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ORIGINAL REPORT

Antibiotic use in ambulatory care in Europe (ESAC data 1997–2002): trends, regional differences and seasonal fluctuations†

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SUMMARY

Purpose The ESAC project (European Study on Antibiotic Consumption) aims to collect antibiotic-use data through a European network of national surveillance systems. This paper reports on the retrospective data collection in ambulatory care for the period 1997–2002.

Methods Valid data of antibiotic consumption of 24 European countries for 2002 and of 18 countries for the entire 6-year period was classified according to the Anatomical Therapeutic Chemical Classification (ATC) and expressed in defined daily dose (DDD) per 1000 inhabitants per day (DID). Overall and subgroup comparison of antibiotic consumption over time as well as between geographical clusters was performed.

Results Total use of antibiotics in Europe remained at a median level of 20 DID in the period 1997–2002 with a wide variation between countries ranging from 9.8 DID in The Netherlands to 32.2 DID in France. A substantial increase in subclass consumption of co-amoxiclav and fluoroquinolones was noted while the use of narrow-spectrum penicillins, erythromycin, quinolones and sulfonamides decreased. Total consumption as well as seasonal fluctuations showed remarkable geographical clustering with low consumption and low variation between summer and winter in the North, high consumption patterns in the South and a mixed model in the East.

Conclusions Within the ESAC project, valid time series of antibiotic-use data are publicly available now, enabling to improve the study of determinants of use, the evaluation of governmental antibiotic consumption policies and the investigation of the associated emergence of antibiotic resistance. Copyright © 2006 John Wiley & Sons, Ltd.

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INTRODUCTION

Until recently, information on antibiotic consumption was limited. Published information focussed only on one country, on specific age and sex categories or on consumption patterns for specific indications. Attempts to present international comparable data were limited to a few countries or biased by rough extrapolation.[1]

Cars were the first to present comparable antibiotic consumption data for 15 European countries.[2] His data, however, were purchased from the Institute for Medical Statistics, limiting the study to a single cross-sectional observation. A second attempt to collect comparable data on antibiotic use was made by the European Drug Utilisation Research group (Euro-DURG) in collaboration with the WHO collaborative centre for Drug Statistics Methodology (Oslo, Norway). This group distributed a spreadsheet through a network of national DUR groups asking to gather publicly available information on antibiotic consumption in the respective countries.[3] Considerable methodological difficulties were encountered, leading to the conclusion that a coordinated and concerted effort of scientific associations and regulatory authorities was needed to produce comprehensive and comparable antibiotic-use data at the European level.

In the mean time, evidence accumulated that antibiotic use, overuse and misuse were important risk factors for the emergence of antibiotic resistance. The lack of a comprehensive, validated database on antibiotic consumption at the European level has clearly pointed out during the EU conference on the problem of anti-microbial resistance, organised in Copenhagen in 1998.[4] The recommendations derived from the conference stated that every Member State should be able to collect national data on the supply and consumption of anti-microbial agents and that an EU strategy should be established to ensure transparency and comparability between national databases.

As a result, the European Commission decided to grant the European Surveillance of Antibiotic Consumption project (ESAC) for a 2-year period (November 2001–October 2003), and funding has been secured until 2007. The project is constructed as an international network of national surveillance systems, aiming to collect comparable and reliable antibiotic-use data.

A first attempt to collect data on antibiotic consumption within the ESAC project focussed on a retrospective data collection for the period 1997–2002, separately for ambulatory care and hospitals. It was the intention to assess the accessibility and validity of the data as well as the strengths and weaknesses of national systems. A first report presented the 2002 data of outpatient consumption.[5] This paper will highlight the trends over the entire 6-year period, the regional differences and the seasonal fluctuations of outpatient antibiotic consumption in Europe.

METHODS

Data collection was organised using a network of dedicated national representatives (predominantly microbiologists) who built a national data collection network with the interested constituencies in their country (data providers, public health authorities and the national body coordinating antibiotic policy). All European countries were invited to take part in the ESAC project and 32 countries participated in 2002.

Antibiotic consumption data were classified according to the Anatomical Therapeutic Chemical (ATC) classification (version 2003), as recommended by the World Health Organisation.[6] Data collection was limited to systemic antibiotics for human use and was collected in an aggregated format at the level of the active ingredient (level 5 of the ATC class J01). The volume of consumption was expressed in defined daily doses (DDDs), that is, the number of assumed average maintenance doses per day for a drug used for its main indication in adults in a given area and time. To enable international comparison, antibiotic consumption per country was standardised for population size expressing the volume in DDD per 1000 inhabitants per day (DID).

A more complete description of the origin of the ESAC data, details of the methodology used and an in-depth discussion on the validity of the collected data was published in a separate article.[7]

In this paper, consumption of antibiotics in ambulatory care will be presented for the 24 countries able to deliver valid and comprehensive data in 2002. Included countries were all EU countries except Cyprus Lithuania and Malta plus two additional countries, Norway and Croatia.

For longitudinal trend analysis, the dataset was limited to 18 countries delivering comprehensive data for at least 5 years. Fourteen of them delivered data for the entire 6-year period. In three countries (Austria, Czech Republic and Hungary) data collection only started in 1998. For these countries, data of 1997 were substituted by the data of 1998. For studying the seasonal variation in antibiotic consumption, 13 datasets with complete data on a quarterly base were used (data not available for France, Germany, Ireland, Luxembourg and Spain).

For in-depth analysis and to follow the evolution over time, the main class of cephalosporins was divided in the four generations of cephalosporins as described in the recent version of the ATC classification.[9]

Statistical analysis

Overall and subgroup comparison of antibiotic consumption between 1997 and 2002 was performed using the non-parametric Wilcoxon signed rank test for related samples. Trend analysis on total consumption was investigated using the General linear model (GLM) statistics for repeated measures.

European countries were geographically clustered in North (Norway, Sweden, Denmark, Finland, Ireland, UK, The Netherlands, Germany, Austria), South (Portugal, Spain, Italy, Greece, France, Belgium, Luxembourg) and East (Estonia, Latvia, Poland, Czech Republic, Slovakia, Hungary, Slovenia, Croatia). Enforced clustering was tested using the canonical discriminant function showing an eigen value of 2.02, a canonical correlation of 0.82 and a $p < 0.001$ for the Wilks Lambda test. Antibiotic consumption between clusters was compared using the non-parametric Kruskal–Wallis test completed with a paired comparison using the Mann–Whitney U test. For all statistical analysis the SPSS statistical package was used and a two-sided p-value of $p < 0.05$ was considered as the significance level.

RESULTS

At the European level, total use of antibiotics in ambulatory care remained at a median level of about 20 DID with a peak consumption in 1999 and a slight tendency to decrease in recent years (Figure 1) (GLM for repeated measures $p = 0.315$, not significant). In Table 1, antibiotic consumption patterns of 1997 and 2002 were compared, for total consumption as well as for the relative frequency of different antibiotic classes. Over the 6-year period, antibiotic use showed a decrease of more than 10% in the United Kingdom and Hungary. An increase of more than 10% was observed in Portugal and Ireland and of more than 20% in Greece and Poland.

A wide variation was observed in the total antibiotic consumption in Europe, ranging from 9.8 DID in The Netherlands to 32.2 DID in France in 2002. A group of countries, showing an extremely high consumption

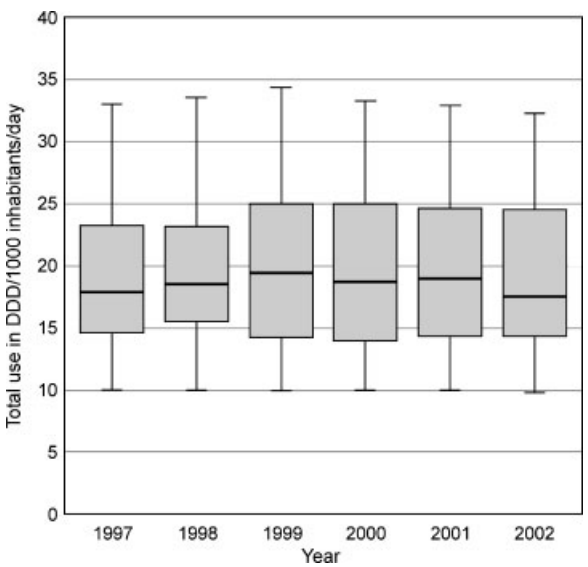

Figure 1. Evolution of total antibiotic use in ambulatory care 1997–2002 ($n = 18$ countries)

Table 1. Antibiotic use in ambulatory care in European countries: evolution 1997–2002

Country	Total use		Total use	Penicillins		Cephalosporins		Tetracyclines		Macrolides		Quinolones		Sulfonamides		Others	
	DDD/1000 in h/day		Index 2002	J01C		J01D		J01A		J01F		J01M		J01E		J01B/G/R/X	
	1997	2002	(1997=100)	% 1997	% 2002	% 1997	% 2002	% 1997	% 2002	% 1997	% 2002	% 1997	% 2002	% 1997	% 2002	% 1997	% 2002
NL	10.2	9.8	96	38	39	1	1	26	24	11	13	8	8	8	7	8	8
AT	13.0	12.3	95	37	41	12	11	10	8	27	24	8	11	5	4	0	0
DE	13.5	13.1	97	32	34	9	9	23	21	18	17	5	9	9	8	3	3
DK	12.2	13.3	109	60	63	0	0	8	8	17	16	2	1	6	6	7	6
UK	16.6	14.3	86	47	46	6	5	20	22	16	15	3	3	7	7	1	2
HU	18.6	15.2	81	44	46	14	12	14	11	15	16	5	8	8	6	0	0
SE	14.6	15.5	106	49	47	4	3	20	20	7	6	7	7	5	5	8	12
SI	17.5	16.4	94	57	58	5	4	5	4	17	18	8	8	7	7	0	0
CZ	18.3	17.1	94	44	43	7	6	16	18	14	14	5	6	9	7	5	6
FI	19.4	18.0	93	30	28	12	13	25	22	9	12	3	5	11	10	9	11
ES	21.3	19.6	91	54	54	12	11	4	4	16	16	10	13	4	2	1	1
IE	17.3	19.0	110	54	49	9	10	19	18	11	13	2	4	4	5	0	1
PL	16.6	21.1	128	35	47	11	10	22	18	9	11	5	5	15	6	2	3
BE	25.4	24.5	97	37	40	16	14	17	11	13	13	7	13	3	2	7	7
PT	23.2	26.5	114	44	49	14	12	8	5	13	13	13	14	5	3	2	3
LU	25.8	26.8	104	34	39	19	18	15	9	18	16	6	10	3	2	5	5
GR	25.1	30.6	122	38	32	25	22	11	9	17	25	4	8	4	2	2	1
FR	33.0	32.2	98	52	51	14	11	9	11	16	16	6	7	2	2	1	3
EE		11.7			39		5		23		10		5		9		10
LV		12.6			56		3		23		2		5		1		9
NO		14.8			38		2		21		13		3		7		16
HR		21.6			52		16		8		8		7		8		0
SK		22.1			55		8		11		16		6		4		0
IT		25.3			44		14		1		20		15		3		3

pattern of more than 25 DID could be distinguished, including three European countries of the Mediterranean area and Luxembourg. On the other hand, a low consumption pattern of less than 15 DID was observed in the Scandinavian countries, the Baltic States, England, The Netherlands, Germany and Austria (Table 1).

In Figure 2, the consumption of the main classes of antibiotics is given for 2002. Penicillins (ATC class J01C) were the most commonly used antibiotics in Europe with a median use of 9.0 DID, representing 46% of total antibiotic consumption. The other classes amounted to smaller segments of consumption: cephalosporins (median 1.9 DID), tetracyclines (median 2.7 DID) and macrolides (median 2.4 DID), quinolones (median 1.5 DID) and sulfonamides (median 0.8 DID). Consumption of most classes of antibiotics varied widely among European countries, with relatively highest variation observed for penicillins, cephalosporins and macrolides (see also Table 1).

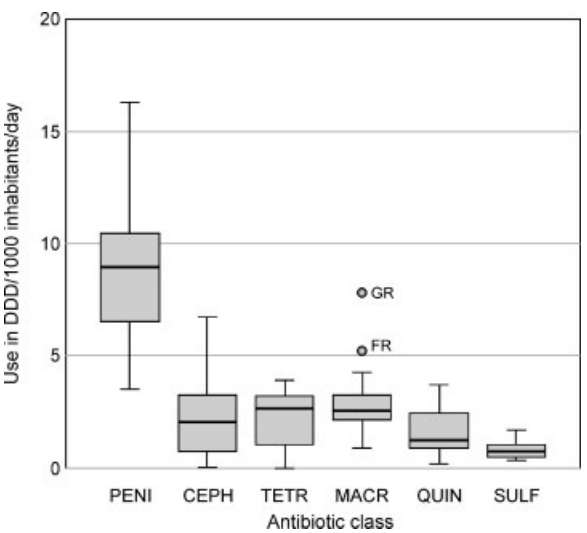

Figure 2. Consumption of main antibiotic classes in ambulatory care in 2002 ($n = 24$ countries)

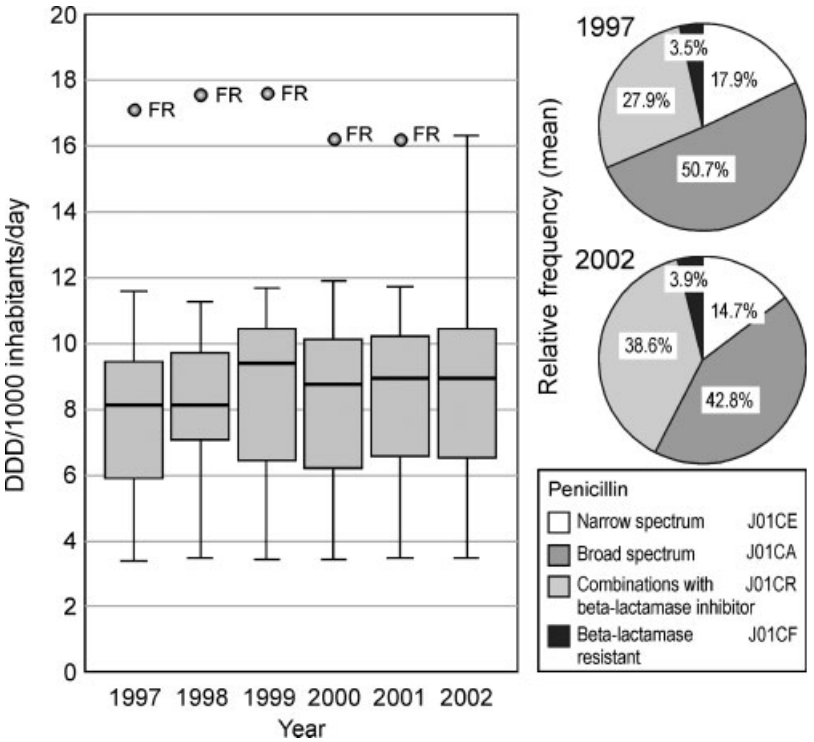

Figure 3. Evolution of penicillin use in ambulatory care 1997–2002 ($n = 18$ countries)

Use of penicillins

The median use of penicillins rose slightly from 8.1 to 9.0 DID in 2002 ($p = 0.500$) (Figure 3) with a peak consumption in 1999. Compared to 1997, the 2002 consumption pattern showed a proportional increase in co-amoxiclav use ($p = 0.001$) compensated by a decrease in narrow-spectrum ($p = 0.004$) as well as broad-spectrum penicillin use ($p = 0.020$) (Figure 3). The relative frequency of penicillin use on total use ranged from 28% in Finland to 63% in Denmark in 2002 (Table 1). This relative frequency remained rather stable per country over the 6-year period except in Poland where penicillin use increased from 35% of total consumption in 1997 to 47% in 2002.

Use of cephalosporins

As shown in Figure 4, median use of cephalosporins remained at the same level in recent years in Europe. A wide variation was observed in AC use of cephalosporins per country ranging from 0.03 in Denmark to 6.74 DID in Greece in 2002. In the latter country, cephalosporin use accounted for 22% of total antibiotic consumption. Comparing 1997 and 2002 consumption per country, the proportional use of cephalosporins remained remarkably stable (Table 1). A decrease in the use of first generation cephalosporins ($p = 0.002$) could be noted (Figure 4), while the consumption of second and third generation cephalosporins slightly increased (not significant). The ambulatory care use of fourth generation cephalosporins accounted for less than 1% of total cephalosporin consumption.

Use of macrolides, which include lincosamides and streptogramins

The median use of macrolides slightly decreased from 2.7 in 1997 to 2.4 DID in 2002 ($p = 0.744$). Also in this class, a peak consumption was noticed in 1999. All countries, except Sweden, showed a decrease in their erythromycin use. The average market segment of erythromycin among the macrolides decreased from 22.0% in 1999 to 12.8% in 2002 ($p < 0.001$) (Figure 5)

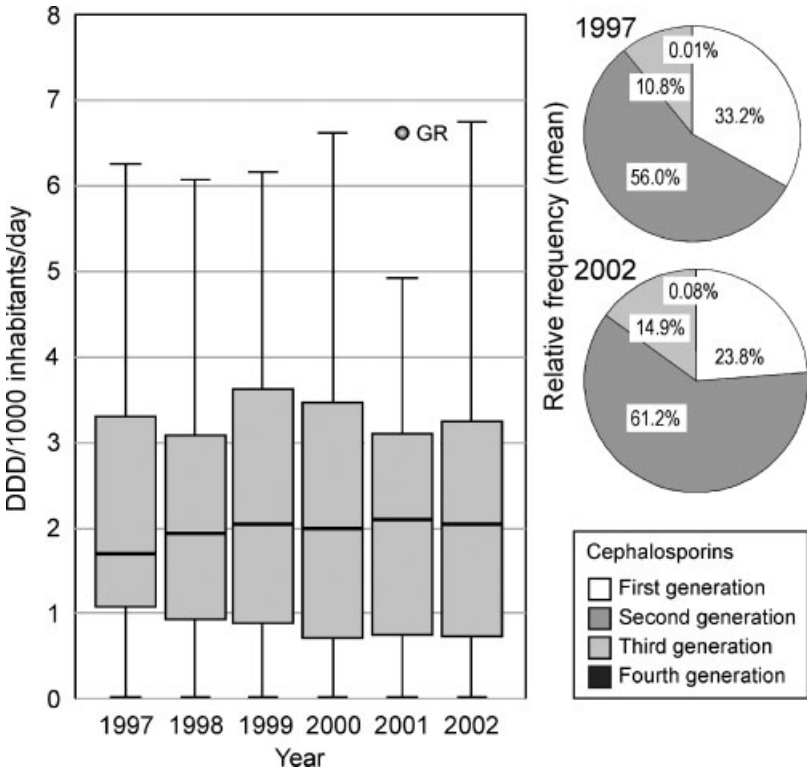

Figure 4. Evolution of cephalosporin use in ambulatory care 1997–2002 ($n = 18$ countries)

Use of quinolones

Quinolone consumption increased from a median of 0.89 in 1997 to 1.23 DID in 2002 ($p < 0.001$) (Figure 6), accounting for 1–14% of total consumption per country (Table 1). The penetration of moxifloxacin was limited to an average market segment among the quinolones of 6.3% in 2002, reaching a more substantial market volume only in Belgium.

Use of other antibiotics

Overall use of tetracyclines slightly decreased from a median of 2.9 in 1997 to 2.7 DID in 2002 ($p = 0.053$). A wide variation in the use of tetracyclines between countries could be observed with a relative frequency ranging from 1% to 23% (Table 1). Per country, only slight variation in the 6-year period could be noted. Consumption of sulfonamides decreased from a median of 0.85 in 1997 to 0.82 DID in 2002 ($p < 0.001$) with limited variation between and within countries.

Regional differences in antibiotic consumption

Total ambulatory care use of 2002 differed significantly between clusters ($p = 0.001$) and was low in the North, moderate in the East and high in the South (Figure 7). Within clusters, variation was limited in the North and the South and more extended in the East. The same analysis performed for each antibiotic class separately, revealed an identical significant pattern of clustering for penicillins ($p = 0.005$), cephalosporins ($p = 0.002$), macrolides ($p = 0.001$), quinolones ($p < 0.001$) and sulfonamides ($p = 0.013$). Only for tetracyclines, regional clustering could not be demonstrated ($p = 0.362$).

Seasonal fluctuation of antibiotic consumption

The seasonal fluctuation of AC antibiotic consumption revealed different patterns of variation between summer and winter consumption (Figure 8). In countries belonging to the Northern cluster, seasonal fluctuations showed a mean variation of 23% between

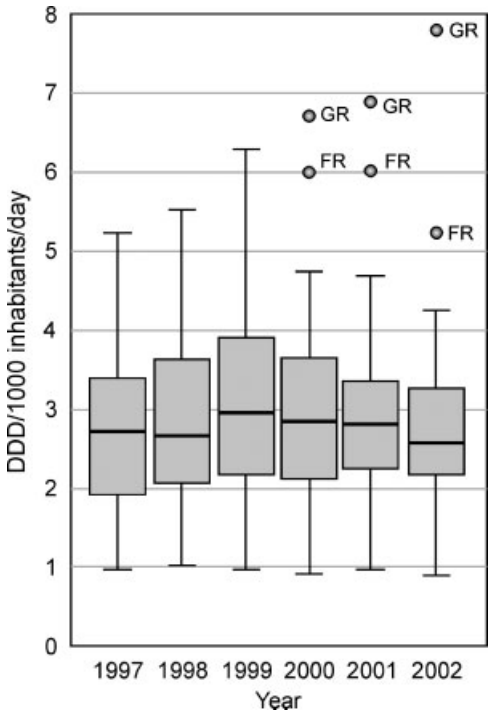

Figure 5. Evolution of macrolide use in ambulatory care 1997–2002 ($n = 18$ countries), including lincosamides and streptogramins.

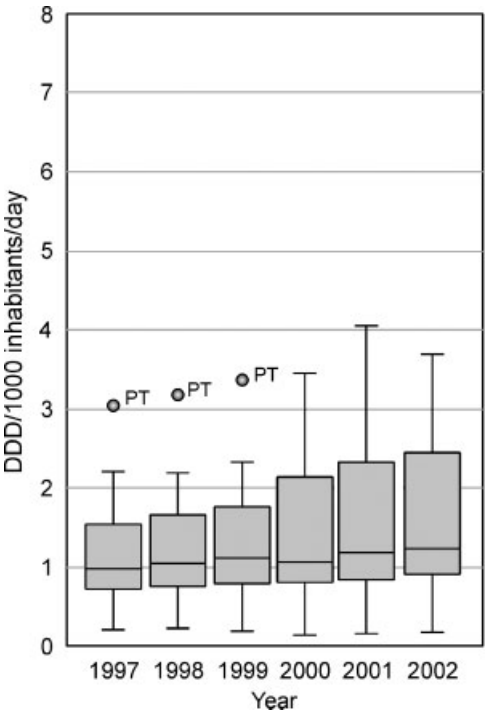

Figure 6. Evolution of quinolone use in ambulatory care 1997–2002 ($n = 18$ countries)

the consumption in the summer period (mean consumption of quarter 2 plus quarter 3) and the winter period (mean consumption of quarter 4 plus quarter 1 of the following year). In contrast, countries of the South with a high total consumption, showed in winter a mean increase of 38% above summer consumption with more pronounced peaks in their consumption patterns. Countries of the East showed a mean winter increase of 42%. From Figure 8, it is clear, however, that in recent years the seasonal fluctuation pattern of Hungary, Czech Republic and Slovenia becomes more comparable with the North, coinciding with a decrease in total use.

DISCUSSION

The retrospective data collection of the ESAC project for the period 1997–2002 revealed a rather constant consumption pattern of antibiotics in Europe over time with a high variation between countries ranging from less than 10 DID (The Netherlands) to more than 30 DID (France). Although a slight decrease in total consumption in recent years was observed, this observation needs to be handled with caution. The small peak in 1999 of the overall consumption as well

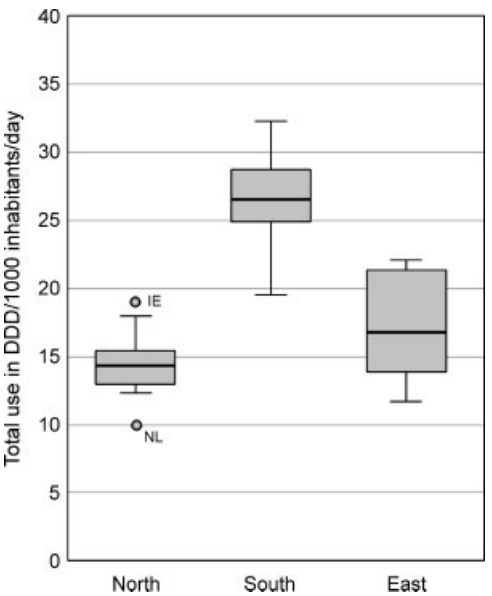

Figure 7. Regional differences in antibiotic use in 2002 ($n = 24$ countries)

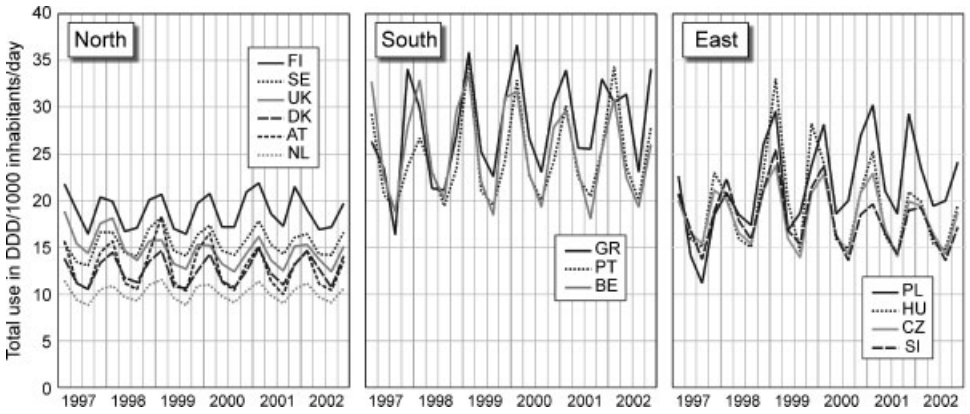

Figure 8. Seasonal fluctuations in antibiotic use 1997–2002 ($n = 13$ countries)

as the consumption of penicillins and macrolides, might have been induced by a higher rate of respiratory tract infections and influenza in that year, as observed in some eastern European countries.[8,9]

ESAC was the first project capable to establish a data collection system on the volume of medicinal consumption at the national level over several years with data deriving from public sources of most of the European countries. There are several reasons why ESAC succeeded. First, within the ESAC project data collection was limited to antibiotics and did not cover total drug consumption as was the case in several other projects. Second, the emergence of resistance and the attention spent to this problem at the European level in recent years, facilitated the willingness of the national official bodies to release and deliver data on antibiotics. Third, the lessons learned from previous attempts were taken into account[3] and the ESAC policy consisted in an approach directed to the real data providers with a close follow-up of all actions at the national level. Fourth, clear guidance was offered for the use of the ATC/DDD classification as for the format of data delivery.

After data collection, data were rigorously checked for validity. Only data considered as valid or with minor bias were used for international comparison.[7] Minor biases were mainly caused by the need for extrapolation to cover the entire population (e.g. The Netherlands, Poland), the underestimation of total consumption due to documented and/or expected over-the-counter sales of antibiotics (e.g. Spain), the overestimation of total consumption due to parallel export (e.g. Greece), difficulties to split between ambulatory care and hospital consumption (e.g. Finland) and the particularities of some reimbursement systems not covering cheap antibiotics (e.g. Austria).

International comparison of antibiotic consumption data for ambulatory care revealed a wide variation in antibiotic use ranging from the low figure of The Netherlands to the threefold in France. This wide variability had an important influence on the amount of antibiotic consumption in particular classes, which could be clearly demonstrated for the AC use of cephalosporines, macrolides and quinolones. The amount of consumption of these classes was highly correlated with the amount of total consumption. This should be kept in mind while exploring the relationship between specific resistance patterns and the exposure to a particular class of antibiotics within each country.

The ESAC project demonstrated once more that there is a huge variability in antibiotic consumption patterns across Europe. On the one hand, we could identify the countries of the North with a stable low consumption pattern, low seasonal variation and rational consumption profiles. On the other hand, there are the countries of the South with known erratic consumption profiles despite national attempts to decrease their antibiotic consumption patterns. Question remains how this wide variability has been established and why it still exists. There is an urgent need for a better understanding of the dynamics of consumption. The remarkable cluster formation of consumption patterns in Europe emphasises the importance of socio-cultural determinants of antibiotic use.[10]

Detailed, reliable and long standing time series of antibiotic consumption data are now publicly available[11] enabling to identify determinants of use, to

evaluate established antibiotic policies and to unravel the complex relationship between consumption and resistance. For researchers in the field of pharmacoepidemiology, the ESAC results shows that drug consumption data can be collected at the European level using the appropriate methods and collaborating with the appropriate organisations within each country.

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