J Antimicrob Chemother 2011; **66** Suppl 6: vi3–vi12
doi:10.1093/jac/dkr453

Journal of Antimicrobial Chemotherapy

European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997–2009)

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Objectives: To describe total outpatient systemic antibiotic use in Europe from 1997 to 2009 and to analyse statistically trends of total use and composition of use over time.

Methods: For the period 1997–2009, data on outpatient use of systemic antibiotics aggregated at the level of the active substance were collected and expressed in defined daily doses (WHO, version 2011) and packages per 1000 inhabitants per day (DID and PID, respectively). Outpatient antibiotic (ATC J01) use in DID in the 33 European countries able to deliver valid data was analysed using longitudinal and compositional data analyses.

Results: Total outpatient antibiotic use in 2009 varied by a factor of 3.8 between the countries with the highest (38.6 DID in Greece) and lowest (10.2 DID in Romania) use. For Europe, a significant increase was found in total outpatient antibiotic use, as well as a significant seasonal variation, which decreased over time from 1997 to 2009. Relative use of penicillins and quinolones significantly increased over time with respect to sulphonamides and trimethoprim, and relative use of quinolones increased with respect to macrolide/lincosamide/streptogramin as well. More detailed analyses of these major antibiotic subgroups will be described in separate papers.

Conclusions: Outpatient antibiotic use in Europe measured as DID has increased since 1997, whereas seasonal variation has decreased over time. European Surveillance of Antimicrobial Consumption (ESAC) data on outpatient antibiotic use in Europe enable countries to audit their antibiotic use. Complemented by longitudinal and compositional data analyses, these data provide a tool for assessing public health strategies aimed at reducing antibiotic resistance and optimizing antibiotic prescribing.

Keywords: drug consumption, pharmacoepidemiology, ambulatory care

Introduction

The European Surveillance of Antimicrobial Consumption (ESAC) project is an international network of surveillance systems with the aim of collecting comparable and reliable data on antimicrobial use in Europe.[1] The ESAC project started in 2001, following the 'Council recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine', in order to accompany analogous surveillance programmes on resistance.[2] Since then, the ESAC network has expanded to a network of 35 European countries. This paper is the first of a series updating an earlier series of papers on outpatient antibiotic use in Europe (1997–2003).[3–7] In this series we will also update brief reports focusing on penicillin, cephalosporin, macrolide and quinolone use, as well as data on indicators to assess the quality of outpatient antibiotic use in Europe developed within ESAC.[8–12] In addition, outpatient use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials will be discussed in a separate paper.[13] Descriptions of trends of use (1997–2009), seasonal variation and composition of use will be completed using modern statistical methods, as described in two tutorial papers.[14,15]

Methods

Participants

Thirty-five countries have been included in the ESAC project, comprising all 27 EU Member States, 3 European Economic Area/European Free Trade Association (EEA/EFTA) countries (Iceland, Norway and Switzerland), 3 candidate countries (Croatia, Former Yugoslavian Republic of Macedonia and Turkey) and 2 other countries (Russian Federation and Israel).

ATC/DDD classification system

Use data of systemic antibiotics for ambulatory care for the period 1997–2009, aggregated at the level of the active substance, were collected in accordance with the Anatomical Therapeutic Chemical (ATC) classification and the defined daily dose (DDD) measurement unit (WHO, version 2011).[16]

Within the ATC subgroup J01 (i.e. antibacterials for systemic use, excluding topical antibiotics), 229 unique chemical substances (ATC-5 level) were listed for antibiotics or their combinations, aggregated into 33 chemical subgroups (ATC-4 level) and subsequently into 10 pharmacological subgroups (ATC-3 level), which were used in this paper.

Data collection

Each country was asked to deliver data at product level, i.e. using a unique identifier for each of the medicinal product packages available in their country. Information on the number of packages consumed for each product had to be accompanied by an exhaustive and valid national register file including information on the number of DDD and route of administration (RoA). In 2009, 16 countries not able to deliver data at product level provided data on the number of DDD at ATC-5 level, including information on RoA.

In addition, information was collected on data source and data coverage (Table S1, available as Supplementary data at *JAC* Online). In 2009, 22 countries provided sales data and 10 countries reimbursement data (for Switzerland only, sales data from 2004 were available). Reimbursement data were collected by the third-party payer on the basis of financial claims from legitimate beneficiaries. Distribution or sales data were based on reports from the pharmaceutical companies, wholesalers, pharmacies or marketing research companies.

Use data were expressed in DDD per 1000 inhabitants per day (DID) and packages per 1000 inhabitants per day (PID). In most of the participating countries, the denominator was based on the WHO mid-year population.[17] Some countries provided denominator data originating from their national statistical office (Cyprus, France, Germany, Portugal, Spain, Sweden and the UK). For Germany, Israel, Luxembourg, the Netherlands and Portugal, the insured population was used as the denominator.

Data coverage in 2009 was 100% for most countries, 98% for Belgium, >95% for Luxembourg, 90% for Germany and the Netherlands, 77% for Portugal and 55% for Israel as only the Haifa region is included.

Some countries were only able to provide total care (TC) data, i.e. including both ambulatory and hospital care data, e.g. Cyprus and Lithuania. Greece provided TC data for 2004–08, Bulgaria and Iceland up to 2005 and Estonia for 2001. These data were, however, also included, because ambulatory care use data represent >90% of the total use.[18]

Data validation

Use data and register files, if provided, were checked for inconsistencies. This was supported by the ESAC Collect Manager Application, which was used to upload the data into the ESAC core database and generate a standard validation report. For each country, this report was sent to the ESAC Lead National Representative for approval. More information on the data collection and validation can be found in the ESAC Yearbook 2009[19] and previous yearbooks.[20–22]

Analysis

To provide a detailed description of outpatient antibiotic use in 2009 in DID and PID, the number of DDD per package was calculated by dividing DID by PID values per country. Quarterly outpatient antibiotic use data in DID were statistically modelled to assess use and seasonal variation of use and their trends from 1997 to 2009 for Europe, using longitudinal data analysis.[14] Through compositional data analysis, annual outpatient use data in DID were modelled to assess trends of the relative proportions of the major antibiotic subgroups from 1997 to 2009 for Europe.[15] For both the longitudinal and compositional data analyses applied in this series, the two tutorial papers provide a practical overview of the methodology.[14,15] In addition, we describe use and seasonal variation of use in DID and their trends, and also trends of the relative proportions of the major antibiotic subgroups from 1997 to 2009 for individual countries.

Results

Of the 35 countries included in the ESAC network, 33 had data that were valid for further analysis (not Former Yugoslavian Republic of Macedonia and Turkey). Table 1 provides data on outpatient antibiotic use in these countries from 1997 to 2009 and shows an increasing availability of valid data, from 14 countries in 1997 to 26 in 2003 and 32 in 2009. Fourteen countries were able to deliver data for all 13 years (1997–2009), of which eight delivered data on a quarterly basis.

Outpatient antibiotic use in 2009

Figure 1 shows total outpatient antibiotic use in 33 European countries for 2009 expressed in DID. For Switzerland, antibiotic use data were delivered in 2004 only and are therefore also depicted in Figure 1 but are not included in further analyses. Consumption is broken down into eight major antibiotic groups according to the ATC classification: penicillins (J0IC; β-lactam antibacterials, penicillins); cephalosporins (J01D; other β-lactam antibacterials); macrolides (J01F; macrolides, lincosamides and streptogramins); quinolones (J01M; quinolone antibacterials); tetracyclines (J01A; tetracyclines); sulphonamides (J01E; sulphonamides and trimethoprim); urinary antiseptics (J01X; other antibacterials); and other antibiotics [concatenation of amphenicols (J01B), aminoglycosides (J01G) and combinations of antibacterials (J01R)].[16] Outpatient antibiotic use varied by a factor of 3.8 between the country with the highest use (38.6 DID in Greece) and the country with the lowest use (10.2 DID in Romania). The median was 19.0 DID and the interquartile range was 15.1–23.1 DID. Penicillins were the most frequently prescribed antibiotics in all countries, ranging from 29% (Germany) to 66% (Slovenia) of total outpatient antibiotic use. The proportion within total outpatient use of cephalosporins ranged from 0.2% (Denmark) to 26%

Table 1. Yearly outpatient antibiotic use in 33 European countries, expressed in DID (1997–2009)

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Austria	—	12.62	13.13	12.29	11.79	11.76	12.48	12.52	14.47	14.28	14.70	15.08	15.93
Belgium	25.44	26.36	26.21	25.26	23.73	23.82	23.80	22.71	24.29	24.16	25.40	27.66	27.52
Bulgaria	—	—	15.11	20.18	22.66	17.29	15.54	16.39	18.00	18.15	19.79	20.56	18.59
Croatia	—	—	—	18.42	18.51	22.65	23.42	22.95	23.38	21.20	22.49	23.37	21.21
Cyprus	—	—	—	—	—	—	—	—	—	31.89	33.86	32.78	34.44
Czech Republic	—	18.21	18.58	—	—	17.14	16.70	15.85	17.32	15.94	16.83	17.41	18.44
Denmark	12.22	12.75	12.13	12.30	12.82	13.24	13.52	14.05	14.62	15.17	16.11	15.97	15.97
Estonia	—	—	—	—	14.37	11.66	11.08	10.40	11.70	11.79	12.68	11.88	11.07
Finland	19.38	18.44	18.44	19.04	19.77	17.90	18.73	17.20	18.11	17.42	18.35	17.91	17.96
France	33.09	33.63	34.13	33.22	33.15	32.23	28.86	26.98	28.89	27.91	28.63	27.99	29.58
Germany	13.05	13.26	13.57	13.64	12.76	12.72	13.90	13.01	14.61	13.61	14.46	14.54	14.90
Greece	25.06	24.86	28.50	29.37	29.56	30.62	31.32	33.01	34.73	41.05	43.18	45.21	38.64
Hungary	—	18.30	23.45	18.53	18.58	17.08	19.14	18.18	19.54	17.19	15.46	15.18	15.98
Iceland	22.19	23.14	21.74	20.47	20.00	20.64	20.34	21.44	23.24	20.01	19.20	20.64	19.46
Ireland	—	16.45	18.02	17.60	18.69	18.70	20.12	20.24	20.54	21.23	22.96	22.42	20.76
Israel	—	—	—	—	—	19.55	20.06	19.64	20.55	22.17	20.23	22.04	22.42
Italy	—	—	24.47	23.98	25.50	24.32	25.61	24.78	26.20	26.66	27.57	28.46	28.66
Latvia	—	—	—	—	—	11.01	—	11.77	12.28	12.01	12.07	10.95	10.48
Lithuania	—	—	—	—	—	—	—	—	—	22.65	24.11	25.10	19.72
Luxembourg	27.23	26.89	28.19	27.14	27.57	27.52	28.58	24.90	26.34	25.06	27.22	27.12	28.19
Malta	—	—	—	—	—	—	—	—	—	—	17.88	20.81	21.59
Netherlands	10.09	9.94	10.02	9.81	9.87	9.81	9.79	9.75	10.51	10.85	11.05	11.24	11.39
Norway	—	15.31	—	—	15.58	15.73	15.61	15.66	16.75	14.81	15.50	15.53	15.23
Poland	—	20.69	22.19	22.65	24.77	21.37	—	19.12	19.61	—	22.15	20.69	23.59
Portugal	23.06	23.33	25.23	24.86	24.52	26.51	25.11	23.78	24.47	22.75	22.10	22.61	22.94
Romania	—	—	—	—	—	—	—	—	—	—	—	—	10.19
Russian Federation	—	—	—	—	—	—	9.75	9.26	9.06	9.58	10.23	9.96	12.20
Slovakia	—	—	25.70	27.60	29.08	26.65	27.64	22.50	25.09	22.49	24.77	23.40	23.78
Slovenia	17.51	19.30	19.76	18.01	17.35	16.32	16.99	16.71	16.26	14.71	16.02	15.03	14.42
Spain	21.34	20.56	19.97	18.96	18.00	18.01	18.93	18.54	19.29	18.71	19.90	19.70	19.68
Sweden	14.64	15.53	15.82	15.52	15.84	15.24	14.66	14.48	14.87	15.28	15.49	14.60	13.95
Switzerland	—	—	—	—	—	—	—	9.03	—	—	—	—	—
UK	17.01	16.16	14.84	14.29	14.80	14.79	15.14	14.96	15.45	15.33	16.47	16.92	17.27

—, no use reported.

(Malta), of macrolides from 5% (Sweden) to 30% (Greece), of quinolones from 3% (UK, Iceland, Denmark and Norway) to 16% (Russian Federation), of tetracyclines from 0.02% (Slovenia) to 26% (Iceland), of sulphonamides from 0.03% (Lithuania) to 10% (Latvia) and of urinary antiseptics from 0.02% (Slovenia) to 19% (Norway).

Figure 2 shows total outpatient antibiotic use in 17 European countries for 2009 expressed in PID. In addition, their ranking in decreasing order is depicted according to both DID and PID. Interestingly, the Russian Federation shifted from position 15 in DID (low-prescribing country) to position 3 in PID, and Belgium from position 3 in DID to position 9 in PID. The DDD per package ranged from 2.6 in Italy to 11.8 in Sweden.

Longitudinal data analysis (1997–2009)

For Europe, a significant increase in total outpatient antibiotic use of 0.05 (SD 0.02) DID per quarter was found, starting from 17.94 (SD 0.91) DID in the first quarter of 1997. There was also significant seasonal variation, with an amplitude of 4.18 (SD 0.37) DID, which decreased over time ($P=0.07$) by 0.01 (SD 0.01) DID per quarter (Figure 3). Furthermore, the longitudinal analysis shows that both the upward winter and downward summer peaks of outpatient antibiotic consumption shifted significantly from one year to another, and that there was a significant positive correlation between the volume of use and the seasonal variation. This means that, in terms of absolute amount, high-consuming countries tended to have high seasonal variation and vice versa.

Of the 20 countries providing comparable data, 8 showed an increase of >1 DID in 2009 compared with 1997 or 1998, whereas 5 showed a decrease of >1 DID in 2009 compared with 1997 or 1998 (Table 1 and Figure 4).

Figure 4 shows the seasonal data on antibiotic use for the 12 countries able to deliver quarterly data for the whole observation period and missing a maximum of 1 year of data. Data for

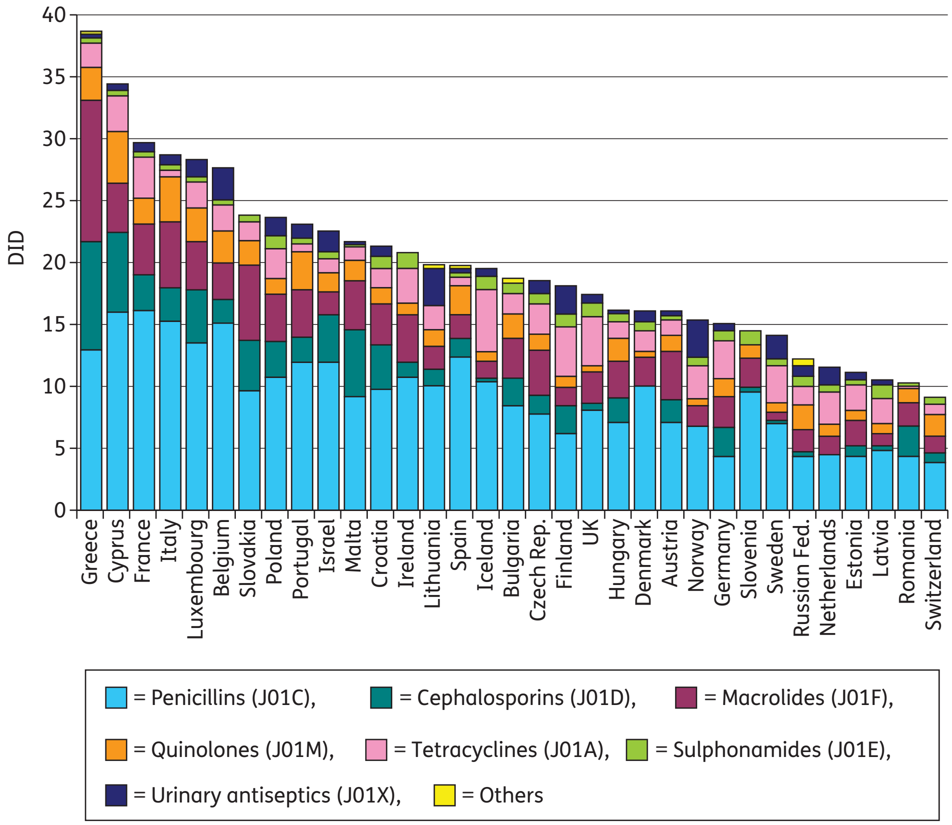


Figure 1. Total outpatient antibiotic use in 33 European countries in 2009 in DID (2004 data for Switzerland). For Cyprus and Lithuania, total care data are used. The category Cephalosporins includes carbapenems and monobactams; Macrolides includes lincosamides and streptogramins; Sulphonamides includes trimethoprim; Urinary antiseptics includes glycopeptide antibacterials, polymyxins, fusidic acid, imidazole derivatives, nitrofuran derivatives and other antibacterials; and Others includes J01B, J01G and J01R.

another 15 countries able to deliver seasonal data but missing more than 1 year of data are available online (Figure S1, available as Supplementary data at *JAC* Online). The median increase in total outpatient antibiotic use in the winter quarters (first and fourth) compared with the summer quarters (second and third) was 30% for 27 countries able to deliver quarterly data for at least 1 year and ranged from 11% in Cyprus to more than 50% in Lithuania and Hungary. In seven Northern European countries this seasonal variation was limited to <20% and in 13 countries it exceeded 30%.

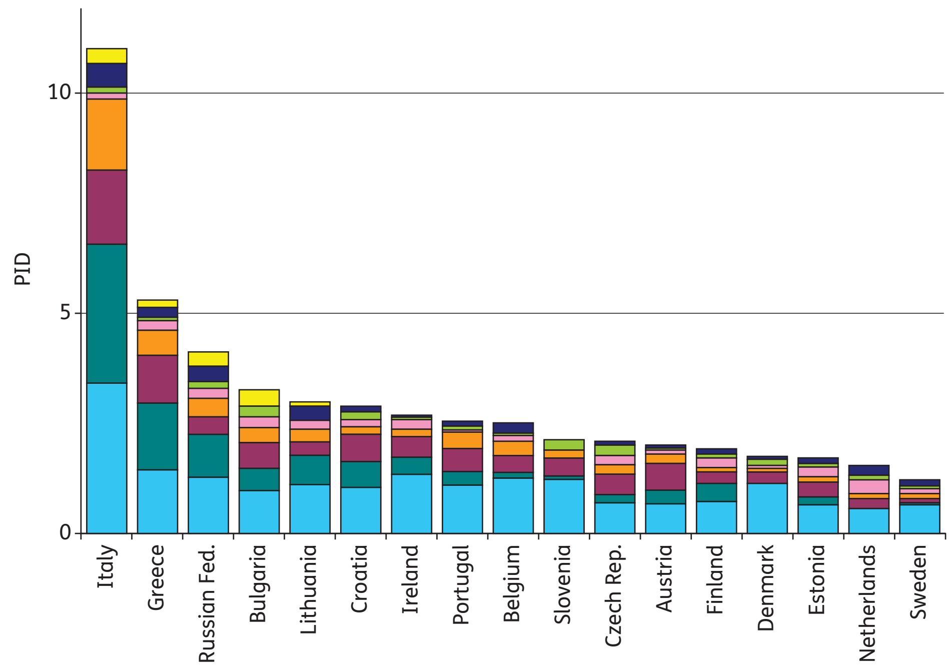
Compositional data analysis (1997–2009)

The relative use of quinolones significantly increased over time with respect to the use of macrolides and sulphonamides (Table 2). The relative use of penicillins increased over time with respect to the use of sulphonamides. No significant change was observed in the relative use of one of the major subgroups relative to another when outpatient antibiotic use increased (Table 3).

Trends of relative proportions of antibiotic subgroups according to the ATC/DDD classification are shown in Figure S2 (available as Supplementary data at *JAC* Online). In many countries the proportion of penicillins and quinolones increased over time, while the proportion of tetracyclines and sulphonamides was steadily decreasing. Some countries maintained a stable pattern of antibiotic use over the period of observation (Denmark, the Netherlands, Norway and the UK), while others showed substantial modifications, i.e. absolute differences of ≥10% between 1997 and 2009 (Belgium, Bulgaria, Greece, Latvia, Luxembourg, Slovakia and the Russian Federation).

Discussion

The volume of outpatient antibiotic use in DID increased in most European countries between 1997 and 2003,[3] and this trend continued between 2004 and 2009. Overall, the ranking of most countries remained the same. In all 33 European countries studied, penicillins were the most-used antibiotics and their proportional use further increased between 2004 and 2009. From 1997 to 2009, proportional use of quinolones increased markedly. Use of cephalosporins, tetracyclines and sulphonamides, three major subgroups of antibiotics, remained the same or decreased in most European countries. Striking geographical variations were observed in the use of various antibiotic subgroups. The narrow-spectrum penicillins and the first-generation cephalosporins are still mainly prescribed in Nordic countries, but their proportion is decreasing. Their use has almost disappeared in most Southern European countries. The increase in use over time of the newer (i.e. broad-spectrum) antibiotics, such as amoxicillin/clavulanic



Country	IT	GR	RU	BG	LT	HR	IE	PT	BE	SI	CZ	AT	FI	DK	EE	NL	SE
Ranking PID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ranking DID	2	1	15	8	7	5	6	4	3	13	9	12	10	11	17	16	14
DDD/package	2.6	7.3	3.0	5.7	6.6	7.4	8.6	9.0	10.9	6.8	8.1	8.1	9.5	9.3	6.5	7.4	11.8

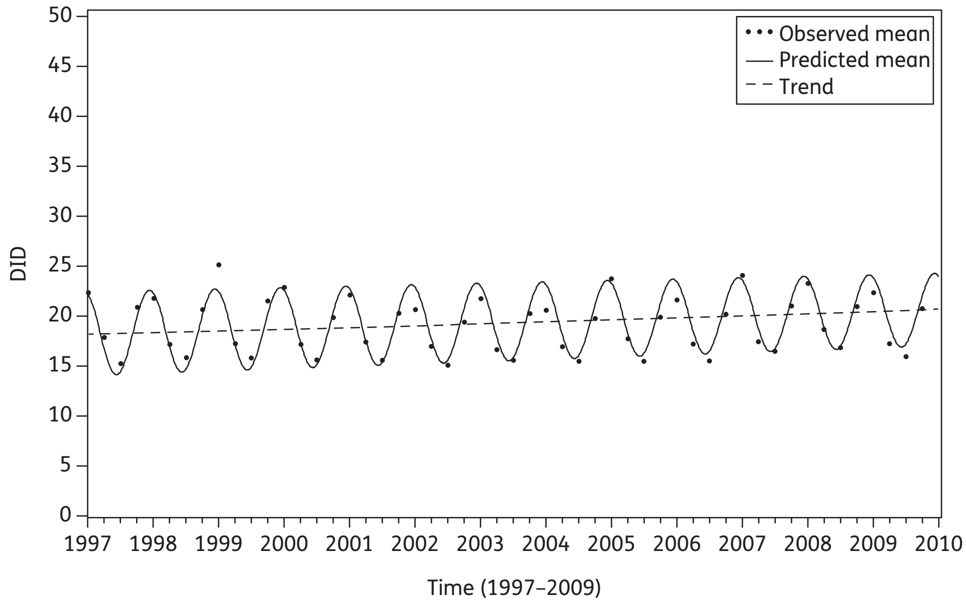
Figure 2. Total outpatient antibiotic use in 17 European countries in 2009 in PID, the ranking in DID versus PID, and the mean number of DDD per outpatient package. For Lithuania, total care data are used. For Italy, 2008 data are used. For the Czech Republic and Ireland, 2007 data are used. The category Cephalosporins includes carbapenems and monobactams; Macrolides includes lincosamides and streptogramins; Sulphonamides includes trimethoprim; Urinary antiseptics includes glycopeptide antibacterials, polymyxins, fusidic acid, imidazole derivatives, nitrofuran derivatives and other antibacterials; and Others includes J01B, J01G and J01R. AT, Austria; BE, Belgium; BG, Bulgaria; CZ, Czech Republic; DK, Denmark; EE, Estonia; FI, Finland; GR, Greece; HR, Croatia; IE, Ireland; IT, Italy; LT, Lithuania; NL, Netherlands; PT, Portugal; RU, Russian Federation; SE, Sweden; SI, Slovenia.

acid, macrolides and quinolones, has continued and will be described in detail in separate papers in this series.[8,10,11]

Seasonality of outpatient antibiotic use was observed in all countries and was significantly correlated with total outpatient antibiotic consumption. The highest seasonal variation (increase of >30% in the first and fourth quarters compared with the second and third quarters) was observed in high-consuming European countries, suggesting unnecessary antibiotic usage for viral infections. Although we observed an increase in outpatient antibiotic use over time in Europe, the seasonal variation of outpatient antibiotic use decreased over time, suggesting more appropriate prescribing.

In addition to the total outpatient antibiotic use in DID and its seasonal variation, other indicators to assess the quality of outpatient antibiotic use in Europe have been proposed by ESAC.[23] Quality assessment of the 2009 outpatient antibiotic use based on these quality indicators is described in a separate paper in this series.[12]

At the start of the project, ESAC opted for the DDD measurement unit, defined as the assumed average maintenance dose per day for its main indication in adults.[16] Because the DDD is a technical unit, albeit based on use in infections of moderate severity, expressing antibiotic use data in DDD is not always optimal. This is the case if the number of DDD per package (or prescription or person or treatment) differs substantially between the elements of a comparison, e.g. when comparing use between adults and children, between different countries or within a country over time. While most antibiotics are being prescribed for children,[24] antibiotic use for children in DID is underestimated as DDD takes into account the dosage used in



ATC	Parameters				
	β_0	β_1	$\beta_0{}^S$	$\beta_1{}^S$	δ
J01	17.941 (0.907)*	0.046 (0.022)*	4.179 (0.366)*	–0.010 (0.005)	0.413 (0.019)*

Figure 3. Estimated linear trend and seasonal variation of outpatient antibiotic use in Europe based on available quarterly data for 1997–2009. β_0 (intercept), predicted average outpatient use in the first quarter of 1997; β_1 (slope), predicted average increase (if positive)/decrease (if negative) in use per quarter; $\beta_0{}^S$ (seasonal variation), predicted average amplitude of the upward winter and downward summer peak in use; $\beta_1{}^S$ (damping effect), predicted average increase (if positive)/decrease (if negative) of the amplitude of the upward winter and downward summer peak in use per quarter; δ (phase shift), shift in timing of the upward winter and downward summer peak from one year to another. *Significant ($P<0.05$).

adults.[25] While the Russian Federation has a much higher antibiotic use in PID, its use in DID is underestimated because of its low number of DDD per package (3.0 DDD per package) (Figure 2). The opposite is true for Belgium, where use in DID is overestimated because of a higher number of DDD per package (10.9 DDD per package). Davey *et al*.[26] also illustrated that Belgium had a similar outpatient antibiotic use compared with the UK, and that it decreased over time in PID but not in DID. The difference in the observed trends in DID or PID for Belgium can again be explained by changes in the number of DDD per package over time. This number increased from 7 in 1997 to 9 in 2004 and to 11 in 2009, which limits the comparison of antibiotic use in DID in Belgium over time. To our knowledge, Sweden is the first country in Europe to set a target for its antibiotic use for each county by 2014 using the number of prescriptions instead of the number of DDD. Because Sweden has the highest DDD per package (11.8 DDD per package), setting a target based on prescriptions rather than DDD is more meaningful. This target has been set at 250 antibiotic prescriptions/1000 inhabitants/year per county, whereas their current national prescribing rate is 360 antibiotic prescriptions/1000 inhabitants/year.[27,28]

However, interpreting results in PID also has important limitations. Not all European countries are able to provide this type of data. Some countries dispense antibiotics in standard pack sizes, while in other countries, e.g. the Netherlands and the UK, single units are dispensed exactly following the doctor's prescription. Packages are used as a proxy for prescription but sometimes only half of the pack is necessary, while for other patients two or more standard packs are necessary. Finally, as mentioned above, pack size can change over years, often according to commercial interest or to guidelines proposing higher dosages to treat infections with antibiotic-resistant bacteria (e.g. β-lactams to treat pneumococci with intermediate resistance to penicillin).

For future surveillance of antibiotic consumption we propose a combination of outcome measures including the number of DID and PID, or prescriptions per 1000 inhabitants per day (PrID), and also information on the number of persons treated. For example, consumption of 1000 DDD per year could represent huge differences in the number of packs and persons treated depending on the number of DDD per package and the number of packages per person treated. It approximates to 300 packages per year in the Russian Federation (3 DDD per package) versus 90 packages per year in Belgium (11 DDD per package), and 90 packages per year could be equal to 90 persons treated per year (1 package per person treated) but could also be equal to 45 persons treated (2 packages per person treated). Therefore, further consolidation and quality enhancement of the surveillance of antibiotic consumption is crucial, e.g. collecting data that allow a more in-depth assessment of the relation between antibiotic consumption and antimicrobial resistance, and the effect of interventions to optimize antibiotic prescribing.

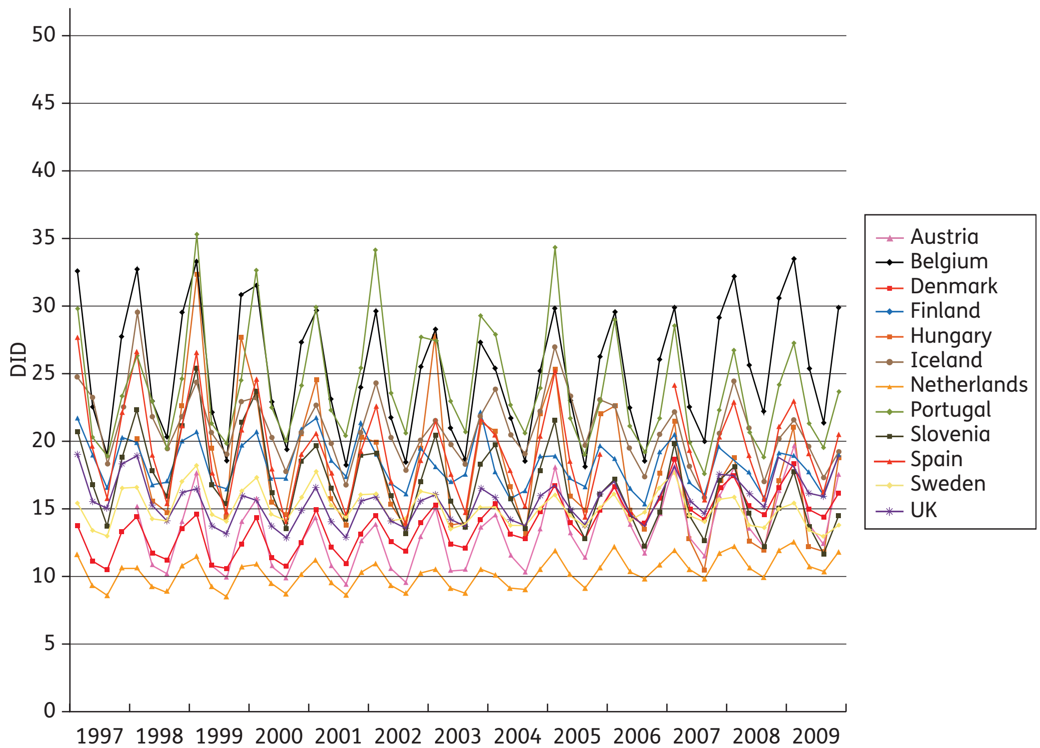


Figure 4. Seasonal variation in outpatient antibiotic use in 12 European countries able to deliver quarterly data for 1997–2009 and missing a maximum of 1 year of data.

Table 2. Change in composition of outpatient antibiotic use in Europe as a function of time

J01	A	C	D	E	F	M	X	Other
A		−0.168	−0.039	0.131	−0.108	−0.276	−0.291	−0.287
C	0.168		0.129	0.299*	0.060	−0.108	−0.123	−0.119
D	0.039	−0.129		0.171	−0.069	−0.237	−0.252	−0.247
E	−0.131	−0.299*	−0.171		−0.240	−0.408*	−0.423	−0.418
F	0.108	−0.060	0.069	0.240		−0.168*	−0.183	−0.179
M	0.276	0.108	0.237	0.408*	0.168*		−0.015	−0.011
X	0.291	0.123	0.252	0.423	0.183	0.015		0.005
Other	0.287	0.119	0.247	0.418	0.179	0.011	−0.005	

A, tetracyclines (J01A; tetracyclines); C, penicillins (J0IC; β-lactam antibacterials, penicillins); D, cephalosporins (J01D; other β-lactam antibacterials); E, sulphonamides (J01E; sulphonamides and trimethoprim); F, macrolides (J01F; macrolides, lincosamides and streptogramins); M, quinolones (J01M; quinolone antibacterials); X, urinary antiseptics (J01X; other antibacterials); other, other antibiotics [concatenation of amphenicols (J01B), aminoglycosides (J01G) and combinations of antibacterials (J01R)].
Values are estimated changes in the log ratio of the row versus column antibiotic type with increasing time.[15] Significant effects are indicated with an asterisk; positive values represent an increase and negative values represent a decrease.

More detailed data on antibiotic use linked to the patient's age and gender, the indication and prescriber characteristics could substantially broaden our interpretation of the striking variations between and within European countries. Linking antibiotic use data with age and gender seems feasible in most countries, while linking antibiotic use with indication is more challenging and mostly reported on sample data in single countries based on prescription databases.[29] Given the substantial non-adherence to antibiotic prescriptions, these prescription data have to be interpreted with caution.[30,31]

Although ESAC focused on national outpatient antibiotic use, regional data can display different and more meaningful results. ESAC collected subnational data for Ireland, Italy, Portugal, Sweden and the UK using the three-level hierarchical Nomenclature of Territorial Units for Statistics (NUTS) classification (data not shown).[32] We found differing rates of penicillin use for the

Table 3. Change in composition of outpatient antibiotic use in Europe as a function of total use

J01	A	C	D	E	F	M	X	Other
A		0.120	0.279	1.188	0.122	0.371	0.030	0.328
C	−0.120		0.158	1.067	0.002	0.251	−0.080	0.207
D	−0.279	−0.158		0.909	−0.157	0.092	−0.248	0.049
E	−1.188	−1.067	−0.909		−1.066	−0.817	−1.157	−0.860
F	−0.122	−0.002	0.157	1.066		0.249	−0.091	0.206
M	−0.371	−0.251	−0.092	0.817	−0.249		−0.340	−0.043
X	−0.030	0.080	0.248	1.157	0.091	0.340		0.297
Other	−0.328	−0.207	−0.049	0.860	−0.206	0.043	−0.297	

A, tetracyclines (J01A; tetracyclines); C, penicillins (J0IC; β-lactam antibacterials, penicillins); D, cephalosporins (J01D; other β-lactam antibacterials); E, sulphonamides (J01E; sulphonamides and trimethoprim); F, macrolides (J01F; macrolides, lincosamides and streptogramins); M, quinolones (J01M; quinolone antibacterials); X, urinary antiseptics (J01X; other antibacterials); other, other antibiotics [concatenation of amphenicols (J01B), aminoglycosides (J01G) and combinations of antibacterials (J01R)].
Values are estimated changes in the log ratio of the row versus column antibiotic type with increasing total use.[15] Significant effects are indicated with an asterisk; positive values represent an increase and negative values represent a decrease.

different regions within Italy, a high-consuming country, but also in low-consuming countries such as Sweden. For instance, in Italy a north–south gradient was observed, with much higher volumes of total outpatient antibiotic (mainly penicillins) use in the south (e.g. 39.9 DID in Campania and 34.9 DID in Sicily) as opposed to the north (e.g. 16.1 DID in the province of Bolzano).[33,34]

Nevertheless, the available ESAC data on outpatient antibiotic use in Europe enable countries to audit their antibiotic use by creating and maintaining a comprehensible, comparable and reliable reference database. The ESAC data have been shown to be a valuable data source not only for ecological studies on the relationship between antibiotic use and resistance,[18,35] but also for the evaluation of adherence to guidelines and policies and for the assessment of the outcomes of national and regional interventions.[36] We invite international organizations, such as WHO, to coordinate a global surveillance programme on outpatient antibiotic use and to propose common indicators of antibiotic use based on the ESAC experience.

Acknowledgements

The ESAC Lead National Representatives, on behalf of their respective ESAC National Networks, are: Helmut Mittermayer (deceased 6 July 2010), Sigrid Metz and Gerhard Fluch (Austria); Sofie Vaerenberg and Mathijs-Michiel Goossens (Belgium); Boyka Markova (Bulgaria); Arjana Tambic Andrašević (Croatia); Antonis Kontemeniotis (Cyprus); Jiří Vlček (Czech Republic); Niels Frimodt-Møller and Ulrich Stab Jensen (Denmark); Ly Rootslane and Ott Laius (Estonia); Jaana Vuopio-Varkila and Outi Lyytikainen (Finland); Philippe Cavalie (France); Winfried Kern (Germany); Helen Giamarellou and Anastasia Antoniadou (Greece); Gábor Ternák and Ria Benko (Hungary); Haraldur Briem and Olafur Einarsson (Iceland); Robert Cunney and Ajay Oza (Ireland); Raul Raz and Hana Edelstein (Israel); Pietro Folino (Italy); Andis Seilis and Uga Dumpis (Latvia); Rolanda Valinteliene (Lithuania); Marcel Bruch (Luxembourg); Michael Borg and Peter Zarb (Malta); Stephanie Natsch and Marieke Kwint (the Netherlands); Hege Salvesen Blix (Norway); Waleria Hryniewics, Anna Olczak-Pienkowska (until 2006), Malgorzata Kravanja and Tomasz Ozorowski (from 2007) (Poland); Mafalda Ribeirinho and Luis Caldeira (Portugal); Anda Băicuş and Gabriel Popescu (Romania); Svetlana Ratchina and Roman Kozlov (the Russian Federation); Viliam Foltán (Slovakia); Milan Čižman (Slovenia); Edurne Lázaro, José Campos and Francisco de Abajo (Spain); Ulrica Dohnhammar (Sweden); Giorgio Zanetti (Switzerland); and Peter Davey and Hayley Wickens (UK). More information on the ESAC project and the members of the ESAC Project Group is available at www.esac.ua.ac.be.

Finally, we would like to thank Klaus Weist [European Centre for Disease Prevention and Control (ECDC)] for his critical reading of the manuscript.

Funding

The 2005 data collection was funded by a grant from DG SANCO of the European Commission (Grant Agreement 2003211), whereas the 2006–09 data collection was funded by the ECDC (Grant Agreement 2007/001).

Transparency declarations

This article is part of a *JAC* Supplement sponsored by the ECDC and the University of Antwerp.

Conflicts of interest: none to declare.

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Supplementary data

Table S1 and Figures S1 and S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org).

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