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

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***Background*: Data on outpatient macrolide, lincosamide and streptogramin (MLS) use in Europe were collected from 25 countries within the ESAC project, funded by DG SANCO of the European Commission, using the WHO ATC/DDD methodology.**

***Methods*: For the period 1997–2003, data on outpatient use of systemic MLS aggregated at the level of the active substance were collected and expressed in DDD (WHO, version 2004) per 1000 inhabitants per day (DID). Macrolide use was analysed in detail, using a classification based on their mean plasma elimination half-life.**

***Results*: Total outpatient MLS use in 2003 varied by a factor of 11 between the country with the highest (9.36 DID in Greece) and lowest (0.85 DID in Sweden) use. MLS use showed high seasonal variation. Short-, intermediate- and long-acting macrolides were used most in 6, 18 and 1 countries, respectively (mainly erythromycin, clarithromyin and azithromycin, respectively). Lincosamide use was observed in all countries (mainly clindamycin) and substantial streptogramin use only in France (pristinamycin). From 1997 to 2003, MLS use increased in 14 countries and was most pronounced in Greece (increase of >5 DID). Except for Sweden, a relative increase of intermediate- (mainly clarithromycin) and/or long-acting (mainly azithromycin) macrolide use was observed, at the expense of short-acting macrolide (mainly erythromycin) use.**

***Conclusion*: The observed differences between European countries in the levels of MLS use and the extreme seasonal variations in their use suggest that this class of antibiotics is prescribed inappropriately in many countries. The MLS classification developed here facilitates a more comprehensive description of macrolide use in Europe. These data (collected as part of ESAC) could promote investigations that lead to a deeper understanding of the link between macrolide use and resistance.**

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

Introduction

In this paper we present a detailed overview of outpatient use of 18 substances classified as macrolides, lincosamides or streptogramins (MLS; Table 1). While several criteria exist to classify macrolides, for instance based on their chemical structure, there is as yet no officially accepted classification for macrolides. We adopted a classification based on their mean plasma elimination half-life, which subdivides them into

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Table 1. Classification of macrolides, lincosamides and streptogramins (MLS) according to WHO ATC codes

Macrolides					
short-acting		intermediate-acting		long-acting	
J01FA01	**erythromycin**	**J01FA06**	**roxithromycin**	**J01FA10**	**azithromycin**
J01FA02	**spiramycin**	J01FA07	josamycin	J01FA13	dirithromycin
J01FA03	**midecamycin**	**J01FA09**	**clarithromycin**		
J01FA05	oleandomycin	J01FA14	flurithromycin		
J01FA08	troleandomycin[a]	**J01FA15**	**telithromycin**		
J01FA11	miocamycin				
J01FA12	rokitamycin				
Lincosamides					
J01FF01	**clindamycin**				
J01FF02	lindamycin				
Streptogramins					
J01FG01	**pristinamycin**				
J01FG02	quinupristin/dalfopristin				

Drugs whose use represents more than 1% of the total MLS use in Europe in 2003 are shown in bold type.
[a]No use of this MLS antibiotic was reported in Europe in 2003.

short-, intermediate- and long-acting macrolides. Additional data are available on the ESAC website (www.ua.ac.be/ESAC).

Methods

The methods for collecting use data of systemic antibiotics have been previously described in the introductory paper of this series[1] and elsewhere.[2,3] Outpatient use of MLS was compared between 25 countries. A classification according to their mean plasma elimination half-life, subdividing macrolides into short- (half-life < 4 h), intermediate- (half-life from 4 to 24 h) and long-acting (half-life > 24 h) macrolides (Table 1), was used to assess outpatient use in more detail. In addition, trends in time and seasonal variation were analysed.

Results

For only nine macrolides, the use represented more than 1% of the total MLS use in 2003 in Europe, while no use was recorded for one substance (troleandomycin) (Table 1). Figure 1 shows the total MLS use in 2003, as well as the use of short-, intermediate- and long-acting macrolides, expressed in defined daily doses (DDD) per 1000 inhabitants per day (DID). Total MLS use varied by a factor of 11 between the country with the highest use (9.36 DID in Greece) and the country with the lowest use (0.85 DID in Sweden). Variations were even more pronounced when use of short- (1.81 DID in the UK versus 0.07 in Austria), intermediate- (8.02 DID in Greece versus 0.08 in Sweden) and long-acting (1.50 DID in Croatia versus 0.04 DID in Sweden) macrolides was compared (Table 2). While lincosamide (J01FF; mainly clindamycin) use was observed in all countries (ranging from 0.01 DID in Denmark to 0.64 DID in Hungary), streptogramin use was restricted to Greece, Belgium, Luxembourg (<0.001 DID) and France (0.82 DID—mainly pristinamycin) (Table S1, Online Supplementary data).

Erythromycin, a short-acting macrolide, accounted for more than 50% of the total MLS use in Iceland, Norway, Sweden and the UK; was the most used MLS in Estonia and Denmark (>40%) in 2003; and represented more than 20% of MLS use in Ireland and Israel. The intermediate-acting macrolides represented the most used subclass in Austria, Belgium, the Czech Republic, France, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Slovakia, Slovenia and Spain (mainly clarithromycin) and in Germany, Finland and Israel (mainly roxithromycin). Clarithromycin and roxithromycin use also represented more than 20% of MLS use in Estonia and Finland and in the Czech Republic, Denmark and Slovakia, respectively. The long-acting macrolides were the most used MLS only in Croatia (mainly azithromycin). Azithromycin accounted for more than 20% of MLS use in another 12 countries (Tables 2 and S1; Figure S1, Online Supplementary data). Lincosamides represented more than 20% of the total MLS use in Hungary, Poland and Sweden, and more than 10% in Germany and Croatia (mainly clindamycin), while substantial streptogramin use was only observed in France (pristinamycin).

Tables 2 and S1 as well as Figure S1 provide an overview of the consumption trends in the participating countries between 1997 and 2003. A total of 14 countries showed increasing MLS use between the first and the last year of observation. Only in one country, however, was there more than 1 DID difference in MLS use between 1997 and 2003; this was in Greece, where an extreme increase from 4.16 to 9.36 DID was observed. The proportional use of the different macrolide subclasses showed more dramatic variations, i.e. absolute differences of

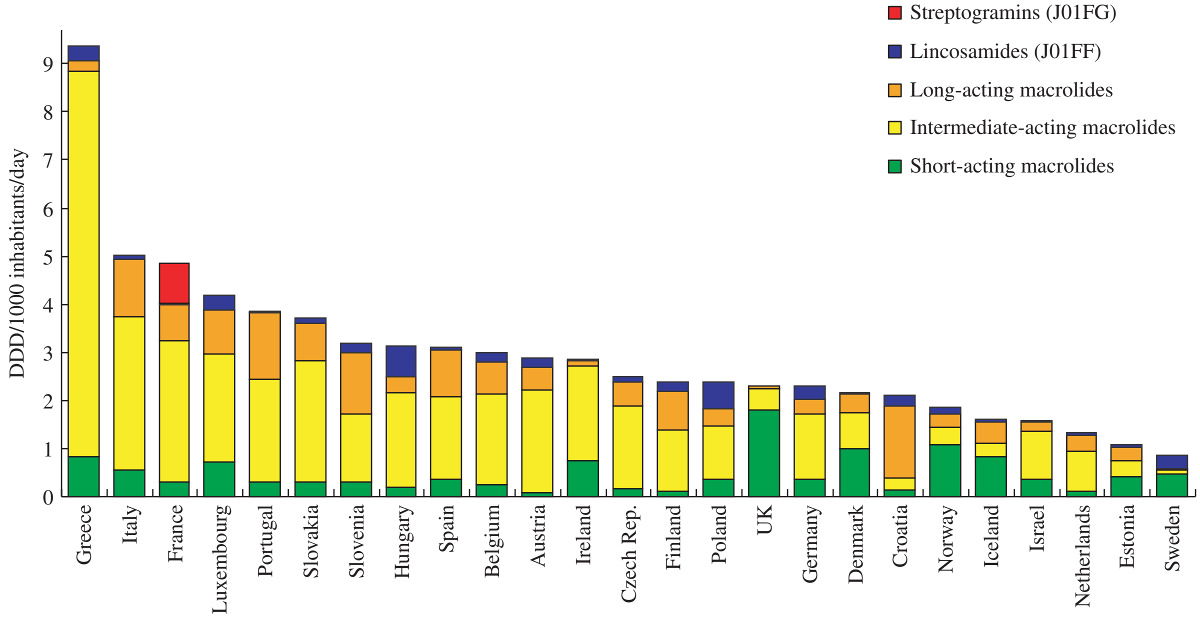

Figure 1. Outpatient use of MLS in 25 European countries in 2003. For Iceland total data are used; for Poland 2002 data are used.

10% or more between 1997 and 2003, in more than half of the countries. Proportional use of short-acting macrolides decreased by more than 30% in Iceland and Portugal; by more than 20% in Ireland; and by more than 10% in Denmark, Spain, Greece, Hungary, Poland, Slovakia and Slovenia. This decrease was mainly the result of decreasing erythromycin use, except for Slovakia (decreasing spiramycin use) 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 Denmark and Slovakia. Overall, intermediate-acting macrolide use increased by more than 20% in Ireland (clarithromycin) and by more than 10% in Iceland, Finland, Greece, Hungary, Portugal and Slovenia (mainly clarithromycin), and long-acting macrolide use increased by more than 20% in Iceland and Portugal and by more than 10% in Spain, Poland and Luxembourg (azithromycin). Intermediate-acting macrolide use only decreased by more than 10% in Sweden (clarithromycin) and Luxembourg (roxithromycin). In Sweden this decrease coincided with an increase of lincosamide use (clindamycin) by more than 10% (Figure S1). Decreasing roxithromycin use was also observed in Belgium, the Czech Republic, Spain, Slovakia and Slovenia.

Figures S2 and S3 (Online Supplementary data) show the seasonal fluctuation of MLS use in 21 European countries that provided quarterly data. The same figures for macrolides only are available at www.ua.ac.be/ESAC. The mean of MLS use in the first and fourth quarter was more than 60% higher than the mean of MLS use in the second and third quarter in Austria, Belgium and Hungary (clarithromycin) and in Germany (roxithromycin). This seasonal variation was more than 50% in Greece, Poland, Portugal, Slovakia, Slovenia, Spain (clarithromycin) and Estonia (erythromycin). Only in Iceland, the Netherlands, Sweden and the UK was it less than 30%. In the Netherlands the increase in antibiotic use in winter quarters was 25% (clarithromycin). In Iceland, Sweden and the UK it was 11%, 17% and 21%, respectively (erythromycin), and, similar to the case in Denmark, decreasing over time.

Discussion

Levels of MLS use and their extreme (also seasonal) variation among European countries suggest that this class of antibiotics is prescribed inappropriately in many countries. The seasonal variations in use observed for this class of antibiotics, which is mostly used to treat respiratory tract infections, were more extreme than previously observed for total as well as for β-lactam antibiotic use.[1,3–5] This may suggest an inappropriate use for conditions such as the common cold, flu and bronchitis. Moreover, variations in macrolide use became even more pronounced when assessing use of short-, intermediate- and long-acting substances. This subgrouping of the macrolides is not supported by ATC codes; however, telithromycin was classified here as a macrolide and not as a ketolide, which is in accordance with the ATC classification. We assigned telithromycin to the intermediate-acting subgroup (mean plasma elimination half-life 4–24 h) based on its 10 h half-life.[6]

This classification enabled us to provide the most lucid overview of MLS use in Europe. Other classifications based on the chemical structure of the macrolides or on differences in mechanisms of action are known. However, stratifying macrolides according to these classifications would not have been as informative or would have compelled us to show data on the substance level or would have had both these drawbacks.

MLS use increased in 14 countries during 1997–2003, most remarkably in Greece (by >5 DID), and in 2003, Greece was the highest consumer of MLS in Europe. This continuous increase of MLS use (mainly clarithromycin) in Greece might be partially explained by parallel exports, as described earlier.[1] Among MLS, macrolides were the most used subclass, and among the macrolides, the intermediate-acting subgroup (mainly clarithromycin) was predominantly used in the majority of the European countries. In a few countries (Denmark, Estonia, Iceland, Norway, Sweden and the UK), however, use of the short-acting macrolides was predominant. Irrespective of the most used subgroup, a shift in prescribing trends from the older to newer analogues, which

Table 2. Trends of macrolide use in 25 European countries, expressed in DDD per 1000 inhabitants per day

Year	97	98	99	00	01	02	03
Austria		3.18	3.39	2.87	2.65	2.54	2.68
short		0.24	0.17	0.12	0.11	0.08	0.07
intermediate		2.41	2.72	2.29	2.10	2.04	2.14
long		0.52	0.51	0.46	0.44	0.42	0.46
Belgium	3.18	3.56	3.50	3.44	3.13	3.03	2.79
short	0.43	0.55	0.48	0.39	0.34	0.30	0.25
intermediate	2.28	2.56	2.48	2.43	2.12	2.01	1.89
long	0.47	0.45	0.54	0.62	0.67	0.72	0.65
Croatia				1.79	1.62	1.65	1.88
short				0.10	0.09	0.13	0.13
intermediate				0.10	0.16	0.14	0.26
long				1.59	1.37	1.38	1.50
Czech Republic		2.45	2.41	2.36	2.41	2.26	2.39
short		0.40	0.40	0.36	0.30	0.18	0.16
intermediate		1.65	1.60	1.57	1.67	1.61	1.73
long		0.41	0.41	0.44	0.44	0.47	0.50
Denmark	2.03	2.27	2.17	2.01	2.09	2.16	2.14
short	1.18	1.25	1.11	1.10	1.09	1.11	1.01
intermediate	0.58	0.62	0.58	0.47	0.53	0.62	0.73
long	0.27	0.40	0.48	0.44	0.46	0.43	0.40
Estonia						1.09	1.01
short						0.69	0.42
intermediate						0.22	0.32
long						0.19	0.28
Finland	1.64	1.64	1.77	1.89	2.07	1.94	2.19
short	0.24	0.20	0.18	0.16	0.15	0.12	0.11
intermediate	0.72	0.77	0.86	1.02	1.17	1.09	1.28
long	0.68	0.67	0.72	0.71	0.76	0.73	0.79
France	4.60	4.84	4.93	5.19	5.14	4.39	4.00
short	0.75	0.72	0.61	0.64	0.60	0.38	0.31
intermediate	3.39	3.59	3.66	3.83	3.68	3.21	2.94
long	0.46	0.53	0.66	0.72	0.86	0.80	0.75
Germany	2.28	2.30	2.33	2.22	2.07	2.01	2.02
short	0.60	0.57	0.56	0.53	0.43	0.40	0.36
intermediate	1.35	1.38	1.41	1.32	1.32	1.31	1.36
long	0.33	0.36	0.37	0.38	0.32	0.29	0.30
Greece	4.02	5.21	6.13	6.53	6.60	7.46	9.07
short	0.94	0.88	0.68	0.96	1.07	0.87	0.83
intermediate	2.85	4.05	5.30	5.52	5.46	6.50	8.02
long	0.24	0.28	0.15	0.05	0.07	0.09	0.22
Hungary		2.47	3.78	3.00	2.76	2.22	2.50
short		0.50	0.58	0.45	0.41	0.29	0.20
intermediate		1.60	2.66	2.08	1.94	1.62	1.96
long		0.37	0.54	0.47	0.41	0.31	0.34
Iceland	1.79	1.84	1.72	1.53	1.49	1.51	1.56
short	1.55	1.47	1.33	1.07	0.97	0.89	0.82
intermediate	0.11	0.12	0.15	0.18	0.20	0.22	0.29
long	0.14	0.25	0.24	0.28	0.32	0.39	0.44
Ireland	1.87	1.96	2.19	2.14	2.33	2.48	2.83
short	1.03	0.93	0.92	0.82	0.77	0.70	0.74
intermediate	0.80	0.98	1.21	1.26	1.49	1.68	1.98
long	0.04	0.04	0.06	0.06	0.07	0.10	0.10
Israel						1.49	1.55
short						0.38	0.35
intermediate						0.95	1.02
long						0.16	0.18
Italy			5.05	4.95	4.98	4.98	4.93
short			0.91	0.83	0.84	0.73	0.56
intermediate			3.08	3.06	2.99	3.10	3.18
long			1.05	1.06	1.15	1.15	1.19
Luxembourg	4.30	4.47	4.69	4.42	4.37	3.90	3.88
short	0.81	0.97	0.85	0.76	0.75	0.66	0.73
intermediate	2.92	3.02	3.21	2.91	2.76	2.36	2.24
long	0.56	0.48	0.63	0.75	0.86	0.89	0.91
Netherlands	1.12	1.16	1.17	1.14	1.23	1.24	1.27
short	0.16	0.14	0.14	0.13	0.12	0.11	0.10
intermediate	0.77	0.79	0.79	0.76	0.82	0.82	0.84
long	0.19	0.23	0.24	0.25	0.29	0.31	0.33
Norway		1.47			1.64	1.80	1.71
short		1.08			1.14	1.20	1.09
intermediate		0.23			0.30	0.36	0.36
long		0.17			0.21	0.24	0.26
Poland	1.17	1.54	1.42	1.70	2.05	1.82	
short	0.45	0.36	0.34	0.40	0.44	0.35	
intermediate	0.66	1.04	0.91	0.98	1.23	1.13	
long	0.06	0.14	0.17	0.31	0.38	0.34	
Portugal	3.06	3.06	3.50	3.38	3.36	3.46	3.81
short	1.26	1.10	1.00	0.83	0.67	0.35	0.29
intermediate	1.35	1.53	1.75	1.73	1.73	1.88	2.14
long	0.45	0.43	0.75	0.82	0.96	1.23	1.37
Slovakia				2.92	3.24	3.33	3.60
short				0.54	0.57	0.38	0.31
intermediate				1.82	1.99	2.20	2.53
long				0.56	0.68	0.74	0.76
Slovenia	2.85	3.53	3.81	3.57	3.18	2.83	3.00
short	0.64	0.59	0.60	0.48	0.38	0.30	0.30
intermediate	0.81	1.55	1.73	1.72	1.46	1.27	1.41
long	1.41	1.39	1.47	1.37	1.34	1.25	1.29
Spain	3.25	3.38	3.30	3.17	3.04	3.01	3.05
short	0.89	0.79	0.69	0.59	0.47	0.41	0.36
intermediate	1.79	1.92	1.80	1.72	1.70	1.68	1.71
long	0.57	0.66	0.81	0.86	0.87	0.92	0.98
Sweden	0.81	0.85	0.79	0.71	0.74	0.66	0.58
short	0.56	0.61	0.58	0.55	0.60	0.53	0.46
intermediate	0.22	0.21	0.17	0.12	0.11	0.10	0.08
long	0.02	0.03	0.03	0.03	0.03	0.03	0.04
UK	2.86	2.70	2.43	2.28	2.31	2.25	2.29
short	2.34	2.19	1.99	1.88	1.87	1.80	1.81
intermediate	0.49	0.47	0.41	0.38	0.41	0.42	0.44
long	0.03	0.03	0.03	0.03	0.03	0.03	0.04

Country: Total national macrolide use.
Short: Short-acting macrolide use.
Intermediate: Intermediate-acting macrolide use.
Long: Long-acting macrolide use.

has also been previously recorded for other antibiotic classes,[5] was observed for all countries except Sweden. There was an increase in the proportional use of the intermediate- (mainly clarithromycin) and/or the long-acting subgroups (mainly azithromycin) at the expense of the short-acting subgroup (mainly erythromycin) during the 7 years studied in this work. Widespread use of the short-acting macrolides, such as erythromycin, which are inferior to the newer analogues clarithromycin and azithromycin in terms of pharmacokinetic profiles and adverse drug reactions, could indicate conservative and cost-conscious antibiotic use. Remarkably, prevalence of macrolide resistance in common respiratory pathogens, *Streptococcus pneumoniae* and *Streptococcus pyogenes*, also tends to be lower in countries that predominantly use the short-acting analogues in comparison with those that use the intermediate-acting analogues.[7,8] However, this ecological link does not prove a cause and effect relationship and could actually relate to more judicious antibiotic prescribing.

In addition, compared with the intermediate-acting (clarithromycin) macrolides, long-acting (azithromycin) macrolides may cause an enhanced resistance selection.[9,10] However, this issue remains, as yet, debatable. In conclusion, the ESAC data presented here could facilitate investigations that lead to a deeper understanding of the link between macrolide use and resistance. Although the current MLS classification might not be ideal, it nevertheless provided ESAC with a tool to describe macrolide use in Europe in a more comprehensive manner than ever before.

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Transparency declarations

The authors have no interests to declare.

Supplementary data

Table S1 and Figures S1–3 are available as Online Supplementary data at http://jac.oxfordjournals.org.

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