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European Surveillance of Antimicrobial Consumption (ESAC): outpatient macrolide, lincosamide and streptogramin (MLS) use in Europe (1997–2009)

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Background: Data on more than a decade of outpatient macrolide, lincosamide and streptogramin (MLS) use in Europe were collected from 33 countries within the European Surveillance of Antimicrobial Consumption (ESAC) project, funded by the European Centre for Disease Prevention and Control (ECDC), using the WHO Anatomical Therapeutic Chemical (ATC)/defined daily dose (DDD) methodology.

Methods: For the period 1997–2009, data on outpatient use of systemic MLS aggregated at the level of the active substance were collected and expressed in DDD (WHO, version 2011) per 1000 inhabitants per day (DID). Using a classification based on mean plasma elimination half-life, macrolide use was analysed for trends over time, seasonal variation and composition.

Results: Total outpatient MLS use in 2009 varied by a factor of 18 between the countries with highest (11.5 DID in Greece) and lowest (0.6 DID in Sweden) use. MLS use showed high seasonal variation. Short-, intermediate- and long-acting macrolides were the most commonly used agents in 2, 25 and 5 countries, respectively (mainly erythromycin, clarithromycin and azithromycin, respectively). In Sweden, mainly lincosamides (clindamycin) were used. Lincosamide use was observed in all countries, while substantial use of a streptogramin was only seen in France (pristinamycin). For Europe, a significant increase in outpatient MLS use was found, as well as a significant seasonal variation, which increased over time from 1997 to 2009. Relative use of long-acting macrolides and lincosamides significantly increased over time with respect to intermediate-acting macrolides, and relative use of the latter increased with respect to short-acting macrolides.

Conclusions: The observed differences between European countries in the levels of MLS use and the extreme seasonal variations in their use suggest that this subgroup of antibiotics is still prescribed inappropriately in many countries.

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

Introduction

This paper presents data from the European Surveillance of Antimicrobial Consumption (ESAC) project on outpatient use of 18 drugs belonging to the macrolide, lincosamide and streptogramin (MLS) group of antibiotics (Table 1) in 2009. As in previous ESAC studies, a classification of macrolides based on their mean plasma elimination half-life, which categorizes them as short-, intermediate- or long-acting, was adopted.[1] The article also reviews temporal trends and seasonal variation in macrolide use.

Methods

The methods for collecting and analysing the data on outpatient use of systemic antibiotics is described elsewhere.[2] Here we provide a detailed description of outpatient MLS use in 2009 in defined daily doses (DDD)

Table 1. Classification of MLS (ATC classification, 2011 version)

Macrolides					
short-acting		intermediate-acting		long-acting	
J01FA01	**erythromycin**	J01FA06	**roxithromycin**	J01FA10	**azithromycin**
J01FA02	**spiramycin**	J01FA07	josamycin	J01FA13	dirithromycin
J01FA03	midecamycin[a]	J01FA09	**clarithromycin**		
J01FA05	oleandomycin[b]	J01FA14	flurithromycin		
J01FA08	troleandomycin[b]	J01FA15	telithromycin[a]		
J01FA11	miocamycin				
J01FA12	rokitamycin				
Lincosamides					
J01FF01	**clindamycin**				
J01FF01	lindamycin				
Streptogramins					
J01FG01	**pristinamycin**				
J01FG02	quinupristin/dalfopristin				

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

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 MLS 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 employed.[3] Through compositional data analysis, annual outpatient use data in DID were modelled to assess trends of the relative proportions of the major MLS subgroups from 1997 to 2009 for Europe.[4]

A classification according to their mean plasma elimination half-life, subdividing macrolides into short-acting (half-life <4 h), intermediate-acting (half-life 4–24 h) and long-acting (half-life >24 h) macrolides (Table 1), was used to assess the composition of outpatient use in more detail.

Results

Outpatient MLS use in 2009

In terms of the agents listed in Table 1, seven macrolides each represented >1% of the total MLS use in 2009, with the remainder of the compounds (apart from oleandomycin and troleandomycin, whose use was not reported) each representing <1% of total macrolide use. Figure 1 shows the total MLS use in 2009, as well as the use of short-, intermediate- and long-acting macrolides, expressed in DID. Total MLS use varied by a factor of 18 between the country with the highest (11.54 DID in Greece) and lowest (0.63 DID in Sweden) use. Variations were even more pronounced when use of short-acting (1.45 DID in the UK versus 0.04 in Austria), intermediate-acting (9.85 DID in Greece versus 0.07 in Sweden) and long-acting (2.24 DID in Slovakia versus 0.06 DID in Sweden; no use in Latvia) macrolides were compared (Table 2). While lincosamide (J01FF; mainly clindamycin) use was observed in all countries (ranging from 0.002 DID in Romania to 0.68 DID in Austria), streptogramin use was restricted to the Czech Republic, Germany, Greece, Switzerland, the UK (<0.001 DID) and France (1.04 DID, pristinamycin) (Table S1, available as Supplementary data at *JAC* Online).

Erythromycin, a short-acting macrolide, represented >49% of the total MLS use in Norway and the UK, and accounted for >20% of use in Denmark, Iceland, Romania and Sweden. The intermediate-acting macrolides represented the most used subgroup in Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia and Switzerland (mainly clarithromycin) and in Denmark and Israel (mainly roxithromycin) (Tables 2 and S1). Clarithromycin and roxithromycin use also represented >30% of MLS use in Croatia, Slovenia, Spain and the UK. The long-acting macrolides were the most used MLS in Croatia, Iceland, the Russian Federation, Slovenia and Spain (mainly azithromycin) (Tables 2 and S1). Azithromycin use represented >20% of total MLS use in another 15 countries. Lincosamides were the most used MLS in Sweden and represented >10% of the total MLS use in Austria, Bulgaria, Finland, Germany, Hungary, Luxembourg, Norway and Poland (mainly clindamycin), while substantial streptogramin use was only observed in France (pristinamycin) (Table S1).

Figure 2 shows total outpatient MLS use in 17 European countries for 2009 expressed in PID. In addition, their ranking is depicted according to both DID and PID. Ireland occupied position 3 in DID but position 8 in PID. The DDD per package ranged from 3.1 in Italy to 10.6 in Greece.

Longitudinal data analysis (1997–2009)

For Europe, a significant increase in total outpatient MLS use of 0.02 (SD 0.01) DID per quarter was found, starting from 2.16

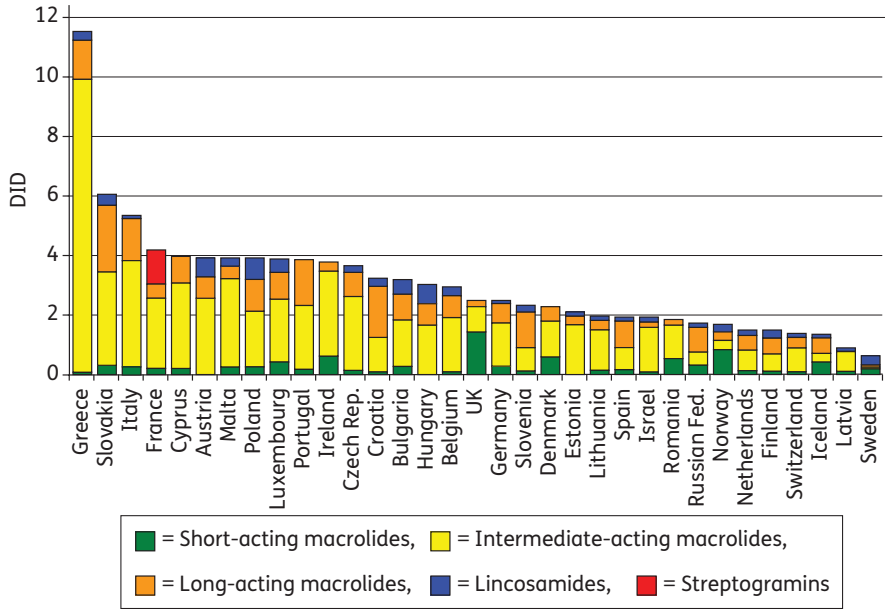


Figure 1. Outpatient use of MLS in 33 European countries in 2009 in DID (2004 data for Switzerland). For Cyprus and Lithuania, total care data are used.

(SD 0.25) DID in the first quarter of 1997, as well as significant seasonal variation with an amplitude of 0.68 (SD 0.13) DID, which increased significantly over time by 0.005 (SD 0.001) DID per quarter (Figure 3). Furthermore, the longitudinal analysis shows that both the upward winter and downward summer peaks of outpatient MLS 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 countries with high and low MLS consumption tend to have high and low seasonal variation in MLS use, respectively.

Tables 2 and S1 provide an overview of the consumption trends in the participating countries between 1997 and 2009. MLS use increased in most countries, and extremely so for Greece, where an increase of >7 DID was observed for macrolides between 1997 and 2009 (from 4.02 to 11.23 DID). In Finland, France, Iceland, Slovenia and Spain a decreasing trend was observed.

Figures S1 and S2 (available as Supplementary data at *JAC* Online) show the seasonal variation of MLS use in the 27 European countries that provided quarterly data. Corresponding figures for macrolides only are available at www.esac.ua.ac.be. The mean of MLS use in the first and fourth quarters was >50% higher than mean MLS use in the second and third quarters in Austria, Belgium, Greece, Germany, Luxembourg, Hungary, Lithuania Slovakia, Portugal, Poland, Estonia (clarithromycin) and Spain (azithromycin). Only in Iceland (azithromycin), Sweden (clindamycin) and the UK (erythromycin) was it <20%.

Compositional data analysis (1997–2009)

For Europe, the relative use of long-acting macrolides as well as lincosamides significantly increased over time with respect to intermediate-acting macrolides, and their relative use significantly increased with respect to the short-acting macrolides (Table 3).

The proportional use of the different macrolide subclasses showed substantial variations, i.e. absolute differences of ≥10% between 1997 and 2009, in more than half of the countries (Figure S3, available as Supplementary data at *JAC* Online). Proportional use of short-acting macrolides decreased by >50% in Iceland, Latvia, Bulgaria and Estonia, by >30% in the Russian Federation, Denmark and Ireland, by >20% in Portugal, Greece and the UK and by >10% in Israel, Spain, Hungary, Norway, Slovenia, Poland, Slovakia, Germany, Italy and the Czech Republic. This decrease was mainly the result of decreasing erythromycin use, except for Italy, the Czech Republic and Slovakia (decreasing spiramycin use) and Bulgaria and Slovenia (decreasing midecamycin use), and was matched by a similar increase in intermediate- and/or long-acting macrolide use in all these countries except for Austria, Finland, Sweden (lincosamides) and France (streptogramins). Overall, intermediate-acting macrolide use increased by >50% in Latvia and Estonia (clarithromycin), by >30% in Croatia and Bulgaria (clarithromycin), by >20% in Lithuania, Ireland, Iceland (clarithromycin) and Denmark (roxithromycin) and by >10% in Greece, Portugal, the Russian Federation, the UK (mainly clarithromycin) and Israel (mainly roxithromycin). It decreased by >10% only in the Netherlands and Spain (mainly clarithromycin).

Long-acting macrolide use (i.e. azithromycin) increased by >30% in Spain, Iceland and the Russian Federation and by >20% in the Netherlands, Poland, Slovakia and Bulgaria. It decreased by >30% in Croatia and by >10% in Lithuania.

Lincosamide use increased by >30% in Sweden (clindamycin) and streptogramin use (pristinamycin) increased by >10% in France.

Table 2. Yearly outpatient macrolide 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	**—**	**3.22**	**3.43**	**2.89**	**2.65**	**2.54**	**2.68**	**2.59**	**2.97**	**2.89**	**3.02**	**3.03**	**3.26**
short	—	0.21	0.16	0.12	0.11	0.08	0.07	0.07	0.07	0.06	0.05	0.05	0.04
intermediate	—	2.41	2.72	2.29	2.10	2.04	2.14	2.08	2.41	2.36	2.39	2.35	2.49
long	—	0.60	0.55	0.48	0.44	0.42	0.46	0.45	0.49	0.47	0.57	0.63	0.73
Belgium	**3.18**	**3.56**	**3.50**	**3.44**	**3.13**	**3.03**	**2.80**	**2.13**	**2.30**	**2.25**	**2.40**	**2.52**	**2.68**
short	0.43	0.55	0.48	0.39	0.34	0.30	0.25	0.17	0.15	0.12	0.14	0.13	0.13
intermediate	2.28	2.56	2.48	2.43	2.12	2.01	1.89	1.53	1.72	1.68	1.72	1.74	1.76
long	0.47	0.45	0.54	0.62	0.67	0.72	0.67	0.43	0.43	0.44	0.53	0.65	0.78
Bulgaria	**—**	**—**	**0.26**	**0.55**	**0.48**	**0.61**	**1.26**	**0.87**	**1.10**	**1.69**	**2.36**	**2.78**	**2.73**
short	—	—	0.19	0.41	0.31	0.33	0.72	0.31	0.40	0.50	0.40	0.33	0.24
intermediate	—	—	0.06	0.08	0.05	0.12	0.31	0.26	0.28	0.64	1.23	1.55	1.60
long	—	—	0.01	0.07	0.12	0.16	0.23	0.30	0.42	0.55	0.74	0.91	0.88
Croatia	**—**	**—**	**—**	**1.79**	**1.70**	**1.73**	**1.88**	**2.01**	**2.48**	**2.43**	**3.06**	**3.05**	**2.98**
short	—	—	—	0.10	0.10	0.13	0.13	0.12	0.10	0.09	0.09	0.08	0.07
intermediate	—	—	—	0.10	0.17	0.15	0.26	0.55	0.81	0.92	1.38	1.38	1.20
long	—	—	—	1.59	1.43	1.44	1.49	1.33	1.57	1.41	1.59	1.59	1.72
Cyprus	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**3.29**	**3.54**	**3.40**	**3.93**
short	—	—	—	—	—	—	—	—	—	0.36	0.30	0.30	0.21
intermediate	—	—	—	—	—	—	—	—	—	2.37	2.56	2.45	2.85
long	—	—	—	—	—	—	—	—	—	0.55	0.68	0.64	0.87
Czech Republic	**—**	**2.44**	**2.40**	**—**	**—**	**2.26**	**2.40**	**2.55**	**3.23**	**2.73**	**3.01**	**3.13**	**3.45**
short	—	0.40	0.40	—	—	0.18	0.16	0.12	0.12	0.23	0.00	0.15	0.14
intermediate	—	1.64	1.60	—	—	1.60	1.74	1.92	2.53	1.98	2.37	2.24	2.50
long	—	0.41	0.41	—	—	0.47	0.51	0.51	0.58	0.52	0.64	0.74	0.81
Denmark	**2.03**	**2.28**	**2.17**	**2.03**	**2.09**	**2.15**	**2.13**	**2.22**	**2.33**	**2.31**	**2.42**	**2.29**	**2.21**
short	1.18	1.25	1.11	1.11	1.09	1.10	1.01	0.94	0.83	0.82	0.75	0.67	0.59
intermediate	0.58	0.62	0.58	0.48	0.53	0.62	0.73	0.89	1.10	1.09	1.20	1.15	1.17
long	0.27	0.40	0.48	0.44	0.46	0.43	0.40	0.39	0.40	0.39	0.47	0.47	0.44
Estonia	**—**	**—**	**—**	**—**	**1.38**	**1.09**	**0.99**	**1.31**	**1.63**	**1.75**	**2.14**	**2.13**	**1.98**
short	—	—	—	—	0.96	0.69	0.41	0.33	0.21	0.18	0.16	0.12	0.04
intermediate	—	—	—	—	0.29	0.22	0.31	0.66	1.13	1.29	1.67	1.68	1.64
long	—	—	—	—	0.14	0.19	0.27	0.32	0.29	0.28	0.31	0.33	0.30
Finland	**1.64**	**1.64**	**1.77**	**1.89**	**2.07**	**1.94**	**2.19**	**1.69**	**1.66**	**1.42**	**1.43**	**1.23**	**1.23**
short	0.24	0.20	0.18	0.16	0.15	0.12	0.11	0.10	0.10	0.09	0.09	0.09	0.09
intermediate	0.72	0.77	0.86	1.02	1.17	1.08	1.28	1.00	0.99	0.80	0.76	0.60	0.60
long	0.68	0.67	0.72	0.71	0.76	0.73	0.79	0.59	0.57	0.53	0.58	0.55	0.55
France	**4.61**	**4.85**	**4.90**	**5.17**	**5.18**	**4.42**	**3.99**	**3.46**	**3.66**	**3.06**	**3.14**	**3.13**	**3.06**
short	0.75	0.72	0.60	0.64	0.60	0.38	0.31	0.32	0.25	0.23	0.24	0.23	0.21
intermediate	3.40	3.60	3.64	3.82	3.71	3.23	2.93	2.46	2.83	2.29	2.35	2.44	2.35
long	0.46	0.53	0.66	0.72	0.87	0.80	0.75	0.68	0.57	0.53	0.55	0.47	0.50
Germany	**2.28**	**2.30**	**2.33**	**2.22**	**2.07**	**2.01**	**2.02**	**1.88**	**2.35**	**2.00**	**2.14**	**2.12**	**2.26**
short	0.60	0.57	0.56	0.53	0.43	0.40	0.36	0.30	0.34	0.34	0.33	0.28	0.27
intermediate	1.35	1.38	1.41	1.32	1.32	1.31	1.36	1.27	1.66	1.34	1.41	1.39	1.46
long	0.33	0.36	0.37	0.38	0.32	0.29	0.30	0.30	0.35	0.32	0.40	0.46	0.52

Continued

Table 2. *Continued*

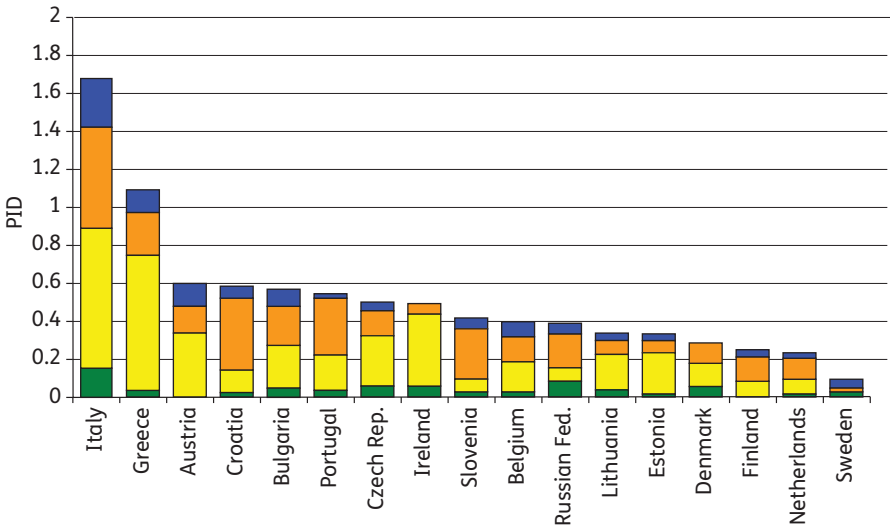
Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Greece	**4.02**	**5.21**	**6.13**	**6.58**	**6.63**	**7.46**	**9.03**	**9.49**	**9.79**	**10.41**	**11.70**	**11.22**	**11.23**
short	0.94	0.88	0.68	0.97	1.07	0.87	0.82	0.65	0.58	0.25	0.18	0.15	0.07
intermediate	2.85	4.05	5.30	5.57	5.49	6.50	7.99	8.36	8.48	9.36	10.40	9.68	9.85
long	0.24	0.28	0.15	0.05	0.07	0.09	0.22	0.48	0.73	0.81	1.11	1.39	1.31
Hungary	**—**	**2.43**	**3.70**	**2.94**	**2.68**	**2.22**	**2.44**	**2.40**	**3.20**	**2.81**	**2.21**	**2.38**	**2.40**
short	—	0.49	0.57	0.44	0.40	0.29	0.20	0.15	0.11	0.08	0.06	0.04	0.05
intermediate	—	1.58	2.61	2.04	1.89	1.62	1.91	1.87	2.51	2.10	1.67	1.71	1.61
long	—	0.37	0.53	0.46	0.40	0.31	0.33	0.38	0.58	0.63	0.48	0.63	0.73
Iceland	**1.79**	**1.85**	**1.74**	**1.53**	**1.47**	**1.48**	**1.56**	**1.60**	**1.73**	**1.52**	**1.57**	**1.51**	**1.25**
short	1.55	1.48	1.34	1.07	0.96	0.88	0.82	0.77	0.76	0.54	0.52	0.42	0.41
intermediate	0.11	0.12	0.16	0.17	0.20	0.22	0.29	0.30	0.35	0.34	0.39	0.39	0.30
long	0.14	0.26	0.24	0.28	0.32	0.39	0.44	0.53	0.63	0.63	0.66	0.69	0.54
Ireland	**—**	**1.93**	**2.16**	**2.12**	**2.30**	**2.44**	**2.78**	**2.84**	**3.10**	**3.51**	**4.01**	**4.07**	**3.76**
short	—	0.92	0.91	0.81	0.76	0.69	0.73	0.68	0.67	0.78	0.74	0.73	0.65
intermediate	—	0.97	1.20	1.24	1.46	1.65	1.95	2.04	2.28	2.56	3.07	3.10	2.85
long	—	0.04	0.06	0.06	0.07	0.09	0.10	0.12	0.15	0.17	0.20	0.24	0.25
Israel	**—**	**—**	**—**	**—**	**—**	**1.49**	**1.55**	**1.46**	**1.58**	**1.84**	**1.67**	**1.73**	**1.82**
short	—	—	—	—	—	0.38	0.35	0.29	0.25	0.24	0.21	0.13	0.10
intermediate	—	—	—	—	—	0.95	1.02	1.00	1.13	1.34	1.15	1.35	1.48
long	—	—	—	—	—	0.16	0.18	0.17	0.20	0.26	0.31	0.25	0.25
Italy	**—**	**—**	**5.04**	**4.94**	**5.04**	**4.96**	**4.91**	**4.69**	**4.91**	**4.79**	**4.84**	**5.21**	**5.27**
short	—	—	0.91	0.83	0.85	0.73	0.56	0.45	0.42	0.40	0.37	0.38	0.28
intermediate	—	—	3.08	3.06	3.03	3.09	3.17	3.06	3.25	3.16	3.19	3.50	3.59
long	—	—	1.05	1.05	1.16	1.15	1.19	1.18	1.25	1.24	1.29	1.32	1.39
Latvia	**—**	**—**	**—**	**—**	**—**	**0.68**	**—**	**0.85**	**1.01**	**0.94**	**1.20**	**0.85**	**0.78**
short	—	—	—	—	—	0.48	—	0.44	0.41	0.30	0.33	0.16	0.10
intermediate	—	—	—	—	—	0.16	—	0.32	0.54	0.50	0.68	0.69	0.68
long	—	—	—	—	—	0.04	—	0.09	0.06	0.13	0.18	—	—
Lithuania	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**1.00**	**1.85**	**1.96**	**1.87**
short	—	—	—	—	—	—	—	—	—	0.14	0.19	0.15	0.12
intermediate	—	—	—	—	—	—	—	—	—	0.50	1.14	1.20	1.38
long	—	—	—	—	—	—	—	—	—	0.35	0.53	0.61	0.37
Luxembourg	**4.54**	**4.72**	**4.94**	**4.64**	**4.56**	**4.06**	**4.06**	**2.38**	**2.68**	**2.62**	**3.43**	**3.41**	**3.46**
short	0.86	1.02	0.90	0.80	0.78	0.69	0.77	0.55	0.59	0.48	0.53	0.46	0.43
intermediate	3.09	3.19	3.38	3.05	2.88	2.45	2.34	1.16	1.31	1.40	2.07	2.10	2.11
long	0.59	0.51	0.66	0.79	0.90	0.92	0.95	0.67	0.79	0.74	0.83	0.85	0.92
Malta	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**2.93**	**3.52**	**3.68**
short	—	—	—	—	—	—	—	—	—	—	0.33	0.24	0.26
intermediate	—	—	—	—	—	—	—	—	—	—	2.25	2.79	2.98
long	—	—	—	—	—	—	—	—	—	—	0.35	0.49	0.45
Netherlands	**1.12**	**1.16**	**1.17**	**1.13**	**1.22**	**1.24**	**1.27**	**1.31**	**1.42**	**1.40**	**1.38**	**1.37**	**1.34**
short	0.16	0.14	0.13	0.12	0.12	0.11	0.10	0.10	0.09	0.10	0.10	0.13	0.11
intermediate	0.77	0.79	0.79	0.76	0.81	0.82	0.84	0.85	0.92	0.86	0.81	0.76	0.72
long	0.19	0.23	0.24	0.25	0.29	0.31	0.33	0.35	0.41	0.44	0.47	0.48	0.52

Continued

Table 2. *Continued*

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Norway	**—**	**1.46**	**—**	**—**	**1.63**	**1.78**	**1.70**	**1.64**	**1.84**	**1.82**	**1.87**	**1.68**	**1.47**
short	—	1.07	—	—	1.13	1.19	1.08	1.02	1.15	1.13	1.11	0.98	0.84
intermediate	—	0.23	—	—	0.30	0.35	0.36	0.35	0.38	0.37	0.40	0.35	0.29
long	—	0.16	—	—	0.21	0.24	0.25	0.27	0.32	0.32	0.36	0.35	0.34
Poland	**—**	**1.54**	**1.42**	**1.70**	**2.05**	**1.84**	**—**	**2.52**	**3.07**	**—**	**3.96**	**3.01**	**3.21**
short	—	0.36	0.34	0.40	0.44	0.35	—	0.93	0.90	—	1.01	0.31	0.27
intermediate	—	1.04	0.91	0.98	1.23	1.14	—	1.25	1.70	—	2.14	1.79	1.87
long	—	0.14	0.17	0.31	0.38	0.35	—	0.34	0.47	—	0.81	0.91	1.07
Portugal	**2.94**	**3.20**	**3.62**	**3.61**	**3.71**	**3.46**	**3.81**	**3.63**	**4.34**	**3.95**	**3.95**	**3.84**	**3.80**
short	0.79	0.69	0.63	0.52	0.42	0.35	0.29	0.25	0.24	0.28	0.23	0.23	0.20
intermediate	1.35	1.53	1.75	1.73	1.73	1.88	2.14	2.08	2.60	2.40	2.30	2.15	2.12
long	0.80	0.98	1.23	1.36	1.56	1.23	1.37	1.30	1.51	1.27	1.42	1.46	1.47
Romania	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**1.83**
short	—	—	—	—	—	—	—	—	—	—	—	—	0.54
intermediate	—	—	—	—	—	—	—	—	—	—	—	—	1.10
long	—	—	—	—	—	—	—	—	—	—	—	—	0.19
Russian Federation	**—**	**—**	**—**	**—**	**—**	**—**	**0.74**	**0.80**	**0.89**	**1.05**	**1.31**	**1.43**	**1.60**
short	—	—	—	—	—	—	0.51	0.48	0.44	0.42	0.41	0.35	0.35
intermediate	—	—	—	—	—	—	0.11	0.15	0.20	0.28	0.35	0.41	0.42
long	—	—	—	—	—	—	0.12	0.17	0.24	0.34	0.54	0.67	0.83
Slovakia	**—**	**—**	**3.31**	**2.98**	**3.31**	**3.40**	**3.70**	**3.14**	**3.75**	**4.73**	**6.01**	**5.58**	**5.68**
short	—	—	0.68	0.53	0.57	0.38	0.32	0.28	0.36	0.34	0.34	0.31	0.30
intermediate	—	—	2.16	1.86	2.04	2.26	2.60	2.19	2.41	3.03	3.56	3.14	3.14
long	—	—	0.48	0.58	0.70	0.76	0.78	0.67	0.98	1.35	2.10	2.13	2.24
Slovenia	**2.85**	**3.53**	**3.81**	**3.57**	**3.18**	**2.81**	**2.98**	**2.99**	**3.04**	**2.31**	**2.44**	**2.23**	**2.12**
short	0.64	0.59	0.60	0.48	0.38	0.30	0.29	0.29	0.25	0.19	0.20	0.16	0.14
intermediate	0.81	1.55	1.73	1.72	1.46	1.27	1.41	1.42	1.44	1.01	1.00	0.84	0.78
long	1.41	1.39	1.47	1.37	1.34	1.25	1.28	1.28	1.36	1.11	1.24	1.22	1.20
Spain	**3.22**	**3.33**	**3.22**	**3.06**	**2.90**	**2.81**	**2.80**	**2.37**	**2.26**	**1.95**	**1.99**	**1.85**	**1.83**
short	0.89	0.79	0.67	0.57	0.45	0.39	0.33	0.26	0.22	0.19	0.18	0.16	0.15
intermediate	1.78	1.90	1.76	1.68	1.64	1.58	1.58	1.31	1.22	0.97	0.94	0.83	0.78
long	0.55	0.64	0.78	0.81	0.82	0.85	0.89	0.80	0.82	0.79	0.88	0.86	0.90
Sweden	**0.81**	**0.85**	**0.79**	**0.71**	**0.74**	**0.65**	**0.57**	**0.55**	**0.58**	**0.58**	**0.58**	**0.12**	**0.31**
short	0.56	0.61	0.58	0.55	0.60	0.52	0.45	0.43	0.46	0.46	0.45	0.00	0.19
intermediate	0.22	0.21	0.17	0.12	0.11	0.10	0.08	0.08	0.08	0.08	0.07	0.07	0.07
long	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.04	0.05	0.05	0.05	0.06	0.06
Switzerland	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**1.25**	**—**	**—**	**—**	**—**	**—**
short	—	—	—	—	—	—	—	0.07	—	—	—	—	—
intermediate	—	—	—	—	—	—	—	0.85	—	—	—	—	—
long	—	—	—	—	—	—	—	0.33	—	—	—	—	—
UK	**2.84**	**2.71**	**2.45**	**2.30**	**2.33**	**2.28**	**2.32**	**2.22**	**2.27**	**2.17**	**2.35**	**2.44**	**2.49**
short	2.31	2.19	1.99	1.86	1.86	1.80	1.79	1.69	1.67	1.55	1.59	1.56	1.45
intermediate	0.49	0.49	0.43	0.41	0.44	0.45	0.48	0.48	0.54	0.55	0.65	0.75	0.88
long	0.04	0.03	0.03	0.03	0.03	0.03	0.04	0.05	0.06	0.07	0.11	0.13	0.15

Country, total national macrolide use; short, short-acting macrolides; intermediate, intermediate-acting macrolides; long, long-acting macrolides; —, no use reported; 0.00, <0.005.



Country	IT	GR	AT	HR	BG	PT	CZ	IE	SI	BE	RU	LT	EE	DK	FI	NL	SE
Ranking PID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ranking DID	2	1	4	6	7	5	8	3	10	9	14	13	12	11	16	15	17
DDD/package	3.1	10.6	6.5	5.5	5.7	7.2	6.4	8.3	5.6	7.6	4.5	5.9	6.4	8.0	6.0	6.6	7.2

Figure 2. Outpatient use of MLS 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.

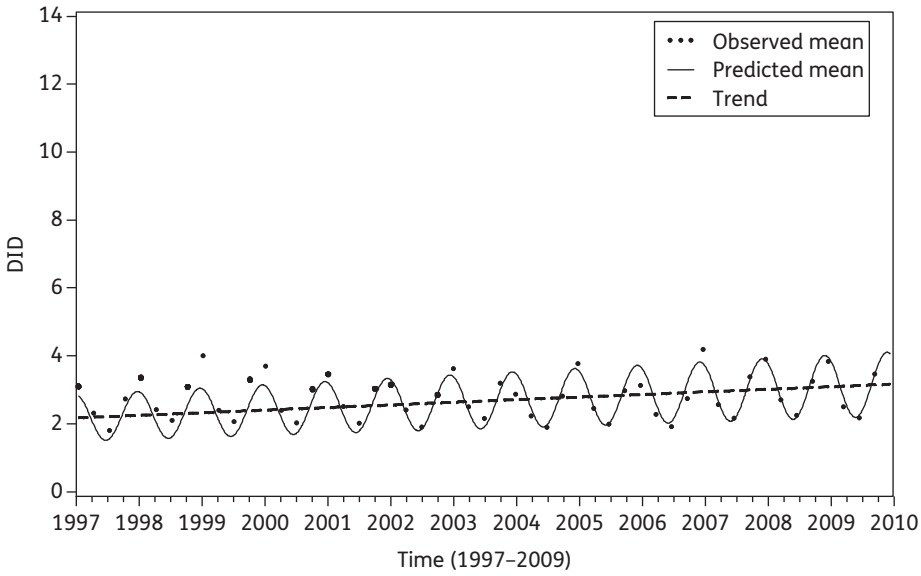
Discussion

Levels of MLS use and their extreme (also seasonal) variation among European countries suggest that this subgroup of antibiotics is still prescribed inappropriately in many countries. The seasonal variations in use observed for this subgroup of antibiotics, which are mostly used to treat respiratory tract infections, were more extreme than observed for total use and for penicillin use.[2,5] This may suggest inappropriate use for conditions such as the common cold, flu and bronchitis. Moreover, variations in macrolide use were more pronounced when assessing the use of short-, intermediate- and long-acting substances. This classification was also used in previous ESAC papers[1] and enabled us to provide the most revealing overview of MLS use in Europe.

In comparison with the 2003 data on MLS use, published in the previous series,[1] midecamycin and telithromycin no longer represented >1% of the total MLS use. For telithromycin, introduced in 2001, a strong increase up to 2005 was followed by a marked decline, which coincided with European Medicines Agency warnings on the safety of telithromycin published in 2006 and 2007.[6,7]

MLS use increased in 10 countries during 1997–2009, most remarkably in Greece (by >7 DID), and in 2009 Greece remained the highest consumer of MLS in DID in Europe. When using PID as the outcome measure instead of DID, we observed no important shifts in ranking except for Ireland (Figure 2). For MLS, there was less variation in DDD per package in each country (average 6.5 DDD per package) compared with penicillins.[5]

Among MLS, macrolides were the most used subgroup (except for Sweden, where lincosamide use predominated), and among the macrolides the intermediate-acting subgroup (mainly clarithromycin) was predominantly used in the majority of the European countries. Only in the UK and Norway did the use of short-acting macrolides (i.e. erythromycin) remain predominant. The lower price of short-acting macrolides could be a possible explanation for their predominant use in the UK, as the NHS provides a financial incentive to prescribe cheaper medicinal products.[8] Reimbursement can be a very powerful tool to control antibiotic use by general practitioners,[9] but a more detailed assessment of the different national reimbursement systems is needed to fully understand their influence on shifts (or lack of shifts) in the choice of antibiotic subgroup or substance. Irrespective of the most used subgroup, a shift in prescribing trends from the older to newer analogues, which has also been recorded for other antibiotic subgroups,[5] was observed for all countries except Sweden. Sweden was the only country with a significant increase in lincosamide use (i.e. clindamycin); the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) network only advises clindamycin for



ATC	Parameters				
	β_0	β_1	$\beta_0{}^S$	$\beta_1{}^S$	δ
J01F	2.159 (0.245)*	0.019 (0.008)*	0.681 (0.131)*	0.005 (0.001)*	0.353 (0.019)*

Figure 3. Estimated linear trend and seasonal variation of outpatient MLS 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 MLS use in Europe as a function of time

J01F	FA short	FA inter	FA long	FF
FA short		−0.131*	−0.167*	−1.755*
FA inter	0.131*		−0.036*	−0.044*
FA long	0.167*	0.036*		−0.008
FF	1.755*	0.044*	0.008	

FA short, short-acting macrolides; FA inter, intermediate-acting macrolides; FA long, long-acting macrolides; FF, lincosamides.
Values are estimated changes in the log ratio of the row versus column antibiotic type with increasing time.[4] Significant effects are indicated with an asterisk; positive values represent an increase and negative values represent a decrease.

recurrent tonsillitis/pharyngotonsillitis within 14 days or as an alternative for penicillin V in case of penicillin allergy in acute tonsillitis/pharyngotonsillitis, skin and soft tissue infection and community-acquired pneumonia in adults.[10] Data linking prescriptions with indications could be helpful in reaching a better understanding of such trends in use.

Overall, there was an increase in the proportional use of the intermediate-acting (mainly clarithromycin) and/or long-acting (mainly azithromycin) subgroups at the expense of the short-acting subgroup (mainly erythromycin) during the 13 years of observation. In Spain, the Russian Federation and Iceland the long-acting macrolides (i.e. azithromycin) became the predominant group. Decreasing use of the short-acting macrolides, like erythromycin, which are inferior to the newer analogues clarithromycin and azithromycin in terms of pharmacokinetic profiles and adverse drug reactions, could be considered a positive trend. However, both clarithromycin and azithromycin have been shown to cause enhanced resistance selection in oral streptococci.[11]

The currently reported ESAC data should contribute to a better understanding of the link between macrolide use and resistance. Although the current MLS classification might not be ideal, it nevertheless provides us with a tool to describe macrolide use in Europe in a more comprehensive manner than before and to assess the future impact of guidelines and interventions in promoting better use of these drugs.

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The information contained in this publication does not necessarily reflect the opinion/position of the European Commission or the ECDC.

Supplementary data

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

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