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

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Background: Data on 13 years (1997–2009) of outpatient penicillin use were collected from 33 European countries within the European Surveillance of Antimicrobial Consumption (ESAC) project and analysed in detail.

Methods: For the period 1997–2009, data on outpatient use of systemic penicillins aggregated at the level of the active substance were collected using the Anatomical Therapeutic Chemical (ATC)/defined daily dose (DDD) method (WHO, version 2011) and expressed in DDD per 1000 inhabitants per day (DID). For detailed analysis of trends over time, seasonal variation and composition of outpatient penicillin use in 33 European countries, we distinguished between narrow-spectrum penicillins (NSP), broad-spectrum penicillins (BSP), penicillinase-resistant penicillins (PRP) and combinations with β-lactamase inhibitors (COP).

Results: Total outpatient penicillin (ATC group J01C) use in 2009 varied by a factor of 3.8 between the countries with the highest (16.08 DID in France) and lowest (4.23 DID in the Russian Federation) use. COP represented 45.8%, BSP 40.7%, NSP 10.8% and PRP 2.6% of total European outpatient penicillin use. Total outpatient penicillin use significantly increased over time by 1.53 (SD 0.71) DID between 1997 and 2009. COP (mainly co-amoxiclav) increased by 2.17 (SD 0.40) DID, which was the result of its absolute increase as well as the observed shift from NSP and BSP towards COP. This increase exceeded 10% in 20 countries, where it coincided with a similar decrease in either BSP (15 countries) or NSP (5 countries).

Conclusions: Penicillins represented the most widely used antibiotic subgroup in all 33 participating countries, albeit with considerable variation in their use patterns. For Europe, a continuous increase in overall penicillin use and of COP use was observed during the period 1997–2009.

Keywords: antibiotic use, co-amoxiclav, pharmacoepidemiology, ambulatory care

Introduction

This paper presents data from the European Surveillance of Antimicrobial Consumption (ESAC) project and reports on the use of penicillins in 2009, classified into five chemical subgroups based on the Anatomical Therapeutic Chemical (ATC) classification. It also reviews temporal trends, seasonal variation and composition of outpatient penicillin use in data collected for the 1997–2009 period from 33 European countries.

Methods

In 2009, 35 countries were included in the ESAC project, of which 33 countries provided valid data. The methods for collecting use data for systemic antibiotics were described in the introductory paper of this series.[1] For the period 1997–2009, data on outpatient antibiotic use, aggregated at the level of the active substance, were collected in accordance with the ATC classification and defined daily dose (DDD) measurement unit (WHO, version 2011).[2] Outpatient antibiotic use data for 2009, expressed in DDD per 1000 inhabitants per day (DID), was available for 32 European countries, including Cyprus and Lithuania, that provided

Table 1. Classification of penicillins and their combinations (ATC classification, 2011 version)

Penicillins with extended spectrum	
J01CA01	ampicillin[a]
J01CA02	pivampicillin
J01CA03	carbenicillin[b]
J01CA04	**amoxicillin**
J01CA05	carindacillin[b]
J01CA06	bacampicillin
J01CA07	epicillin[b]
J01CA08	**pivmecillinam**
J01CA09	azlocillin
J01CA10	mezlocillin
J01CA11	mecillinam
J01CA12	piperacillin
J01CA13	ticarcillin
J01CA14	metampicillin[b]
J01CA15	talampicillin[b]
J01CA16	sulbenicillin[b]
J01CA17	temocillin[b]
J01CA18	hetacillin[b]
J01CA20	combinations[b]
J01CA51	ampicillin, comb.
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	benzathine phenoxymethylpenicillin
J01CE30	combinations
β-Lactamase-resistant penicillins	
J01CF01	dicloxacillin[a]
J01CF02	cloxacillin
J01CF03	methicillin[b]
J01CF04	oxacillin
J01CF05	**flucloxacillin**
β-Lactamase inhibitors	
J01CG01	sulbactam
J01CG02	tazobactam[b]
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

Bold type indicates that use represented >1% of total penicillin use in 2009.
[a]Use represented >1% of total penicillin use in 2003.
[b]No use of this penicillin was reported in 2009.

total use data. In addition, 2004 data for Switzerland are presented. Beside the DID outcome measurement unit, the number of packages/1000 inhabitants/day (PID) was utilized (*n*=17 countries). Package data became available from 2006. The calculated DID/PID ratio allowed assessment of the number of DDD available per package.

The WHO Collaborating Centre for Drug Statistics Methodology has assigned 44 unique ATC codes for penicillins; no new substances were added compared with earlier descriptions of outpatient penicillin use in Europe (Table 1).[3] The ATC group J01C (β-lactam antibacterials, penicillins) comprises penicillins, β-lactamase inhibitors and their combinations categorized into five chemical subgroups. Since β-lactamase inhibitors are given in conjunction with broad-spectrum penicillins, outpatient use of four main subgroups of penicillins was analysed in this paper: broad-spectrum penicillins (BSP; ATC subgroup J01CA); narrow-spectrum penicillins (NSP; J01CE); penicillinase-resistant penicillins (PRP; J01CF); and combinations of penicillins with β-lactamase inhibitors (COP; J01CR). Importantly, the DDD for the parenteral use of amoxicillin and enzyme inhibitor (J01CR02) changed from 1 g to 3 g in 2005. To enable comparability for subsequent years, ESAC has updated data for the previous years.

The methods used for analysing temporal trends, seasonal variation and changes in composition of outpatient penicillin use are described in two tutorials in this series.[4,5]

Results

Outpatient penicillin use in 2009

Five penicillins represented 96.1% of the total outpatient penicillin use in 2009 in Europe: amoxicillin and enzyme inhibitor (co-amoxiclav) (44.9%); amoxicillin (39.0%); phenoxymethylpenicillin (8.9%); flucloxacillin (1.7%); and pivmecillinam (1.6%). Other substances represented <1% each, and no use at all was recorded for 11 substances (Table 1).

Penicillins represented 47% of total outpatient use in 2009.[1] Figure 1 shows total outpatient penicillin use subdivided into the four main subgroups in 2009 for 33 European countries, including two countries (Cyprus and Lithuania) with total use data and Swiss data for 2004, expressed in DID. Total penicillin use varied by a factor of 3.8 between the countries with the highest (16.1 DID in France) and lowest (4.2 DID in the Russian Federation) use.

NSP represented 10.8% of total European outpatient penicillin use. Large variations in outpatient NSP use were found, ranging from 5.1 DID in Denmark to 0.003 DID in Italy. Phenoxymethylpenicillin, commonly known as penicillin V, was the most widely used NSP in most countries. Its use represented >50% of total outpatient penicillin use in Denmark (5.1 DID), Norway (3.6 DID) and Sweden (3.9 DID). In contrast, this substance represented <1% of total penicillin use in Belgium, Cyprus, France, Israel, Luxembourg, Malta, the Netherlands, the Russian Federation and Spain (representing <0.07 DID). No use was reported for Croatia, Italy and Portugal. Instead, a wide variety of other NSP substances were reported. For example, benzathine phenoxymethylpenicillin was mainly used in Austria, Croatia and the Czech Republic, and penamecillin in Hungary and Slovakia. Pheneticillin was exclusively used in the Netherlands. The long-acting parenteral benzylpenicillin was mainly used in the Czech Republic, Greece and Lithuania.

BSP represented 40.7% of total European outpatient penicillin use. Outpatient BSP use ranged from 9.0 DID in France to 1.1 DID in Malta. Amoxicillin was the most commonly used BSP. The

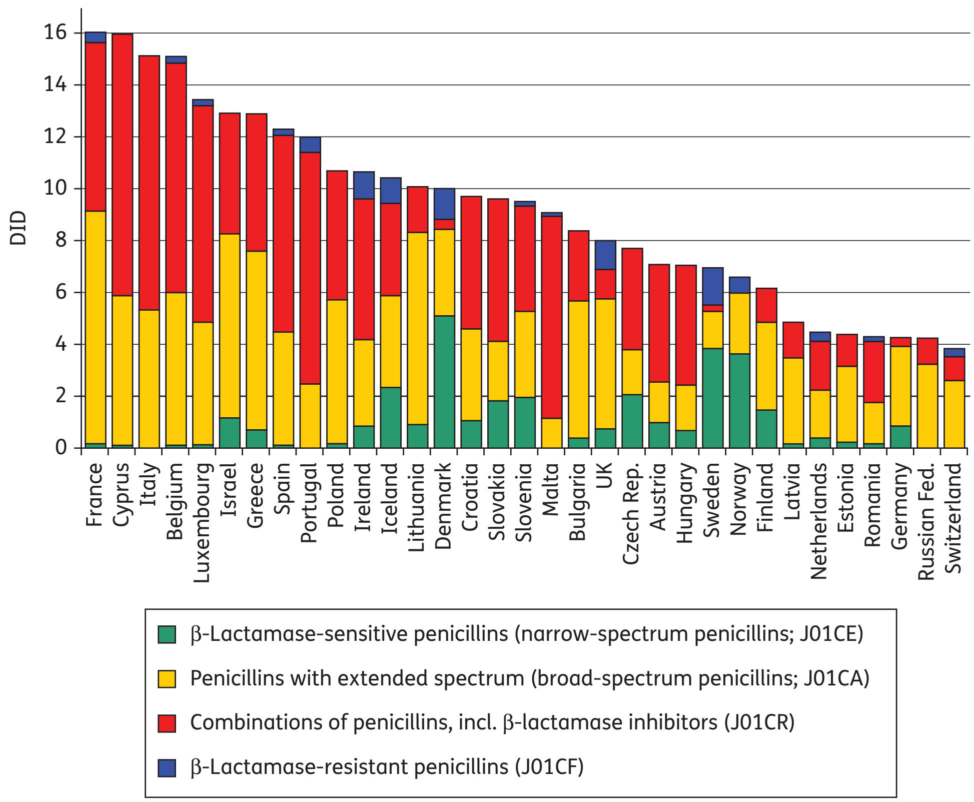


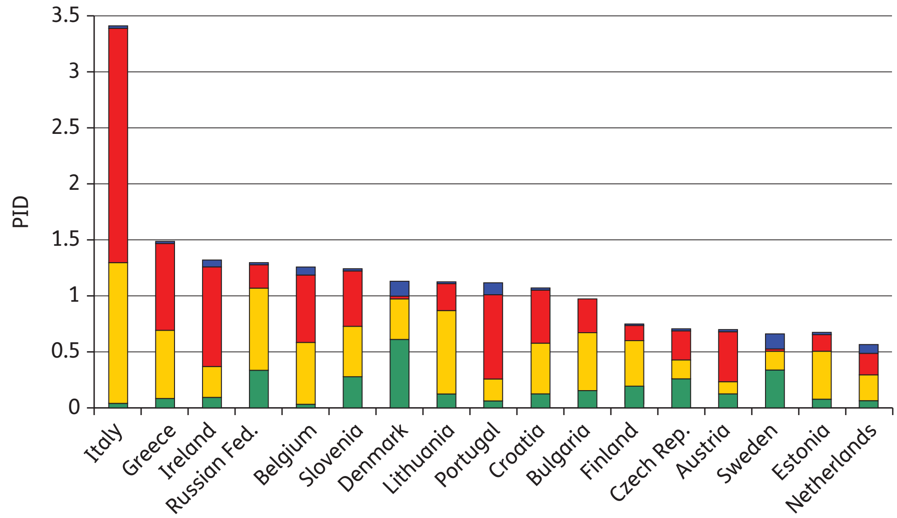
Figure 1. Outpatient use of penicillins in 33 European countries in 2009 in DID (2004 data for Switzerland). For Cyprus and Lithuania, total care data are reported.

highest proportional outpatient BSP use was observed for the Russian Federation (75.9%), followed by Estonia, Germany, Latvia and Lithuania (>65%) (range 2.9–7.4 DID). Proportional use was >50% in 11 countries. Malta had the lowest proportional use (12.3%) (1.1 DID). Pivmecillinam was commonly used in the Nordic countries Norway, Denmark, Finland and Sweden as well as in Israel (20.3%, 15.7%, 11.2%, 7.6% and 5.2%, respectively). The use of ampicillin represented 9.1% (0.4 DID) of total outpatient penicillin use in the Russian Federation and 7.7% (0.8 DID) of total outpatient penicillin use in Lithuania. Bacampicillin was only used in Italy and pivampicillin only in Denmark.

COP represented 45.8% of total European outpatient penicillin use. In 2009, the highest use of COP was observed in Cyprus (10.1 DID) (total care data) followed by Italy (9.8 DID) and the lowest in Norway (0.002 DID). The most commonly used COP substance was amoxicillin and enzyme inhibitor (co-amoxiclav). Its proportional use ranged from 86.6% in Malta (7.9 DID) to 0.03% in Norway (0.002 DID). Co-amoxiclav use represented >50% of total penicillin use in Austria (4.5 DID), Belgium (8.9 DID), Croatia (5.1 DID), Cyprus (10.0 DID; hospital use data are included), Hungary (4.6 DID), Ireland (5.5 DID), Italy (9.8 DID), Luxembourg (8.4 DID), Portugal (9.0 DID), Romania (2.3 DID), Slovakia (5.2 DID) and Spain (7.6 DID). In contrast, a low proportional use of co-amoxiclav was seen in Denmark (0.4 DID), Germany (0.2 DID) and Sweden (0.2 DID) (all <6%). It represented 10%–20% of total penicillin use in Finland (1.2 DID), Lithuania (1.6 DID) and the UK (1.1 DID). Sultamicillin represented >1% of total outpatient penicillin use in Estonia, Germany, Lithuania and Slovakia.

PRP represented 2.6% of total European outpatient penicillin use. Their proportional use in 2009 varied from 20.5% in Sweden to no use in Hungary and Bulgaria. PRP represented >1% of total outpatient penicillin use in 14 countries. All these countries only reported the use of one particular substance except for France. Flucloxacillin was used in Sweden, the UK, Ireland, the Netherlands, Portugal, Belgium and Luxembourg (20.5%, 14.2%, 9.2%, 8.4%, 4.6%, 1.7% and 1.4%, respectively); dicloxacillin in Denmark, Iceland and Norway (11.3%, 9.2% and 8.4%, respectively); cloxacillin in Slovenia, Spain and France (1.6%, 1.6% and 1.5%, respectively); and oxacillin in Romania and France (3.2% and 1.1%, respectively). Methicillin use was not recorded in 2009.

Figure 2 shows total outpatient penicillin use expressed in PID for 17 countries for 2009 (Italy, 2008 data; Ireland and the Czech Republic, 2007 data). Based on package data, Italy showed the highest use of penicillin (3.4 PID), followed by Greece, Ireland and the Russian Federation (1.5, 1.3 and 1.3 PID, respectively). Lowest PID figures were seen for the Netherlands, Estonia and Sweden (0.6–0.7 PID). Based on ranking, the Russian Federation shifted from position 17 in DID (low-prescribing country) to position 4 in PID (high-prescribing country), Portugal from position 4 in DID to position 9 in PID and Belgium from position 2 in DID to position 5 in PID. The ranking was similar for the Czech Republic, Denmark, Estonia and Italy. Consequently, the lowest mean DDD per package was found in the Russian Federation (3.3 DDD/pack)



Country	BE	PT	SE	AT	CZ	HR	LT	DK	GR	IE	BG	FI	NL	SI	EE	IT	RU
Ranking PID	5	9	15	14	13	10	8	7	2	3	11	12	17	6	16	1	4
Ranking DID	2	4	12	11	13	8	6	7	3	5	10	14	15	9	16	1	17
DDD/package J01C	12.1	10.8	10.6	10.4	9.9	9.2	9.1	8.9	8.8	8.7	8.6	8.3	7.9	7.7	6.7	4.5	3.3
DDD/package J01	10.9	9.0	11.8	8.1	8.1	7.4	6.6	9.3	7.3	8.6	5.7	9.5	7.4	6.8	6.5	2.6	3.0

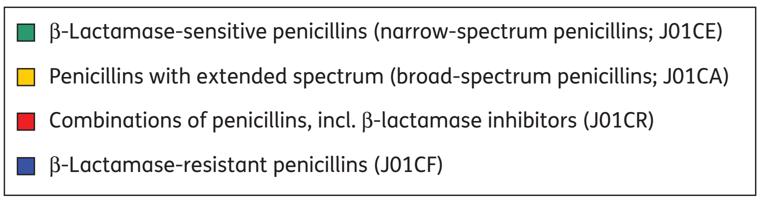


Figure 2. Total outpatient penicillin use in 17 European countries in 2009 in PID, the ranking in DID versus PID, and the number of DDD per outpatient penicillin package. For Lithuania, total care data are used. For Italy, 2008 data are used. For the Czech Republic and Ireland, 2007 data are used. Countries are shown in order (left to right) of decreasing DDD/package J01C, as shown in the table. 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.

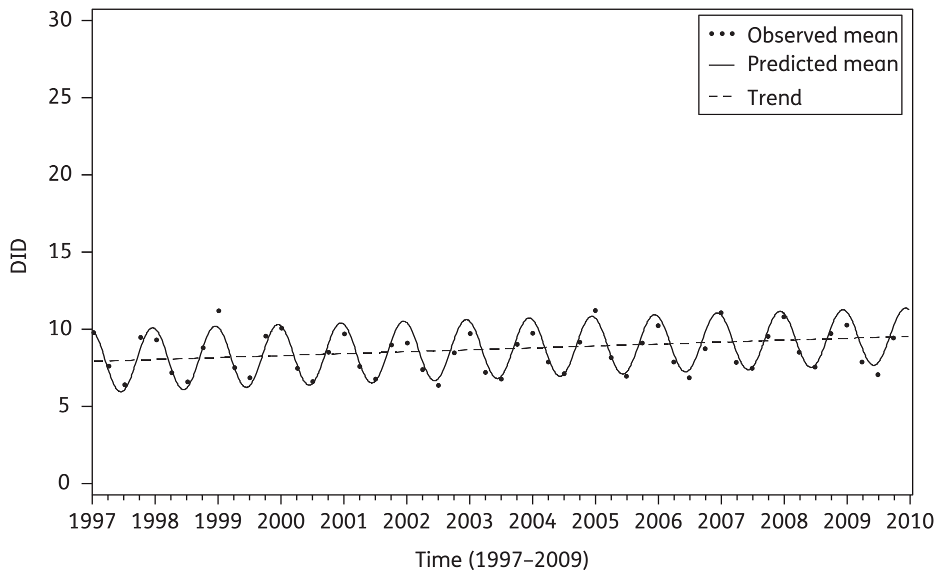
and the highest in Belgium (12.1 DDD/pack), followed by Portugal and Sweden (10.8 and 10.6 DDD/pack, respectively). The mean DDD for a penicillin package was higher in all countries compared with the overall mean DDD for an antibiotic package (J01), except for the northern countries Denmark, Finland and Sweden.

Longitudinal data analysis (1997–2009)

For Europe, a significant increase in total outpatient penicillin use of 0.03 (SD 0.01) DID per quarter was found, starting from 8.09 (SD 0.62) DID in the first quarter of 1997, and there was a significant seasonal variation with an amplitude of 1.87 (SD 0.20) DID, which decreased non-significantly over time by 0.001 (SD 0.004) DID per quarter (Figure 3). Furthermore, the longitudinal analysis showed that both upward winter and downward summer peaks of outpatient penicillin consumption shifted significantly from one year to another and that there was a positive correlation between volume of use and seasonal variation. This means that, in terms of absolute amount, high and low penicillin-consuming countries tend to have high and low seasonal variation in penicillin use, respectively.

Table 2 provides an overview of outpatient penicillin use for all 33 participating European countries between 1997 and 2009. Outpatient use of penicillins was stable or increasing in most countries. The highest continuous increase since 2003 was observed in the Russian Federation, with a rise of 100% (from 2.1 DID to 4.2 DID), followed by Austria, showing an increase of 62% (from 4.4 DID to 7.1 DID), and Belgium, with an increase of 61% (from 9.4 DID to 15.1 DID). In Ireland, Luxembourg and Italy, penicillin use steadily increased by >40%. In Slovakia, however, a large drop of 7 DID (a decrease of 76%) was observed in overall penicillin use between its peak in 2001 and 2009. Penicillin use decreased in Slovakia by 76% since 2001 (from 16.8 DID to 9.6 DID), in Lithuania by 49% since 2006 (from 15.1 DID to 10.1 DID) and in Croatia by 27% since 2003 (from 12.3 to 9.7). In the other countries, no remarkable trends were observed.

The overall increase in penicillin use was mainly the result of the increased use of COP. For Europe, a significant increase in total COP use of 0.04 (SD 0.01) DID per quarter was found, starting from 1.98 (SD 0.34) DID in the first quarter of 1997, and there was a significant seasonal variation with an amplitude of 0.58



Parameters				
β_0	β_1	$\beta_0{}^S$	$\beta_1{}^S$	δ
8.0902 (0.6158)*	0.0295 (0.0136)*	1.8696 (0.1976)*	−0.0014 (0.0045)	0.3825 (0.0234)*

Figure 3. Estimated linear trend and seasonal variation of outpatient penicillin use 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 ($P<0.05$).

(SD 0.12) DID, which increased significantly over time by 0.004 (SD 0.002) DID per quarter (Figure 4). This trend was observed for most countries, mainly due to an increase in co-amoxiclav use. Countries with an initial low use of co-amoxiclav increased their use more than 3-fold; these were Austria, Bulgaria, Estonia, Finland, Germany, Norway and Poland. Almost all other countries doubled their co-amoxiclav use over the years.

Figures S1 and S2 (available as Supplementary data at *JAC* Online) show the seasonal variation of outpatient penicillin use in 27 European countries able to deliver quarterly data (no quarterly data were available for Bulgaria, France, Malta and Norway). Seasonal variation was less pronounced in low penicillin-consuming countries (Denmark, Iceland, the Netherlands, Sweden and the UK) compared with higher penicillin-consuming countries (Austria, Belgium, Portugal and Spain). Iceland and Sweden in Northern Europe and the Czech Republic decreased both their total penicillin use and seasonal variation over time. Austria, Belgium, Italy, Lithuania, Luxembourg, Poland and the Russian Federation increased both their overall and seasonal variation over time. For the other countries different yearly and seasonal variations were observed.

Seasonal variations of penicillin use correlated to a high degree with the total antibiotic use described in the introductory paper in all but two countries; the UK showed substantially higher seasonal variation of penicillins compared with all antibiotics, whereas in the Netherlands the seasonality of penicillin use was lower than for antibiotics in general, mainly due to the increased use of tetracyclines (country-specific results not shown).

Compositional data analysis (1997–2009)

For Europe, higher outpatient penicillin use resulted in a significant increase in the proportional use of COP relative to NSP and BSP. Proportional use of NSP was significantly smaller relative to the other three main subgroups when total penicillin use was higher (Table 3). The relative use of COP and BSP significantly increased over time with respect to that of NSP and PRP, and the relative use of COP significantly increased over time with respect to BSP (Table 4).

Trends of proportional outpatient penicillin use in individual countries are shown in Figure S3 (available as Supplementary data at *JAC* Online). The proportion of COP increased continuously in most European countries between 1997 and 2009. This increase exceeded 10% in 20 countries, where it coincided with a similar decrease in either BSP in 15 countries or NSP in 5 countries. Its proportional use was stable in Spain, France, Luxembourg and Slovenia since 2005–06. Denmark, Germany and Sweden had the lowest proportional COP use since 1997 (<10%). COP use in Norway was negligible.

The Northern European countries Denmark, Norway and Sweden had the highest proportional use of NSP, with a constant 60% of total penicillin use over time, but their proportion decreased over time. In contrast, proportional NSP use was low since 1997 in Belgium, France, Italy, Latvia, Luxembourg, Malta, Portugal and Spain (<2%). NSP use in the Russian Federation and Poland decreased to <2% over the last 3 years.

Table 2. Yearly outpatient penicillin 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	**—**	**4.42**	**4.41**	**4.37**	**4.40**	**4.49**	**5.14**	**5.08**	**6.00**	**6.15**	**6.23**	**6.60**	**7.09**
BSP	—	1.26	1.24	1.19	1.18	1.05	1.07	0.99	1.42	1.44	1.49	1.45	1.59
NSP	—	1.49	1.32	1.32	1.23	1.12	1.14	1.05	0.99	1.02	1.00	1.04	0.99
PRP	—	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
COP	—	1.67	1.85	1.85	1.98	2.33	2.91	3.04	3.58	3.68	3.73	4.10	4.50
Belgium	**9.43**	**9.70**	**9.96**	**9.62**	**9.37**	**9.63**	**10.32**	**10.51**	**11.93**	**12.44**	**13.57**	**15.48**	**15.13**
BSP	4.02	4.08	4.17	3.85	3.54	3.57	3.53	3.71	4.64	5.26	5.78	6.80	5.88
NSP	0.18	0.15	0.18	0.19	0.17	0.17	0.16	0.14	0.13	0.11	0.10	0.11	0.10
PRP	0.30	0.29	0.28	0.28	0.27	0.25	0.24	0.22	0.23	0.23	0.22	0.25	0.26
COP	4.93	5.18	5.33	5.31	5.40	5.64	6.39	6.44	6.93	6.84	7.47	8.33	8.89
Bulgaria	**—**	**—**	**7.64**	**8.67**	**10.97**	**8.52**	**6.67**	**7.71**	**8.13**	**8.94**	**9.65**	**9.75**	**8.40**
BSP	—	—	5.96	4.76	5.71	5.07	4.62	5.45	5.55	6.62	6.83	6.70	5.36
NSP	—	—	1.37	3.17	4.40	2.68	0.73	0.85	0.65	0.57	0.56	0.46	0.36
PRP	—	—	0.04	0.10	0.09	0.04	0.04	0.02	0.00	—	—	—	—
COP	—	—	0.27	0.63	0.76	0.73	1.27	1.39	1.92	1.75	2.26	2.59	2.67
Croatia	**—**	**—**	**—**	**8.70**	**9.03**	**11.88**	**12.32**	**11.78**	**11.55**	**10.10**	**10.70**	**10.99**	**9.69**
BSP	—	—	—	4.02	4.05	4.90	4.82	5.05	4.91	4.20	4.21	3.93	3.57
NSP	—	—	—	1.05	1.17	1.76	1.59	1.69	1.38	1.40	1.30	1.26	1.06
PRP	—	—	—	0.06	0.06	0.06	0.06	0.06	0.05	0.06	0.05	0.05	0.00
COP	—	—	—	3.56	3.74	5.16	5.84	4.99	5.21	4.45	5.13	5.75	5.06
Cyprus	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**14.46**	**15.80**	**14.86**	**16.01**
BSP	—	—	—	—	—	—	—	—	—	6.65	7.03	5.82	5.77
NSP	—	—	—	—	—	—	—	—	—	0.12	0.12	0.11	0.12
PRP	—	—	—	—	—	—	—	—	—	0.03	0.03	0.02	0.03
COP	—	—	—	—	—	—	—	—	—	7.66	8.62	8.90	10.09
Czech Republic	**—**	**7.98**	**8.17**	**—**	**—**	**7.29**	**6.92**	**6.80**	**7.24**	**6.47**	**6.87**	**7.25**	**7.73**
BSP	—	3.31	3.57	—	—	2.68	2.60	2.20	2.53	2.00	2.00	1.57	1.75
NSP	—	2.68	2.53	—	—	2.31	2.25	1.92	1.89	1.99	2.04	2.01	2.06
PRP	—	0.14	0.12	—	—	0.10	0.10	0.09	0.00	0.00	0.00	0.03	0.04
COP	—	1.85	1.95	—	—	2.19	1.97	2.60	2.83	2.48	2.83	3.63	3.89
Denmark	**7.31**	**7.61**	**7.26**	**7.58**	**8.04**	**8.31**	**8.49**	**8.81**	**9.09**	**9.48**	**10.15**	**9.99**	**10.00**
BSP	2.39	2.38	2.29	2.30	2.47	2.50	2.52	2.63	2.78	2.94	3.25	3.27	3.31
NSP	4.56	4.80	4.47	4.72	4.90	4.99	5.07	5.20	5.26	5.38	5.62	5.32	5.14
PRP	0.34	0.40	0.48	0.53	0.65	0.77	0.85	0.92	0.97	1.04	1.09	1.13	1.14
COP	0.02	0.03	0.02	0.02	0.03	0.04	0.05	0.06	0.08	0.12	0.19	0.27	0.41
Estonia	**—**	**—**	**—**	**—**	**5.49**	**4.50**	**4.42**	**4.12**	**4.50**	**4.52**	**4.91**	**4.73**	**4.37**
BSP	—	—	—	—	4.51	3.82	3.58	3.12	3.24	3.28	3.40	3.16	2.93
NSP	—	—	—	—	0.41	0.30	0.23	0.31	0.40	0.29	0.31	0.31	0.24
PRP	—	—	—	—	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
COP	—	—	—	—	0.52	0.39	0.61	0.69	0.85	0.94	1.19	1.26	1.20
Finland	**5.90**	**5.46**	**5.31**	**5.57**	**6.06**	**5.07**	**5.72**	**5.09**	**5.67**	**5.44**	**6.00**	**6.12**	**6.14**
BSP	3.12	2.74	2.72	2.98	3.20	2.76	3.02	2.66	3.07	2.92	3.22	3.43	3.44
NSP	2.52	2.41	2.23	2.13	2.10	1.54	1.79	1.56	1.59	1.57	1.62	1.44	1.44
PRP	0.06	0.06	0.06	0.06	0.05	0.05	0.05	0.05	0.04	0.04	0.04	0.02	0.02
COP	0.19	0.25	0.30	0.41	0.70	0.71	0.87	0.82	0.97	0.91	1.13	1.23	1.23
France	**17.15**	**17.59**	**17.51**	**16.18**	**16.33**	**16.40**	**13.94**	**12.78**	**14.40**	**14.61**	**14.96**	**14.73**	**16.08**
BSP	12.38	12.72	12.42	10.80	10.08	9.22	7.89	6.98	7.73	7.98	8.12	8.19	9.02
NSP	0.33	0.29	0.24	0.21	0.19	0.28	0.16	0.17	0.15	0.15	0.15	0.14	0.15
PRP	0.56	0.51	0.58	0.54	0.54	0.49	0.46	0.47	0.46	0.44	0.43	0.43	0.43
COP	3.88	4.08	4.27	4.63	5.51	6.40	5.43	5.17	6.07	6.05	6.27	5.97	6.49

Continued

Table 2. *Continued*

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Germany	**4.23**	**4.51**	**4.54**	**4.80**	**4.29**	**4.38**	**4.50**	**4.01**	**4.38**	**4.27**	**4.46**	**4.38**	**4.27**
BSP	2.29	2.47	2.54	2.66	2.54	2.67	2.88	2.63	3.03	2.94	3.19	3.15	3.11
NSP	1.81	1.89	1.83	1.93	1.53	1.47	1.44	1.17	1.10	1.09	1.00	0.94	0.85
PRP	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.01	0.01	0.01
COP	0.11	0.13	0.15	0.18	0.20	0.22	0.17	0.19	0.23	0.23	0.26	0.28	0.30
Greece	**9.42**	**7.90**	**10.26**	**10.21**	**10.15**	**9.91**	**10.35**	**10.35**	**11.13**	**13.70**	**13.14**	**14.92**	**12.89**
BSP	6.52	4.72	6.03	5.58	5.70	5.22	5.35	4.95	5.61	6.33	6.45	7.87	6.88
NSP	0.53	0.53	0.53	0.53	0.50	0.37	0.26	0.25	0.26	2.16	1.89	1.65	0.73
PRP	0.02	0.02	0.01	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.00	0.00	0.00
COP	2.34	2.63	3.68	4.10	3.96	4.32	4.74	5.14	5.26	5.21	4.79	5.39	5.28
Hungary	**—**	**8.07**	**10.23**	**8.15**	**8.48**	**7.89**	**9.10**	**8.36**	**8.64**	**7.28**	**7.01**	**6.14**	**7.06**
BSP	—	3.24	3.99	3.03	3.20	2.88	3.23	2.76	2.62	1.82	2.00	1.84	1.79
NSP	—	1.15	1.34	1.09	1.09	0.97	1.31	1.09	0.81	0.83	0.84	0.73	0.67
PRP	—	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
COP	—	3.69	4.89	4.02	4.20	4.04	4.56	4.52	5.22	4.63	4.17	3.57	4.61
Iceland	**10.59**	**11.20**	**10.40**	**10.45**	**10.12**	**10.69**	**10.48**	**11.07**	**11.97**	**10.51**	**9.85**	**10.88**	**10.41**
BSP	4.33	4.60	4.35	4.19	3.95	4.19	4.03	4.07	4.34	3.89	3.72	3.68	3.56
NSP	3.81	3.97	3.25	3.08	2.92	2.92	2.52	2.92	3.05	2.46	1.95	2.66	2.35
PRP	1.26	1.30	1.39	1.34	1.28	1.28	1.35	1.33	1.37	1.05	1.06	1.03	0.95
COP	1.19	1.33	1.40	1.84	1.98	2.31	2.57	2.74	3.22	3.12	3.11	3.52	3.55
Ireland	**—**	**7.91**	**8.96**	**8.79**	**9.26**	**9.09**	**10.00**	**9.76**	**10.21**	**10.50**	**11.51**	**11.34**	**10.66**
BSP	—	4.07	4.39	3.97	3.92	3.53	3.87	3.42	3.53	3.57	3.79	3.57	3.33
NSP	—	0.78	0.81	0.82	0.77	0.72	0.76	0.82	0.81	0.86	0.97	0.90	0.85
PRP	—	0.68	0.72	0.79	0.80	0.82	0.85	0.87	0.93	0.95	1.07	1.02	0.98
COP	—	2.37	3.04	3.21	3.78	4.01	4.52	4.65	4.95	5.11	5.69	5.85	5.51
Israel	**—**	**—**	**—**	**—**	**—**	**11.29**	**11.56**	**11.63**	**11.74**	**12.33**	**10.20**	**11.70**	**12.94**
BSP	—	—	—	—	—	6.41	6.54	6.54	6.60	6.83	5.29	6.54	7.10
NSP	—	—	—	—	—	1.57	1.59	1.60	1.46	1.58	1.48	1.32	1.20
PRP	—	—	—	—	—	0.23	0.21	0.11	0.04	0.03	0.22	0.01	0.01
COP	—	—	—	—	—	3.07	3.21	3.37	3.63	3.90	3.21	3.82	4.63
Italy	**—**	**—**	**10.56**	**10.48**	**11.50**	**11.19**	**12.31**	**12.11**	**13.00**	**13.63**	**14.59**	**15.17**	**15.18**
BSP	—	—	6.51	6.25	6.76	6.35	6.52	6.19	6.41	6.28	6.18	5.98	5.34
NSP	—	—	0.06	0.05	0.04	0.03	0.01	0.01	0.01	0.01	0.00	0.00	0.00
PRP	—	—	0.01	0.03	0.04	0.03	0.02	0.02	0.02	0.01	0.01	0.01	0.01
COP	—	—	3.98	4.16	4.66	4.77	5.76	5.90	6.57	7.32	8.39	9.18	9.82
Latvia	**—**	**—**	**—**	**—**	**—**	**4.98**	**—**	**5.36**	**5.47**	**5.44**	**5.95**	**5.01**	**4.80**
BSP	—	—	—	—	—	3.92	—	3.98	3.83	3.76	3.79	3.32	3.34
NSP	—	—	—	—	—	0.15	—	0.19	0.18	0.16	0.14	0.13	0.16
PRP	—	—	—	—	—	0.01	—	0.01	0.00	0.00	0.00	0.00	0.00
COP	—	—	—	—	—	0.91	—	1.19	1.46	1.52	2.02	1.56	1.31
Lithuania	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**15.07**	**13.90**	**13.04**	**10.08**
BSP	—	—	—	—	—	—	—	—	—	6.17	8.65	8.87	7.42
NSP	—	—	—	—	—	—	—	—	—	7.06	3.33	2.35	0.92
PRP	—	—	—	—	—	—	—	—	—	0.78	0.00	0.01	0.03
COP	—	—	—	—	—	—	—	—	—	1.06	1.91	1.81	1.71
Luxembourg	**9.29**	**9.38**	**9.91**	**9.64**	**10.28**	**10.92**	**11.96**	**10.81**	**11.70**	**11.65**	**12.63**	**12.63**	**13.47**
BSP	4.67	4.65	4.73	4.57	4.56	4.63	4.71	3.95	4.12	3.95	4.35	4.44	4.74
NSP	0.19	0.17	0.16	0.18	0.15	0.14	0.16	0.17	0.17	0.14	0.14	0.12	0.09
PRP	0.22	0.21	0.20	0.20	0.20	0.19	0.17	0.18	0.19	0.19	0.17	0.18	0.19
COP	4.21	4.35	4.82	4.69	5.38	5.97	6.91	6.52	7.23	7.37	7.96	7.90	8.44

Continued

Table 2. *Continued*

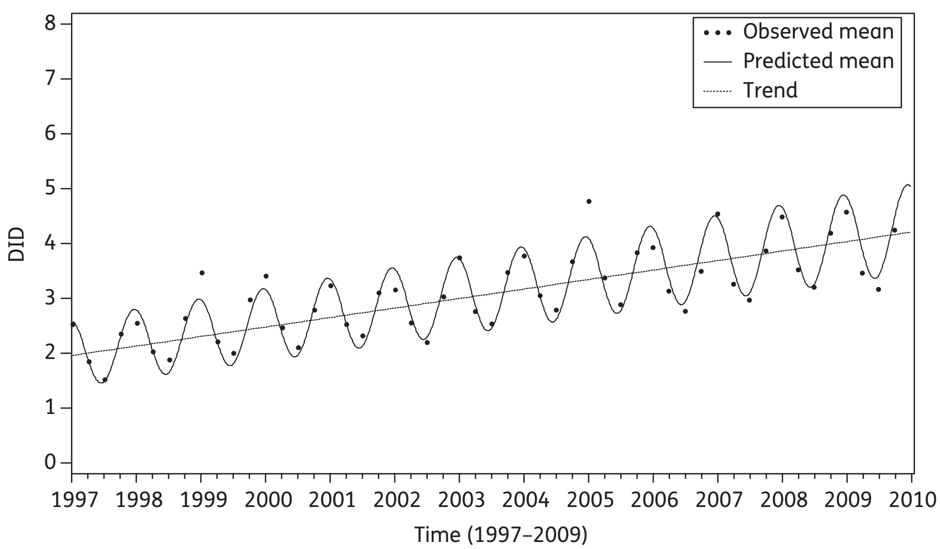
Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Malta	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**8.75**	**9.00**	**9.08**
BSP	—	—	—	—	—	—	—	—	—	—	1.39	1.26	1.12
NSP	—	—	—	—	—	—	—	—	—	—	0.08	0.02	0.03
PRP	—	—	—	—	—	—	—	—	—	—	0.09	0.07	0.07
COP	—	—	—	—	—	—	—	—	—	—	7.18	7.66	7.86
Netherlands	**3.89**	**3.83**	**3.85**	**3.78**	**3.81**	**3.82**	**3.86**	**3.76**	**4.09**	**4.32**	**4.33**	**4.42**	**4.48**
BSP	2.18	2.13	2.06	1.87	1.82	1.78	1.77	1.69	1.86	1.89	1.90	1.89	1.89
NSP	0.56	0.53	0.52	0.52	0.49	0.45	0.44	0.42	0.44	0.50	0.46	0.41	0.39
PRP	0.23	0.22	0.23	0.24	0.25	0.25	0.27	0.28	0.29	0.32	0.32	0.36	0.38
COP	0.92	0.95	1.04	1.15	1.25	1.34	1.39	1.38	1.50	1.61	1.66	1.77	1.82
Norway	**—**	**6.68**	**—**	**—**	**6.63**	**6.59**	**6.59**	**6.54**	**7.00**	**6.28**	**6.61**	**6.76**	**6.59**
BSP	—	1.73	—	—	1.96	2.06	2.10	2.15	2.34	2.06	2.23	2.34	2.36
NSP	—	4.77	—	—	4.38	4.15	4.04	3.88	4.22	3.75	3.85	3.85	3.65
PRP	—	0.17	—	—	0.28	0.37	0.45	0.50	0.44	0.47	0.53	0.56	0.58
COP	—	0.01	—	—	0.01	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Poland	**—**	**8.27**	**9.40**	**9.68**	**11.14**	**9.97**	**—**	**7.19**	**7.57**	**—**	**10.50**	**10.13**	**10.68**
BSP	—	5.29	6.35	7.39	7.85	7.28	—	6.28	6.65	—	5.96	5.47	5.60
NSP	—	1.39	1.59	0.59	1.08	0.48	—	0.29	0.30	—	0.17	0.16	0.15
PRP	—	0.12	0.08	0.06	0.04	0.03	—	0.01	0.01	—	0.00	0.01	0.01
COP	—	1.47	1.38	1.63	2.17	2.18	—	0.61	0.62	—	4.37	4.50	4.93
Portugal	**10.12**	**10.56**	**11.63**	**11.86**	**11.67**	**13.04**	**11.83**	**11.18**	**12.00**	**11.58**	**11.30**	**11.60**	**12.00**
BSP	5.46	5.07	5.07	4.63	4.11	3.75	3.47	3.12	3.21	3.01	2.61	2.49	2.43
NSP	0.05	0.05	0.05	0.05	0.04	0.10	0.01	0.09	0.02	0.01	0.02	0.02	0.02
PRP	0.67	0.69	0.69	0.68	0.66	0.64	0.70	0.67	0.62	0.61	0.56	0.55	0.55
COP	3.94	4.74	5.82	6.50	6.86	8.53	7.65	7.30	8.16	7.95	8.11	8.55	9.00
Romania	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**4.31**
BSP	—	—	—	—	—	—	—	—	—	—	—	—	1.61
NSP	—	—	—	—	—	—	—	—	—	—	—	—	0.16
PRP	—	—	—	—	—	—	—	—	—	—	—	—	0.14
COP	—	—	—	—	—	—	—	—	—	—	—	—	2.40
Russian Federation	**—**	**—**	**—**	**—**	**—**	**—**	**2.10**	**2.15**	**2.28**	**2.68**	**3.14**	**3.30**	**4.23**
BSP	—	—	—	—	—	—	1.68	1.72	1.79	2.08	2.26	2.48	3.21
NSP	—	—	—	—	—	—	0.19	0.16	0.12	0.09	0.07	0.02	0.06
PRP	—	—	—	—	—	—	0.03	0.02	0.01	0.01	0.01	0.01	0.01
COP	—	—	—	—	—	—	0.20	0.25	0.36	0.50	0.80	0.79	0.95
Slovakia	**—**	**—**	**15.46**	**16.27**	**16.81**	**14.69**	**15.58**	**12.54**	**13.04**	**10.24**	**10.57**	**9.53**	**9.56**
BSP	—	—	7.40	6.49	6.27	4.76	5.31	4.52	4.44	3.53	3.16	2.52	2.33
NSP	—	—	4.40	6.00	6.25	5.50	5.55	4.58	4.45	2.41	2.29	1.98	1.84
PRP	—	—	0.03	0.06	0.07	0.07	0.06	0.04	0.00	0.00	0.00	0.00	0.00
COP	—	—	3.63	3.71	4.22	4.37	4.66	3.41	4.15	4.30	5.12	5.03	5.40
Slovenia	**10.05**	**11.25**	**11.61**	**10.36**	**10.22**	**9.50**	**10.07**	**9.85**	**9.41**	**8.90**	**9.95**	**9.37**	**9.51**
BSP	3.37	3.23	3.11	3.05	3.09	2.75	3.21	3.17	3.22	3.09	3.48	3.19	3.34
NSP	2.88	2.92	2.57	2.44	2.62	2.34	2.59	2.49	1.90	1.97	2.18	2.07	1.95
PRP	0.12	0.12	0.12	0.13	0.13	0.14	0.16	0.16	0.17	0.17	0.14	0.03	0.15
COP	3.67	4.99	5.81	4.73	4.37	4.27	4.11	4.02	4.12	3.67	4.16	4.07	4.07
Spain	**11.53**	**10.92**	**10.73**	**10.18**	**9.60**	**9.81**	**10.62**	**10.78**	**11.73**	**11.54**	**12.14**	**12.23**	**12.31**
BSP	6.60	5.85	5.44	5.05	4.51	4.26	4.18	3.97	3.92	4.07	4.37	4.39	4.42
NSP	0.20	0.18	0.17	0.14	0.12	0.11	0.10	0.09	0.08	0.08	0.09	0.09	0.09
PRP	0.28	0.28	0.26	0.26	0.26	0.25	0.24	0.21	0.20	0.20	0.19	0.19	0.19
COP	4.45	4.62	4.86	4.73	4.71	5.19	6.10	6.51	7.53	7.19	7.49	7.56	7.61

Continued

Table 2. *Continued*

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Sweden	**7.20**	**7.60**	**7.44**	**7.26**	**7.48**	**7.20**	**6.76**	**6.52**	**6.66**	**6.97**	**7.16**	**7.37**	**6.98**
BSP	1.11	1.23	1.30	1.27	1.34	1.33	1.26	1.27	1.35	1.41	1.45	1.50	1.44
NSP	4.85	5.12	4.82	4.71	4.76	4.42	4.09	3.88	3.91	4.08	4.22	4.17	3.87
PRP	0.99	1.00	1.08	1.07	1.15	1.23	1.21	1.18	1.17	1.25	1.24	1.44	1.43
COP	0.25	0.26	0.24	0.21	0.22	0.22	0.20	0.19	0.22	0.24	0.25	0.25	0.24
Switzerland	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**3.84**	**—**	**—**	**—**	**—**	**—**
BSP	—	—	—	—	—	—	—	0.92	—	—	—	—	—
NSP	—	—	—	—	—	—	—	0.27	—	—	—	—	—
PRP	—	—	—	—	—	—	—	0.02	—	—	—	—	—
COP	—	—	—	—	—	—	—	2.63	—	—	—	—	—
UK	**7.76**	**7.26**	**6.63**	**6.37**	**6.71**	**6.69**	**6.99**	**6.80**	**7.16**	**7.10**	**7.73**	**7.95**	**8.03**
BSP	4.95	4.65	4.26	4.05	4.33	4.31	4.48	4.29	4.57	4.53	5.02	5.12	5.04
NSP	0.75	0.70	0.65	0.65	0.66	0.64	0.68	0.65	0.66	0.68	0.72	0.71	0.74
PRP	0.58	0.61	0.65	0.70	0.77	0.81	0.86	0.89	0.91	0.98	1.02	1.07	1.14
COP	1.48	1.30	1.08	0.97	0.96	0.94	0.97	0.96	1.01	0.91	0.98	1.05	1.11

Country, total national penicillin use, including β-lactamase inhibitors; BSP, broad-spectrum penicillins (J01CA); NSP, narrow-spectrum penicillins (J01CE); PRP, penicillinase-resistant penicillins (J01CF); COP, combinations of penicillins, including β-lactamase inhibitors (J01CR); —, no use reported; 0.00, <0.005.



Parameters				
β_0	β_1	$\beta_0{}^S$	$\beta_1{}^S$	δ
1.9817 (0.3381)*	0.0418 (0.0077)	0.5807 (0.1187)*	0.0037 (0.0015)*	0.3490 (0.0238)*

Figure 4. Estimated linear trend and seasonal variation of outpatient COP use 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 ($P<0.05$).

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

J01C	BSP	NSP	COP	PRP
BSP		1.111*	−1.033*	−0.318
NSP	−1.111*		−2.144*	−1.428*
COP	1.033*	2.144*		0.716
PRP	0.318	1.428*	−0.716	

J01C, β-lactam antibacterials, penicillins; BSP, broad-spectrum penicillins; NSP, narrow-spectrum penicillins; COP, combinations with β-lactamase inhibitors; PRP, β-lactamase-resistant penicillins.
Values are estimated changes in the log ratio of the row versus column antibiotic type with increasing total use. Significant effects are indicated with an asterisk; positive values represent an increase and negative values represent a decrease.

Table 4. Change in composition of outpatient penicillin use in Europe as a function of time

J01C	BSP	NSP	COP	PRP
BSP		0.051*	−0.064*	0.050*
NSP	−0.051*		−0.115*	−0.001
COP	0.064*	0.115*		0.114*
PRP	−0.050*	0.001	−0.114*	

J01C, β-lactam antibacterials, penicillins; BSP, broad-spectrum penicillins; NSP, narrow-spectrum penicillins; COP, combinations with β-lactamase inhibitors; PRP, β-lactamase-resistant penicillins.
Values are estimated changes in the log ratio of the row versus column antibiotic type with increasing time. Significant effects are indicated with an asterisk; positive values represent an increase and negative values represent a decrease.

The proportional use of BSP remained high and increased continuously in Germany, Latvia, Lithuania and the Russian Federation, coinciding with a decrease in NSP or COP.

Discussion

Penicillins were the most frequently used antibiotics in Europe.[1] Their use remained high and increased in most countries from 1997 to 2009. Overall, European seasonal variation in outpatient penicillin use was found to increase significantly over time by 1.53 (SD 0.71) DID between the first quarter of 1997 and the last of 2009. The increase in penicillin use was mainly due to the increase in the COP subgroup. COP use increased by 2.17 (SD 0.40) DID. The increase in COP use exceeded the overall penicillin increase, meaning that in addition to the absolute increase in COP there was also a substantial shift from NSP and BSP use towards COP use. This was confirmed by compositional data analyses.

Penicillin use and the use of its four analysed subgroups differed substantially between countries. NSPs remained one of the most commonly used antibiotics to date in Sweden, Norway and Denmark, whereas in the Southern European countries their use decreased since 1997 and was negligible in 2009. Only 12 countries reported the use of PRPs, and their use remained low over time.[3]

Ampicillin, the first aminopenicillin, was almost entirely superseded by amoxicillin. Only four countries still reported ampicillin use of >0.1 DID in 2009. Amoxicillin was the second most commonly used antibiotic in Europe (39%). Overall, the use of BSPs showed a non-significant decreasing trend. In most countries, BSP (mainly amoxicillin) use decreased in favour of COP. The combinations of β-lactamase inhibitors (clavulanic acid and sulbactam) with aminopenicillins represented the most frequently used penicillin subgroup, and co-amoxiclav represented 45% of total outpatient penicillin use. Most countries doubled their use of co-amoxiclav during the period 1997–2009, reaching 7–10 DID in the high-consuming countries. This finding raises concern regarding the appropriate prescribing of co-amoxiclav for respiratory tract infections, which are one of the main drivers of antibiotic prescribing in outpatients.[6,7] For instance, the recommended antibiotic treatment for community-acquired lower respiratory tract infections, following the European Respiratory Society guidelines, remains amoxicillin or a tetracycline.[8] However, Butler *et al.*[9] showed that antibiotic prescriptions virtually never benefit patients with acute cough, which is one of the most common reasons for antibiotic prescribing in the community.

Next to the overall significant increase in outpatient penicillin use, a non-significant decrease in seasonal variation was observed. This outcome could be relevant for assessing the quality of antibiotic use expressed in DID in ambulatory care settings. Total outpatient antibiotic use and its seasonal variation are both driven by outpatient penicillin use and quality indicators for outpatient antibiotic use.[10–12] A high seasonal variation (higher use during the winter period compared with the summer period) is mainly caused by outpatient penicillin use, due to prescribing for respiratory tract infections during winter periods. This is clearly observed for the UK due to the increase in amoxicillin use for respiratory tract infections in the winter period (1.5 DID). In contrast, the Netherlands showed an increase in tetracyclines for the treatment of respiratory tract infections (country-specific results not shown).

A decrease in seasonal variation over time could be considered an improvement of the quality of appropriate antibiotic use. We observed increased outpatient penicillin use over time in Cyprus, Denmark, Greece, Ireland and Spain, but their seasonal variations decreased over time (results not shown).

Using both outcome measures, DID and PID, allows us to better understand differences in antibiotic use between countries. Italy, a country with high rates of prescribing, consumed the highest number of penicillin packages. Greece, Ireland and the Russian Federation, on the other hand, consumed proportionally twice as many penicillin packages compared with Austria, the Czech Republic, Estonia, the Netherlands and Sweden. Furthermore, the mean DDD in one penicillin package was lowest in the Russian Federation and considerably higher in Portugal. As a result, the Russian Federation had a higher penicillin use when expressed in PID (1.3) and a lower use when expressed in DID (4.2) compared with Portugal (1.1 PID and 12.0 DID). Therefore, for future surveillance we suggest comparing both the PID and DID outcome measures simultaneously. The example shows that the application of DID alone may not correctly reflect outpatient antibiotic use. Outcome measures such as the number of prescriptions and persons could improve our understanding of the differences found, as explained in the introductory paper of this series.[1] Furthermore, the DDD per package for outpatient penicillin use was higher compared with that of total outpatient antibiotic use, meaning that penicillin packages contained more DDD compared with packages of any other antibiotic. The northern countries Denmark, Finland and Sweden, however, deviated from this observation.

In conclusion, striking quantitative and qualitative yearly and seasonal variations in penicillin use suggest inappropriate use of penicillins for respiratory tract infections, mainly and increasingly with co-amoxiclav. The ESAC data allow auditing of country-specific penicillin consumption patterns over time and the formulation of country-specific recommendations, e.g. on the use of co-amoxiclav. In future the ESAC data should permit the evaluation of guideline adherence and the development of educational and other interventions.

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Supplementary data

Figures S1, S2 and S3 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org).

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