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

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Background: Data on more than a decade of outpatient quinolone 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).

Methods: For the period 1997–2009, data on outpatient use of systemic quinolones 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 and packages per 1000 inhabitants per day (DID and PID, respectively). Using a classification based on pharmacokinetic and *in vitro* potency profiles, quinolone use was analysed with regard to trends over time, seasonal variation and composition.

Results: Total outpatient quinolone use in 2009 varied by a factor of 7.5 between the country with the highest (Italy, 3.61 DID) and the country with the lowest (the UK, 0.48 DID) quinolone use. The second-generation quinolones accounted for >50% of quinolone use (mainly ciprofloxacin), except for Croatia, where first-generation quinolones (mainly norfloxacin) were mostly used. A significant increase in outpatient quinolone use was found for Europe, as well as a large seasonal variation, which increased significantly over time from 1997 to 2009. Relative use of third-generation quinolones significantly increased over time with respect to the use of second-generation quinolones, while the relative use of both significantly increased with respect to the first-generation quinolones. Levofloxacin and moxifloxacin (respiratory quinolones) represented >10% of quinolone outpatient use in 17 countries, with extreme seasonal variation in all countries.

Conclusions: There was a substantial increase and change in the pattern of quinolone use between 1997 and 2009, a period during which quinolones that are effective for the treatment of respiratory tract infections were introduced. These quinolones are not the first-line antibiotics for this indication and their use should generally be limited, and quinolones should ideally show no substantial seasonal variation in terms of their use.

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

Introduction

Since the introduction of nalidixic acid for the treatment of Gram-negative urinary tract infections in 1962, the quinolones have become important and effective agents in the treatment of bacterial infections. Two major groups of compounds have been developed from the basic quinine molecule: the quinolones and naphthyridones.[1] After a slow start, derivatives were developed that had increased potency and improved bioavailability and pharmacokinetic characteristics. However, some of these structural changes have been found to correlate with specific side effects, which resulted in the withdrawal of several agents after marketing or in late development.[2] One of the earliest and most important changes was the addition of a fluorine atom at position 6 of the quinine-based pharmacore; this single alteration provided a large increase in potency, and

many currently used fluoroquinolones were derived from this molecule. Of these, ciprofloxacin became the benchmark against which all future quinolones would be measured. However, increasing antibiotic resistance among respiratory pathogens has prompted the introduction of alternative therapeutic options for respiratory infections, most prominent among which are the 'new' fluoroquinolones levofloxacin and moxifloxacin. The new fluoroquinolones possess increased activity against Gram-positive bacteria as well as superior pharmacokinetic/pharmacodynamic properties compared with the older quinolones.[3]

An in-depth analysis of quinolone use was performed using a classification based on their pharmacokinetic and *in vitro* potency profiles, which determine the area of clinical use. This paper reports on outpatient quinolone use in 2009 in Europe, based on the consumption data collected from 33 European countries. It also reviews the seasonal variation, temporal trends and composition of quinolone use in 1997–2009, focusing in particular on the new so-called respiratory quinolones.

Methods

In 2009, 35 countries were included in the European Surveillance of Antimicrobial Consumption (ESAC) project of which 33 provided valid data. The methods for collecting use data on systemic antibiotics are described elsewhere.[4] For the period 1997–2009, data on the use of systemic antibiotics for ambulatory care aggregated at the level of the active substance were collected, in accordance with the Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) measurement unit (WHO, version 2011).[5] To provide a detailed description of outpatient quinolone use in 2009, data are reported as DDD per 1000 inhabitants per day (DID) and packages per 1000 inhabitants per day (PID); the number of DDD per package was calculated by dividing DID by PID values for each country. Quarterly outpatient quinolone use data in DID were statistically modelled to assess seasonal variation and trends in use from 1997 to 2009 for Europe, using longitudinal data analysis.[6] Through compositional data analysis, annual outpatient use data in DID were modelled to assess trends of the relative proportions of the major quinolone subgroups from 1997 to 2009 for Europe.[7] For comparison of outpatient quinolone use, quinolones were classified into three generations, as introduced by Ball,[1] based on their chemical structure and antimicrobial activity (Table 1).[8]

Results

Outpatient quinolone use in 2009

The WHO Collaborating Centre for Drug Statistics Methodology has assigned 26 unique ATC codes for quinolones, which now include three new compounds (prulifloxacin, pazufloxacin and garenoxacin) not included in earlier descriptions of quinolone use in Europe (Table 1). Only five quinolones had >1% of the total outpatient quinolone use in 2009, while no use was recorded for 10 other quinolones (Table 1).

Figure 1 shows the total outpatient quinolone use as well as the relative use of each of the three quinolone generations in 2009 expressed in DID for 32 European countries [including Cyprus and Lithuania with total use data (i.e. both ambulatory and hospital use)] and 2004 data for Switzerland. Outpatient quinolone use varied by a factor of 7.5 between the countries with the highest (3.61 DID in Italy; 4.13 DID in Cyprus is total use data) and lowest (0.48 DID in the UK) use. In 2009, first-generation quinolones (mostly norfloxacin) still represented 55% of the total outpatient quinolone use in Croatia, >30% in the Czech Republic, Cyprus, Estonia, Switzerland and Poland, and >10% in all but 11 countries (<10% of total use Belgium, Germany, Luxembourg, Portugal, Sweden, UK; no use in Denmark, Ireland, Norway, Israel and Iceland). Use of first-generation quinolones varied from 0.74 DID in Croatia and 1.5 DID in Cyprus (total use) to 0.02 DID in the UK, with no reported use in Denmark, Iceland, Ireland, Israel and Norway. Pipedimic acid was used in 10 countries, DID ranging from 0.001 in Germany to 0.14 in Italy. Among the other first-generation quinolones, nalidixic acid was used in Hungary, the Russian Federation, Romania and the UK (1.8%, 0.2%, 0.1% and 0.04% of total quinolone use, respectively), cinoxacin was used only in Italy (0.4% of total quinolone use) and flumequine was only used in France (0.6% of total use). Second-generation quinolones were by far the most widely used quinolones in Europe, their use

Table 1. Classification of quinolones into three generations (ATC classification, 2011 version)

First-generation		Second-generation		Third-generation	
J01MB01	rosoxacin[a]	J01MA01	**ofloxacin**	J01MA05	temafloxacin[a]
J01MB02	nalidixic acid	J01MA02	**ciprofloxacin**	J01MA13	trovafloxacin[a]
J01MB03	piromidic acid[a]	J01MA03	pefloxacin	J01MA14	**moxifloxacin**
J01MB04	pipemidic acid[b]	J01MA04	enoxacin	J01MA15	gemifloxacin
J01MB05	oxolinic acid[a]	J01MA07	lomefloxacin	J01MA16	gatifloxacin[a]
J01MB06	cinoxacin	J01MA08	fleroxacin[a]	J01MA17	prulifloxacin
J01MB07	flumequine	J01MA09	sparfloxacin	J01MA18	pazufloxacin[a]
J01MA06	**norfloxacin**	J01MA10	rufloxacin	J01MA19	garenoxacin[a]
		J01MA11	grepafloxacin[a]		
		J01MA12	**levofloxacin**		

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

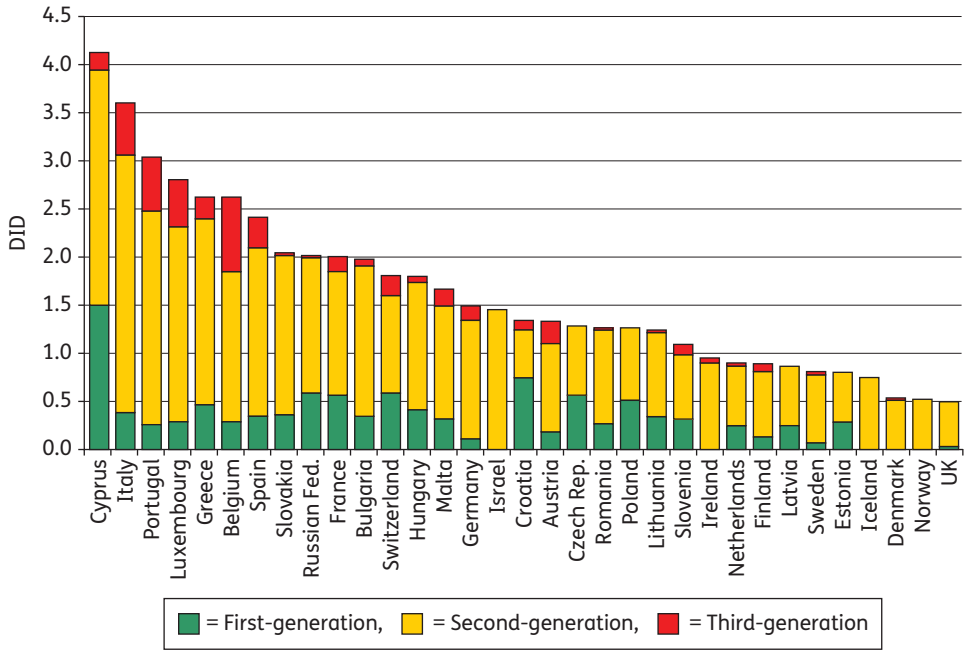


Figure 1. Outpatient use of quinolones in 33 European countries in 2009 in DID (2004 data for Switzerland). For Cyprus and Lithuania, total care data are used.

exceeding 50% (median 73%) of total quinolone use in all countries except Croatia. Their use varied from 2.7 DID in Italy to 0.46 in the UK. Ciprofloxacin accounted for 50% of total quinolone use in 20 countries and was the most frequently used quinolone in 26 countries. Its use varied from 0.35 DID in Iceland to 1.73 DID in Portugal. Ofloxacin was the most commonly used quinolone in Israel, while its purified *S*-enantiomer, levofloxacin, was the predominant quinolone used in Italy. Among the third-generation quinolones, only prulifloxacin and moxifloxacin were widely prescribed in Europe during 1997–2009. Their use was recorded in all countries except Iceland and varied from 0.78 DID in Belgium to 0.000002 DID in the Czech Republic (Table 2) Moxifloxacin represented 81.3% of the third-generation quinolones use in 2009 and prulifloxacin the remainder (18.7%).

Figure 2 shows total outpatient quinolone use in 17 European countries for 2009 expressed in PID. In addition, their ranking in decreasing order is depicted according to both DID and PID. No major shifts in ranking were observed. The number of DDD per package ranged from 2.2 in Italy to 8.5 in Sweden.

Longitudinal data analysis (1997–2009)

A significant increase in total outpatient quinolone use of 0.01 (SD 0.003) DID per quarter was found, starting from 1.11 (SD 0.17) DID in the first quarter of 1997. There was also a significant seasonal variation with an amplitude of 0.06 (SD 0.03) DID, which increased significantly over time by 0.002 (SD 0.0005) DID per quarter (Figure 3). Furthermore, the longitudinal analysis showed that both the upward winter and downward summer peaks of outpatient quinolone 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 amounts, high quinolone-consuming countries tend to have a high seasonal variation in quinolone use and vice versa.

Table 2 provides an overview of the quinolone consumption trends in the participating countries between 1997 and 2009. Only two countries (Slovenia and Sweden) showed a decrease in quinolone use over time. The use of quinolones increased by >1 DID in Greece (1.51 DID), Luxembourg (1.18 DID) and Italy (1.08 DID). The seasonal variation in outpatient quinolone use in 12 European countries missing a maximum of 1 year of quarterly data for 1997–2009 is shown in Figure S1 (available as Supplementary data at *JAC* Online). Data for another 15 countries able to deliver quarterly data for 1997–2009 but missing more than 1 year of data are in Figure S2 (available as Supplementary data at *JAC* Online). In all countries except Germany, Italy and Luxembourg, mean quinolone use in the first and fourth quarters did not exceed mean use in the second and third quarters by >20%. The high seasonal variation in Germany, Italy and Luxembourg resulted from the relatively frequent use of levofloxacin, moxifloxacin and in Italy also of prulifloxacin in the winter quarters. In most countries seasonal variation was highest for moxifloxacin, except for the Czech Republic, Slovakia and the UK (levofloxacin). However, other quinolones also showed an increase in use in the winter months. Ciprofloxacin variation was >20% in Slovakia and Poland and >15% in Hungary, Latvia and the Russian Federation. Ofloxacin variation was >15% in the Czech Republic, Poland and Slovakia, while norfloxacin variation was >15% in Latvia.

Compositional data analysis (1997–2009)

For Europe, the relative use of third-generation quinolones significantly increased over time with respect to the use of second-generation quinolones, whilst the use of both significantly increased relative to the use of first-generation quinolones

Table 2. Yearly outpatient quinolone 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	**—**	**1.05**	**1.14**	**1.25**	**1.35**	**1.39**	**1.32**	**1.49**	**1.42**	**1.41**	**1.43**	**1.31**	**1.33**
first	—	0.42	0.41	0.39	0.37	0.35	0.33	0.27	0.24	0.22	0.20	0.18	0.17
second	—	0.63	0.72	0.83	0.85	0.89	0.81	1.00	0.91	0.92	0.94	0.91	0.93
third	—	0.00	0.00	0.04	0.12	0.15	0.19	0.22	0.27	0.26	0.29	0.22	0.23
Belgium	**1.79**	**1.88**	**2.10**	**2.26**	**2.61**	**2.68**	**2.73**	**2.46**	**2.47**	**2.36**	**2.27**	**2.41**	**2.61**
first	0.83	0.75	0.65	0.55	0.51	0.45	0.42	0.38	0.35	0.31	0.28	0.28	0.26
second	0.97	1.13	1.45	1.71	2.10	1.86	1.64	1.52	1.50	1.45	1.40	1.56	1.57
third	—	—	—	—	—	0.38	0.67	0.55	0.62	0.60	0.59	0.57	0.78
Bulgaria	**—**	**—**	**0.03**	**1.23**	**1.60**	**1.35**	**0.44**	**1.60**	**2.29**	**1.81**	**1.95**	**2.08**	**1.97**
first	—	—	0.01	0.01	0.03	0.03	0.05	0.12	0.15	0.32	0.34	0.36	0.32
second	—	—	0.02	1.22	1.57	1.32	0.37	1.46	2.10	1.46	1.58	1.67	1.58
third	—	—	0.00	0.00	0.00	0.00	0.02	0.02	0.04	0.02	0.03	0.05	0.07
Croatia	**—**	**—**	**—**	**1.41**	**1.33**	**1.53**	**1.52**	**1.46**	**1.52**	**1.53**	**1.37**	**1.44**	**1.33**
first	—	—	—	1.31	1.20	1.36	1.29	1.22	1.21	1.15	0.90	0.86	0.74
second	—	—	—	0.10	0.13	0.15	0.18	0.18	0.22	0.29	0.38	0.48	0.50
third	—	—	—	0.00	0.00	0.02	0.05	0.06	0.09	0.09	0.09	0.10	0.09
Cyprus	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**3.85**	**3.79**	**4.29**	**4.13**
first	—	—	—	—	—	—	—	—	—	1.70	1.57	1.67	1.50
second	—	—	—	—	—	—	—	—	—	2.12	2.09	2.50	2.46
third	—	—	—	—	—	—	—	—	—	0.02	0.14	0.12	0.17
Czech Republic	**—**	**0.97**	**1.08**	**—**	**—**	**1.09**	**1.09**	**1.27**	**1.37**	**1.15**	**1.20**	**1.24**	**1.27**
first	—	0.69	0.66	—	—	0.52	0.53	0.67	0.71	0.57	0.59	0.56	0.55
second	—	0.28	0.42	—	—	0.56	0.57	0.60	0.66	0.58	0.61	0.68	0.72
third	—	—	—	—	—	—	0.00	0.00	—	—	—	0.00	0.00
Denmark	**0.22**	**0.24**	**0.20**	**0.15**	**0.17**	**0.18**	**0.25**	**0.28**	**0.32**	**0.37**	**0.44**	**0.52**	**0.52**
first	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	—	—	—	—	—
second	0.22	0.23	0.20	0.15	0.17	0.17	0.24	0.28	0.32	0.36	0.43	0.50	0.50
third	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.02	0.02
Estonia	**—**	**—**	**—**	**—**	**0.82**	**0.55**	**0.62**	**0.70**	**0.76**	**0.82**	**0.87**	**0.88**	**0.79**
first	—	—	—	—	0.16	0.16	0.17	0.20	0.23	0.27	0.29	0.30	0.27
second	—	—	—	—	0.66	0.39	0.45	0.49	0.52	0.55	0.58	0.58	0.52
third	—	—	—	—	0.00	0.00	0.00	—	0.00	—	0.00	0.00	0.00
Finland	**0.65**	**0.64**	**0.64**	**0.72**	**0.83**	**0.90**	**0.84**	**0.83**	**0.83**	**0.83**	**0.90**	**0.87**	**0.87**
first	0.27	0.25	0.15	0.15	0.16	0.16	0.17	0.17	0.15	0.14	0.14	0.11	0.11
second	0.38	0.39	0.49	0.57	0.67	0.73	0.66	0.64	0.65	0.65	0.69	0.69	0.70
third	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.03	0.03	0.04	0.07	0.07	0.07
France	**1.83**	**1.85**	**1.90**	**2.13**	**2.34**	**2.08**	**2.04**	**2.07**	**2.17**	**2.18**	**2.19**	**2.08**	**2.00**
first	1.03	0.96	0.97	0.95	0.93	0.93	0.83	0.82	0.81	0.77	0.71	0.66	0.56
second	0.80	0.89	0.93	1.18	1.41	1.07	1.04	1.05	1.15	1.22	1.27	1.26	1.28
third	0.00	0.00	0.00	0.00	0.00	0.08	0.16	0.20	0.21	0.19	0.21	0.17	0.16
Germany	**0.72**	**0.87**	**0.93**	**1.00**	**1.12**	**1.12**	**1.05**	**1.15**	**1.36**	**1.25**	**1.41**	**1.42**	**1.48**
first	0.13	0.11	0.12	0.16	0.18	0.15	0.15	0.15	0.15	0.13	0.12	0.11	0.10
second	0.59	0.74	0.74	0.68	0.74	0.72	0.66	0.76	0.90	0.88	1.02	1.11	1.24
third	0.00	0.01	0.06	0.15	0.20	0.25	0.24	0.24	0.31	0.24	0.27	0.20	0.14
Greece	**1.11**	**1.36**	**1.65**	**1.82**	**2.16**	**2.45**	**1.85**	**1.87**	**1.89**	**2.18**	**3.01**	**3.05**	**2.63**
first	0.69	0.74	0.93	0.88	0.87	0.84	0.64	0.51	0.54	0.54	0.52	0.48	0.45
second	0.42	0.62	0.72	0.93	1.25	1.52	1.15	1.33	1.27	1.59	2.23	2.28	1.94
third	0.00	0.00	0.00	0.02	0.04	0.09	0.05	0.03	0.08	0.06	0.26	0.29	0.23

Continued

Table 2. *Continued*

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Hungary	**—**	**0.87**	**1.09**	**1.03**	**1.20**	**1.35**	**1.52**	**1.65**	**1.91**	**1.80**	**1.51**	**1.75**	**1.79**
first	—	0.31	0.35	0.34	0.38	0.46	0.49	0.48	0.52	0.52	0.42	0.41	0.40
second	—	0.56	0.74	0.69	0.81	0.84	0.96	1.06	1.22	1.14	1.01	1.28	1.34
third	—	0.00	0.00	0.00	0.01	0.05	0.07	0.11	0.17	0.14	0.08	0.06	0.06
Iceland	**0.43**	**0.55**	**0.62**	**0.62**	**0.71**	**0.71**	**0.72**	**0.65**	**0.80**	**0.65**	**0.71**	**0.77**	**0.73**
first	0.00	0.00	0.00	0.00	0.00	0.00	0.00	—	—	—	—	—	—
second	0.43	0.55	0.62	0.62	0.71	0.71	0.72	0.65	0.80	0.65	0.71	0.77	0.73
third	0.00	0.00	0.00	0.00	0.00	0.00	0.00	—	—	—	—	—	—
Ireland	**—**	**0.52**	**0.56**	**0.57**	**0.64**	**0.65**	**0.72**	**0.75**	**0.84**	**0.94**	**1.04**	**1.04**	**0.94**
first	—	0.10	0.09	0.08	0.08	0.08	0.04	0.01	0.01	0.00	0.00	—	—
second	—	0.42	0.47	0.45	0.51	0.54	0.64	0.70	0.80	0.88	0.96	0.96	0.88
third	—	0.00	0.00	0.03	0.05	0.04	0.04	0.04	0.04	0.06	0.08	0.08	0.06
Israel	**—**	**—**	**—**	**—**	**—**	**0.88**	**0.93**	**1.09**	**1.19**	**1.34**	**1.34**	**1.39**	**1.44**
first	—	—	—	—	—	0.00	0.00	0.00	0.00	0.00	0.00	0.00	—
second	—	—	—	—	—	0.88	0.93	1.09	1.19	1.34	1.32	1.39	1.44
third	—	—	—	—	—	0.00	0.00	0.00	0.00	0.00	0.02	0.00	0.00
Italy	**—**	**—**	**2.53**	**2.66**	**3.01**	**2.84**	**3.01**	**2.97**	**3.30**	**3.46**	**3.53**	**3.46**	**3.61**
first	—	—	0.79	0.73	0.88	0.74	0.68	0.61	0.55	0.51	0.45	0.41	0.37
second	—	—	1.75	1.86	1.86	1.85	2.05	2.02	2.04	2.14	2.32	2.55	2.69
third	—	—	0.00	0.07	0.26	0.25	0.28	0.34	0.71	0.81	0.76	0.49	0.55
Latvia	**—**	**—**	**—**	**—**	**—**	**0.87**	**—**	**0.90**	**1.03**	**1.10**	**1.06**	**0.98**	**0.85**
first	—	—	—	—	—	0.30	—	0.25	0.28	0.26	0.27	0.26	0.22
second	—	—	—	—	—	0.57	—	0.65	0.75	0.84	0.79	0.72	0.62
third	—	—	—	—	—	—	—	0.00	—	0.00	0.00	0.00	0.00
Lithuania	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**0.83**	**1.46**	**1.56**	**1.23**
first	—	—	—	—	—	—	—	—	—	0.32	0.47	0.48	0.34
second	—	—	—	—	—	—	—	—	—	0.52	0.99	1.07	0.88
third	—	—	—	—	—	—	—	—	—	—	0.00	0.01	0.02
Luxembourg	**1.63**	**1.52**	**1.86**	**2.28**	**2.61**	**2.48**	**2.81**	**2.48**	**2.66**	**2.62**	**2.80**	**2.77**	**2.81**
first	0.60	0.56	0.53	0.47	0.40	0.34	0.32	0.31	0.29	0.28	0.26	0.27	0.26
second	1.03	0.96	1.33	1.81	2.21	1.93	2.14	1.84	1.92	1.89	2.02	2.03	2.04
third	0.00	0.00	0.00	0.00	0.00	0.21	0.36	0.33	0.44	0.46	0.52	0.47	0.51
Malta	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**1.70**	**1.78**	**1.66**
first	—	—	—	—	—	—	—	—	—	—	0.34	0.33	0.31
second	—	—	—	—	—	—	—	—	—	—	1.20	1.29	1.19
third	—	—	—	—	—	—	—	—	—	—	0.16	0.16	0.16
Netherlands	**0.84**	**0.84**	**0.89**	**0.84**	**0.83**	**0.81**	**0.81**	**0.84**	**0.86**	**0.91**	**0.93**	**0.90**	**0.89**
first	0.43	0.41	0.40	0.37	0.34	0.32	0.31	0.31	0.29	0.30	0.28	0.26	0.24
second	0.40	0.43	0.49	0.47	0.49	0.48	0.49	0.51	0.53	0.56	0.59	0.61	0.61
third	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.04	0.05	0.06	0.03	0.04
Norway	**—**	**0.25**	**—**	**—**	**0.35**	**0.40**	**0.40**	**0.43**	**0.48**	**0.44**	**0.48**	**0.50**	**0.51**
first	—	0.01	—	—	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	—
second	—	0.24	—	—	0.34	0.40	0.40	0.43	0.48	0.44	0.48	0.50	0.51
third	—	0.00	—	—	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Poland	**—**	**1.24**	**1.12**	**0.97**	**1.04**	**1.11**	**—**	**1.00**	**1.14**	**—**	**1.15**	**1.21**	**1.25**
first	—	0.67	0.59	0.55	0.54	0.52	—	0.41	0.51	—	0.47	0.49	0.49
second	—	0.56	0.53	0.41	0.50	0.59	—	0.59	0.63	—	0.68	0.72	0.76
third	—	0.00	0.00	0.00	0.00	0.00	—	0.00	0.00	—	0.00	0.00	0.00

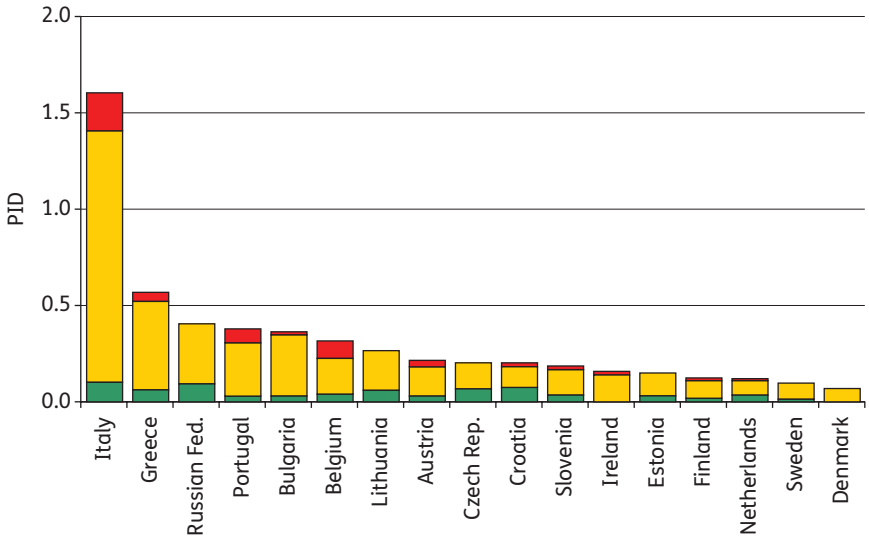
Continued

Table 2. *Continued*

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Portugal	**3.04**	**2.98**	**3.09**	**3.19**	**3.65**	**3.70**	**3.10**	**3.04**	**3.04**	**2.92**	**3.16**	**3.05**	**3.04**
first	0.56	0.59	0.63	0.66	0.65	0.58	0.42	0.40	0.33	0.30	0.26	0.24	0.23
second	2.48	2.39	2.46	2.53	2.91	2.82	2.29	2.27	2.35	2.35	2.34	2.22	2.24
third	0.00	0.00	0.00	0.00	0.08	0.31	0.38	0.37	0.36	0.27	0.57	0.59	0.56
Romania	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**1.26**
first	—	—	—	—	—	—	—	—	—	—	—	—	0.25
second	—	—	—	—	—	—	—	—	—	—	—	—	0.98
third	—	—	—	—	—	—	—	—	—	—	—	—	0.03
Russian Federation	**—**	**—**	**—**	**—**	**—**	**—**	**1.13**	**1.29**	**1.39**	**1.56**	**1.70**	**1.89**	**2.01**
first	—	—	—	—	—	—	0.34	0.38	0.41	0.47	0.49	0.55	0.57
second	—	—	—	—	—	—	0.79	0.90	0.97	1.08	1.21	1.33	1.43
third	—	—	—	—	—	—	0.00	0.00	0.01	0.01	0.01	0.01	0.01
Slovakia	**—**	**—**	**1.23**	**1.55**	**1.74**	**1.67**	**1.58**	**1.33**	**1.67**	**1.70**	**1.97**	**2.00**	**2.03**
first	—	—	0.42	0.48	0.43	0.41	0.35	0.40	0.41	0.36	0.35	0.37	0.35
second	—	—	0.81	1.06	1.31	1.26	1.23	0.93	1.27	1.33	1.60	1.61	1.67
third	—	—	0.00	—	—	—	—	—	—	0.00	0.01	0.02	0.02
Slovenia	**1.44**	**1.66**	**1.62**	**1.39**	**1.34**	**1.38**	**1.18**	**1.12**	**1.15**	**1.08**	**1.12**	**1.11**	**1.08**
first	0.94	1.06	1.01	0.81	0.69	0.63	0.48	0.40	0.37	0.35	0.34	0.33	0.30
second	0.50	0.59	0.61	0.58	0.58	0.66	0.60	0.61	0.64	0.62	0.65	0.67	0.67
third	0.00	0.00	0.00	0.00	0.07	0.09	0.10	0.10	0.14	0.11	0.13	0.11	0.11
Spain	**2.18**	**2.12**	**2.17**	**2.17**	**2.22**	**2.20**	**2.24**	**2.24**	**2.26**	**2.32**	**2.47**	**2.42**	**2.42**
first	0.96	0.86	0.79	0.77	0.70	0.61	0.58	0.52	0.47	0.44	0.39	0.36	0.33
second	1.23	1.26	1.33	1.27	1.31	1.30	1.32	1.37	1.40	1.52	1.64	1.72	1.76
third	0.00	0.00	0.05	0.14	0.21	0.29	0.34	0.35	0.38	0.36	0.44	0.35	0.33
Sweden	**1.01**	**1.04**	**1.07**	**1.05**	**1.09**	**1.01**	**1.00**	**0.98**	**0.99**	**0.98**	**0.92**	**0.83**	**0.79**
first	0.57	0.57	0.56	0.54	0.52	0.47	0.43	0.38	0.31	0.24	0.17	0.10	0.05
second	0.44	0.47	0.50	0.51	0.56	0.52	0.55	0.58	0.66	0.72	0.73	0.72	0.72
third	0.00	0.00	0.00	0.01	0.01	0.02	0.03	0.02	0.02	0.02	0.02	0.01	0.01
Switzerland	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**1.80**	**—**	**—**	**—**	**—**	**—**
first	—	—	—	—	—	—	—	0.57	—	—	—	—	—
second	—	—	—	—	—	—	—	1.03	—	—	—	—	—
third	—	—	—	—	—	—	—	0.20	—	—	—	—	—
UK	**0.48**	**0.47**	**0.43**	**0.42**	**0.44**	**0.45**	**0.45**	**0.48**	**0.52**	**0.53**	**0.62**	**0.52**	**0.48**
first	0.06	0.05	0.05	0.04	0.04	0.04	0.03	0.03	0.03	0.03	0.07	0.02	0.02
second	0.42	0.42	0.39	0.37	0.40	0.41	0.42	0.44	0.49	0.50	0.53	0.49	0.46
third	—	—	—	—	—	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01

Country, total national quinolone use; first, first-generation quinolones; second, second-generation quinolones; third, third-generation quinolones; —, no use reported; 0.00, <0.005.

(Table 3). In more than half of the countries, the proportional use of the different quinolone generations showed substantial variation, i.e. differences of ≥10%, between 1997 and 2009 (Figure S3, available as Supplementary data at *JAC* Online). Only in Estonia did proportional use of the first-generation quinolones increase by >10%. It decreased by >50% in Sweden, by >30% in Spain, Belgium, Slovenia, Croatia and Greece, and by >10% in Finland, France, the Czech Republic, Austria, Luxembourg, the Netherlands, Italy, Bulgaria, Ireland, Slovakia, Poland, Hungary, Germany, Portugal and Lithuania. This decrease can mainly be explained by a decrease in norfloxacin use, except for Ireland (nalidixic acid). For France, Luxembourg, the Netherlands, Italy, Poland and Lithuania it also resulted from decreasing use of pipedimic acid, and for Finland from decreasing use of cinoxacin (no longer used from 2000 onwards). This decrease was matched by a similar increase in use of the third-generation quinolones in Austria, Belgium, Denmark, Greece, Finland, Luxembourg, Portugal, Slovenia and the Russian Federation,



Country	IT	GR	RU	PT	BG	BE	LT	AT	CZ	HR	SI	IE	EE	FI	NL	SE	DK
Ranking PID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ranking DID	1	3	5	2	6	4	9	8	10	7	11	12	16	14	12	15	17
DDD/package	2.2	4.6	5.0	8.1	5.5	8.4	4.7	6.2	6.2	6.9	5.9	6.5	5.5	7.4	7.9	8.5	7.6

Figure 2. Outpatient use of quinolones in 17 European countries in 2009 in PID, the ranking in DID versus PID, and the mean number of DDD per outpatient package. For Lithuania, total care data are used. For Italy, 2008 data are used. For the Czech Republic and Ireland, 2007 data are used. 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 of the second-generation quinolones in the Czech Republic, Latvia, Norway, Poland, Sweden and Slovakia. In Germany, Spain, France, Hungary, Italy and the Netherlands the initial increase in third-generation quinolones has stabilized or decreased again in favour of second-generation quinolones.

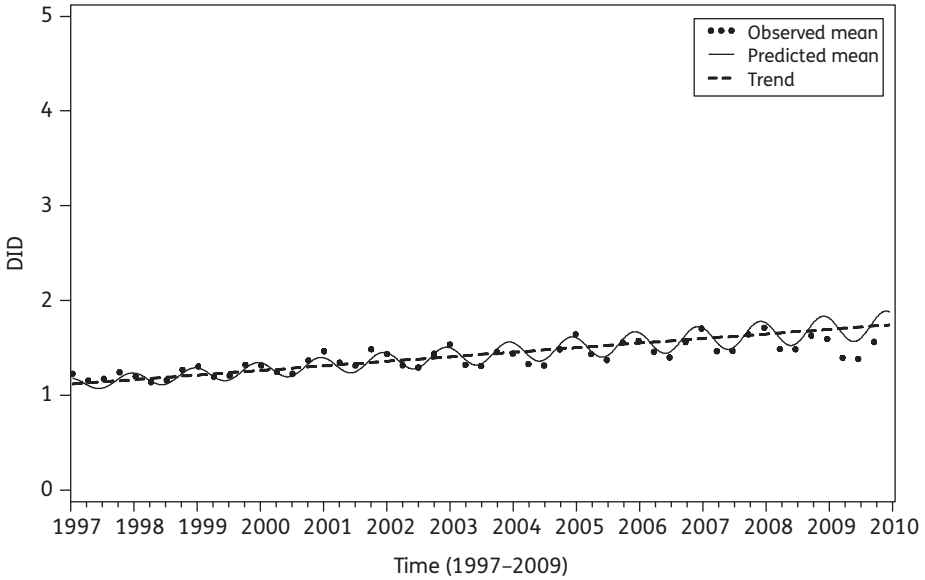
Discussion

This study describes outpatient use in Europe of quinolones (J01M), which has been one of the fastest growing antibiotic classes since the start of the ESAC survey in 1997.[4] There was striking variation in outpatient prescribing, with Italy having the highest outpatient quinolone use (mainly levofloxacin) in 2009, which was part of a continuously increasing trend, and Belgium showing the highest third-generation (mainly moxifloxacin) quinolone use. In Portugal (highest user in 2003) stable total consumption (still mainly ciprofloxacin) was seen, despite a substantial increase in moxifloxacin use since 2002. However, in general the use of quinolones remained highest in Southern Europe, followed by Eastern Europe, and was lowest in Northern Europe. In contrast to total outpatient antibiotic use of all classes of antibiotics, no important shifts in ranking were observed for outpatient quinolone use when using PID as the outcome measure instead of DID (Figure 2). This reflects the fact that the number of DDD per package for quinolones shows much less inter-country variation relative to that seen for total outpatient antibiotic use and for the other major antibiotic classes.[4,9–13]

The nomenclature of the quinolones is complex and we again used a classification based on their pharmacokinetic and *in vitro* potency profiles, which determine the area of clinical use. The increased *in vitro* potency profiles of newer quinolones has resulted in a shift away from those agents used predominantly for the treatment of urinary tract infections in the 1960s/70s (first-generation quinolones) to quinolones developed in the 1980s/90s and used systemically (second-generation quinolones), through to quinolones used for the treatment of respiratory tract infections in the current millennium (third-generation quinolones). Substantial use (>0.1 DID) of other quinolones was observed only in Italy (prulifloxacin and pipemidic acid) and Portugal (prulifloxacin).

During the 1990s, the use of the second-generation quinolones steadily increased at the expense of the first-generation compounds in most countries. This trend has changed, especially in the countries with the highest quinolone use in Europe, due to the introduction of newer agents such as levofloxacin (second-generation) and moxifloxacin (third-generation). In some countries the proportion of moxifloxacin is continuously increasing, while in Germany, France, Hungary, Spain, Italy and the Netherlands this initial increase was followed by a decrease starting in 2005–06. It is not clear whether this decrease was initiated by clinicians' changed perceptions of resistance, which is known to influence their choice of antibiotic.[14]

In some countries (such as Belgium, Luxembourg and Portugal) these so-called respiratory quinolones (levofloxacin



ATC	Parameters				
	β_0	β_1	$\beta_0{}^S$	$\beta_1{}^S$	δ
J01M	1.106 (0.170)*	0.012 (0.003)*	0.064 (0.029)*	0.002 (0.0005)*	0.416 (0.044)*

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

Table 3. Change in composition of outpatient quinolone use in Europe as a function of time

J01M	M1	M2	M3
M1		−0.655*	−3.533*
M2	0.655*		−2.878*
M3	3.533*	2.878*	

M1, first-generation quinolones; M2, second-generation quinolones; M3, third-generation quinolones.
Values are estimated changes in the log ratio of the row versus column antibiotic type with increasing time.[7] Significant effects are indicated with an asterisk; positive values represent an increase and negative values represent a decrease.

and moxifloxacin) are prescribed in large amounts. That is why seasonal variation of quinolones has significantly increased in Europe during the period of observation. Other countries are still largely prescribing the older quinolones, such as norfloxacin (high use in Croatia) and ofloxacin (especially in Israel). However, in general, their consumption is decreasing in most countries. Ciprofloxacin is still the most widely prescribed quinolone in clinical practice and its consumption increased in many countries during 1997–2009. Its use was probably boosted by patent expiry in 2003 followed by the introduction of generic equivalents in many European countries.

Since in most, if not all, European countries quinolones are not recommended as first-line antibiotics for the treatment of lower respiratory tract infections in ambulatory care,[15] the substantial increase in use of respiratory quinolones in the winter months should ideally not have occurred. Moreover, infections caused by atypical bacteria or pneumococci with intermediate resistance to β-lactam antibiotics can still be successfully treated with high doses of β-lactams.[16]

What was more striking is that outpatient use of so-called urinary quinolones with wide activity against Gram-negative bacteria but only marginal activity against Gram-positives also showed an increase in use in the winter months, e.g. ciprofloxacin in Slovakia, Poland, Hungary, Latvia and the Russian Federation. This inappropriate use of both the older and respiratory quinolones will inevitably lead to emergence of resistant pneumococci and also of resistant Gram-negative organisms.[17] That is why seasonal variation of quinolone use is among the final set of ESAC drug-specific quality indicators for outpatient antibiotic use in Europe.[18] The 2009 values for these quality indicators are reported in an accompanying paper.[19]

A recent publication listed a set of disease-specific quality indicators for outpatient antibiotic prescribing for the six main indications for antibiotic prescribing (acute otitis media, acute upper respiratory infection, acute/chronic sinusitis, acute tonsillitis, acute bronchitis/bronchiolitis and cystitis/other urinary infection) and for pneumonia.[20] This set was scored by 40 experts from 25 countries, and suggests that for each of these

indications quinolones should be prescribed in only 0%–5% of patients prescribed an antibiotic. Using (seasonal) quinolone use as a quality indicator has also been suggested by Altiner *et al*.,[21] and has been implemented already in Scotland.[22] Although quinolones do not represent the first-line therapy for most adult respiratory tract infections in Europe, a substantial change in the prescribing pattern of these agents was noted in the ESAC project. As quinolone use should be restricted and mainly reserved for well-defined indications, such high use probably indicates non-adherence to prescribing guidelines. From a public health perspective, this is an important consideration, as excessive and inappropriate use of quinolones is associated with the development of resistance, requires more resources and exposes patients to the additional risk of side effects.

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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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