Hospital consumption of antibiotics in 15 European countries: results of the ESAC Retrospective Data Collection (1997–2002)

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Objectives: To collect reliable, comparable and publicly available data on hospital use of antibiotics in Europe aggregated at the national level (1997–2002).

Methods: Consumption data of systemic antibiotics in Anatomical Therapeutic Chemical (ATC) class J01 were collected and expressed in defined daily doses (DDD) per 1000 inhabitants per day. Valid data for 2002 were available for 15 countries, and 6 year trends for 10 countries. Comparison with ambulatory care (AC) consumption data was possible in 14 countries.

Results: In 2002, median national hospital antibiotic consumption in Europe was 2.1 DDD/1000 inhabitants/day in Europe, ranging from 3.9 in Finland and France to 1.3 in Norway and Sweden. Hospital care (HC) consumption as a proportion of total antibiotic consumption ranged from 17.8% to 6.4%. The consumption of hospital-specific antibiotics ranged from 0.43 DDD/1000 inhabitants/day in Greece and 0.08 in Sweden.

Six-year trends in consumption were stable, except for rising co-amoxiclav exposure and more rapid market penetration of new antibiotics (e.g. levofloxacin) in some countries. There was a strong, positive correlation between the extent of antibiotic use in AC and in HC (Spearman coefficient 0.745; $P=0.002$), both for overall use and for use of five main classes (not macrolides and ‘others’). In contrast to AC consumption no substantial seasonal variation in consumption was observed.

Conclusions: It was cumbersome but feasible to collect ecological data on hospital antibiotic consumption in a set of 15 European countries on a retrospective basis, illustrating substantial cross-national variations in the extent and distribution of exposure to antibiotics in hospital care.

Keywords: antibacterial agents, data collection, hospitals, drug utilization, Europe, factual databases, microbial drug resistance

Introduction

The hospital is often considered as the epicentre of antibiotic resistance.1,2 Hospitalized patients often suffer from a debilitated physical condition and deficiencies of the immune system, requiring intense antibiotic therapy for longer periods and for severe infectious complications. Prophylaxis with antibiotics is often required for invasive diagnostic and therapeutic procedures. There is a higher risk for cross-colonization and infection, because of the frequent contacts between healthcare workers and patients, and the intense use of medical devices for life support. Hence, the pressure among the hospitalized patients in terms of number of patients exposed in the population over time is high. This may lead to higher prevalence of antimicrobial resistance in hospital populations and to higher rates of failure to initial empirical therapy. This in turn may result in increased fatality figures, and to selection of germs with multiple resistance to antibiotics of second and third lines of defence.3–5

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Healthcare policy makers are worried that, despite efforts to limit excessive use of antibiotics, consumption as well as resistance might escalate.\(^6\)\(^{-8}\) It is increasingly feared that spending large sums of money on costly and potentially harmful antibiotics of last defence will not protect hospitals from being confronted with epidemics of resistant germs, a bad reputation, excessive expenditures and avoidable loss of human lives.

On 15 November 2001, a European Council Recommendation\(^9\) stated that specific strategies should be pursued to collect data on antibiotic use.

This paper reports on the first cross-national retrospective comparison in the European region of antibiotic consumption in hospital care (HC) for the years 1997–2002. We present data from the European Surveillance of Antimicrobial Consumption (ESAC) project, an international network of surveillance systems, aiming to collect reliable and comparable antibiotic use data in Europe. ESAC was established in 2001 with support of the European Commission.

### Materials and methods

The approach to data collection and validation in the ESAC project is extensively described elsewhere.\(^10\)

For the period 1997–2002, consumption data of systemic antibiotics for hospital care aggregated at the level of the active substance were collected, in accordance with the Anatomic Therapeutic Chemical (ATC) classification and defined daily dose (DDD) measurement unit (WHO, version 2003).\(^1.1\)

For each available antibiotic substance from ATC class J01 (which does not include antifungals, antibacterials for tuberculosis and topical antibiotics) the total consumption in DDVs was collected per country and per year. National hospital consumption in this study was expressed on a population basis as DDD per 1000 inhabitants per day.

Data were collected through a network of national representatives (most often microbiologists), working closely together with government officials, hospital pharmacists and drug utilization research groups, and supported by a multidisciplinary ESAC management team located at the University of Antwerp, Belgium.

Prior to the interpretation of the consumption data, validity of the provided consumption data was evaluated by means of a checklist including possible sources of bias. The methodology for this validity check in ambulatory care (AC) and in hospital care as well as its results on a country by country basis is extensively described in a previous technical paper on the methodological issues of this data collection.\(^10\) All data sets were checked for comprehensiveness of census data or for bias in sampling data. We assessed the correctness of the coding of medicinal products on the market into the ATC classification. We checked the absence of data collection bias due to peculiarities in reimbursement systems or to allocation of subsets (nursing homes, prescribing by specialists to outpatients) to either ambulatory care or hospital care. Only valid data sets are included in the present analysis. We included one data set (Finland) with minor bias in ambulatory/hospital care mix, but we clearly indicate the presence of this bias in the text and in the figures.

Hospital consumption was broken down into seven main antibiotic groups in analogy with previous descriptions of antibiotic consumption in ambulatory care: penicillins (J01C); cephalosporins + carbapenems + monobactams (J01D); tetracyclines (J01A); macrolides + lincosamides + streptogramins (J01F); quinolones (J01M); sulphonamides + trimethoprim (J01E); and others (J01B + J01G + J01X), including e.g. amphenicols, aminoglycosides and glycopeptides.

Penicillins (J01C) were broken down further into four subclasses: narrow-spectrum penicillins (J01CE), extended-spectrum penicillins, such as ampicillin and amoxicillin (J01CA), combinations with \(\beta\)-lactamase inhibitor, such as co-amoxiclav (J01CR), and \(\beta\)-lactamase-resistant penicillins (J01CF). Cephalosporins were broken down into four generations (as defined recently in the 2005 version of the ATC classification).\(^1.1\)

Because this article focuses on hospital care, we took special interest in antibiotics that are not or very seldom used in ambulatory care, such as third- and fourth-generation cephalosporins, carbenems, monobactams, aminoglycosides and glycopeptides. To explore the cross-national differences in the use of these antibiotics, we gathered them in a single group, and labelled this group ‘hospital-specific antibiotics’.

Valid data for 2002 was available for 15 countries; seven of the 15 former traditional EU states: Belgium (BE), Denmark (DK), Greece (GR), Finland (FI), France (FR), Luxembourg (LU) and Sweden (SE); six of the 10 new member states: Estonia (EE), Hungary (HU), Malta (MT), Poland (PL), Slovakia (SK) and Slovenia (SI); and two non-EU states: Croatia (HR) and Norway (NO).

From the 15 countries providing valid data, five countries (EE, FI, HR, NO, SK) were not able to provide a consecutive series of at least 5 years of data. For the 10 other countries, data were available for six consecutive years, with missing data for Slovenia (1997) substituted by 1998 data.

Of the 15 data sets of 2002, three were considered to be with minor bias: Finland because of a contamination of hospital data with primary care data; Poland because of an extrapolation procedure of a sample covering 60% of the population; and Greece because of the slight overestimation by parallel trading and a slight underestimation by possible inclusion of a limited number of small regional hospitals in primary care data (see Supplementary data; available at JAC Online).

Other countries participating in ESAC, which were not able to provide data or provided some data but not a valid estimate of total exposure, are listed in the Supplementary data (available at JAC Online).

Data were most often provided by governmental health policy institutions, stemming from manufacturers (two countries), wholesalers (four countries), hospital pharmacists (seven countries), marketing research organizations (one country), and the reimbursement system (one country). Only in Belgium, data stem from a fee for service reimbursement system. In all other countries, the State or health insurers provide a fixed budget for drug expenditures in the hospital. For 14 of the 15 sets of valid hospital data (all except Malta) the ambulatory care data were also available within the ESAC data collection systems, and hence total antibiotic exposure could be calculated, as well as the mix between ambulatory and hospital care.

The evolution of yearly consumption is graphically presented with a classical Tukey Box and Whisker Plot for each year. Longitudinal time trend analysis over the 6 year period was performed using the General Linear Model (GLM) for repeated measures.

The relation between hospital care consumption and ambulatory care consumption was investigated using the non-parametric Spearman Rank Correlation test, with the \(a\) priori alpha-level of significance set at \(P = 0.05\). In addition, for each of the seven main antibiotic classes, the percentage of that class in total volume was compared between hospital and ambulatory care in each country.

Data were analysed with the statistical package SPSS\(^8\).

### Results

#### Hospital use of antibiotics in 2002

In 2002, the median national hospital antibiotic consumption in Europe was 2.1 DDD/1000 inhabitants/day, ranging from 3.9 in
Finland and France to 1.3 in Norway and Sweden. In Figure 1, a rank order graph of total hospital consumption in 15 European countries is given.

HC consumption as a proportion of total (hospital + ambulatory care) antibiotic consumption ranged in 2002 from 10.7% in France to 6.4% in Slovakia, with Finland and Estonia as outliers at respectively 17.8% and 15.5% (results not shown, data missing for Malta).

However, data from Finland include primary healthcare centres and nursing homes. Countries with high HC consumption generally also have high outpatient consumption of antibiotics (see Figure 2), with a Spearman Rank Correlation Coefficient of 0.745 ($P = 0.002$).

**Proportional hospital use of main antibiotic classes in 2002**

The proportion of penicillin use ranged from 57% to 36% in 13 countries, but was much lower in Greece (28%) and in Finland (13%).

The proportion of cephalosporin use was high in Greece (31%) and Luxembourg (30%) and low in France (8%). Tetracycline use was proportionally high (10% or more) in two countries (12% in Sweden, 11% in Poland). Macrolide use (including lincosamides and streptogramins) ranged between 13% in Malta and 3% in Poland; and quinolone use ranged between 17% in Finland and 4% in Norway.

A high (20% or more) proportional use of ‘other antibiotics’ was reported in three countries (27% in FI, 24% in EE, 21% in FR); intermediate (between 19% and 10%) in five countries (GR, PL, MT, NO, DK); and low (between 9% and 6%) in the seven remaining countries. In the high fraction ‘others’ in Finland, the use of methenamine and nitrofurantoin predominated.

The consumption of hospital-specific antibiotics (see the Materials and methods section for definition) ranged between 0.43 DDD/1000 inhabitants/day in Greece and 0.08 in Sweden (median 0.27). In Figure 3, the distribution of the subclasses is shown.

Adding HC to AC consumption provides an estimate of the total exposure of humans to antibiotics in a country. This ranged from 36.09 DDD per 1000 inhabitants per day in France to 13.80 in Estonia (median 23).

The rank correlation between the proportions in ambulatory care and hospital care of penicillins, cephalosporins, tetracyclines, macrolides and sulphonamides were respectively...
There was no significant correlation between the proportions of quinolones in AC and HC (mainly because quinolones are used very little in AC in Nordic countries), or between the proportions in the group ‘others’ (mainly because of minimal outpatient use of this group in Eastern European countries, such as HU, SK, HR and SI).

### Proportional use within penicillins, cephalosporins and quinolones

Within penicillins (J01C), the proportion of co-amoxiclav was high (85% and more) in two countries (BE, LU), between 75% and 45% in eight countries and low (less than 12%) in five countries (FI, EE, NO, SE, DK). The use of narrow-spectrum penicillins was only substantial (19% or more) in six countries (DK, NO, SE, FI, HR, EE), and ranged between 12% and 1% in the remaining countries. Exposure to β-lactam-resistant penicillins was high in Norway and Sweden (both 40%), and ranged between 21% and 1% in the remaining countries (see Figure 4).

Within the cephalosporins, the proportion of third- and fourth-generation cephalosporins ranged between 50% and 10% (see Figure 5), with Belgium using the highest proportion of fourth-generation cephalosporins (19%), while Denmark was almost exclusively (87%) using second-generation cephalosporins.

Within the quinolones, the proportion of ciprofloxacin in 2002 was more than 50% in most countries. In some countries (FI, BE) a relative breakthrough was observed of levofloxacin (>40%), and to a much lesser extent of moxifloxacin (less than 2% in all countries).

### Evolution of consumption over 6 years

In Figure 6 national hospital antibiotic consumption in Europe between 1997 and 2002 is represented by box plots with a relatively stable mean (hovering around 2 DDD/1000 inhabitants/day), without significant trends.
In Table 1, hospital use of all antibiotics and the relative distribution of this hospital consumption over seven groups is compared between 1997 and 2002. Overall hospital use and the proportion of major antibiotic groups remained relatively stable in all the countries. The share of penicillins decreased by five percentage points (pp) only in three countries (MT, GR and LU). Within the penicillins the mean proportion of co-amoxiclav rose from 54% to 60% from 1997 to 2002 (data not shown). The share of quinolones decreased by 5 pp in France, and increased by 5 pp or more in Slovenia, Greece and Finland.
The boxplots of the national consumption of hospital-specific antibiotics (carbapenems, glycopeptides and aminoglycosides) and of the third- and fourth-generation cephalosporins are given in Figure 7. The use of glycopeptides and carbapenems was increasing to some extent in all countries (especially in Greece, Malta and Slovenia), but remained below 0.05 DDD/1000 inhabitants/day in all countries (GLM for trend $P = 0.003$ and $P = 0.002$, respectively). The median national aminoglycoside consumption was between 0.07 and 0.08 DDD/1000 inhabitants/day. Substantial

Table 1. Hospital antibiotic use in 15 European countries (evolution of exposure to antibiotics in hospital care in defined daily doses per 1000 inhabitants and of proportional use of major antibiotic classes between 1997 and 2002)

<table>
<thead>
<tr>
<th></th>
<th>1997 DDD/1000</th>
<th>% Penicillins J01C</th>
<th>% Cephalosporins J01D</th>
<th>% Tetracyclines J01A</th>
<th>% Macrolides J01F</th>
<th>% Quinolones J01M</th>
<th>% Sulphonamides J01E</th>
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<tr>
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<td></td>
<td></td>
<td></td>
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<td>SE</td>
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<td>38</td>
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Figure 7. Evolution of the use of hospital-specific antibiotics in Europe (1997–2002) ($n = 10$ countries). Open circles indicate extreme values.
Hospital antibiotics in Europe

decreases (more than 10% difference between 1997 and 2001) were seen in four countries (PL, BE, FI, DK) and increases in two countries (FR, SI). The use of monobactams was very limited in most countries, except Belgium (however, also regressing to zero) (data not shown).

For the third- and fourth-generation cephalosporins, a gradual increase in consumption was observed, consistently in all countries (GLM for trend \( P = 0.003 \)).

Seasonal variation

In the seven countries able to provide quarterly data for 6 years (DK, ES, GR, FI, PL, SE, SI), no substantial seasonal variation in hospital antibiotic consumption (<20% difference in use between autumn–winter quarters and spring–summer quarters) was observed (data not shown).

Discussion

With comparable and valid data sets from 15 countries, the data collection from the ESAC project was not as successful in HC as in AC, where data sets from 23 countries within Europe were collected. However, this is the first valid, comparable and publicly available set of cross-national drug consumption data in the hospital sector, not only for antibiotics but also for medicines in general.

There are several limitations to the study. First, a number of European countries were not able to submit national, longitudinal data in this data collection effort, including larger countries such as Germany, the UK, Italy and Spain.

Second, the validity of the hospital data is vulnerable to biases in ambulatory/hospital case mix. This is illustrated by the data from Finland, distorted to some extent by the inclusion into the hospital data of the consumption data of primary healthcare centers in remote areas and nursing homes. The antibiotic group ‘others’ comprises more than 20% of all antibiotics in Finland and includes drugs used for urinary tract infections (e.g. methenamine and nitrofurantoin). Thus the true rank of antibiotic consumption in Finnish hospitals may be better illustrated in Figure 3 with hospital-specific antibiotics.

Third, the reliability of the estimation of national aggregates of hospital drug consumption must be critically evaluated. Some countries derive a reliable estimate for national hospital exposure to antibiotics from wholesalers’ data; others from detailed consumption registration in all hospitals. In other countries, national consumption data are derived from a sample of hospitals, expressed in DDD per 100 bed days.13–20 Interesting cross-national comparisons have been published based on comparisons between single hospitals or groups of hospitals in different countries.21–29 However, extrapolation of these sample data to a national aggregate of hospital antibiotic use is difficult, because consumption patterns may differ substantially in university hospitals, large regional hospitals with intensive care and/or haematology units and small local hospitals with limited capabilities as to invasive diagnostic or therapeutic interventions.17–19 Hence, in this overview we included only fairly complete national data sets, with which it was possible to produce a reliable aggregated estimation of national exposure of humans to antibiotics.

Fourth, there is the problem of the denominator in expressing hospital consumption. In this cross-national comparison, we were forced to express the aggregated national antibiotic consumption data as a function of the population of the country (DDD/1000 inhabitants per day) and not as a function of the number of bed days in the country (DDD/100 bed days), as recommended by the WHO and as customary in previous publications of hospital drug consumption. The healthcare data collection systems in Europe are not able to provide trustworthy, timely and comparable national data on the number of hospital bed days for all European countries.30 As the population trends in Europe are relatively stable, we decided that for this cross-national surveillance study it was more appropriate to use country population as the denominator for aggregated national estimates of antibiotic exposure.

For national studies aiming to assess variability between individual hospitals in the country we recommend that consumption data are expressed as DDD per 100 bed days (or in relation to the number of hospital admissions or treatment courses20,31), however, with explicit provision of the number of bed days per hospital and per country, and also expressing the estimate of overall national exposure of hospital consumption in DDD/1000 inhabitants per day. An additional advantage is that with this expression of exposure HC use can be added to AC use to produce a more sophisticated estimation of total antibiotic exposure of the human population in a particular country.32

A final limitation of the study is the aggregation of consumption data for antibiotics, which can be administered both parenterally and orally. In the first phase of the ESAC project, data were collected at the level of the active substance. This precluded advanced analysis of route of administration in the hospital, an important element in the evaluation of appropriateness of use.13 In the second phase of the ESAC project, the data collection protocol will stipulate separation between oral and parenteral use.

The most striking feature of the findings presented here is the huge variation in the total exposure to antibiotics in hospital care in Europe, with a 3- to 4-fold difference between the low and high range. Although demographic and epidemiological determinants may explain part of the variance, it is a clear indication that antibiotics are overprescribed in the hospitals of some European countries.

Hospital consumption remained relatively stable over the period of registration, in terms of absolute level of exposure and in terms of distribution over the seven main groups. The rise in exposure to co-amoxiclav may be due to more treatment courses (more frequent first choice in empirical therapy), or to higher doses and longer duration per treatment course, in an attempt to curb resistance to Streptococcus pneumoniae. It is important to note that the recent 2004 change of the DDD for parenteral co-amoxiclav from 1 to 3 g/day was not implemented in these data. Implementing this change in methodology may reduce the estimate of overall exposure to antibiotics in some countries.

Also, the use of third- and fourth-generation cephalosporins, and of carbapenems and glycopeptides seems to be on the rise in all countries. The patterns for the use of aminoglycosides are more complex and merit further attention.

In contrast to ambulatory care consumption, the hospital data showed minimal seasonal variation, indicating that the level of HC use is not dominated by seasonal fluctuations in the incidence of upper respiratory diseases.

Unfortunately, the number of European countries providing valid HC data sets was too small to perform a cluster analysis of regional differences, as was performed in the ambulatory care setting.8
We observed a significant relationship between the extent of the total exposure to antibiotics and between the distribution over five main classes (not quinolones and ‘others’) in ambulatory and hospital care. First, when the use of antibiotics in one country is high in AC, it is also likely to be high in HC and vice versa. Second, if a main class of antibiotics is predominantly used in ambulatory care in a particular country, it is likely that the same class will be used to a similar extent in hospital care. This points to a fundamental observation. Despite the huge variation of antibiotic consumption across the countries of Europe, both in ambulatory and in hospital care, the basic characteristics of use (extent and nature) are strongly correlated between the two healthcare settings within each country. This may indicate that within countries, common determinants influence antibiotic use both in AC and HC.

Our data indicate that hospital care consumption is only 5–10% of the total exposure to antibiotics in many European countries. Within the hospital consumption, the percentage of hospital-specific antibiotics (see the Materials and methods section for definition) is around 10%. However, hospital exposure is more concentrated in terms of number of patients in the population exposed and intensity of treatment (dosage and duration). This may provide the ecological pressure for the emergence of hospital-specific resistant germs, which may cause serious impediments to the prophylactic treatment of invasive diagnostic and therapeutic interventions in the affected hospital or spread back into the community.

The relationship between hospital antibiotic consumption and antimicrobial resistance both in the hospital and in the community is a complex issue, and requires a thorough and historical perspective on the medical traditions in the ambulatory care sector of the country. Specific resistance patterns in the community may change the nature of empirical therapy of patients hospitalized with community-acquired infections and in turn induce national differences in the prevalence of methicillin-resistant Staphylococcus aureus, Enterobacteriaceae and Pseudomonas aeruginosa and Acinetobacter baumannii, leading to different profiles of use of hospital-specific antibiotics. In this study, we have collected aggregated national data on consumption in hospital care, which provide ecological comparisons between national aggregates over time. There are many pitfalls in the ecological study of the association between antibiotic use and resistance across healthcare settings and time. Moreover, significant associations are not proof of causality, and do not reveal what is cause and what is effect. However, collecting reliable and comparable utilization data for cross-national comparison is a first step in demonstrating and understanding variability in medical practices. This has been the achievement of the ESAC project.

In conclusion, it was cumbersome but feasible to collect ecological data on hospital antibiotic consumption in a set of 15 European countries on a retrospective basis. There are huge cross-national variations in extent and distribution of exposure to antibiotics in the hospital care sector of these 15 countries. Within countries, there is a relationship in extent and distribution of exposure to antibiotics between hospital and ambulatory care. In countries with high AC consumption, HC consumption tends to be high too and to display a similar distribution over main classes in both settings (except for quinolones and ‘others’).

To continue and expand this routine data collection effort, sustained logistic support at the EU level, national commitment of regulatory authorities, continued rigor in checking validity of data sets for possible bias, and cooperation between professional associations of microbiologists, drug utilization researchers and hospital pharmacists will be necessary.

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Transparency declarations

The authors have no interests to declare.

Supplementary data

Supplementary data are available at JAC Online (http://jac.oxfordjournals.org/).

References

Hospital antibiotics in Europe