

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

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Background: Data on 13 years of outpatient cephalosporin use were collected from 33 European countries within the European Surveillance of Antimicrobial Consumption (ESAC) project, funded by the European Centre for Disease Prevention and Control (ECDC), and analysed in detail.

Methods: For the period 1997–2009, data on outpatient use of systemic cephalosporins 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 cephalosporin use in 33 European countries, we distinguished between first-generation (J01DB), second-generation (J01DC), third-generation (J01DD) and fourth-generation (J01DE) cephalosporins.

Results: Total outpatient cephalosporin use in 2009 varied from 8.7 DID in Greece to 0.03 DID in Denmark. In general, use was higher in Southern and Eastern European countries than in Northern European countries. Total outpatient cephalosporin use increased over time by 0.364 (SD 0.473) DID between 1997 and 2009. Cephalosporin use increased for half of the countries. Low-consuming Northern European countries and the UK further decreased their use. Second-generation cephalosporins increased by >20% in seven countries (mainly cefuroxime), coinciding with a decrease in first-generation cephalosporins. Substantial parenteral use of third-generation substances (mainly ceftriaxone) was observed in France, Italy and the Russian Federation.

Conclusions: Since 1997, the use of the older (narrow-spectrum) cephalosporins decreased in favour of the newer (i.e. broad-spectrum) cephalosporins in most countries. Extreme variations between European countries in cephalosporin use over time suggest that they are to a large extent inappropriately used.

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

Introduction

This paper presents data from the European Surveillance of Antimicrobial Consumption (ESAC) project and reports on the use of cephalosporins in 2009, comprising 45 substances assigned to the Anatomical Therapeutic Chemical (ATC) group J01D and grouped into four generations based on their spectrum of antimicrobial activity (Table 1).^{1,2} It also reviews temporal

trends, the seasonal variation and composition of outpatient cephalosporin use on 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 on

Table 1. Four generations of cephalosporins following the ATC classification

First-generation		Second-generation		Third-generation		Fourth-generation	
J01DB01	cefalexin	J01DC01	cefoxitin	J01DD01	cefotaxime	J01DE01	cefepime
J01DB02	cefaloridine ^a	J01DC02	cefuroxime	J01DD02	ceftazidime	J01DE02	ceftiofime
J01DB03	cefalotin	J01DC03	cefamandole	J01DD03	cefsulodin ^a	J01DE03	ceftiofime
J01DB04	cefazolin	J01DC04	cefaclor	J01DD04	ceftriaxone		
J01DB05	cefadroxil	J01DC05	cefotetan ^a	J01DD05	cefmenoxime ^a		
J01DB06	cefazidone ^a	J01DC06	cefonicide	J01DD06	latamoxef ^a		
J01DB07	cefatrizine ^b	J01DC07	cefotiam	J01DD07	ceftizoxime		
J01DB08	cefapirin ^a	J01DC08	loracarbef	J01DD08	cefixime		
J01DB09	cefradine ^b	J01DC09	cefmetazole ^a	J01DD09	cefodizime		
J01DB10	cefacerile ^a	J01DC10	cefprozil	J01DD10	cefetamet		
J01DB11	cefroxadine ^a	J01DC11	ceforanide	J01DD11	ceftiofime ^a		
J01DB12	ceftezole ^a			J01DD12	cefoperazone		
				J01DD13	cefpodoxime		
				J01DD14	ceftibuten		
				J01DD15	cefdinir ^a		
				J01DD16	cefditoren		
				J01DD17	cefcapene ^a		
				J01DD54	ceftriaxone, combinations		
				J01DD62	cefoperazone, combinations		

Bold type indicates that use represented >1% of total outpatient cephalosporin use in Europe in 2009.

^aNo use of this cephalosporin in Europe was reported in 2009.

^bUse represented >1% of total penicillin use in 2003.

systemic antibiotics were described in the introductory paper of this series.³ For a detailed analysis, i.e. temporal trends ($n=31$ countries), seasonal variation ($n=27$ countries) and the changes in composition of outpatient cephalosporin use ($n=31$ countries), we distinguished between first-generation (J01DB), second-generation (J01DC), third-generation (J01DD) and fourth-generation cephalosporins (J01DE).^{4,5}

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).⁶ Outpatient antibiotic use data for the year 2009, expressed in DDD per 1000 inhabitants per day (DID), were available for 32 European countries (including Cyprus and Lithuania who provided total use data). For complementary reasons, data for Switzerland (only for the year 2004) are presented as well. Besides the DID outcome measurement unit, the number of packages/1000 inhabitants/day (PID) was utilized ($n=17$ countries). Package data have been available since 2006. The calculated DID/PID ratio allows assessment of the number of DDD available per package.

Results

Outpatient cephalosporin use in 2009

The WHO Collaborating Centre for Drug Statistics Methodology has assigned 45 unique ATC codes for cephalosporins; compared with the previous description of outpatient cephalosporin use in Europe,² one of these 45 cephalosporins is a newly introduced second-generation substance, three are new third-generation substances and one is a fourth-generation substance. Ten cephalosporins represented 97.0% of total outpatient cephalosporin use in Europe in 2009: cefuroxime (57.4%), cefalexin (10.1%), cefaclor (9.6%), cefixime (6.9%), cefprozil (4.1%), cefpodoxime

(2.9%), cefadroxil (2.6%), ceftriaxone (1.4%), ceftibuten (1.0%) and cefazolin (1.0%). Other substances represented <1% of total outpatient cephalosporin use. No use was recorded for 15 cephalosporin substances (Table 1).

Cephalosporins represented 11.4% of total outpatient use of antibacterials for systemic use in 2009. Figure 1 shows total outpatient cephalosporin use expressed in DID subdivided into the four cephalosporin generations in 2009 for 33 European countries, including two countries (Cyprus and Lithuania) with total use data and the Swiss 2004 data. Outpatient cephalosporin use varied by a factor of 267 between the countries with the highest (8.7 DID in Greece) and lowest (0.03 DID in Denmark) use (Table 2).

The first-generation cephalosporins represented 14.6% of total European outpatient cephalosporin use. A large variation in outpatient first-generation use was found, ranging from 2.2 DID in Finland to 0.004 DID in Slovenia (Table 2). The highest proportional first-generation use within total cephalosporin use was found for Norway (96.5%). First-generation cephalosporins represented >50% of the total outpatient cephalosporin use in six countries. Their use was mostly represented by just one substance, namely cefalexin (J01DB01), in Norway (96.4% or 0.1 DID), Finland (94.4% or 2.2 DID), the UK (74.6% or 0.4 DID) and Iceland (69.4% or 0.2 DID). Cefadroxil (J01DB05) was most used in Sweden (73.7% or 0.2 DID) and Latvia (27.1% or 0.1 DID). Cefradine (J01DB09) was most used by Ireland (12.7% or 0.2 DID), the UK (8.3% or 0.05 DID) and Portugal (5.5% or 0.1 DID). Minor use of first-generation cephalosporins was reported by France, Germany, Greece, Hungary, Italy, Luxembourg, Malta, Slovenia and Spain (<5% of their total outpatient cephalosporin use).

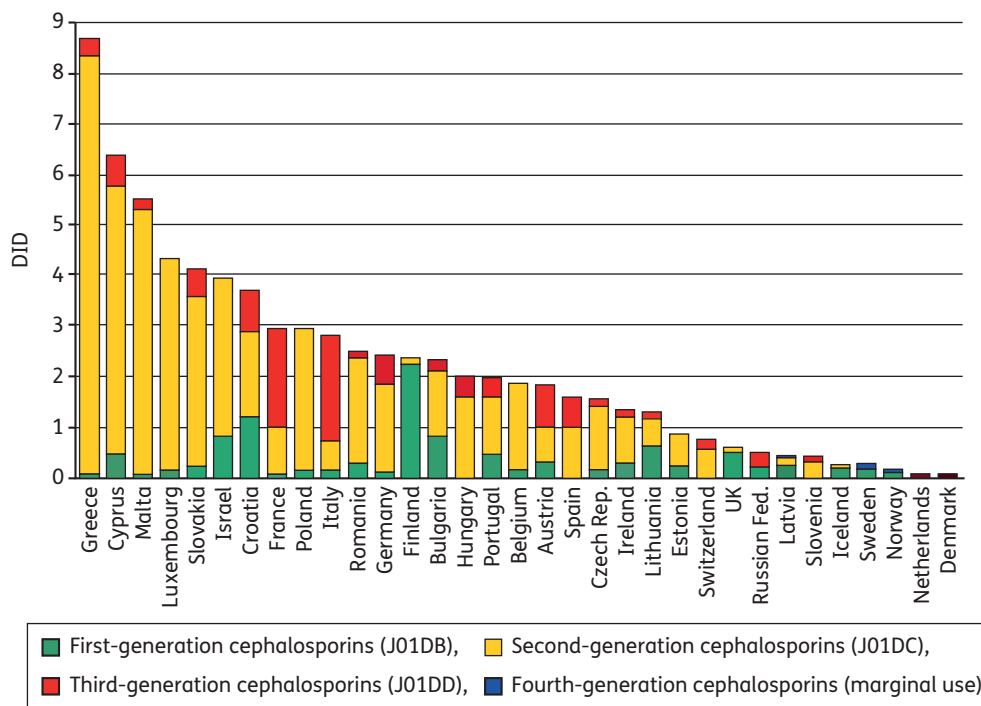


Figure 1. Outpatient use of cephalosporins in 33 European countries in 2009 in DID (2004 data for Switzerland). For Cyprus and Lithuania, total care data are reported. For Switzerland, only 2004 outpatient data are reported.

The second-generation cephalosporins represented 71.3% of total European outpatient cephalosporin use. Second-generation use ranged from 8.3 DID in Greece to 0.0003 DID in Norway (Table 2). The highest proportional second-generation use was observed for Luxembourg (96.7%). The second-generation cephalosporins were most frequently used in 20 countries (>50% of total outpatient cephalosporin use). Their use was mostly represented by cefuroxime (J01DC02) for Belgium (90.3% or 1.6 DID), Luxembourg (90.2% or 3.9 DID), Malta (85.2% or 4.7 DID), Poland (82.9% or 2.4 DID), Israel and Slovakia (78.4% and 74.5%, both 3.1 DID), the Czech Republic (70.0% or 1.1 DID) and Cyprus (67.9% or 4.3 DID, total care data). Greek use was mainly represented by cefuroxime (57.9% or 5.0 DID) and cefaclor (J01DC04) (20.6% or 1.8 DID). Ireland had the highest proportional use of cefaclor (57.4% or 0.76 DID). Countries with the highest cefprozil (J01DC10) use were Greece (16.0%), Estonia (14.8%), the Czech Republic (12.4%) and Hungary (11.4%). Greece was the only country using ceforanide (J01DC11).

The third-generation cephalosporins represented 14.0% of total outpatient cephalosporin use in Europe (mainly cefixime and cefpodoxime), of which 14.3% was for parenteral use (mainly ceftriaxone). Except for Iceland, all countries used third-generation cephalosporins in 2009 (Table 2). Their use represented 73.9% of total use in Italy (2.1 DID, mainly ceftibuten, of which 0.42 DID was for parenteral use, mainly ceftriaxone), 65.0% in France (1.9 DID, mainly cefpodoxime and cefixime, of which 0.1 DID was for parenteral use, mainly ceftriaxone), 50.9% in the Russian Federation (0.2 DID, of which 0.17 DID was for parenteral use, mainly ceftriaxone) and 43.7% in Austria (0.8 DID, mainly cefixime and cefpodoxime for oral use).

Fourteen countries prescribed fourth-generation cephalosporins in the year 2009; their use was very low, representing 0.03% of total European outpatient cephalosporin use. Highest use was observed for Italy, with 0.009 DID. Proportional use was highest in the Czech Republic (0.4%, 0.006 DID) and lowest in Germany (0.01%). No use was reported for 18 countries (Table 2). The most frequently used fourth-generation cephalosporin was cefepime. Austria and Bulgaria prescribed ceftipime as well.

Figure 2 shows total outpatient cephalosporin use expressed in PID for 17 countries for the year 2009 (Italy, 2008 data; Ireland and the Czech Republic, 2007 data). Italy prescribed the most cephalosporin packages (3.2 PID), followed by Greece, the Russian Federation and Lithuania (1.5, 1.0 and 0.7 PID). Lowest PID figures were found for Denmark and the Netherlands (<0.01 PID), followed by Sweden (<0.05 PID). According to the ranking shown, the Russian Federation shifted from position 13 in DID (low-prescribing country) to position 3 in PID (high-prescribing country) and Belgium from position 8 in DID to position 13 in PID. The ranking was similar for Austria, Denmark, Slovenia, Sweden and the Netherlands. Consequently, the lowest mean DDD per package was found in the Russian Federation (0.5 DDD/package) and the highest in Belgium (12.6 DDD/package), followed by Slovenia and Portugal (7.1 and 6.7 DDD/package, respectively). The mean number of DDD for a cephalosporin package in all countries was considerably lower compared with the overall mean number of DDD for an antibiotic package (J01), except for Belgium and Slovenia. In the Russian Federation, Lithuania and Italy, the mean number of DDD per package was 6, 3.5 and 2.8 times lower compared with the mean DDD of total J01 use.

Table 2. Yearly outpatient use of first- to fourth-generation cephalosporins in 33 European countries, expressed in DID (1997–2009)

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Austria	—	1.584	1.735	1.490	1.395	1.389	1.628	1.555	1.675	1.573	1.696	1.699	1.804
1st gen.	—	0.317	0.307	0.292	0.292	0.294	0.310	0.292	0.291	0.292	0.295	0.302	0.308
2nd gen.	—	0.533	0.635	0.500	0.394	0.348	0.462	0.499	0.609	0.568	0.613	0.639	0.707
3rd gen.	—	0.733	0.792	0.697	0.708	0.748	0.855	0.764	0.774	0.713	0.788	0.759	0.788
4th gen.	—	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Belgium	3.969	4.407	4.200	3.871	3.182	3.381	3.269	3.135	3.046	2.579	2.363	2.019	1.816
1st gen.	0.998	0.887	0.675	0.527	0.405	0.327	0.274	0.230	0.182	0.164	0.153	0.156	0.147
2nd gen.	2.971	3.520	3.525	3.343	2.777	3.053	2.994	2.905	2.864	2.415	2.209	1.862	1.668
3rd gen.	0.001	0.000	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
4th gen.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Bulgaria	—	—	1.376	2.515	2.500	1.426	1.383	1.675	2.071	1.697	1.865	2.077	2.303
1st gen.	—	—	1.207	1.574	2.083	0.883	1.008	1.161	1.450	1.166	1.116	1.036	0.827
2nd gen.	—	—	0.110	0.590	0.337	0.342	0.227	0.363	0.469	0.501	0.697	0.923	1.309
3rd gen.	—	—	0.057	0.345	0.073	0.194	0.137	0.121	0.141	0.030	0.052	0.118	0.166
4th gen.	—	—	0.002	0.006	0.007	0.007	0.011	0.030	0.010	0.000	0.000	0.001	0.001
Croatia	—	—	—	3.282	3.141	3.650	3.875	3.415	3.543	3.251	3.512	3.988	3.703
1st gen.	—	—	—	1.711	1.653	2.022	2.076	1.846	1.791	1.621	1.806	1.596	1.212
2nd gen.	—	—	—	1.015	1.115	1.284	1.359	1.180	1.344	1.212	1.050	1.671	1.674
3rd gen.	—	—	—	0.556	0.374	0.344	0.440	0.388	0.408	0.418	0.655	0.721	0.816
4th gen.	—	—	—	—	0.000	—	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cyprus	—	—	—	—	—	—	—	—	—	6.203	6.945	6.486	6.376
1st gen.	—	—	—	—	—	—	—	—	—	0.665	0.664	0.577	0.473
2nd gen.	—	—	—	—	—	—	—	—	—	5.091	5.694	5.343	5.325
3rd gen.	—	—	—	—	—	—	—	—	—	0.446	0.587	0.566	0.578
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	—
Czech Republic	—	1.346	1.260	—	—	1.069	0.996	0.954	1.188	0.913	1.052	1.362	1.521
1st gen.	—	0.506	0.427	—	—	0.280	0.241	0.180	0.172	0.113	0.099	0.125	0.139
2nd gen.	—	0.834	0.829	—	—	0.786	0.752	0.771	1.013	0.799	0.951	1.147	1.305
3rd gen.	—	0.006	0.004	—	—	0.002	0.002	0.003	0.003	0.002	0.002	0.085	0.071
4th gen.	—	0.000	0.000	—	—	0.000	0.000	0.000	0.000	0.000	—	0.005	0.006
Denmark	0.025	0.026	0.023	0.024	0.027	0.026	0.023	0.023	0.027	0.027	0.029	0.033	0.032
1st gen.	0.005	0.004	0.004	0.004	0.005	0.005	0.005	0.006	0.007	0.006	0.006	0.006	0.005
2nd gen.	0.019	0.021	0.018	0.019	0.020	0.019	0.015	0.016	0.018	0.018	0.020	0.022	0.021
3rd gen.	0.001	0.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.004	0.005	0.006
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	—
Estonia	—	—	—	—	0.676	0.579	0.595	0.657	0.715	0.783	0.807	0.849	0.825
1st gen.	—	—	—	—	0.355	0.312	0.325	0.325	0.326	0.318	0.250	0.263	0.222
2nd gen.	—	—	—	—	0.297	0.267	0.269	0.331	0.388	0.464	0.557	0.585	0.602
3rd gen.	—	—	—	—	0.023	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
4th gen.	—	—	—	—	0.000	—	—	0.000	0.000	—	0.000	0.000	—
Finland	2.257	2.134	2.242	2.237	2.324	2.273	2.292	2.128	2.210	2.215	2.376	2.319	2.325
1st gen.	1.804	1.802	1.949	1.988	2.086	2.085	2.119	1.993	2.080	2.110	2.283	2.232	2.238
2nd gen.	0.438	0.321	0.286	0.244	0.234	0.187	0.173	0.134	0.129	0.105	0.092	0.086	0.086
3rd gen.	0.015	0.011	0.007	0.005	0.004	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.000
4th gen.	—	—	—	—	—	0.000	—	0.000	—	—	—	—	—

Continued

Table 2. Continued

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
France	4.661	4.549	4.818	4.550	4.242	3.692	3.331	3.055	3.210	2.763	2.959	2.530	2.915
1st gen.	1.903	1.698	1.747	1.222	0.850	0.575	0.381	0.255	0.224	0.167	0.120	0.095	0.086
2nd gen.	1.656	1.627	1.748	1.744	1.692	1.424	1.309	1.257	1.273	0.976	0.965	0.715	0.934
3rd gen.	1.102	1.225	1.324	1.584	1.700	1.692	1.641	1.542	1.713	1.620	1.874	1.719	1.895
4th gen.	—	—	—	—	—	—	—	—	—	—	0.000	0.000	0.001
Germany	0.940	1.030	0.951	0.928	0.863	0.893	1.206	1.252	1.457	1.359	1.591	1.921	2.386
1st gen.	0.165	0.183	0.166	0.172	0.146	0.137	0.128	0.122	0.119	0.121	0.112	0.109	0.091
2nd gen.	0.380	0.393	0.361	0.341	0.326	0.369	0.703	0.762	0.929	0.895	1.090	1.390	1.785
3rd gen.	0.394	0.454	0.424	0.415	0.390	0.387	0.375	0.368	0.409	0.344	0.388	0.422	0.509
4th gen.	—	0.000	—	—	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Greece	6.257	6.064	6.159	6.665	6.646	6.731	6.210	7.072	7.715	7.674	8.859	9.385	8.651
1st gen.	2.330	1.453	1.396	0.936	0.654	0.495	0.373	0.303	0.227	0.190	0.190	0.090	0.064
2nd gen.	3.858	4.520	4.712	5.684	5.934	6.159	5.767	6.528	7.268	7.183	8.113	8.820	8.291
3rd gen.	0.066	0.086	0.049	0.044	0.054	0.070	0.067	0.219	0.199	0.287	0.533	0.454	0.293
4th gen.	0.002	0.005	0.002	0.002	0.004	0.007	0.002	0.022	0.021	0.014	0.023	0.022	0.002
Hungary	—	2.522	3.353	2.526	2.426	2.091	2.259	2.196	2.320	2.087	1.635	1.855	1.979
1st gen.	—	0.377	0.401	0.241	0.198	0.157	0.133	0.107	0.088	0.066	0.048	0.042	0.036
2nd gen.	—	1.915	2.509	1.886	1.768	1.510	1.691	1.655	1.746	1.547	1.230	1.430	1.558
3rd gen.	—	0.230	0.442	0.400	0.460	0.424	0.436	0.434	0.486	0.474	0.357	0.383	0.385
4th gen.	—	—	—	—	—	—	0.000	0.000	—	—	—	—	—
Iceland	0.551	0.547	0.568	0.554	0.514	0.526	0.480	0.422	0.496	0.191	0.102	0.261	0.260
1st gen.	0.105	0.092	0.103	0.120	0.110	0.136	0.142	0.168	0.176	0.082	0.102	0.174	0.180
2nd gen.	0.398	0.412	0.421	0.386	0.345	0.336	0.283	0.196	0.250	0.110	0.103	0.086	0.079
3rd gen.	0.047	0.043	0.044	0.048	0.059	0.055	0.055	0.058	0.069	0.000	—	0.000	—
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	—
Ireland	—	1.721	1.972	1.899	2.013	1.894	2.001	1.901	1.816	1.872	1.960	1.557	1.324
1st gen.	—	0.406	0.412	0.371	0.365	0.341	0.347	0.327	0.302	0.303	0.300	0.304	0.277
2nd gen.	—	1.130	1.359	1.349	1.481	1.398	1.493	1.429	1.422	1.466	1.542	1.136	0.945
3rd gen.	—	0.185	0.201	0.179	0.167	0.156	0.161	0.145	0.092	0.103	0.119	0.118	0.102
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	—
Israel	—	—	—	—	—	3.431	3.496	3.485	3.793	4.262	3.651	4.082	3.960
1st gen.	—	—	—	—	—	0.656	0.647	0.721	0.725	0.817	0.762	0.840	0.819
2nd gen.	—	—	—	—	—	2.766	2.837	2.752	3.057	3.431	2.772	3.228	3.124
3rd gen.	—	—	—	—	—	0.009	0.010	0.009	0.011	0.014	0.118	0.015	0.016
4th gen.	—	—	—	—	—	0.001	0.002	0.002	0.000	0.000	—	—	—
Italy	—	—	3.885	3.651	3.691	3.439	3.362	3.083	3.107	2.887	2.729	2.765	2.779
1st gen.	—	—	0.256	0.217	0.212	0.182	0.173	0.155	0.141	0.134	0.129	0.131	0.122
2nd gen.	—	—	1.890	1.743	1.552	1.360	1.228	1.099	0.991	0.896	0.760	0.681	0.598
3rd gen.	—	—	1.710	1.662	1.877	1.868	1.936	1.811	1.960	1.845	1.831	1.945	2.050
4th gen.	—	—	0.030	0.029	0.050	0.028	0.025	0.018	0.015	0.011	0.009	0.008	0.009
Latvia	—	—	—	—	—	0.400	—	0.327	0.427	0.526	0.577	0.493	0.433
1st gen.	—	—	—	—	—	0.274	—	0.219	0.274	0.321	0.341	0.265	0.228
2nd gen.	—	—	—	—	—	0.110	—	0.095	0.122	0.133	0.185	0.190	0.157
3rd gen.	—	—	—	—	—	0.016	—	0.013	0.031	0.072	0.051	0.038	0.049
4th gen.	—	—	—	—	—	0.000	—	0.000	0.000	0.000	0.000	0.000	—

Continued

Table 2. Continued

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Lithuania	—	—	—	—	—	—	—	—	—	0.867	1.797	3.186	1.258
1st gen.	—	—	—	—	—	—	—	—	—	0.771	1.318	2.231	0.619
2nd gen.	—	—	—	—	—	—	—	—	—	0.060	0.355	0.709	0.551
3rd gen.	—	—	—	—	—	—	—	—	—	0.035	0.123	0.244	0.086
4th gen.	—	—	—	—	—	—	—	—	—	0.001	0.001	0.002	0.002
Luxembourg	5.258	5.393	5.782	5.364	5.151	5.108	5.427	4.724	5.034	4.300	4.477	4.214	4.328
1st gen.	1.739	1.661	1.387	1.137	0.873	0.675	0.614	0.444	0.359	0.180	0.163	0.138	0.133
2nd gen.	3.511	3.724	4.387	4.220	4.265	4.419	4.800	4.270	4.665	4.110	4.303	4.063	4.184
3rd gen.	0.007	0.008	0.008	0.007	0.012	0.014	0.012	0.010	0.010	0.010	0.011	0.013	0.011
4th gen.	—	—	—	—	0.000	0.000	0.000	0.000	0.000	0.000	—	—	—
Malta	—	—	—	—	—	—	—	—	—	—	2.965	4.888	5.504
1st gen.	—	—	—	—	—	—	—	—	—	—	0.085	0.036	0.049
2nd gen.	—	—	—	—	—	—	—	—	—	—	2.798	4.697	5.274
3rd gen.	—	—	—	—	—	—	—	—	—	—	0.082	0.155	0.181
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	—
Netherlands	0.129	0.112	0.095	0.081	0.072	0.065	0.056	0.047	0.047	0.045	0.046	0.043	0.041
1st gen.	0.022	0.020	0.019	0.021	0.020	0.019	0.015	0.011	0.009	0.008	0.007	0.005	0.004
2nd gen.	0.092	0.068	0.054	0.045	0.038	0.035	0.034	0.029	0.031	0.030	0.031	0.030	0.029
3rd gen.	0.015	0.023	0.022	0.016	0.013	0.011	0.007	0.007	0.007	0.007	0.008	0.009	0.008
4th gen.	—	—	—	0.000	—	0.000	—	—	—	—	—	—	—
Norway	—	0.230	—	—	0.251	0.272	0.292	0.275	0.234	0.155	0.157	0.142	0.125
1st gen.	—	0.230	—	—	0.251	0.272	0.292	0.275	0.234	0.153	0.155	0.139	0.121
2nd gen.	—	—	—	—	—	—	—	—	—	0.000	0.000	0.000	0.000
3rd gen.	—	—	—	—	—	—	—	—	—	0.002	0.003	0.003	0.004
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	—
Poland	—	2.111	2.098	2.050	2.293	2.056	—	2.523	1.723	—	2.043	2.206	2.893
1st gen.	—	0.710	0.665	0.618	0.698	0.472	—	0.385	0.264	—	0.166	0.140	0.152
2nd gen.	—	1.356	1.379	1.377	1.558	1.557	—	2.137	1.459	—	1.877	2.066	2.741
3rd gen.	—	0.045	0.054	0.054	0.036	0.026	—	0.000	0.000	—	0.000	0.000	0.000
4th gen.	—	—	0.001	0.001	0.001	0.001	—	0.000	—	—	0.000	—	—
Portugal	3.299	3.109	3.513	3.466	3.104	3.255	3.764	3.215	3.349	2.716	2.234	1.980	1.956
1st gen.	0.987	0.814	0.894	0.862	0.844	0.842	0.878	0.751	0.790	0.720	0.572	0.467	0.443
2nd gen.	1.463	1.503	1.719	1.663	1.527	1.768	2.231	1.956	2.075	1.619	1.273	1.153	1.134
3rd gen.	0.850	0.792	0.900	0.942	0.733	0.644	0.654	0.508	0.483	0.377	0.389	0.359	0.379
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	—
Romania	—	—	—	—	—	—	—	—	—	—	—	—	2.473
1st gen.	—	—	—	—	—	—	—	—	—	—	—	—	0.281
2nd gen.	—	—	—	—	—	—	—	—	—	—	—	—	2.094
3rd gen.	—	—	—	—	—	—	—	—	—	—	—	—	0.095
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	0.003
Russian Federation	—	—	—	—	—	—	0.151	0.210	0.230	0.264	0.315	0.370	0.472
1st gen.	—	—	—	—	—	—	0.123	0.148	0.163	0.172	0.179	0.176	0.218
2nd gen.	—	—	—	—	—	—	0.004	0.005	0.008	0.010	0.012	0.012	0.013
3rd gen.	—	—	—	—	—	—	0.024	0.057	0.058	0.081	0.123	0.181	0.240
4th gen.	—	—	—	—	—	—	0.000	0.000	0.001	0.000	0.000	0.000	0.000

Continued

Table 2. Continued

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Slovakia	—	—	1.954	2.486	2.733	2.475	2.484	2.155	3.397	3.041	3.862	3.893	4.117
1st gen.	—	—	1.239	1.122	1.139	0.788	0.664	0.427	0.369	0.287	0.289	0.250	0.234
2nd gen.	—	—	0.666	1.237	1.437	1.561	1.697	1.630	2.916	2.417	3.079	3.110	3.346
3rd gen.	—	—	0.049	0.125	0.155	0.126	0.121	0.098	0.112	0.337	0.494	0.533	0.536
4th gen.	—	—	0.000	0.001	0.001	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.000
Slovenia	0.914	0.732	0.645	0.594	0.520	0.680	0.707	0.717	0.704	0.522	0.544	0.435	0.420
1st gen.	0.281	0.192	0.122	0.110	0.100	0.087	0.089	0.072	0.061	0.059	0.029	0.005	0.004
2nd gen.	0.531	0.477	0.469	0.428	0.342	0.505	0.532	0.583	0.606	0.402	0.411	0.314	0.305
3rd gen.	0.102	0.063	0.054	0.056	0.078	0.087	0.086	0.062	0.037	0.061	0.104	0.117	0.111
4th gen.	—	—	—	—	—	—	—	—	—	—	—	—	—
Spain	2.572	2.623	2.543	2.327	2.064	1.983	2.041	1.805	1.826	1.671	1.789	1.651	1.555
1st gen.	0.084	0.074	0.059	0.051	0.039	0.032	0.026	0.021	0.017	0.016	0.014	0.015	0.014
2nd gen.	1.825	1.931	1.883	1.693	1.476	1.398	1.463	1.305	1.274	1.129	1.185	1.076	0.998
3rd gen.	0.664	0.618	0.602	0.583	0.550	0.553	0.551	0.479	0.536	0.526	0.589	0.560	0.543
4th gen.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Sweden	0.612	0.617	0.580	0.537	0.512	0.473	0.437	0.396	0.378	0.373	0.341	0.302	0.242
1st gen.	0.395	0.406	0.396	0.379	0.372	0.349	0.329	0.300	0.282	0.281	0.256	0.228	0.183
2nd gen.	0.175	0.178	0.156	0.135	0.119	0.103	0.087	0.076	0.077	0.070	0.063	0.049	0.034
3rd gen.	0.041	0.033	0.029	0.023	0.021	0.022	0.021	0.019	0.020	0.022	0.022	0.025	0.026
4th gen.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	—	—	—	—	—
Switzerland	—	—	—	—	—	—	—	0.750	—	—	—	—	—
1st gen.	—	—	—	—	—	—	—	0.000	—	—	—	—	—
2nd gen.	—	—	—	—	—	—	—	0.549	—	—	—	—	—
3rd gen.	—	—	—	—	—	—	—	0.200	—	—	—	—	—
4th gen.	—	—	—	—	—	—	—	0.001	—	—	—	—	—
UK	1.077	0.956	0.811	0.756	0.780	0.767	0.769	0.759	0.780	0.792	0.800	0.710	0.580
1st gen.	0.823	0.821	0.678	0.634	0.657	0.646	0.647	0.640	0.608	0.630	0.653	0.589	0.495
2nd gen.	0.218	0.112	0.117	0.111	0.113	0.112	0.114	0.112	0.166	0.156	0.142	0.116	0.081
3rd gen.	0.036	0.023	0.016	0.012	0.010	0.009	0.007	0.007	0.006	0.006	0.005	0.005	0.004
4th gen.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	—	—	—	—	—

Country, total national cephalosporin use; gen., generation; —, no use reported; 0.000, <0.0005.

Longitudinal data analysis (1997–2009)

For Europe, a non-significant increase in total outpatient cephalosporin use of 0.007 (SD 0.009) DID per quarter was found, starting from 1.85 (SD 0.51) DID in the first quarter of 1997, but there was significant seasonal variation with an amplitude of 0.59 (SD 0.11) DID, which decreased significantly over time by 0.003 (SD 0.001) DID per quarter (Figure 3). Furthermore, the longitudinal analysis showed that the winter peak of outpatient cephalosporin consumption shifted significantly from one year to another and that there was a positive correlation between the volume of use and the seasonal variation. This means that, in terms of absolute amount, high and low cephalosporin-consuming countries tend to have high and low seasonal variation in cephalosporin use, respectively.

Table 2 provides an overview of outpatient cephalosporin use for all 33 participating European countries between 1997 and 2009. Total outpatient use of cephalosporins increased for half

of the participating countries. The highest continuous increase since first participation was observed in Germany (with a rise of 154% from 0.9 to 2.4 DID), followed by Slovakia (with a rise of 111% since 1999 from 2.0 to 4.1 DID), Malta (with a rise of 86% since 2007 from 3.0 to 5.5 DID), Bulgaria (with a rise of 67% since 1999 from 1.4 to 2.3 DID), Lithuania (total care use, with a rise of 45% since 2006 from 0.9 to 1.3 DID) and Greece (with a rise of 39% from 6.3 to 8.7 DID). The Russian Federation, however, a low-prescribing country, almost tripled its use from 2003 to 2009, from 0.15 to 0.47 DID; this was mainly the result of the rise in third-generation substances (ceftriaxone, cefixime and cefotaxime). The increase in cephalosporin use for the other countries (Croatia, Cyprus, Estonia and Israel) was mainly the result of the rise in second-generation substances (cefuroxime and cefaclor).

Fourteen countries decreased their overall outpatient cephalosporin use. The highest decrease was observed for Belgium.

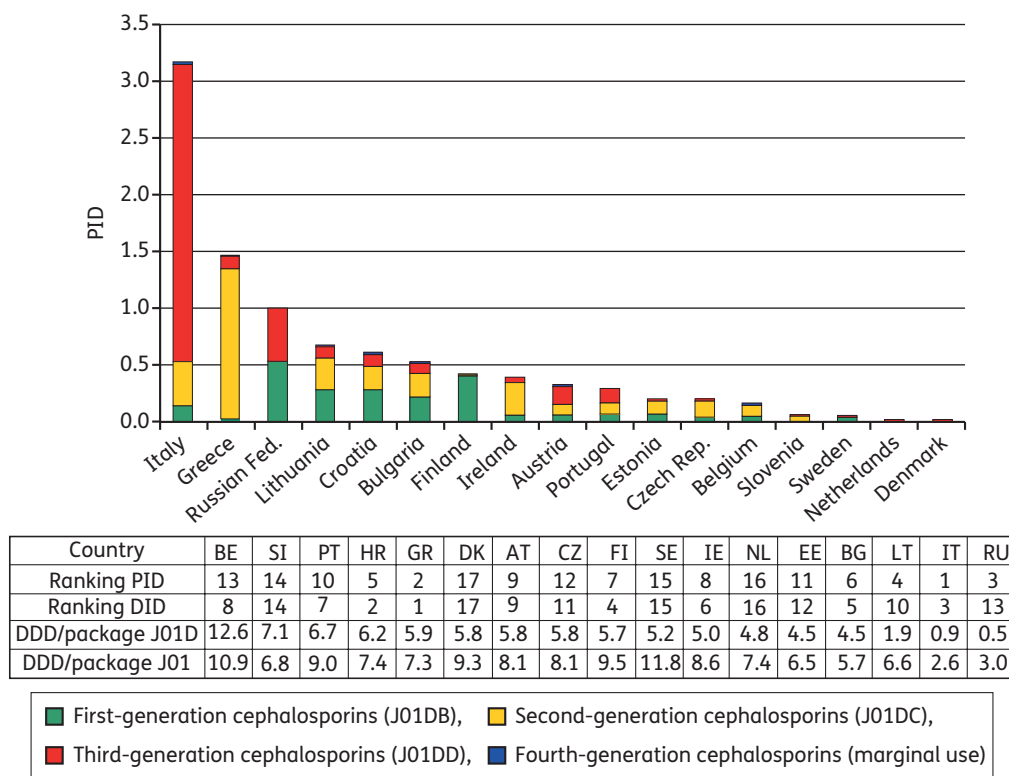


Figure 2. Outpatient use of cephalosporins in 17 European countries in 2009 in PID, the ranking in DID versus PID, and the mean number of DDD per outpatient cephalosporin package. For Lithuania, total care data are used. For Italy, 2008 data are used. For the Czech Republic and Ireland, 2007 data are used. Countries are shown in order (left to right) of decreasing DDD/package J01D, 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.

Four countries more than halved their use: Belgium (from 4.4 to 1.8 DID), Norway (from 0.29 DID in 2003 to 0.13 DID), Slovenia (from 0.91 to 0.42 DID) and Sweden (from 0.62 to 0.24 DID). Minor decreases in overall outpatient cephalosporin use were observed for France, Hungary, Iceland, Ireland, Italy, Latvia, Luxembourg, Portugal, Spain and the UK.

Denmark and the Netherlands had the lowest use in absolute numbers (on average in time 0.03 DID and <0.2 DID, respectively). Use in the Netherlands decreased 3-fold (from 0.13 in 1997 to 0.04 DID), mainly due to the continuous decrease in the second-generation cephalosporin cefaclor.

Fourth-generation cephalosporins were prescribed in 24 countries during the period 1997–2009. However, Estonia, Hungary, Israel, Latvia, Luxembourg, the Netherlands, Poland, Sweden and the UK discontinued their use over time. Denmark, Iceland, Ireland, Norway, Portugal and Slovenia have never prescribed fourth-generation cephalosporins.

Figures S1 and S2 (available as Supplementary data at JAC Online) show the seasonal variation of outpatient cephalosporin use in 27 European countries that were able to provide quarterly data. Seasonal variations were observed in all countries, except for the lowest prescribing countries, Denmark and the Netherlands. The seasonal variation was less pronounced or absent in the low-prescribing countries Iceland, Slovenia, Sweden and UK. Finland also showed a lower seasonal variation compared with the higher prescribing countries.

Compositional data analysis (1997–2009)

For Europe, the relative use of first-generation cephalosporins significantly decreased over time with respect to the second-, third- and fourth-generation cephalosporins (Table 3).

Proportional use of first-generation cephalosporins decreased by $\geq 50\%$ in Bulgaria (mainly cefalexin and cefazolin) and Slovakia, by $\geq 40\%$ in Lithuania (mainly cefazolin), by $\geq 30\%$ in France (mainly cefaloxin and cefadroxil), Greece (mainly cefadroxil), Luxembourg (mainly cefatrizine, no use in 2009), the Russian Federation (no absolute decrease) and Slovenia (mainly cefalexin), by $\geq 20\%$ in Croatia, Estonia (cefazolin and no use of cefalexin since 2007) and Poland, and by $>10\%$ in Belgium, the Czech Republic (mainly cefalexin, no use in 2009), Germany, Hungary and Latvia (mainly cefalexin). This decrease was matched by increasing use of second-generation cephalosporins (mainly cefuroxime) in all these countries, except for France, where the decrease was compensated by an equal increase in the use of third-generation cephalosporins (mainly the oral cefpodoxime). The decrease in Belgium was mainly related to an overall decrease in cephalosporin use.

Proportional use of first-generation cephalosporins increased by 50% in Iceland by the single use of cefalexin at the expense of the use of cefuroxime. Proportional use of first-generation cephalosporins increased by $>10\%$ in Finland and the UK (mainly cefalexin). This increase coincided with a

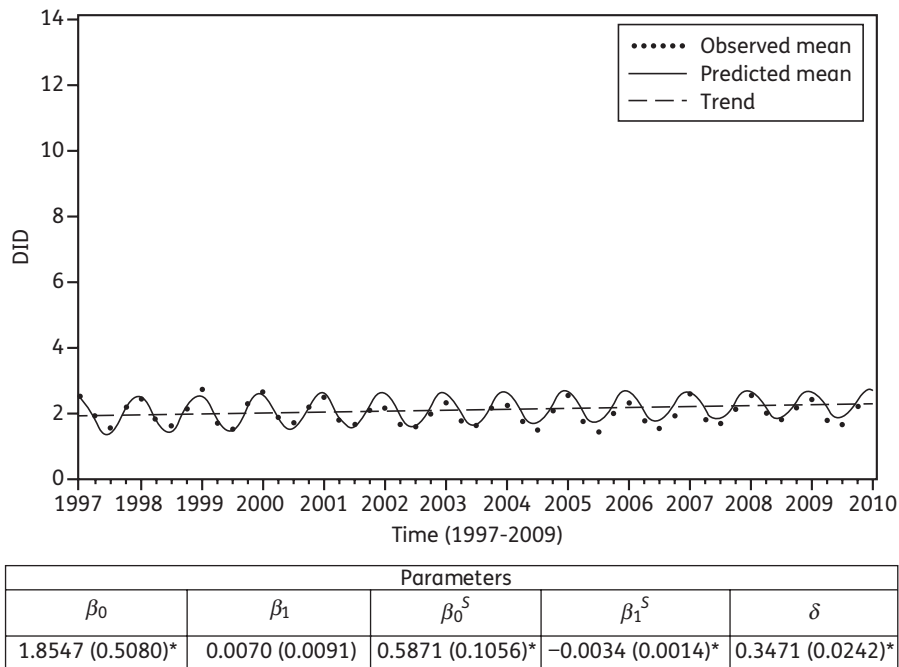


Figure 3. Estimated linear trend and seasonal variation of outpatient cephalosporin use based on available quarterly data for 1997–2009. β_0 (intercept), predicted average outpatient use in the first quarter of 1997; β_1 (slope), predicted average increase (if positive)/decrease (if negative) in use per quarter; β_0^S (seasonal variation), predicted average amplitude of the upward winter and downward summer peak in use; β_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 cephalosporin use in Europe as a function of time

	J01DB	J01DC	J01DD	J01DE
J01DB		-0.133*	-0.128*	-0.118*
J01DC	0.133*		0.005	0.015
J01DD	0.128*	-0.005		0.010
J01DE	0.118*	-0.015	-0.010	

J01DB, first-generation cephalosporins; J01DC, second-generation cephalosporins; J01DD, third-generation cephalosporins; J01DE, fourth-generation cephalosporins.

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.

decrease in second-generation cephalosporin use (mainly cefuroxime).

In most countries with the highest proportions of first-generation cephalosporin use, this proportion continued to increase (Finland and Sweden). Also, Iceland substantially increased the use of first-generation cephalosporins. In countries with the lowest proportions of first-generation use, this proportion further decreased (Figure S3, available as Supplementary data at JAC Online).

Second-generation cephalosporin use increased by >70% in Slovakia due to the 9-fold increase in cefuroxime at the

expense of cefalexin use. The use of second-generation cephalosporins increased by >20% in Bulgaria (since 2006), Estonia, Germany, Greece (5-fold increase in cefuroxime), Luxembourg and Poland (mainly cefuroxime). This coincided mainly with a drop in cefalexin, cefazolin or cefadroxil. A proportional increase in the use of third-generation cephalosporins was observed for France (mainly cefpodoxime and cefixime) and Italy (mainly ceftriaxone and cefpodoxime) and coincided with a decrease in the use of first- and second-generation cephalosporins in France and Italy, respectively.

Austria, Cyprus, Ireland, Israel, Malta, Norway and Portugal showed minor changes in proportional use of the different generations of cephalosporins ($\leq 10\%$) over time. Norway did not introduce second- and third-generation cephalosporins until 2006 and their use is still marginal.

Discussion

Overall, European outpatient cephalosporin use significantly increased between the first quarter of 1997 and the last of 2009 by 0.36 (SD 0.47) DID, mainly due to the proportional and absolute increases in second-, third- and fourth-generation cephalosporins in most countries. Seasonal variation of cephalosporin use, however, decreased significantly over time.

Various overall trends in cephalosporin use were observed. The high cephalosporin-consuming countries Greece and Malta continued to increase their use. Moreover, the highest sudden increase was observed for Malta, where use almost doubled in only 2 years (from 3 DID in 2007 to 5.5 DID in 2009). A considerable increase was observed also for Slovakia and Germany. However,

the highest proportional increase was observed for the Russian Federation, a low cephalosporin-consuming country. Cephalosporin use decreased in several countries between 1997 and 2009, especially in Belgium, France and Italy. The lowest cephalosporin use was observed in Denmark and The Netherlands. In general, use and seasonal variation were higher in Southern and Eastern European countries than in Northern European countries.

Since our first observations in 1997, administration of the first-generation cephalosporin cefazolin increased to 1% of total European cephalosporin use. However, since 1997, the use of the older (narrow-spectrum) cephalosporins decreased in favour of the newer (i.e. broad-spectrum) cephalosporins in most countries. All countries used second-generation cephalosporins. An increase in second-generation use (mainly cefuroxime and cefaclor) by >20% occurred in six countries, while in Slovakia use increased by 70% due to the large increase in the use of cefuroxime. Observed increases in the use of higher generations of cephalosporins were due not only to the proportional decrease in use of first-generation cephalosporins (mainly cefalexin) but also to the absolute increase in the use of more extended-spectrum cephalosporins. Only a few countries consumed significant proportions of third-generation cephalosporins, and their use increased over time. Fourth-generation cephalosporins were used in 24 countries during the period 1997–2009. However, only 14 of these countries still used them in 2009. The northern countries and the UK (since 2005) deviated from all other European countries. Their first-generation use increased and/or second-generation use decreased substantially.

High proportions of parenterally administered substances were observed for Italy, France and the Russian Federation (mainly ceftriaxone). Outpatient parenteral cephalosporin treatment is particularly common in Italy.⁷ Ceftriaxone use increased continuously in Italy, and its use almost doubled since the first observation in 1997. A large percentage of the antibiotic courses were given intramuscularly, albeit with the convenience of once-daily administration due to its prolonged half-life. In addition, clinical outcomes were excellent, and patient and physician satisfaction was found to be high.^{8–10}

First-generation cephalosporins are predominantly active against Gram-positive bacteria. Successive generations, however, have shown increased activity against Gram-negative bacteria. They are used to treat a wide variety of bacterial infections, including respiratory tract infections, skin infections and urinary tract infections. Given the observed increase in use of oral second-generation (mainly cefuroxime) and third-generation (cefixime and cefpodoxime) cephalosporins, the appropriateness of their use should be questioned. Cephalosporin use has been increasing for the treatment of uncomplicated respiratory tract infections with a presumed aetiology, despite no recommendation for cephalosporin use in such circumstances.^{11,12} Drug utilization studies could provide valuable data on the usage of particular drugs.

The extreme variations between countries and over time suggest that cephalosporins, in particular the more extended-spectrum cephalosporins, are inappropriately used to a large extent. In Austria, for example, a continuous and steep increase in the percentage of invasive *E. coli* isolates resistant to third-generation cephalosporins was observed from 2001 to 2007 (from 0.0% to 8.8%). The increased use of fluoroquinolones¹³ and the traditionally frequent use of oral third-generation

cephalosporins (Figure 1) may have contributed to the emergence of resistant microorganisms in Austria.¹⁴

As described in the other papers of this series, remarkable differences in volume of use were observed, depending on the outcome measurement unit used (DID or PID). The mean DDD in one cephalosporin package was low in the Russian Federation and considerably higher in Belgium. Consequently, the Russian Federation had a higher cephalosporin use when expressed in PID (1.0) and a lower use when expressed in DID (0.5) compared with Belgium (0.2 PID and 1.8 DID respectively). Therefore, for future surveillance we suggest that the PID and DID outcome measures are compared with each other.

In conclusion, the trends in time and the shift between generations in cephalosporin use in Europe need further exploration. These ESAC results can be used as a historical reference to gauge future interventions to optimize prescribing, and call for future research to gain a deeper understanding of antibiotic use, and cephalosporin use in particular.

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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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