antimicrobial agents for 1025 patients admitted to five university hospitals

	Rijeka	Tartu	Riga	Vilnius	Huddinge
Consultation with IDS	7.9%	7.4%	12.7%	17.1%	50.0%
Indication for treatment with AB in medical records	27.2%	76.5%	72.9%	90.8%	92.3%
Culture/susceptibility testing	28.5%	26.5%	21.2%	19.7%	64.5% <sup>a</sup>

<sup>a</sup>Antimicrobial agents may have been prescribed before the results of the culture were available, but the empirical choice was confirmed by susceptibility reports and treatment was considered as targeted.

IDS, infectious disease specialist; AB, antimicrobial agent.

Rijeka (48 patients, 21% of those receiving antibiotics), 5.3% in Tartu (40 patients, 18% of those receiving antibiotics), 3.0% in Riga (28 patients, 12% of those receiving antibiotics), 3.4% in Vilnius (30 patients, 24% of those receiving antibiotics), and 9.3% in Huddinge (61 patients, 30% of those receiving antibiotics). The most common nosocomial infections were: urinary tract infections (27%) and surgical site infections (20%) in Rijeka; lower respiratory tract infections (33%), urinary tract infections and intra-abdominal infections (13% each) in Tartu; surgical site infections (32% and 37%, respectively) and fever of unknown origin (25% and 23%, respectively) in Riga and Vilnius; and fever of unknown origin (30%), followed by sepsis (21%), in Huddinge.

The proportion of patients receiving antimicrobial surgical prophylaxis was 24% in Rijeka, 14% in Tartu, 18% in Riga, 19% in Vilnius and 18% in Huddinge (Table 2). The drugs used most commonly for surgical prophylaxis were: cefuroxime (30% of patients) followed by cefazolin and cefepime (15% and 13%, respectively) in Rijeka; cefazolin (84%) and cefoxitin (13%) in Tartu; cefazolin (65% and 40%, respectively) and cefuroxime (26% and 36%, respectively) in Riga and Vilnius; and cefuroxime in Huddinge.

## DISCUSSION

This study surveyed antimicrobial drug use in five politically, economically and geographically diverse countries. Antimicrobial drug use policies in the four newly formed countries (Croatia, Estonia, Latvia and Lithuania) were based mostly on administrative measures and restrictions, while at Huddinge (Sweden) the antimicrobial drug use policy was based on recommendations and educational activities.

In other studies reported previously, the frequency of antimicrobial drug use varied between 17% and 78% of patients [16–18]. Compared with these studies, the frequency of antimicrobial drug use at the hospitals in the present study was not high, even though they were tertiary referral university centres. The number of treatment courses per patient in the five hospitals surveyed was similar to that in other reports [19,20]. The lowest frequency of antimicrobial drug use (14%) was in Vilnius; this was a reduction from a frequency of 24% reported for 2002 (8th World Congress on Clinical Pharmacology and Therapeutics, Brisbane, 2004, abstract PO 150). Several point-prevalence studies during a single year would probably give a more accurate picture of the hospital's antimicrobial drug use.

Almost one-third of the patients in Riga had received an antimicrobial agent without a clear indication for its use. This finding may, in part, reflect differences of opinion among the investigators, which was a limitation of the present study. In the absence of clinical signs of infection, some investigators (UD, PM) classified a duration of antimicrobial prophylaxis of >48 h as an unclear reason for antimicrobial therapy, while others classified it as prophylaxis, regardless of its appropriateness.

At Huddinge, antimicrobial agents were administered intravenously and orally in equal proportions, while in the low-income countries, they were administered intravenously two-fold, or three-fold (Riga), more often than orally. This could not be explained simply by the severity of disease, and may reflect a psychological assumption that intravenous antibiotics are more effective, despite the lack of evidence to support this general approach.

Although the hospitals in Rijeka and Riga had similar antimicrobial policies, and the prevalence of antimicrobial drug use was similar, the pattern of use differed substantially. The number of different antimicrobial agents used in Riga was the lowest among all the hospitals surveyed. Almost one-third of the prescribed antimicrobial agents in Rijeka were those with restricted release, mostly third-generation cephalosporins. Within the DU90% in Riga, there were only two third-generation cephalosporins listed, as restricted release, which accounted for 6% of the treatment courses. Although not restricted, these broad-spectrum  $\beta$ -lactams were not prescribed as

extensively in Tartu, Vilnius and Huddinge as they were in Rijeka. In comparison, a Norwegian study reported low use of third-generation cephalosporins [20], while studies from the Mediterranean region have shown a greater proportion of broad-spectrum antimicrobial use [21–23]. Results from the European Surveillance on Antimicrobial Consumption (ESAC) project for outpatient antibiotic use have shown a higher consumption, especially of broad-spectrum antimicrobial agents, in southern and eastern Europe than in northern Europe [24]. The high frequency of broad-spectrum antimicrobial prescriptions in Rijeka could not be explained by high bacterial resistance rates, as the percentage of patients treated with these agents exceeded the percentage of patients treated according to susceptibility testing, suggesting that they were given empirically. One-half of the patients had already received an antimicrobial agent upon admission for community-acquired infections, which raises questions about the rationality of their use. The same pattern of antimicrobial use in Rijeka has been described previously [25–27]. The hospitals in Rijeka, Huddinge and Tartu had the widest range of available antimicrobial agents and, correspondingly, 90% of the patients at these centres were treated with a wider range of agents. Interestingly, little vancomycin use was recorded in Riga and Tartu, probably because of an absence of methicillin-resistant *Staphylococcus aureus* at the time of the survey.

The finding that most patients in the surgical departments in Vilnius, Riga and Tartu received antimicrobial agents for treatment rather than prophylaxis, and that most patients received an antimicrobial agent >2 days after admission, suggests a high rate of surgical site infection in these centres. However, in Vilnius, patients are commonly hospitalised a few days before scheduled elective surgery, and prophylaxis might have been extended for >24 or 48 h, contrary to guidelines. A retrospective review of indications for antimicrobial treatment in Riga showed that patients with diagnoses such as pancreatitis, cholecystitis, cellulitis and chronic ulcers are treated in surgical departments, even if they do not need surgical intervention. In Tartu, Vilnius and Riga, cefazolin was the agent used most commonly for surgical prophylaxis, which is in accord with published guidelines [28,29]. Although not recommended as a drug of choice for surgical prophylaxis, cefu-

roxime was used mostly for this purpose in Rijeka. Cefuroxime is recommended for use with abdominal surgery in Huddinge, but was also used for other indications, contrary to guidelines. Cefazolin was not approved for use in Sweden at the time of this survey.

Prevalence studies are often used to provide baseline information concerning the occurrence of hospital infections and to help in establishing priorities for their control. It has been estimated that up to 10% of hospitalised patients acquire an infection [30–32], and the prevalence of nosocomial infections in the hospitals included in the present study was within the same range.

The study has several limitations. Although the same protocol was used in all study centres, patients with identical diagnoses were sometimes treated in different departments, thus giving different reflections of the use of antimicrobial agents. Interpretation of findings was also biased in certain cases by the opinions of the local investigator and by differences in record-keeping. As in all other point-prevalence studies, day-by-day and seasonal variations in antimicrobial drug use could not be monitored. Nevertheless, this benchmarking study, using a simple and inexpensive point-prevalence method, revealed several differences in antimicrobial drug prescription among the various centres that could indicate potential problem areas. The high rates of intravenous administration, poor compliance with published guidelines, and prolonged surgical prophylaxis were general problems that deserve specific attention in all centres.

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