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European Surveillance of Antimicrobial Consumption (ESAC): outpatient use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials in Europe (1997–2009)

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Background: Data on more than a decade of outpatient use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials in Europe were collected from 33 countries as part of 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 tetracyclines, sulphonamides and trimethoprim, and other antibacterials aggregated at the level of the active substance were collected and expressed in defined daily doses (DDD; WHO, version 2011) per 1000 inhabitants per day (DID). Using the Anatomical Therapeutic Chemical (ATC) classification, trends in the use of tetracyclines (J01A), sulphonamides and trimethoprim (J01E) and other antibacterials (J01X) over time, seasonal variation and composition of use were analysed.

Results: In 2009, the variations in outpatient use of systemic tetracyclines, sulphonamides and trimethoprim, and other antibacterials between countries, and also in the composition of use over time, were huge. For tetracyclines a significant and for sulphonamides and trimethoprim a non-significant decrease in use was observed between 1997 and 2009 in Europe. The seasonal variation in their use significantly decreased over time. For the other antibacterials, no significant changes in the volume of use or its seasonal variation were seen.

Conclusions: As for all other major antibiotic subgroups, a striking variation in use and composition of use between countries in Europe was observed for outpatient use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials. In combination with the decreasing use, especially of recommended substances, this represents an opportunity not only to reduce antibiotic use but also to improve its quality.

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

Introduction

Both total outpatient antibiotic use in Europe and the use of four major antibiotic subgroups, namely penicillins, cephalosporins, macrolides and quinolones, have previously been reported,[1–5] and are updated in a series of articles to accompany this one.[6–10] This paper reports for the first time outpatient use in Europe of antibacterials for systemic use classified as tetracyclines, sulphonamides and trimethoprim, and other antibacterials according to the Anatomical Therapeutic Chemical (ATC) classification.[11] In addition to a detailed account of their use in 2009, the trends over time, seasonal variation and composition of their use are also reported. Tetracyclines and amoxicillin have been recommended as first-choice antibiotics in community-acquired lower respiratory tract infection, which is one of the most common conditions encountered in primary care.[12] Trimethoprim and nitrofurantoin, which belong to the other two antibiotic subgroups addressed in this paper, are recommended for the treatment of lower urinary tract infections and methenamine is recommended for its prevention.[13] In Sweden outpatient use is often reported without the urinary antiseptic methenamine.[14] This has to be taken into account when comparing outpatient antibiotic use in Europe.

Methods

In 2009, 35 countries were included in the European Surveillance of Antimicrobial Consumption (ESAC) project, of which 33 provided valid data on antibiotic use. The methods for collecting use data on systemic antibiotics are described elsewhere.[6] 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 ATC classification and defined daily dose (DDD) measurement unit (WHO, version 2011).[11] For 2009, outpatient antibiotic use data, expressed in DDD per 1000 inhabitants per day (DID) and packages per 1000 inhabitants per day (PID), were available from 32 countries (and 2004 data for Switzerland) and 17 countries in Europe, respectively, and the outpatient use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials was compared between these countries. The ATC group 'Tetracyclines' is not subdivided into subgroups, but for both 'Sulphonamides and trimethoprim' (J01E) and 'Other antibacterials' (J01X) subgroups have been defined, and will be applied to assess outpatient use in more detail (Table 1). The number of DDD per package was calculated by dividing DID by PID values for each country. Quarterly outpatient use data in DID were statistically modelled to assess use and seasonal variation of use and their trends from 1997 to 2009 for Europe. Longitudinal data analysis was performed.[15] Through compositional data analysis, annual outpatient use data in DID were modelled to assess trends of the relative proportions of the available subgroups from 1997 to 2009 for Europe.[16] In addition, we describe trends and seasonal variation in the use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials in DID, and trends of their relative proportions from 1997 to 2009 for individual countries.

Results

The WHO Collaborating Centre for Drug Statistics Methodology has assigned 14, 33 and 23 unique ATC codes for substances classified as tetracyclines, sulphonamides and trimethoprim, and other antibacterials, respectively (Table 1). Only 5, 4 and 7 of these substances accounted for >1% of the total outpatient use in 2009 in Europe of tetracyclines, sulphonamides and trimethoprim, and other antibacterials, respectively, while no use was recorded for 5, 21 and 5 substances, respectively. Figure 1(a–c) shows the total outpatient use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials in 2009 for 32 European countries, including two countries (Cyprus and Lithuania) with total antibiotic use data expressed in DID. The data shown for Switzerland are for 2004.

Tetracyclines

Outpatient tetracycline use in 2009

Outpatient tetracycline use varied by a factor of 1649 between the countries with the highest (5.1 DID in Iceland) and the lowest (0.003 DID in Slovenia) use and by a factor of 44 between the countries with the highest and the second lowest use (0.11 DID in Romania) (Figure 1a). Doxycycline represented >50% of the total outpatient tetracycline use in all but five countries (Belgium, Denmark, Ireland, Sweden and the UK, but even there use was >30%), and it was the most used tetracycline in all but two countries. In Denmark tetracycline was used most often (>40%) and in the UK lymecycline was used most often (>30%). Use of tetracycline was >20% in Finland, Germany and Norway as well, and lymecycline was also used in Belgium, Denmark, Ireland, Italy and Sweden. Use of minocycline was >20% in Belgium, Ireland, Israel, Italy, Malta and Portugal.

Figure 2(a) shows total outpatient tetracycline use in 17 European countries for 2009 expressed in PID. In addition, their ranking is depicted according to both DID and PID. The DDD per package ranged from 3.8 in Italy to 22.8 in Denmark. Higher values were associated with higher ranking in DID than in PID. Denmark and Sweden appeared higher in the ranking in DID than in that in PID, because of their high number of DDD per package, while for Bulgaria and the Russian Federation the opposite was observed.

Longitudinal data analysis (1997–2009)

A significant decrease in total outpatient tetracycline use of 0.01 (SD 0.003) DID per quarter was found, starting from 2.60 (SD 0.25) DID in the first quarter of 1997, and there was large seasonal variation with an amplitude of 0.62 (SD 0.07) DID, which decreased significantly over time by 0.006 (SD 0.002) DID per quarter (Figure 3a). Furthermore, the longitudinal analysis showed that the winter peak of outpatient antibiotic consumption shifted significantly in timing from one year to another, and that there was a significant positive correlation between the volume of use and the seasonal variation. Thus, in terms of absolute amounts, countries with high tetracycline use tended to have a high seasonal variation in tetracycline use and vice versa.

Table 2 provides an overview of the consumption trends in the participating countries between 1997 and 2009. Two countries showed an increase in tetracycline use of >0.50 DID between the first and last years of observation, and 12 countries showed a similar decrease in use. In Hungary, Luxembourg, Poland and Portugal tetracycline use decreased by >1 DID, whereas in Belgium and Bulgaria use decreased by >2 DID.

The seasonal variation of outpatient tetracycline use in 12 European countries able to deliver quarterly data from 1997 to 2009 and missing a maximum of 1 year of data is shown in Figure S1(a) (available as Supplementary data at *JAC* Online). Another 15 countries were able to deliver seasonal data but were missing more than 1 year of data (Figure S2a, available as Supplementary data at *JAC* Online). In eight countries (Austria, Belgium, Croatia, Finland, Hungary, the Netherlands, Poland and Sweden) use in the first and fourth quarters was >40% higher than that in the second and third quarters. In another three countries (Germany, Estonia and Slovenia) this seasonal variation was >30%. In 16 countries it was <30%, but still >20% (Cyprus, the Czech Republic, Iceland, Italy, Latvia, Luxembourg, Portugal, Spain and Slovakia), >10% (Denmark, Greece, Lithuania and Israel) or <10% (Ireland, the Russian Federation and the UK). Seasonal variation of tetracyclines was mainly driven by doxycycline, but was also observed for minocycline [>20% in seven countries, amongst which were Cyprus (41%) and the Czech Republic (110%)].

Table 1. Classification of tetracyclines, sulphonamides and trimethoprim, and other antibacterials (ATC classification, version 2011)

Tetracyclines	
J01AA01	demeclocycline
J01AA02	**doxycycline**
J01AA03	chlortetracycline[a]
J01AA04	**lymecycline**
J01AA05	metacycline
J01AA06	**oxytetracycline**
J01AA07	**tetracycline**
J01AA08	**minocycline**
J01AA09	rolitetracycline[a]
J01AA10	penimepicycline[a]
J01AA11	clomocycline[a]
J01AA12	tigecycline
J01AA20	combinations of tetracyclines[a]
J01AA56	oxytetracycline, combinations
Sulphonamides and trimethoprim	
Trimethoprim and derivatives	
J01EA01	**trimethoprim**
J01EA02	brodimoprim[a]
J01EA03	iclaprim[a]
Short-acting sulphonamides	
J01EB01	sulfaisodimidine[a]
J01EB02	**sulfamethizole**
J01EB03	sulfadimidine
J01EB04	sulfapyridine
J01EB05	sulfafurazole
J01EB06	sulfanilamide[a]
J01EB07	sulfathiazole
J01EB08	sulfathiourea[a]
J01EB20	combinations[a]
Intermediate-acting sulphonamides	
J01EC01	sulfamethoxazole[a]
J01EC02	sulfadiazine
J01EC03	sulfamoxole[a]
J01EC20	combinations[a]
Long-acting sulphonamides	
J01ED01	**sulfadimethoxine**
J01ED02	sulfalene
J01ED03	sulfametomidine[a]
J01ED04	sulfametoxydiazine[a]
J01ED05	sulfamethoxypyridazine
J01ED06	sulfaperin[a]
J01ED07	sulfamerazine[a]
J01ED08	sulfaphenazole[a]
J01ED09	sulfamazon[a]
J01ED20	combinations[a]
Combinations of sulphonamides and trimethoprim, including derivatives	
J01EE01	**sulfamethoxazole and trimethoprim**
J01EE02	sulfadiazine and trimethoprim[a]
J01EE03	sulfametrole and trimethoprim
J01EE04	sulfamoxole and trimethoprim[a]
J01EE05	sulfadimidine and trimethoprim[a]

Continued

Table 1. *Continued*

Sulphonamides and trimethoprim	
J01EE06	sulfadiazine and tetroxoprim[a]
J01EE07	sulfamerazine and trimethoprim[a]
Other antibacterials	
Glycopeptide antibacterials	
J01XA01	vancomycin
J01XA02	teicoplanin
J01XA03	televancin[a]
J01XA04	dalbavacin[a]
J01XA05	oritavancin[a]
Polymyxins	
J01XB01	colistin
J01XB02	polymyxin B
Steroid antibacterials	
J01XC01	**fusidic acid**
Imidazole derivatives	
J01XD01	**metronidazole**
J01XD02	tinidazole
J01XD03	ornidazole
Nitrofuran derivatives	
J01XE01	**nitrofurantoin**
J01XE02	**nifurtoinol**
Other antibacterials	
J01XX01	**fosfomycin**
J01XX02	xibornol[a]
J01XX03	clofoctol
J01XX04	spectinomycin
J01XX05	**methenamine**
J01XX06	mandelic acid
J01XX07	**nitroxoline**
J01XX08	linezolid
J01XX09	daptomycin
J01XX10	bacitracin[a]

Bold type indicates that use represented >1% of the total use of tetracyclines, sulphonamides and trimethoprim, or other antibacterials, respectively, in Europe in 2009.
[a]No use of this antibiotic in Europe was reported in 2009.

Compositional data analysis (1997–2009)

The relative use of tetracyclines decreased non-significantly over time with respect to all other antibiotic subclasses except sulphonamides.[6] Variation in relative use among the different tetracycline substances was not assessed statistically. Between 1997 and 2009, differences in the proportional use of the different tetracycline substances of ≥10% were observed in 16 countries (Figure S3a, available as Supplementary data at *JAC* Online). The proportional use of doxycycline decreased in nine countries (>10% in Austria, Finland, Germany, Luxembourg, Norway, Portugal and Sweden, >20% in Malta and >30% in Belgium) and increased in five (>10% in Bulgaria, Denmark and Spain, and >30% in France and Ireland). The proportional use of limecycline decreased by >20% in France and increased in eight countries (>10% in Finland, Luxembourg, Norway and Sweden, and

>20% in Belgium, Ireland, Italy and the UK). The proportional use of minocycline decreased by >10% in Italy and the UK, while it increased by >10% in Austria, Malta and Portugal. The proportional use of tetra- and oxytetracycline decreased by >20% in Denmark and the UK, and by >50% in Ireland. It increased in Germany (>10%). The proportional use of other tetracyclines decreased by >20% in Bulgaria.

Sulphonamides and trimethoprim

Outpatient sulphonamide and trimethoprim use in 2009

Outpatient sulphonamide and trimethoprim use varied by a factor of 205 between the countries with the highest (1.18 DID in the UK) and the lowest (0.006 DID in Lithuania) use and by a factor of 7 between the countries with the highest and the second lowest use (0.16 DID in Romania) (Figure 1b).

Combinations of sulphonamides and trimethoprim, including derivatives, represented >90% of the total outpatient use of sulphonamides and trimethoprim in 21 countries and >80% in the Czech Republic (mainly sulfamethoxazole and trimethoprim). Use of these combinations was lower in Austria (37%), Denmark (0%), Finland (0%), Ireland (26%), Iceland (47%), Lithuania (0%), the Netherlands (62%), Norway (34%), the Russian Federation (64%), Sweden (46%) and the UK (0%). Trimethoprim and derivatives were the most widely used subgroup in Austria (63%), Denmark (64%), Finland (100%), Ireland (74%), Iceland (53%), Lithuania (100%), Norway (66%), Sweden (54%) and the UK (99%) (mainly trimethoprim). In the Netherlands this was also a

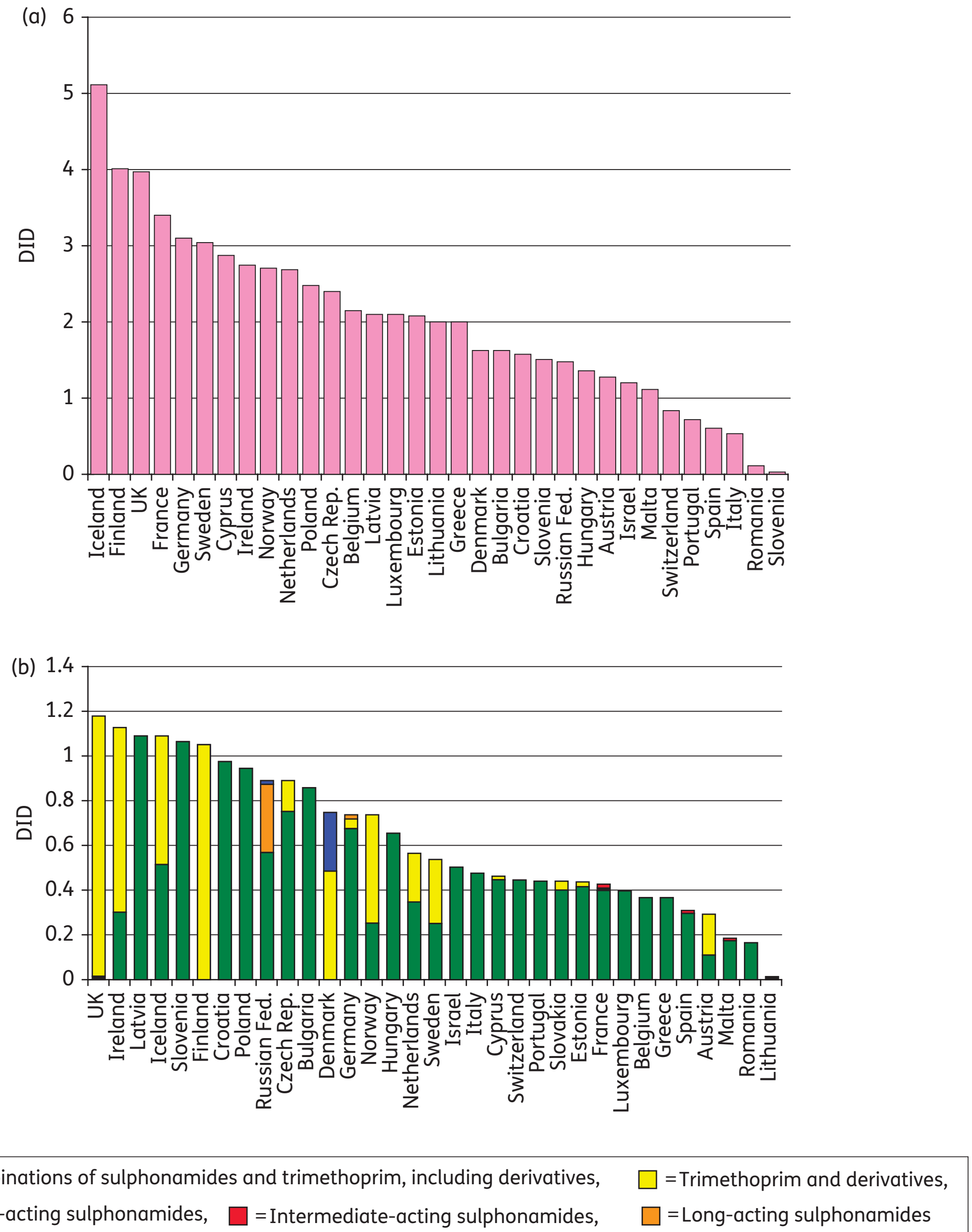


Figure 1. Outpatient use of tetracyclines (a), sulphonamides and trimethoprim (b), and other antibacterials (c) in 33 European countries in 2009 in DID (2004 data for Switzerland). For Cyprus and Lithuania, total care data are used.

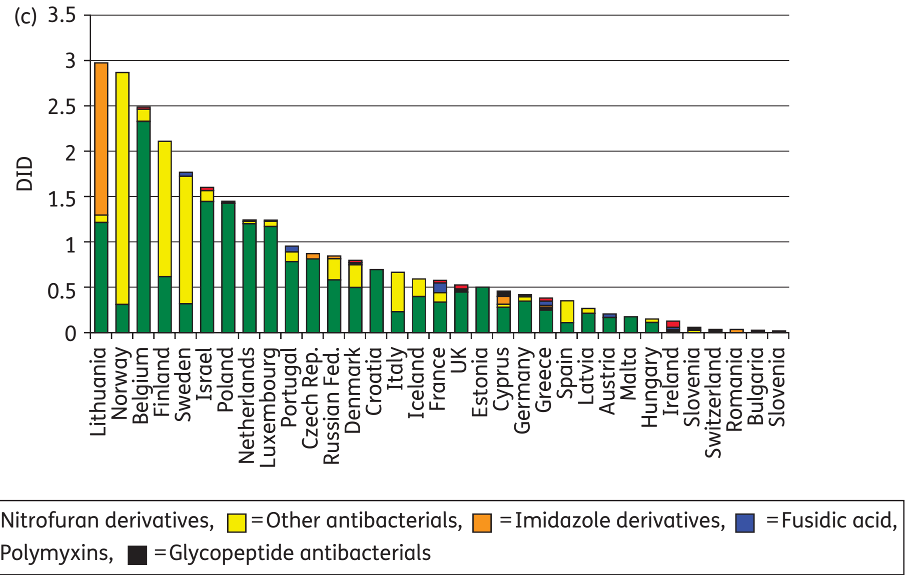


Figure 1. *Continued*

commonly used subgroup (38%; trimethoprim). Denmark was the only country using a substantial proportion of short-acting sulphonamides (35%; sulfamethizole). Use of intermediate-acting sulphonamides was <1% in all but four countries. Only in the Russian Federation was a substantial proportion of long-acting sulphonamides used (34%; sulfadimethoxine).

Figure 2(b) shows total outpatient sulphonamide and trimethoprim use in 17 European countries for 2009 expressed in PID. Their ranking is depicted according to both DID and PID. The DDD per package ranged from 3.7 in Bulgaria and Italy to 26.9 in Ireland. Higher values were associated with higher ranking in DID than in PID. Ireland appeared higher in the ranking in DID than in that in PID, because of its high number of DDD per package, and in Bulgaria and Italy the opposite was seen.

Longitudinal data analysis (1997–2009)

A non-significant decrease in total outpatient sulphonamide and trimethoprim use of 0.007 (SD 0.005) DID per quarter was found, starting from 0.98 (SD 0.24) DID in the first quarter of 1997. A large seasonal variation with an amplitude of 0.17 (SD 0.03) DID was seen, which decreased significantly over time by 0.002 (SD 0.0004) DID per quarter (Figure 3b). The longitudinal analysis showed that the winter peak of outpatient antibiotic consumption shifted in timing significantly from one year to another. The correlation between volume of use and seasonal variation was not significant.

An increase in the use of sulphonamides and trimethoprim of >0.50 DID between the first and the last years of observation was not observed, but in 14 countries use decreased by >0.50 DID. In Iceland, Poland and Slovakia the use of sulphonamides and trimethoprim decreased by >1 DID (Table 3).

The seasonal variation in the 12 European countries able to deliver quarterly data from 1997 to 2009 and missing a maximum of 1 year of data, is shown in Figure S1(b) (available as Supplementary data at *JAC* Online). Another 15 countries were able to deliver seasonal data but were missing more than 1 year of data (Figure S2b, available as Supplementary data at *JAC* Online). In five countries (the Czech Republic, Estonia, Israel, Latvia and Poland) use in the first and fourth quarters was >40% higher than that in the second and third quarters. In another two countries (Hungary and the Russian Federation) this seasonal variation was >30%. In 20 countries it was <30%, but it was >20% in Belgium and the UK, and >10% in Cyprus, Germany, Croatia, Italy, Luxembourg, Slovenia and Spain. Seasonal variation of sulphonamides and trimethoprim was mainly driven by sulfamethoxazole and trimethoprim.

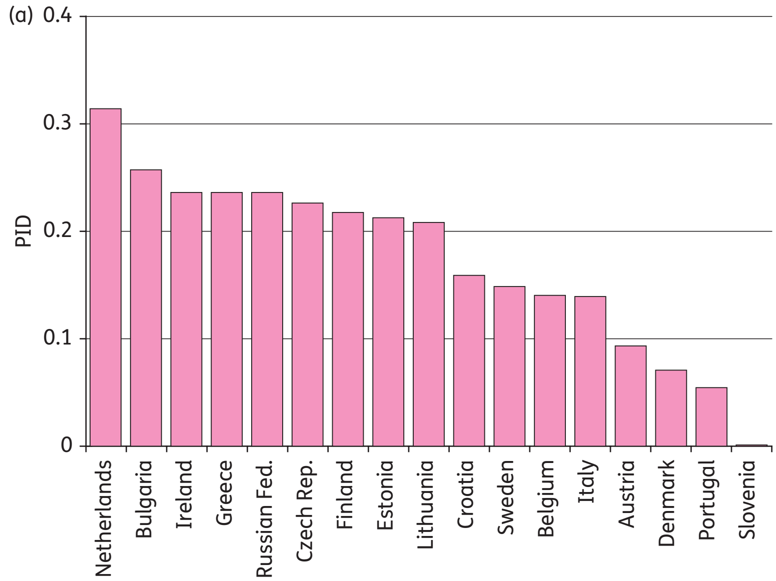
Compositional data analysis (1997–2009)

For Europe, the relative use of combinations of sulphonamides and trimethoprim, including derivatives (J01EE), significantly decreased over time with respect to that of the concatenation of short-, intermediate- and long-acting sulphonamides (J01EB, J01EC and J01ED) (Table 4). Between 1997 and 2009, differences of ≥10% in the proportional use of the different sulphonamide and trimethoprim subclasses were observed in seven countries (Figure S3b, available as Supplementary data at *JAC* Online). The proportional use of trimethoprim and derivatives decreased in Sweden by >20% and increased in four countries (>10% in Austria and Iceland, >20% in Denmark and >40% in Finland). The proportional use of short-acting sulphonamides decreased by >10% in Denmark. The proportional use of intermediate-acting sulphonamides did not vary by >10% in any country. The proportional use of long-acting sulphonamides decreased by >10% in Bulgaria. The proportional use of combinations of sulphonamides and trimethoprim, including derivatives, decreased in three countries (>10% in Austria and Iceland, and >40% in Finland) and increased in four countries (>10% in Bulgaria, France and Italy, and >20% in Sweden).

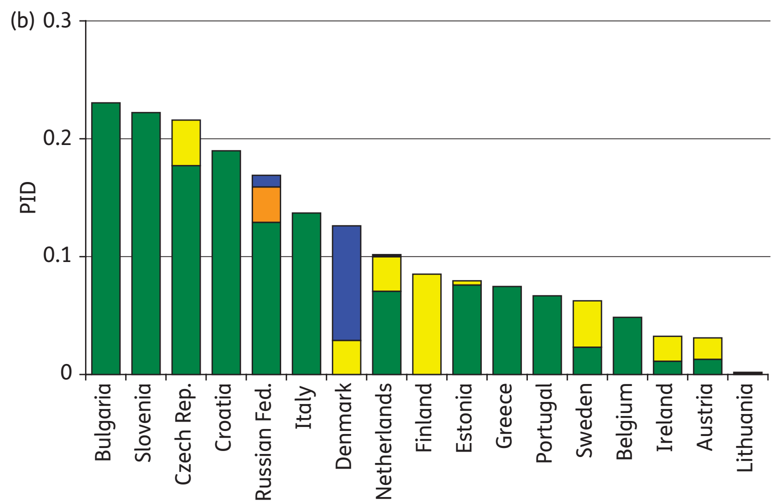
Other antibacterials

Outpatient use of other antibacterials in 2009

Outpatient use of other antibacterials varied by a factor of 3689 between the countries with the highest (2.97 DID in Lithuania)



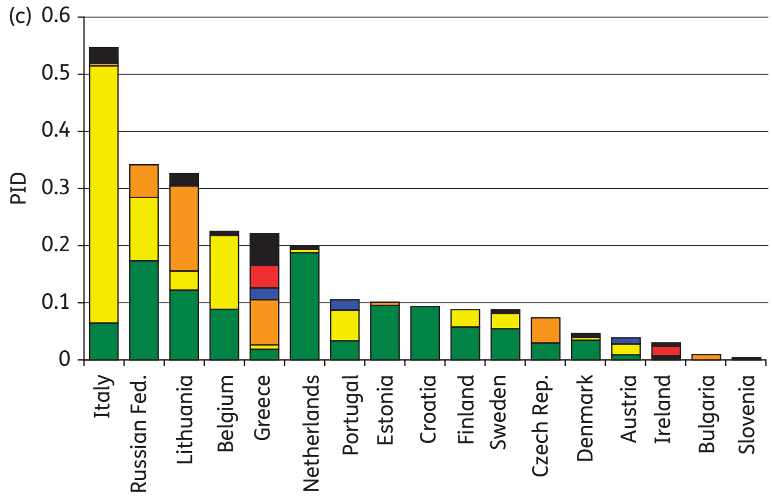
Country	NL	BG	IE	GR	RU	CZ	FI	EE	LT	HR	SE	BE	IT	AT	DK	PT	SI
Ranking PID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ranking DID	5	11	2	9	13	4	1	7	8	12	3	6	16	14	10	15	17
DDD/package	8.5	6.3	14.0	8.5	6.2	11.9	18.4	9.7	9.6	9.9	20.3	15.2	3.8	13.8	22.8	13.3	21.5



Country	BG	SI	CZ	HR	RU	IT	DK	NL	FI	EE	GR	PT	SE	BE	IE	AT	LT
Ranking PID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ranking DID	7	2	1	4	5	11	8	9	3	13	15	12	10	14	6	16	17
DDD/package	3.7	4.8	5.1	5.2	5.3	3.7	6.0	5.6	12.4	5.5	5.0	6.6	8.7	7.6	26.9	9.2	7.8

■ = Combinations of sulphonamides and trimethoprim, including derivatives, ■ = Trimethoprim and derivatives,
■ = Short-acting sulphonamides, ■ = Intermediate-acting sulphonamides, ■ = Long-acting sulphonamides

Figure 2. Outpatient use of tetracyclines (a), sulphonamides and trimethoprim (b), and other antibacterials (c) 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.



Country	IT	RU	LT	BE	GR	NL	PT	EE	HR	FI	SE	CZ	DK	AT	IE	BG	SI
Ranking PID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ranking DID	11	7	1	2	13	5	6	12	10	3	4	9	8	14	15	16	17
DDD/package	1.2	2.4	9.2	11.1	1.7	6.3	8.9	4.8	7.5	23.7	19.9	10.5	17.5	5.4	5.0	0.4	5.1

=Nitrofuran derivatives, =Other antibacterials, =Imidazole derivatives, =Fusidic acid, =Polymyxins, =Glycopeptide antibacterials

Figure 2. *Continued*

and the lowest (0.001 DID in Slovenia) use. It varied by a factor of 928 between the countries with the highest and the second lowest use (0.003 DID in Bulgaria) and by a factor of 144 between the countries with the highest and the third lowest use (0.02 DID in Romania) (Figure 1c).

Nitrofuran derivatives represented >50% of the total outpatient use of other antibacterials in 20 countries (>90% in Belgium, Croatia, the Czech Republic, Estonia, Israel, Luxembourg, Malta, the Netherlands and Poland, >80% in Germany, Portugal and the UK, >70% in Austria, Hungary and Latvia, >60% in Cyprus, Denmark, Greece and the Russian Federation, and >50% in France). In Iceland, Israel and Italy nitrofuran derivatives represented >30%, whilst in Finland and Spain they represented >20% of outpatient use. In all but two countries only nitrofurantoin was used [nifurtoinol in Belgium (44%) and Luxembourg (17%)]. The chemical subgroup other antibacterials (J01XX) represented >60% of total outpatient use of the pharmacological subgroup other antibacterials (J01X) in seven countries (Finland, Italy, Norway, Slovakia, Slovenia, Spain and Sweden). In Denmark, Hungary, Iceland, Latvia and the Russian Federation it represented >20%. Methenamine and fosfomycin, and to a lesser extent nitroxoline and linezolid, were used, each country using a substantial proportion of only one of these substances.

In Ireland, Slovakia and Switzerland the use of polymyxins was >20%. Steroid antibacterials (= fusidic acid; see Table 1) represented >40% of all outpatient use of other antibacterials in Switzerland. Imidazole derivatives were the most used subgroup in Bulgaria (81%), Lithuania (56%) and Romania (97%).

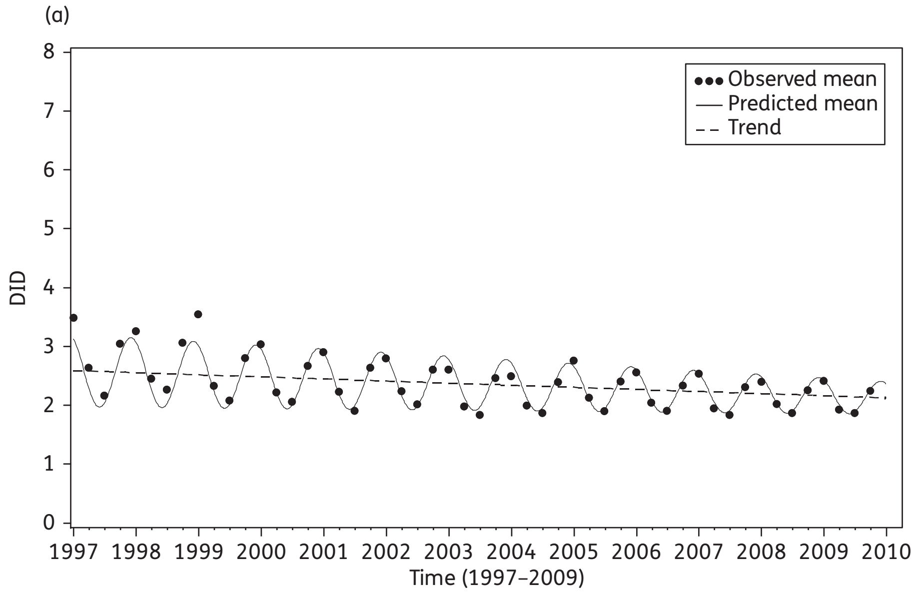
Figure 2(c) shows total outpatient use of other antibacterials in 17 European countries for 2009 expressed in PID. In addition, their ranking is depicted according to both DID and PID. The number of DDD per package ranged from 1.2 in Italy to 23.7 in Finland. Higher values were associated with higher ranking in DID than in PID. Finland and Sweden appeared higher in the ranking in DID than in that in PID, because of their high number of DDD per package, while in Italy and Greece the opposite was observed.

Longitudinal data analysis (1997–2009)

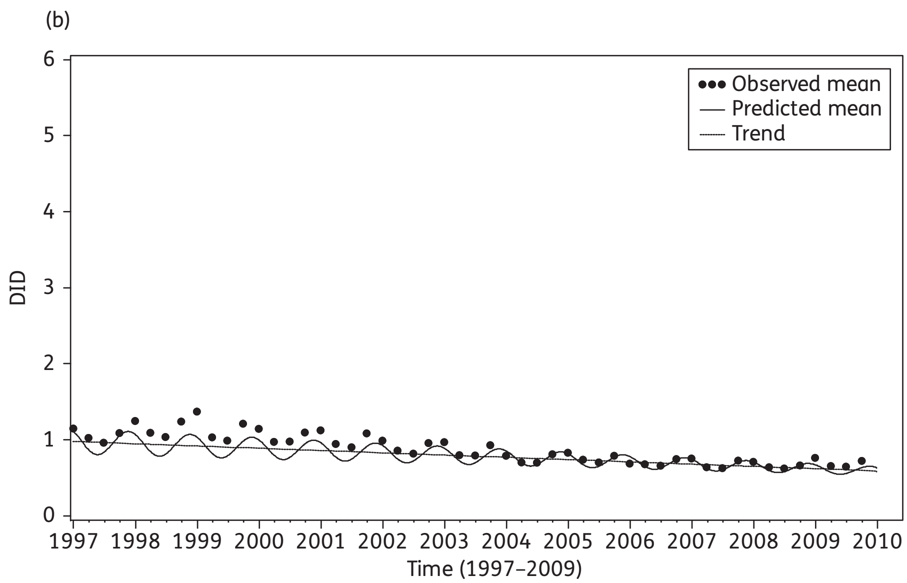
A non-significant increase in total outpatient use of other antibacterials of 0.009 (SD 0.005) DID per quarter was found, starting from 0.42 (SD 0.17) DID in the first quarter of 1997, and seasonal variation was not significant (Figure 3c).

An increase in the use of other antibacterials of >0.50 DID between the first and last years of observation was observed in eight countries. A similar decrease in use was seen in Estonia (Table 5).

The seasonal variation of outpatient use of other antibacterials in 12 European countries able to deliver quarterly data from 1997 to 2009 and missing a maximum of 1 year of data is shown in Figure S1(c) (available as Supplementary data at *JAC* Online). Another 15 countries were able to deliver seasonal data but were missing more than 1 year of data (Figure S2c, available as Supplementary data at *JAC* Online). In none of these countries was use in the first and fourth quarters >20% higher than that in the second and

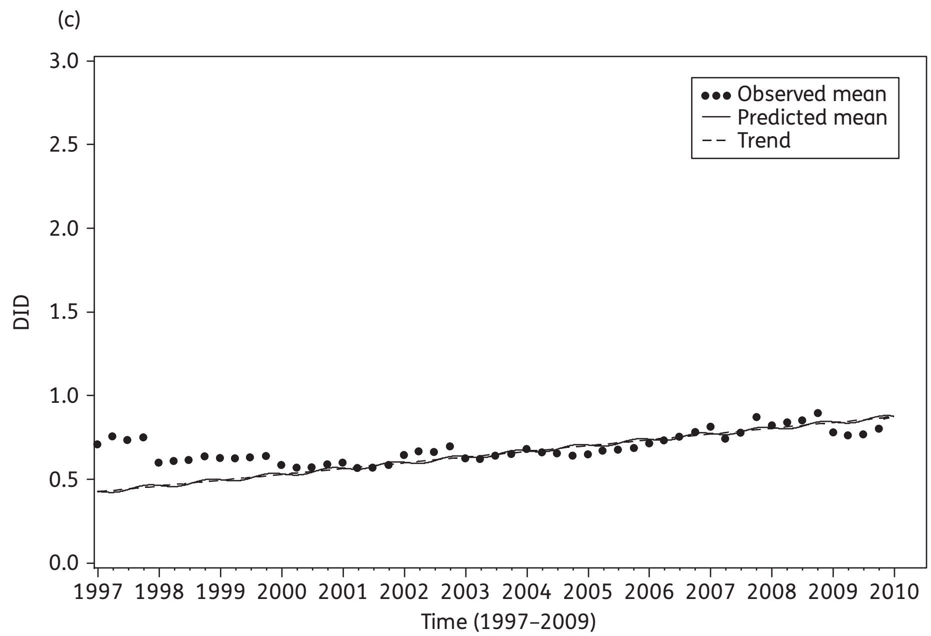


ATC	Parameters				
	β_0	β_1	$\beta_0{}^S$	$\beta_1{}^S$	δ
J01A	2.604 (0.251)*	−0.009 (0.003)*	0.623 (0.072)*	−0.006 (0.002)*	0.495 (0.024)*



ATC	Parameters				
	β_0	β_1	$\beta_0{}^S$	$\beta_1{}^S$	δ
J01E	0.985 (0.239)*	−0.007 (0.005)	0.167 (0.028)*	−0.002 (0.0004)*	0.663 (0.042)*

Figure 3. Estimated linear trend and seasonal variation of outpatient tetracycline (a), sulphonamide and trimethoprim (b), and other antibacterial (c) 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 ($P<0.05$).



ATC	Parameters				
	β_0	β_1	$\beta_0{}^S$	$\beta_1{}^S$	δ
J01X	0.417 (0.171)*	0.009 (0.005)	0.013 (0.008)	-	1.219 (0.609)

Figure 3. *Continued*

third quarters. Only in six countries (Croatia, the Czech Republic, Hungary, Latvia, the Russian Federation and Slovenia) was this seasonal variation >10%. Seasonal variation of other antibacterials was driven by nitrofurantoin rather than by methenamine use.

Compositional data analysis (1997–2009)

For Europe, the relative use of imidazole derivatives (J01XD) significantly decreased over time with respect to that of fusidic acid (J01XC) and the chemical subgroup other antibacterials (J01XX) (Table 6). Between 1997 and 2009, differences of ≥10% in the proportional use of the different subclasses of other antibacterials were observed in 20 countries (Figure S3c, available as Supplementary data at *JAC* Online). Six countries showed differences of >50%. The use of imidazole derivatives shifted to nitrofuran derivatives in Croatia and Estonia, and to polymyxins and other antibacterials in Slovakia. In Austria, use shifted from fusidic acid to nitrofuran derivatives, in Hungary from other antibacterials to nitrofuran derivatives and in Ireland from nitrofuran derivatives to polymyxins and fusidic acid. The proportional use of nitrofuran derivatives also decreased by >10% in Greece and Italy, decreased by >20% in Lithuania and Spain, increased by >10% in Cyprus, Germany and Poland, increased by >20% in Denmark, Latvia and Luxembourg, and increased by >30% in Malta. The proportional use of other antibacterials also decreased by >10% in Germany and Luxembourg, decreased by >20% in Denmark, increased by >10% in Bulgaria, Iceland and Italy, and increased by >20% in Spain.

Discussion

This paper describes in detail for the first time outpatient use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials in Europe. It complements descriptions of the other major antibiotic subgroups: penicillins; cephalosporins; macrolides, lincosamides and streptogramins; and quinolones.[7–10] In contrast to most of these antibiotic subgroups, for tetracyclines a significant and for sulphonamides and trimethoprim a non-significant decrease in use was observed between 1997 and 2009. Similar to the other major substances, seasonal variation of these substances was also substantial and significantly decreasing. For the other antibacterials (ATC J01X), including substances that are mostly used in ambulatory care to treat and prevent lower urinary tract infections, no significant change was observed in the volume of use or in their seasonal variation. However, the variation in use between countries and in the composition of use over time was huge. The latter findings should, however, be interpreted with caution, given the low use in DID of many of the substances studied. The low use in DID also magnifies the impact of total care data, i.e. data including hospital consumption. Also for countries moving from delivering total care data to ambulatory care data, and for countries moving, for example, from delivering sales data to reimbursement data, the impact of these changes is more visible. These changes were described in the introductory paper of this series and in the ESAC yearbooks.[6,17–20]

For the tetracyclines, no classification into chemical subgroups is available within the ATC classification.[11] To provide a better understanding of their outpatient use in Europe, we grouped the tetracyclines close to the substance level. This

Table 2. Yearly outpatient tetracycline 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	—	1.35	1.40	1.28	1.12	1.04	1.08	0.98	1.47	1.26	1.27	1.33	1.27
Belgium	4.41	4.17	3.82	3.47	2.94	2.65	2.29	2.06	1.96	1.85	1.96	2.19	2.14
Bulgaria	—	—	4.24	3.25	3.64	2.80	3.07	2.83	2.61	2.51	2.35	2.16	1.62
Croatia	—	—	—	1.38	1.41	1.80	1.89	1.89	1.95	1.70	1.77	1.77	1.57
Cyprus	—	—	—	—	—	—	—	—	—	3.11	2.51	2.74	2.87
Czech Republic	—	2.89	3.13	—	—	2.53	2.86	2.68	2.91	2.81	2.70	2.51	2.39
Denmark	0.98	0.98	0.92	0.99	0.99	1.04	1.07	1.17	1.27	1.37	1.47	1.55	1.62
Estonia	—	—	—	—	2.89	2.65	2.61	2.42	2.42	2.28	2.31	2.17	2.07
Finland	4.90	4.60	4.53	4.61	4.54	3.90	—	3.57	3.95	3.76	3.97	4.00	4.01
France	2.99	2.96	3.11	3.28	3.10	3.43	3.33	3.45	3.40	3.33	3.34	3.43	3.39
Germany	3.09	2.89	3.07	2.96	2.75	2.68	3.48	3.17	3.45	3.23	3.32	3.21	3.09
Greece	2.73	2.70	2.84	2.80	2.68	2.75	2.55	2.64	2.56	2.52	2.46	2.41	2.00
Hungary	—	2.63	3.11	2.28	2.19	1.93	1.94	1.77	1.74	1.44	1.40	1.39	1.35
Iceland	5.36	5.45	5.17	4.73	4.63	4.81	4.76	5.17	5.46	5.13	5.08	5.29	5.09
Ireland	—	3.15	3.15	3.02	3.23	3.44	3.64	3.82	3.26	3.34	3.32	3.18	2.74
Israel	—	—	—	—	—	1.21	1.25	1.31	1.25	1.30	1.07	1.18	1.20
Italy	—	—	0.53	0.51	0.53	0.33	0.49	0.48	0.47	0.49	0.50	0.54	0.52
Latvia	—	—	—	—	—	2.04	—	2.42	2.61	2.50	2.60	2.28	2.10
Lithuania	—	—	—	—	—	—	—	—	—	1.72	2.47	2.36	2.00
Luxembourg	4.04	3.47	3.28	2.91	2.75	2.61	2.40	2.27	2.21	2.05	2.09	2.16	2.08
Malta	—	—	—	—	—	—	—	—	—	—	0.93	1.11	1.10
Netherlands	2.64	2.55	2.49	2.46	2.39	2.33	2.23	2.21	2.41	2.39	2.55	2.63	2.68
Norway	—	3.24	—	—	3.05	3.05	2.95	2.88	3.04	2.76	2.86	2.79	2.71
Poland	—	3.90	3.90	4.06	4.15	3.90	—	2.84	2.91	—	2.77	2.49	2.47
Portugal	1.97	1.84	1.76	1.56	1.37	1.24	1.22	1.07	1.01	0.90	0.83	0.82	0.72
Romania	—	—	—	—	—	—	—	—	—	—	—	—	0.11
Russian Federation	—	—	—	—	—	—	1.81	1.57	1.37	1.32	1.29	0.90	1.46
Slovakia	—	—	1.92	2.07	2.23	2.37	2.53	2.35	2.29	1.92	1.52	1.54	1.50
Slovenia	0.93	0.86	0.85	0.81	0.77	0.70	0.71	0.61	0.57	0.55	0.58	0.52	0.00
Spain	0.82	0.75	0.67	0.61	0.62	0.62	0.62	0.61	0.59	0.59	0.59	0.60	0.60
Sweden	2.97	3.35	3.33	3.27	3.27	3.10	3.03	3.05	3.25	3.32	3.37	3.22	3.03
Switzerland	—	—	—	—	—	—	—	0.83	—	—	—	—	—
UK	3.45	3.41	3.20	3.15	3.22	3.29	3.30	3.34	3.34	3.34	3.51	3.72	3.96

—, no use reported; 0.00, <0.005.

enabled us to distinguish between substances like doxycycline, used for respiratory infections, with high seasonal variation, and minocycline, which shows much lower seasonal variation and is used for the longer-term treatment of acne. For the combinations of sulphonamides and trimethoprim, as for many other combination products, assignment of the DDD value was not straightforward, but the participating networks were supported in doing this according to the WHO guidelines for ATC classification and DDD assignment to provide comparable and reliable data.[11,20] For the pharmacological subgroup of other antibacterials (ATC J01X), as for all other antibacterial substances collected in ESAC, no topical use data were collected. Reported outpatient use of fusidic acid, polymyxins (mainly colistin) and glycopeptide antibacterials (e.g. vancomycin) is therefore very limited in most European countries. Yet, there are exceptions, such as France, Greece and Portugal using fusidic acid, and Greece and Ireland using polymyxins (mainly colistin). In Greece and Italy, and this is especially visible when use is expressed in PID, outpatient glycopeptide use was observed, as it was also in Lithuania and Cyprus, two countries providing total care data. In the Czech Republic and Greece imidazole derivatives (mainly metronidazole) were used in ambulatory care. The visibility of their use when expressed in PID instead of DID was probably related to the parenteral use of these substances, each package representing only 1 DDD. This also explains why Italy and the Russian Federation, for example, were ranked high when outpatient use was expressed in PID. They have high outpatient parenteral antibiotic use.[21] Use of oral vancomycin as an intestinal anti-infective (ATC A07AA09) is not reported here. Historically, the urinary antiseptics and anti-infectives were moved from ATC G04A to J01MB (other quinolones) and J01X (other antibacterials). Therefore, in Nordic countries, especially in Sweden, the commonly used urinary antiseptic methenamine has not been included in total antibiotic consumption figures.[14] This would mean that their total outpatient antibiotic use in 2009 presented by Adriaenssens *et al*.[6] should be reduced by 2.54 DID for Norway, 1.47 DID for Finland, 1.39 DID for Sweden, 0.26

Table 3. Yearly outpatient sulphonamide and trimethoprim 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	—	0.69	0.68	0.66	0.50	0.48	0.40	0.32	0.32	0.31	0.31	0.29	0.29
Belgium	0.71	0.67	0.63	0.56	0.49	0.44	0.39	0.36	0.35	0.35	0.37	0.38	0.37
Bulgaria	—	—	0.00	1.13	1.31	0.94	1.08	0.97	0.88	0.98	0.99	0.99	0.86
Croatia	—	—	—	1.64	1.68	1.84	1.71	1.62	1.52	1.32	1.37	1.20	0.98
Cyprus	—	—	—	—	—	—	—	—	—	0.44	0.35	0.41	0.46
Czech Republic	—	1.69	1.62	—	—	1.00	1.18	1.18	1.24	1.02	1.10	0.87	0.89
Denmark	0.79	0.77	0.74	0.73	0.74	0.75	0.76	0.77	0.79	0.82	0.81	0.77	0.75
Estonia	—	—	—	—	1.39	1.06	0.79	0.62	0.56	0.62	0.63	0.47	0.43
Finland	2.09	1.96	1.99	1.90	1.83	1.72	—	1.67	1.60	1.52	1.53	1.05	1.05
France	0.72	0.66	0.60	0.56	0.53	0.49	0.45	0.47	0.47	0.46	0.48	0.47	0.42
Germany	1.24	1.12	1.16	1.13	1.09	1.02	0.96	0.93	0.94	0.89	0.86	0.81	0.73
Greece	0.91	0.98	0.79	0.68	0.59	0.55	0.61	0.68	0.69	0.48	0.41	0.42	0.36
Hungary	—	1.39	1.52	1.16	1.11	1.01	1.24	1.08	0.99	0.82	0.73	0.69	0.65
Iceland	2.43	2.50	2.16	2.20	2.13	1.97	1.92	1.90	1.97	1.55	1.40	1.35	1.08
Ireland	—	0.92	0.92	0.90	0.91	0.93	0.68	0.82	0.90	0.90	0.87	0.99	1.13
Israel	—	—	—	—	—	0.23	0.21	0.00	0.32	0.00	0.15	0.00	0.50
Italy	—	—	1.08	0.87	0.81	0.73	0.70	0.62	0.59	0.56	0.53	0.50	0.47
Latvia	—	—	—	—	—	1.08	—	1.03	1.04	0.84	0.00	0.84	1.09
Lithuania	—	—	—	—	—	—	—	—	—	0.01	0.01	0.01	0.01
Luxembourg	0.76	0.66	0.64	0.52	0.49	0.46	0.42	0.37	0.36	0.36	0.36	0.36	0.39
Malta	—	—	—	—	—	—	—	—	—	—	0.20	0.20	0.18
Netherlands	0.77	0.75	0.76	0.71	0.70	0.68	0.67	0.65	0.63	0.62	0.58	0.58	0.56
Norway	—	1.27	—	—	1.11	1.09	1.03	1.05	1.02	0.81	0.79	0.77	0.73
Poland	—	2.72	2.99	2.59	2.62	1.25	—	0.59	0.59	—	1.04	0.95	0.95
Portugal	1.08	1.05	1.03	0.99	0.90	0.88	1.24	0.86	0.58	0.51	0.44	0.43	0.43
Romania	—	—	—	—	—	—	—	—	—	—	—	—	0.16
Russian Federation	—	—	—	—	—	—	1.79	1.43	1.25	1.12	0.93	0.86	0.89
Slovakia	—	—	1.70	1.33	1.22	1.04	0.85	0.79	0.72	0.60	0.52	0.48	0.43
Slovenia	1.22	1.17	1.14	1.20	1.21	1.09	1.15	1.24	1.21	1.16	1.16	1.12	1.06
Spain	0.77	0.60	0.41	0.38	0.35	0.34	0.33	0.31	0.30	0.29	0.29	0.30	0.30
Sweden	0.75	0.75	0.78	0.76	0.75	0.74	0.72	0.70	0.67	0.67	0.75	0.57	0.54
Switzerland	—	—	—	—	—	—	—	0.44	—	—	—	—	—
UK	1.17	1.13	1.09	1.08	1.09	1.06	1.06	1.07	1.07	1.05	1.08	1.13	1.18

—, no use reported; 0.00, <0.005.

Table 4. Change in composition of outpatient sulphonamide and trimethoprim use in Europe as a function of time

J01E	A	BCD	E
A		−0.346	0.224
BCD	0.346		0.570*
E	−0.224	−0.570*	

A, trimethoprim and derivatives (J01EA); BCD, concatenation of short-, intermediate- and long-acting sulphonamides (J01EB, J01EC and J01ED); E, sulphonamides and trimethoprim, including derivatives, (J01EE).
Values are estimated changes in the log ratio of the row versus column antibiotic type with increasing time.[16] Significant effects are indicated with an asterisk; positive values represent an increase and negative values represent a decrease.

DID for Denmark and 0.19 DID for Iceland. Within the ESAC project, however, use of all substances classified within ATC J01 has been reported when describing antibiotic use in Europe.

The most used substances reported in this paper were mainly used for respiratory and urinary tract infections. The decrease in the use of tetracyclines and its seasonal variation might be related to the fact that the need to prescribe antibiotics for respiratory tract infection has been shown to be limited,[22,23] as well as the need to cover for atypical pathogens, i.e. *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* or *Legionella pneumophila*.[23] Although well studied in the Netherlands,[24] doxycycline is no longer among the recommended antibiotics for lower respiratory tract infections by the Dutch College for General Practitioners, because of problems of resistance,[25] and this recommendation might be adopted by other countries and societies. Among the substances studied, the tetracyclines are still the most commonly used. As the European population is

Table 5. Yearly outpatient use of other antibacterials in 33 European countries, expressed in DID (1997–2009)

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Austria	—	0.01	0.03	0.03	0.03	0.03	0.02	0.05	0.13	0.15	0.17	0.18	0.20
Belgium	1.69	1.72	1.74	1.77	1.76	1.78	1.76	1.83	1.99	2.07	2.20	2.36	2.47
Bulgaria	—	—	0.41	0.37	0.35	0.05	0.14	0.12	0.23	0.00	0.00	0.00	0.00
Croatia	—	—	—	0.00	0.00	0.01	0.01	0.54	0.56	0.61	0.46	0.64	0.68
Cyprus	—	—	—	—	—	—	—	—	—	0.36	0.38	0.38	0.45
Czech Republic	—	0.85	0.85	—	—	0.84	1.16	0.30	0.01	0.71	0.75	0.74	0.87
Denmark	0.85	0.84	0.81	0.79	0.75	0.77	0.77	0.75	0.76	0.77	0.77	0.78	0.79
Estonia	—	—	—	—	1.33	1.12	0.97	0.40	1.00	0.91	0.87	0.51	0.48
Finland	1.80	1.85	1.82	1.95	1.93	1.92	—	2.03	1.98	2.01	1.92	2.09	2.10
France	0.41	0.41	0.44	0.46	0.50	0.83	0.89	0.80	0.60	0.55	0.53	0.54	0.56
Germany	0.30	0.29	0.29	0.28	0.29	0.29	0.33	0.33	0.36	0.36	0.37	0.38	0.40
Greece	0.19	0.22	0.24	0.24	0.27	0.29	0.28	0.29	0.16	0.63	0.71	0.75	0.38
Hungary	—	0.00	0.01	0.01	0.01	0.03	0.03	0.03	0.04	0.29	0.28	0.28	0.14
Iceland	0.92	0.94	1.00	0.29	0.32	0.34	0.31	0.50	0.66	0.38	0.41	0.48	0.76
Ireland	—	0.27	0.28	0.29	0.32	0.24	0.27	0.30	0.37	0.14	0.14	0.13	0.11
Israel	—	—	—	—	—	0.97	1.01	0.61	0.60	1.02	1.85	1.87	1.58
Italy	—	—	0.53	0.56	0.61	0.61	0.63	0.64	0.63	0.66	0.65	0.66	0.67
Latvia	—	—	—	—	—	0.60	—	0.60	0.55	0.48	0.47	0.32	0.26
Lithuania	—	—	—	—	—	—	—	—	—	1.44	2.19	2.51	2.97
Luxembourg	1.31	1.32	1.38	1.37	1.27	1.47	1.15	1.47	1.29	1.09	1.05	1.11	1.23
Malta	—	—	—	—	—	—	—	—	—	—	0.14	0.12	0.18
Netherlands	0.68	0.67	0.72	0.76	0.79	0.80	0.82	0.85	0.95	1.05	1.10	1.17	1.24
Norway	—	2.09	—	—	2.43	2.40	2.46	2.68	2.93	2.34	2.51	2.66	2.86
Poland	—	0.13	0.39	0.66	0.66	0.52	—	1.94	2.01	—	0.00	0.00	1.44
Portugal	0.53	0.52	0.52	0.13	0.07	0.89	0.10	0.74	0.11	0.14	0.14	0.84	0.95
Romania	—	—	—	—	—	—	—	—	—	—	—	—	0.02
Russian Federation	—	—	—	—	—	—	0.92	0.87	0.83	0.81	0.84	0.92	0.83
Slovakia	—	—	0.00	0.74	0.80	0.82	0.73	0.01	0.01	0.02	0.03	0.03	0.04
Slovenia	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Spain	0.11	0.12	0.13	0.14	0.16	0.17	0.20	0.23	0.25	0.27	0.29	0.32	0.34
Sweden	1.12	1.16	1.64	1.73	1.76	1.82	1.87	2.01	2.06	2.07	2.06	1.86	1.74
Switzerland	—	—	—	—	—	—	—	0.02	—	—	—	—	—
UK	0.21	0.21	0.20	0.21	0.22	0.23	0.24	0.26	0.28	0.31	0.35	0.41	0.52

—, no use reported; 0.00, <0.005.

Table 6. Change in composition of outpatient use of other antibacterials in Europe as a function of time

J01X	A	B	C	D	E	X
A		−0.047	−0.263	0.272	−0.207	−0.214
B	0.047		−0.216	0.319	−0.160	−0.167
C	0.263	0.216		0.534*	0.056	0.049
D	−0.272	−0.319	−0.534*		−0.479	−0.486*
E	0.207	0.160	−0.056	0.479		−0.007
X	0.214	0.167	−0.049	0.486*	0.007	

A, glycopeptide antibacterials (J01XA); B, polymyxins (J01XB); C, steroid antibacterials (J01XC) or fusidic acid; D, imidazole derivatives (J01XD); E, nitrofuran derivatives (J01XE); X, other antibacterials (J01XX).
Values are estimated changes in the log ratio of the row versus column antibiotic type with increasing time.[16] Significant effects are indicated with an asterisk; positive values represent an increase and negative values represent a decrease.

ageing, however, the use of recommended substances for the treatment and prevention of urinary tract infections might become important as well. Currently, methenamine and nitrofurantoin represent the most commonly used substances in European nursing homes, but quinolones are prescribed as well.[26]

In conclusion, as for all other major antibiotic subgroups, there was striking variation between European countries in the outpatient use and composition of use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials. In combination with the decreasing use, especially of recommended substances, this represents another opportunity to not only reduce antibiotic use, but also to improve its quality for respiratory, urinary and skin infections.

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Supplementary data

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

References

1 Ferech M, Coenen S, Malhotra-Kumar S *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. *J Antimicrob Chemother* 2006; **58**: 401–7.

2 Ferech M, Coenen S, Dvorakova K *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient penicillin use in Europe. *J Antimicrob Chemother* 2006; **58**: 408–12.

3 Coenen S, Ferech M, Dvorakova K *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient cephalosporin use in Europe. *J Antimicrob Chemother* 2006; **58**: 413–7.

4 Coenen S, Ferech M, Malhotra-Kumar S *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient macrolide, lincosamide and streptogramin (MLS) use in Europe. *J Antimicrob Chemother* 2006; **58**: 418–22.

5 Ferech M, Coenen S, Malhotra-Kumar S *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient quinolone use in Europe. *J Antimicrob Chemother* 2006; **58**: 423–7.

6 Adriaenssens N, Coenen S, Versporten A *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997–2009). *J Antimicrob Chemother* 2011; **66** Suppl 6: vi3–12.

7 Versporten A, Coenen S, Adriaenssens N *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient penicillin use in Europe (1997–2009). *J Antimicrob Chemother* 2011; **66** Suppl 6: vi13–23.

8 Versporten A, Coenen S, Adriaenssens N *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient cephalosporin use in Europe (1997–2009). *J Antimicrob Chemother* 2011; **66** Suppl 6: vi25–35.

9 Adriaenssens N, Coenen S, Versporten A *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient macrolide, lincosamide and streptogramin (MLS) use in Europe (1997–2009). *J Antimicrob Chemother* 2011; **66** Suppl 6: vi37–45.

10 Adriaenssens N, Coenen S, Versporten A *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient quinolone use in Europe (1997–2009). *J Antimicrob Chemother* 2011; **66** Suppl 6: vi47–56.

11 WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment 2011*. Oslo. www.whocc.no/filearchive/publications/2011guidelines.pdf (26 October 2011, date last accessed).

12 Woodhead M, Blasi F, Ewig S *et al*. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; **26**: 1138–80.

13 Scottish Intercollegiate Guidelines Network (SIGN). *Management of Suspected Bacterial Urinary Tract Infection in Adults: A National Clinical Guideline*. Edinburgh: Scottish Intercollegiate Guidelines Network, 2006.

14 *SWEDRES 2010: A Report on Swedish Antimicrobial Utilisation and Resistance in Human Medicine*. Solna, Sweden: The Swedish Strategic Programme against Antibiotic Resistance and the Swedish Institute for Infectious Disease Control, 2010.

15 Minalu G, Aerts M, Coenen S *et al*. Application of mixed-effects models to study the country-specific outpatient antibiotic use in Europe: a tutorial on longitudinal data analysis. *J Antimicrob Chemother* 2011; **66** Suppl 6: vi79–87.

16 Faes C, Molenberghs G, Hens N *et al*. Analysing the composition of outpatient antibiotic use: a tutorial on compositional data analysis. *J Antimicrob Chemother* 2011; **66** Suppl 6: vi89–94.

17 ESAC Management Team, ESAC Scientific Advisory Board and ESAC National Networks. *ESAC Yearbook 2009*. Antwerp: University of Antwerp, 2011. www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50036 (26 October 2011, date last accessed).

18 ESAC Management Team, ESAC Scientific Advisory Board and ESAC National Networks. *ESAC Yearbook 2008*. Antwerp: University of Antwerp, 2009. www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50036 (26 October 2011, date last accessed).

19 ESAC Management Team, ESAC Scientific Advisory Board and ESAC National Networks. *ESAC Yearbook 2007*. Antwerp: University of Antwerp, 2008. www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50036 (26 October 2011, date last accessed).

20 ESAC Management Team, ESAC Scientific Advisory Board and ESAC National Networks. *ESAC Yearbook 2006*. Antwerp: University of Antwerp, 2007. www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50036 (26 October 2011, date last accessed).

21 Coenen S, Muller A, Adriaenssens N *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient parenteral antibiotic treatment in Europe. *J Antimicrob Chemother* 2009; **64**: 200–5.

22 Smith S, Fahey T, Smucny J *et al*. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2004; **issue 4**: CD000245.

23 Mills GD, Oehley MR, Arrol B. Effectiveness of β lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. *BMJ* 2005; **330**: 456–62.

24 Verheij T, Hermans J, Mulder J. Effects of doxycycline in patients with acute cough and purulent sputum: a double blind placebo controlled trial. *Br J Gen Pract* 1994; **44**: 400–4.

25 Verheij T, Hopstaken R, Prins J *et al*. NHG standaard acuut hoesten [Guideline on acute cough]. *Huisarts Wet* 2011; **54**: 68–92.

26 McClean P, Hughes C, Tunney M *et al*. Antimicrobial prescribing in European nursing homes. *J Antimicrob Chemother* 2011; **66**: 1609–16.