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European Surveillance of Antimicrobial Consumption (ESAC): outpatient penicillin use in Europe

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***Background*: Data on outpatient penicillin use in Europe were collected from 25 countries within the ESAC project, funded by DG SANCO of the European Commission, using the WHO ATC/DDD methodology.**

***Methods*: For the period 1997–2003, data on outpatient use of systemic penicillins aggregated at the level of the active substance were collected and expressed in DDD (WHO, version 2004) per 1000 inhabitants per day (DID). Of the 'Penicillins' (J01C), outpatient use of narrow-spectrum penicillins (J01CE), broad-spectrum penicillins (J01CA), penicillinase-resistant penicillins (J01CF) and combinations with β-lactamase inhibitors (J01CR) in 25 European countries was analysed in detail.**

***Results*: Total outpatient penicillin use in 2003 varied by a factor of 4 between the country with the highest (15.27 DID in Slovakia) and lowest use (3.86 DID in the Netherlands). Narrow-spectrum penicillins, broad-spectrum penicillins and combinations with β-lactamase inhibitors were used most in 4, 12 and 9 countries, respectively. Penicillin use increased by more than 1 DID in nine countries, whereas it decreased by more than 1 DID in two countries (Czech Republic, France). An increase of the use of combinations with β-lactamase inhibitors by more than 10% in 10 countries coincided with an equal decrease of broad-spectrum penicillins in seven countries and narrow-spectrum penicillins in three countries.**

***Conclusion*: Penicillins represent the most widely used antibiotic class in all 25 participating countries; albeit with considerable variation of their use patterns. A distinct shift from narrow-spectrum penicillins to broad-spectrum penicillins, and specifically their combinations with β-lactamase inhibitors, was observed during the period 1997–2003.**

Keywords: antibiotic use, penicillins, drug consumption, pharmacoepidemiology, ambulatory care, Europe

Introduction

This paper describes outpatient use of 44 substances assigned to the ATC group J01C (comprising penicillins, β-lactamase inhibitors and their combinations)[1] and classified into five subgroups. Inter-country differences, temporal trends and seasonal variation of their use in 25 European countries are analysed in detail. Additional data are available on the ESAC website (www.ua.ac.be/ESAC).

Methods

The methods for collecting usage data of systemic antibiotics were described in the introductory paper of this series[2] and elsewhere.[3,4]

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Data on outpatient antibiotic use for the period 1997–2003 were collected in accordance with the ATC/DDD methodology. (WHO, version 2004)[1] and expressed in DDD per 1000 inhabitants per day (DID).

The 'Beta-lactam antibacterials, Penicillins' consists of five subgroups fully depicted in Table 1. As β-lactamase inhibitors are used almost entirely in combination with broad-spectrum penicillins, outpatient use of four major penicillin subgroups is analysed in this paper: narrow-spectrum penicillins (ATC class J01CE), broad-spectrum penicillins (J01CA), penicillinase-resistant penicillins (J01CF) and combinations of penicillins with β-lactamase inhibitors (J01CR).

Results

The use of only six penicillins represented more than 1% of the total outpatient penicillin use in 2003 in Europe (their cumulative share was 95.9%), while no use was recorded for 11 substances (Table 1). Figure 1 shows total outpatient penicillin use as well as the use of the four major subgroups. Total penicillin use in 2003 varied by a factor of 3.95 between the country with the highest (15.27 DID in Slovakia) and lowest (3.86 in the Netherlands) use.

Outpatient use varied even more for the narrow-spectrum penicillins (5.49 DID in Slovakia versus 0.01 in Italy), the broad-spectrum penicillins (8.14 DID in France versus 1.07 in Austria), combinations of penicillins with β-lactamase inhibitors (7.65 DID in Portugal versus 0.01 in Norway) and penicillinase-resistant penicillins (1.35 DID in Iceland versus 0.0001 in Greece; Table 2).

We observed that narrow-spectrum penicillins (mainly phenoxymethylpenicillin) still represented more than 60% of penicillin use in Norway, Sweden and Denmark, whereas in Belgium, France, Italy, Luxemburg, Portugal and Spain these drugs represented less than 2% of the total penicillin use. Penicillin-V (phenoxymethylpenicillin) was by far the most widely prescribed narrow-spectrum penicillin in most countries, except for Croatia, where benzathine phenoxymethylpenicillin (J01CE10) was largely used. Among the other oral narrow-spectrum penicillins, penamecillin was used in Hungary, Slovakia and the Czech Republic, clometocillin in Belgium and Luxembourg, whereas pheneticillin was exclusively prescribed in the Netherlands. Considerable use of long-acting parenteral antibiotics was recorded in Portugal, Germany, Slovakia, Estonia, Israel, the Netherlands, Italy and Croatia.

In most countries, the broad-spectrum penicillins (mainly amoxicillin) have become the most popular penicillins. Combinations of penicillins with β-lactamase inhibitors (mainly co-amoxiclav) represented in 2003 more than 50% of penicillin use in Austria, Belgium, Hungary, Luxemburg, Portugal and Spain, whereas this was the case in 1997 only in Belgium. The proportion of their use of the total outpatient antibiotic use varied from 0.2% in Norway to 64.3% in Portugal in 2003. Sultamicillin, another combination of penicillins with β-lactamase inhibitors available in some countries, was only used substantially in Slovakia (0.39 DID).

Use of ampicillin has been constantly decreasing in all European countries, even though more than 0.1 DID was still used in Hungary, Ireland, Italy, Estonia, Poland and Greece in 2003. Other broad-spectrum penicillins commonly used in

Table 1. Penicillins and their combinations classified in ATC J01C

Penicillins with extended spectrum	
J01CA01	**ampicillin**
J01CA02	pivampicillin
J01CA03	carbenicillin
J01CA04	**amoxicillin**
J01CA05	carindacillin[a]
J01CA06	bacampicillin
J01CA07	epicillin[a]
J01CA08	**pivmecillinam**
J01CA09	azlocillin
J01CA10	mezlocillin
J01CA11	mecillinam
J01CA12	piperacillin
J01CA13	ticarcillin[a]
J01CA14	metampicillin[a]
J01CA15	talampicillin[a]
J01CA16	sulbenicillin
J01CA17	temocillin[a]
J01CA18	hetacillin[a]
J01CA20	combinations[a]
J01CA51	ampicillin, comb.[a]
β-Lactamase-sensitive penicillins	
J01CE01	benzylpenicillin
J01CE02	**phenoxymethylpenicillin**
J01CE03	propicillin
J01CE04	azidocillin
J01CE05	pheneticillin
J01CE06	penamecillin
J01CE07	clometocillin
J01CE08	benzathine benzylpenicillin
J01CE09	procaine penicillin
J01CE10	benzath. phenoxymethylpen.
J01CE30	combinations
β-Lactamase-resistant penicillins	
J01CF01	**dicloxacillin**
J01CF02	cloxacillin
J01CF03	methicillin[a]
J01CF04	oxacillin
J01CF05	**flucloxacillin**
β-Lactamase inhibitors	
J01CG01	sulbactam
J01CG02	tazobactam[a]
Combinations of penicillins with β-lactamase inhibitor	
J01CR01	ampicillin and enzyme inhibitor
J01CR02	**amoxicillin and enzyme inhibitor**
J01CR03	ticarcillin and enzyme inhibitor
J01CR04	sultamicillin
J01CR05	piperacillin and enzyme inhibitor
J01CR50	combinations of penicillins

Drugs whose use represents more than 1% of the total penicillin use in Europe in 2003 are shown in bold type.
[a]No use of this penicillin was reported in Europe in 2003.

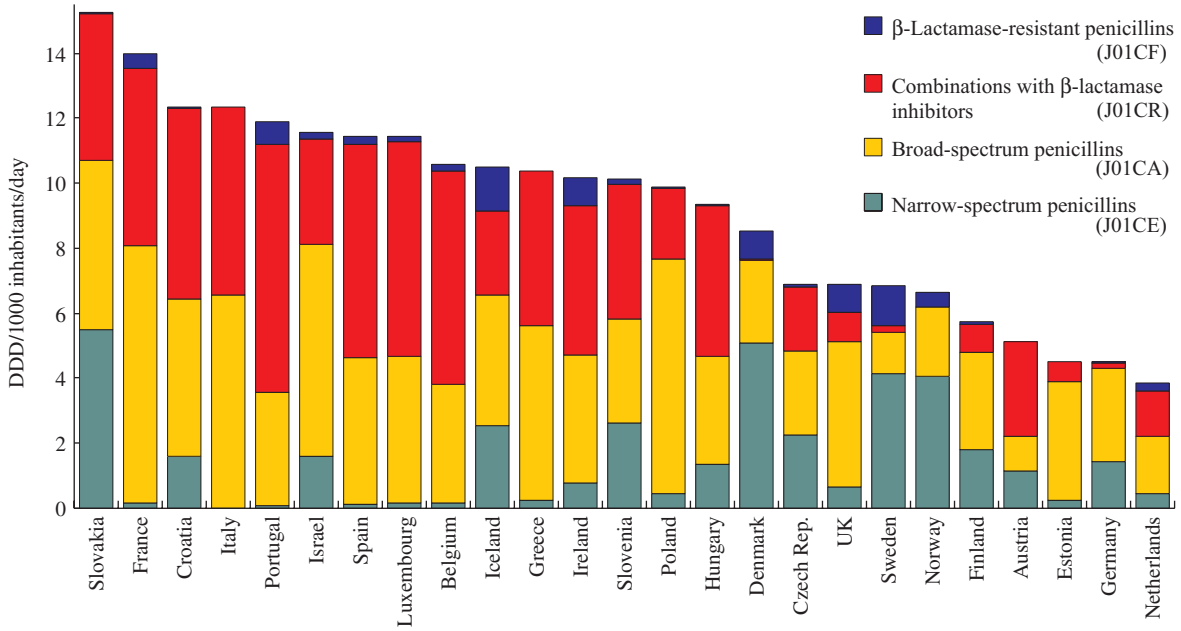

Figure 1. Outpatient use of penicillins in 25 European countries in 2003. For Iceland total data are used; for Poland 2002 data are used.

Europe were pivmecillinam in all Nordic countries, bacampicillin in Italy and France and pivampicillin in Denmark and Norway.

Penicillinase-resistant penicillins were widely used in the UK and Nordic countries, whereas in 10 European countries their share was less than 1%. Methicillin use was not recorded in any country in 2003. Flucloxacillin was mostly used in Sweden, Ireland, the UK, Portugal, the Netherlands, Belgium and Luxembourg; dicloxacillin in Iceland, Denmark and Norway; cloxacillin in Spain, France, Iceland, Israel and Slovenia; and oxacillin in France, the Czech Republic and Slovakia.

Table 2 provides the overview of consumption over time in participating countries between 1997 and 2003. Use of penicillins was increasing in most countries and increased by more than 1 DID in nine countries between the first and the last year of observation. Only in France and the Czech Republic did we observe a decrease in penicillin use of more than 1 DID, particularly after its peak in 1999. The proportion of combinations with β-lactamase inhibitors within total penicillin use has been constantly increasing in all European countries between 1997 and 2003, except Sweden and the UK, as shown in Figure S1 (Online Supplementary data). This increase exceeded 10% in 10 countries, where it coincided with a similar decrease of either broad-spectrum penicillins in seven countries or narrow-spectrum penicillins in three countries. The use of narrow-spectrum penicillins remained relatively constant or decreased in all countries, except Croatia, where the use of benzathine phenoxymethylpenicillin was constantly increasing. The proportional use of broad-spectrum penicillins increased only in Germany, Poland, Sweden and Norway, in all cases coinciding with a decrease of narrow-spectrum penicillins. In only Denmark, Iceland, Sweden and the UK, did penicillinase-resistant penicillins represent more than 10% of total penicillin use, and their proportion was further increasing in these countries.

Figures S2 and S3 (Online Supplementary data) depict the seasonal fluctuation of outpatient penicillin use in 21 European countries that provided quarterly data. In Slovakia, Hungary, Estonia, the Czech Republic, Poland, Belgium, Germany, Spain, Portugal, Greece, Slovenia and Croatia the mean of the use in the first and fourth quarter was more than 30% higher than the mean of the use in the second and third quarter. Seasonal fluctuations of penicillin use correlated to a great degree with seasonal fluctuations of total antibiotic use described in the introductory paper in all but two countries: the UK shows substantially higher seasonal fluctuations of penicillins compared with all antibiotics, whereas in the Netherlands the seasonality of penicillin use is lower than for antibiotics in general.

Discussion

Penicillins represent the most frequently prescribed antibiotics in all 25 European countries and their use remained high and even increased in most countries during the period 1997–2003. In 2003, the highest absolute penicillin use was observed in Slovakia and France, while the highest proportional use was observed in Denmark where penicillins accounted for 63% of total antibiotic use. Penicillin use and the use of their five subclasses differed substantially between countries.

Despite increased bacterial resistance and the development of newer antibiotic classes, the old narrow-spectrum penicillins (mostly penicillin-V) remain one of the most prescribed antibiotics today in northern and several central European countries, which could be considered as a marker of their conservative policy regarding antibiotic prescribing. The use of benzathine and procaine salt forms of parenteral penicillins, designed for slow absorption and long-standing action, was low, but could be underreported in some countries due to the missing DDD value.

Use of penicillinase-resistant penicillins showed remarkable geographic variations and was virtually negligible in 10 countries. In the Nordic countries and the UK, the use of these drugs showed a consistent increase during the summer season (data not shown), reflecting the prescription of these drugs to treat skin infections, which have a higher incidence during this period.[5] This detailed analysis of the seasonal variation of

Table 2. Trends of penicillin use in 25 European countries, expressed in DDD per 1000 inhabitants per day

Year	97	98	99	00	01	02	03
Austria		4.41	4.55	4.57	4.63	4.63	5.14
NSP		1.49	1.32	1.32	1.23	1.12	1.15
BSP		1.28	1.25	1.19	1.18	1.05	1.07
COP		1.63	1.97	2.05	2.21	2.46	2.91
PRP		0.01	0.01	0.01	0.01	0.01	0.01
Belgium	9.43	9.70	9.96	9.62	9.37	9.63	10.60
NSP	0.18	0.15	0.18	0.19	0.17	0.17	0.16
BSP	4.02	4.08	4.17	3.85	3.54	3.57	3.63
COP	4.93	5.18	5.33	5.31	5.40	5.64	6.57
PRP	0.30	0.29	0.28	0.28	0.27	0.25	0.24
Croatia				8.70	8.61	11.34	12.36
NSP				1.05	1.12	1.68	1.60
BSP				4.02	3.86	4.68	4.84
COP				3.56	3.56	4.92	5.86
PRP				0.06	0.06	0.06	0.06
Czech Republic		8.01	8.19	8.12	8.02	7.29	6.89
NSP		2.69	2.54	2.39	2.33	2.31	2.24
BSP		3.32	3.57	3.55	3.36	2.69	2.59
COP		1.86	1.95	2.06	2.21	2.19	1.96
PRP		0.14	0.12	0.12	0.11	0.10	0.10
Denmark	7.31	7.61	7.26	7.51	8.04	8.36	8.53
NSP	4.56	4.80	4.47	4.68	4.90	5.02	5.09
BSP	2.39	2.38	2.28	2.28	2.47	2.52	2.53
COP	0.02	0.03	0.02	0.02	0.03	0.04	0.05
PRP	0.34	0.40	0.48	0.52	0.65	0.77	0.86
Estonia						4.50	4.52
NSP						0.30	0.23
BSP						3.82	3.67
COP						0.39	0.62
PRP						0.00	0.00
Finland	5.90	5.46	5.31	5.57	6.07	5.08	5.72
NSP	2.52	2.41	2.23	2.13	2.10	1.55	1.79
BSP	3.12	2.74	2.72	2.98	3.21	2.77	3.02
COP	0.19	0.25	0.30	0.41	0.70	0.71	0.87
PRP	0.06	0.06	0.06	0.06	0.05	0.05	0.05
France	17.12	17.55	17.61	16.22	16.21	16.31	14.00
NSP	0.32	0.29	0.24	0.21	0.19	0.28	0.16
BSP	12.36	12.69	12.49	10.83	10.01	9.17	7.92
COP	3.87	4.07	4.29	4.64	5.47	6.37	5.46
PRP	0.56	0.51	0.58	0.54	0.54	0.49	0.46
Germany	4.23	4.51	4.54	4.80	4.29	4.38	4.50
NSP	1.81	1.89	1.83	1.93	1.53	1.47	1.44
BSP	2.29	2.47	2.54	2.66	2.54	2.67	2.88
COP	0.11	0.13	0.15	0.18	0.20	0.22	0.17
PRP	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Greece	9.42	7.90	10.26	10.13	10.11	9.91	10.39
NSP	0.53	0.53	0.53	0.52	0.50	0.37	0.26
BSP	6.52	4.72	6.03	5.54	5.67	5.22	5.37
COP	2.34	2.63	3.68	4.07	3.94	4.32	4.76
PRP	0.02	0.02	0.01	0.00	0.00	0.00	0.00
Hungary		8.21	10.43	8.32	8.73	7.89	9.33
NSP		1.17	1.37	1.11	1.12	0.97	1.34
BSP		3.29	4.07	3.10	3.29	2.88	3.31
COP		3.75	4.99	4.11	4.32	4.04	4.67
PRP		0.00	0.00	0.00	0.00	0.00	0.00
Iceland	10.59	11.14	10.34	10.46	10.27	10.87	10.49
NSP	3.81	3.95	3.23	3.08	2.96	2.96	2.52
BSP	4.33	4.58	4.33	4.20	4.00	4.26	4.04
COP	1.19	1.32	1.40	1.84	2.01	2.35	2.58
PRP	1.26	1.29	1.38	1.34	1.30	1.30	1.35
Ireland	8.42	8.00	9.05	8.89	9.41	9.26	10.16
NSP	0.79	0.79	0.81	0.83	0.78	0.73	0.77
BSP	4.82	4.12	4.44	4.01	3.98	3.60	3.93
COP	2.21	2.40	3.07	3.25	3.84	4.09	4.59
PRP	0.59	0.69	0.73	0.80	0.81	0.84	0.87
Israel						11.29	11.56
NSP						1.57	1.59
BSP						6.41	6.54
COP						3.07	3.21
PRP						0.23	0.21
Italy			10.57	10.51	11.34	11.22	12.35
NSP			0.06	0.05	0.04	0.03	0.01
BSP			6.52	6.26	6.67	6.37	6.54
COP			3.98	4.17	4.60	4.78	5.78
PRP			0.01	0.03	0.04	0.03	0.02
Luxembourg	8.80	8.89	9.41	9.19	9.84	10.49	11.44
NSP	0.18	0.16	0.15	0.17	0.14	0.13	0.16
BSP	4.42	4.40	4.49	4.36	4.36	4.44	4.51
COP	3.99	4.12	4.58	4.47	5.15	5.74	6.61
PRP	0.21	0.20	0.19	0.19	0.19	0.18	0.16
Netherlands	3.87	3.84	3.85	3.79	3.83	3.83	3.86
NSP	0.56	0.53	0.52	0.52	0.49	0.46	0.44
BSP	2.17	2.13	2.05	1.88	1.83	1.78	1.77
COP	0.92	0.95	1.04	1.15	1.25	1.34	1.39
PRP	0.23	0.22	0.23	0.24	0.25	0.25	0.27
Norway		6.74			6.67	6.64	6.64
NSP		4.81			4.40	4.18	4.06
BSP		1.74			1.97	2.07	2.11
COP		0.01			0.01	0.01	0.01
PRP		0.17			0.29	0.37	0.45
Poland	5.79	8.27	9.40	9.68	11.14	9.86	
NSP	0.93	1.39	1.59	0.59	1.08	0.47	
BSP	3.98	5.29	6.35	7.39	7.85	7.21	
COP	0.77	1.47	1.38	1.63	2.17	2.16	
PRP	0.12	0.12	0.08	0.06	0.04	0.03	
Portugal	10.17	10.38	11.68	11.91	11.72	13.04	11.90
NSP	0.10	0.10	0.10	0.10	0.10	0.10	0.08
BSP	5.46	5.07	5.07	4.63	4.10	3.75	3.47
COP	3.94	4.51	5.82	6.50	6.86	8.53	7.65
PRP	0.67	0.70	0.69	0.68	0.66	0.64	0.70
Slovakia				15.67	16.54	14.34	15.27
NSP				5.62	6.18	5.42	5.49
BSP				6.35	6.17	4.63	5.21
COP				3.66	4.14	4.24	4.52
PRP				0.04	0.05	0.05	0.05
Slovenia	10.05	11.25	11.61	10.36	10.22	9.55	10.14
NSP	2.88	2.92	2.57	2.44	2.62	2.35	2.61
BSP	3.37	3.23	3.11	3.05	3.09	2.77	3.23
COP	3.67	4.99	5.81	4.73	4.37	4.29	4.14
PRP	0.12	0.12	0.12	0.13	0.13	0.14	0.16

Table 2. (*continued*)

Year	97	98	99	00	01	02	03
Spain	11.58	11.09	10.97	10.36	9.88	10.46	11.45
NSP	0.22	0.19	0.19	0.16	0.14	0.13	0.12
BSP	6.63	5.94	5.56	5.22	4.72	4.58	4.53
COP	4.45	4.68	4.96	4.71	4.76	5.49	6.55
PRP	0.28	0.28	0.27	0.26	0.27	0.26	0.26
Sweden	7.20	7.60	7.44	7.26	7.48	7.29	6.86
NSP	4.85	5.12	4.82	4.71	4.76	4.47	4.15
BSP	1.11	1.23	1.30	1.27	1.34	1.34	1.28
COP	0.25	0.26	0.24	0.21	0.22	0.23	0.20
PRP	0.99	1.00	1.08	1.07	1.15	1.25	1.23
UK	7.71	7.08	6.45	6.23	6.57	6.56	6.88
NSP	0.73	0.67	0.62	0.62	0.63	0.61	0.66
BSP	4.98	4.60	4.19	4.02	4.30	4.28	4.47
COP	1.42	1.20	1.00	0.89	0.87	0.86	0.89
PRP	0.58	0.60	0.64	0.70	0.76	0.81	0.86

Country: Total national penicillin use, including β-lactamase inhibitors.
NSP: Narrow-spectrum penicillins (J01CE).
BSP: Broad-spectrum penicillins (J01CA).
COP: Combinations of penicillins (J01CR).
PRP: Penicillinase-resistant penicillins (J01CF).

particular penicillins underscores the potential to use such data for evaluation of guideline adherence.

Ampicillin, the first aminopenicillin, was almost entirely superseded by amoxicillin with better oral absorption, but its use was still notable (more than 0.1 DID) in six European countries. Amoxicillin solely or in combination with clavulanic acid now represents the most prescribed antibiotic in Europe.

The β-lactamase inhibitors (clavulanic acid, sulbactam and tazobactam) have no intrinsic antimicrobial activity and their use is negligible (traces of sulbactam use were recorded in Germany and Austria). However, their combinations with aminopenicillins (mainly co-amoxiclav) represented the most dynamic penicillin subclass, replacing the narrow- and broad-spectrum penicillins (mainly amoxicillin) in many countries. However, this rapid increase of co-amoxiclav use, expressed in DDDs, could also be explained by its increasing dosage in some countries[6] and not only by increased prescribing. Hence, considering the diversity of co-amoxiclav formulations available in different countries over time (ranging from 0.75 to 4.0 DDD adult daily dose),[7,8] driven by reduced susceptibility of micro-organisms to β-lactam antibiotics and marketing strategies of pharmaceutical companies, further analysis of prescribing regimens is crucial.

In conclusion, striking quantitative and qualitative variations in penicillin use, depicted in this paper, suggest appropriate as well as inappropriate use of penicillins. The ESAC data allow auditing of penicillin prescribing patterns, evaluation of guideline adherence, and of educational and other interventions.

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Transparency declarations

The authors have no interests to declare.

Supplementary data

Figures S1–3 are available as Online Supplementary data at http://jac.oxfordjournals.org.

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