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European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe

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***Background*: The ESAC project, granted by DG SANCO of the European Commission, is an international network of surveillance systems, aiming to collect comparable and reliable data on antibiotic use in Europe. Data on outpatient antibiotic use were collected from 34 countries using the ATC/DDD methodology.**

***Methods*: For the period 1997–2003, data on outpatient use of systemic antibiotics aggregated at the level of the active substance were collected and expressed in DDD (WHO, version 2004) per 1000 inhabitants per day (DID). Outpatient antibiotic (ATC J01) use in 25 European countries, able to deliver valid data, was analysed.**

***Results*: Total outpatient antibiotic use in 2003 varied by a factor of 3 between the country with the highest (31.4 DID in Greece) and the country with the lowest (9.8 DID in the Netherlands) use. General use patterns in individual countries as well as trends during the period 1997–2003 are described in this paper, while major antibiotic classes (penicillins, cephalosporins, macrolides/lincosamides/streptogramins and quinolones) will be analysed in detail in separate papers.**

***Conclusion*: The ESAC project established for the first time a credible alternative to industry sources for the collection of internationally comparable data on antibiotic use in Europe, based on cooperation between regulatory authorities, scientific societies, health insurers and professional organizations. These data provide a tool for assessing public health strategies aiming to optimize antibiotic prescribing.**

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

Introduction

The European Surveillance of Antimicrobial Consumption (ESAC) project, granted by DG SANCO of the European Commission, is an international network of surveillance systems, aiming to collect comparable and reliable data on antibiotic use in Europe. Monitoring of antimicrobial consumption was pursued by the 'Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine', in order to accompany analogous surveillance programmes on resistance.[1]

The first phase of the ESAC project focussed on a retrospective data collection for the period 1997–2002. The first results and the methodology used have been published previously.[2,3]

This paper presents an update of the ESAC data and introduces complementary brief reports focussing on penicillin, cephalosporin, macrolide/lincosamide/streptogramin and quinolone use, respectively.[4–7] Trends of use (1997–2003), seasonal variation and special features related to each particular antibiotic class will be discussed in addition to detailed description of outpatient use patterns in 2003 in each of the articles, supplemented by

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Table 1. Availability of data on the volume of outpatient antibiotic use in Europe within the ESAC project

Country	1997	1998	1999	2000	2001	2002	2003
European Union countries							
Austria		O	O	O	O	O	O
Belgium	●	●	●	●	●	●	●
Cyprus			participant not yet able to provide data				
Czech Republic	·	●	●	●	●	●	●
Denmark	●	●	●	●	●	●	●
Estonia	·	·	·	·	·	●	●
Finland	●	●	●	●	●	●	●
France	●	●	●	●	●	●	●
Germany	●	●	●	●	●	●	●
Greece	O	O	O	O	O	O	O
Hungary	·	●	●	●	●	●	·
Ireland	●	●	●	●	●	●	●
Italy	·	·	●	●	●	●	●
Latvia	·	·	·	·	○	○	·
Lithuania	·	·	·	○	○	·	·
Luxembourg	●	●	●	●	●	●	●
Malta	·	·	·	·	·	·	·
Netherlands	●	●	●	●	●	●	●
Poland	O	O	O	O	O	O	·
Portugal	●	●	●	●	●	●	●
Slovakia	·	·	●	●	●	●	●
Slovenia	●	●	●	●	●	●	●
Spain	O	O	O	O	O	O	O
Sweden	●	●	●	●	●	●	●
UK	●	●	●	●	●	●	●
Applicant countries							
Bulgaria		·	·	·	TC only	TC only	TC only
Croatia		·	·	●	●	●	●
Romania			participant not yet able to provide data				
Turkey	○	○	○	○	○	○	·
Other European countries							
Iceland	TC only	TC only	TC only	TC only	TC only	TC only	TC only
Israel	·	·	·	·	·	O	O
Norway	·	O	·	·	O	●	●
Russia			participant not yet able to provide data				
Switzerland			participant not yet able to provide data				

TC = total care data, including hospital use.
· = no data provided.
○ = data with major bias, invalidating exposure estimation.
O = data available in DDD, but with minor bias, not invalidating exposure estimation.
● = valid data available in DDD.

additional data published on the ESAC website (www.ua.ac.be/ESAC).

Methods

In 2005, 34 countries participated in the ESAC project, including all 25 EU countries, 4 applicant countries (Bulgaria, Croatia, Romania and Turkey), 3 of the 4 members of the European Free Trade Association (Iceland, Norway and Switzerland, not Liechtenstein), Israel and Russia. Use data of systemic antibiotics for ambulatory care for the period 1997–2003 aggregated at the level of the active substance were collected, in accordance with the Anatomic Therapeutic Chemical (ATC) classification and Defined Daily Dose (DDD) measurement unit (WHO, version 2004).[8] Adherence to the ATC/DDD 2004 version was mandatory because of continuous updates, i.e. introduction of new ATC codes and modification of DDD values reflecting real dosage of certain antibiotics in medical practice.

Within the ATC J01 class (i.e. antibacterials for systemic use, excluding antifungals, antibacterials for tuberculosis and topical antibiotics) 209 unique ATC-5 codes were listed for antibiotics or their combinations, aggregated into 32 ATC-4 classes and subsequently into 10 ATC-3 groups, which were applied in this paper.

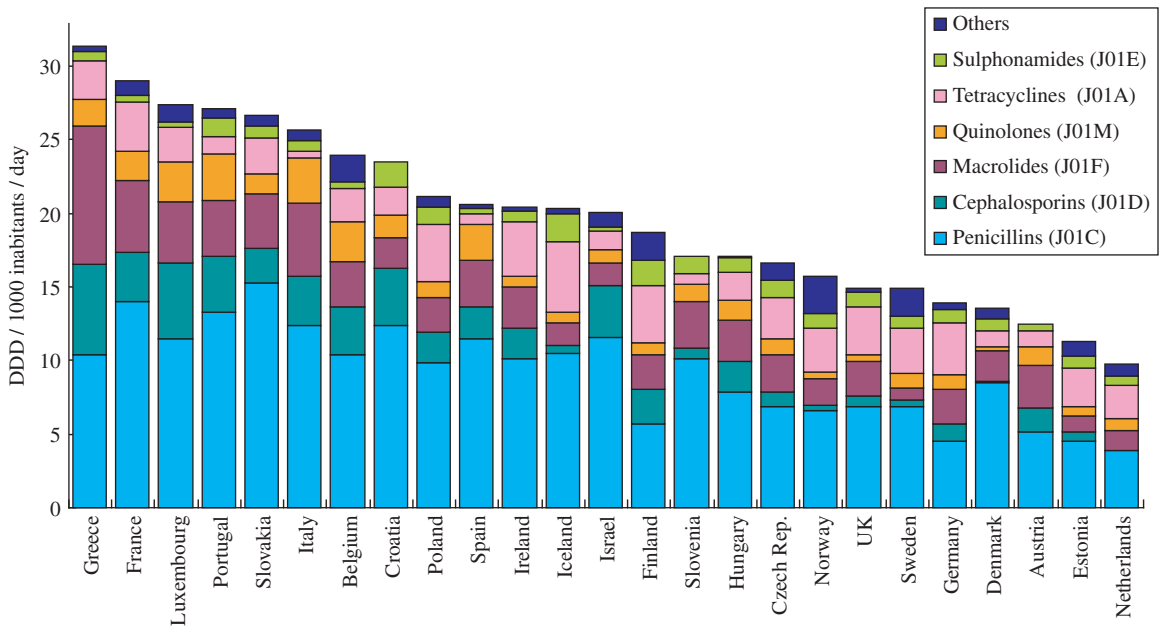

Figure 1. Total outpatient antibiotic use in 25 European countries in 2003. Cephalosporins includes monobactams and carbapenems; macrolides includes lincosamides and streptogramins; sulphonamides includes trimethoprim; and others includes J01B, J01G, J01R and J01X. For Iceland total data are used; for Poland 2002 data are used.

Use data were expressed in DDD per 1000 inhabitants per day (DID). The number of inhabitants in the European countries was based on the midyear population of the country.[9]

Ambulatory care data were collected from 24 countries, whereas Iceland was only able to provide aggregated total use data (data were however also included because ambulatory care use data represented 90–94% of the total use data for the countries providing separate data). Data on antibiotic use in 2003 for Poland have not been delivered and therefore were substituted by 2002 data in Figure 1. For the UK, only data from England were used, which covers 83.6% of the UK population. Of the 34 participating countries, outpatient antibiotic use data from 25 were suitable for further analysis.

Antibiotic use data were reimbursement data in 12 countries and distribution or sales data in 13 countries. Reimbursement data were collected by the third-party payer on the basis of financial claims from legitimate beneficiaries, from prescribers or from dispensing pharmacies. Distribution or sales data was based on reports from the pharmaceutical companies, wholesalers, pharmacies or marketing research companies. In 23 countries, census data were provided (covering at least 90% of the population); in 2 countries, sample data were collected and extrapolated to 100%: Poland (60% coverage of data) and the Netherlands (83% coverage of data). Fourteen countries were able to deliver valid data for all 7 years (1997–2003), of which 11 were on a quarterly basis.

Information was collected from the ESAC national representatives on the characteristics of the data sources and data providers. Validity of the data collection process was evaluated by means of a checklist assessing (i) coverage bias in census data, (ii) sampling bias in sample data, (iii) bias by unaccounted over-the-counter sales in reimbursement data, (iv) parallel trade or inadequate registration of non-reimbursed antibiotics and (v) bias by shifts in the mix of antibiotic use between ambulatory and hospital care. Prior to their interpretation, available datasets were scored into three categories: valid data; data considered valid but with minor biases not invalidating the estimate of exposure; and invalid data with major biases invalidating the estimate of exposure (Table 1).

A complete description of the data providers, details of the methodology used and the associated problems, and in-depth discussions of the validity of the collected data were published previously.[3]

Results

Figure 1 shows total outpatient antibiotic use in 25 European countries for 2003 expressed in DID. Consumption is broken down into seven major antibiotic groups according to the ATC classification: penicillins (J01C), cephalosporins (J01D), macrolides (J01F), quinolones (J01M), tetracyclines (J01A), sulphonamides (J01E) and other antibiotics [concatenation of amphenicols (J01B), aminoglycosides (J01G), combinations of antibacterials (J01R) and other antibacterials (J01X)].[8] Outpatient antibiotic use varied by a factor of 3 between the country with the highest (31.4 DID in Greece) and the country with the lowest (9.8 DID in the Netherlands) use. The median use was 20.1 DID and interquartile range 14.9–25.4 DID. Penicillins represented the most frequently prescribed antibiotics in all countries, ranging from 31% (Finland) to 63% (Denmark) of the total outpatient antibiotic use. For cephalosporins, the proportional use ranged from 0.2% (Denmark) to 20% (Greece), for macrolides from 6% (Sweden) to 30% (Greece) and for quinolones from 2% (Denmark) to 12% (Spain, Portugal and Italy) of the total outpatient antibiotic use.

Table 2 provides the trends of outpatient antibiotic use in 25 countries from 1997 to 2003. Several temporal patterns were observed: continuous increase in Greece, Croatia, Ireland,

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

	1997	1998	1999	2000	2001	2002	2003
Austria	NA	12.51	13.19	12.34	11.86	11.75	12.49
Belgium	25.44	26.36	26.21	25.26	23.73	23.82	24.22
Croatia	NA	NA	NA	18.42	17.65	21.61	23.50
Czech Republic	NA	18.27	18.62	18.56	18.49	17.09	16.65
Denmark	12.22	12.74	12.13	12.19	12.82	13.32	13.58
Estonia	NA	NA	NA	NA	NA	11.67	11.34
Finland	19.38	18.44	18.41	18.97	19.70	17.83	18.73
France	33.02	33.56	34.33	33.24	32.71	32.05	28.97
Germany	14.57	14.63	14.94	14.89	13.82	13.76	13.90
Greece	25.06	24.86	28.50	29.13	29.43	30.53	31.40
Hungary	NA	18.62	23.92	18.91	19.11	17.05	19.63
Iceland	22.12	22.98	21.58	20.47	20.28	20.98	20.36
Ireland	17.34	17.21	19.03	18.52	19.87	19.82	20.48
Israel	NA	NA	NA	NA	NA	19.55	20.06
Italy	NA	NA	24.50	24.03	25.16	24.38	25.63
Luxembourg	25.78	25.48	26.72	25.68	26.08	26.42	27.34
Netherlands	10.21	10.07	10.09	9.86	9.93	9.83	9.78
Norway	NA	15.45	NA	NA	15.67	14.78	15.72
Poland	16.56	20.70	22.18	22.64	24.77	21.14	NA
Portugal	23.22	23.20	24.98	24.93	24.25	26.14	27.10
Slovakia	NA	NA	NA	25.59	27.99	25.56	26.63
Slovenia	17.51	19.30	19.76	18.01	17.36	16.40	17.10
Spain	21.39	20.90	20.45	19.43	18.70	19.35	20.58
Sweden	14.64	15.53	15.82	15.50	15.81	15.42	14.88
UK	16.87	15.76	14.46	13.98	14.48	14.49	14.90

NA, not available.

Portugal, Luxembourg and Denmark; an initial increase followed by a decrease in Belgium, France, Czech Republic, Hungary, Poland, Slovenia and Sweden; and an initial decrease followed by an increase in the UK and Spain. Sudden changes could be observed in Germany (drop in 2001), Poland (drop in 2002) and Greece (rise in 1999). Once-off increase was recorded in Hungary in 1999 and in Finland and Slovakia in 2001.

Trends of relative proportions of antibiotic classes according to the ATC/DDD classification are shown in Figure S1 (Online Supplementary data). In many countries the proportion of penicillins and quinolones increased over time, while the proportion of tetracyclines and sulphonamides was steadily decreasing. Some countries maintained a stable pattern of antibiotic use over the period of observation (the Netherlands, the UK), while others showed significant modifications between 1997 and 2003 (Poland, Greece).

Figure 2 shows seasonal data of antibiotic use for 11 countries able to deliver quarterly data for the whole period of observation. Data for another 10 countries able to deliver seasonal data for at least 1 year of data collection are available as Online Supplementary data (Figure S2). The median increase of total outpatient antibiotic use in winter quarters (the first and fourth) compared with summer quarters (the second and third) was 33% for 21 countries able to deliver quarterly data at least for 1 year and ranged from 17% in Sweden to more than 50% in two countries (Hungary and Slovakia). While in 7 Northern European countries the seasonal fluctuation was limited to <23%, in all remaining 14 countries it exceeded 30%.

Discussion

The volume of outpatient antibiotic use expressed in DID was increasing in most European countries between 1997 and 2003. In particular France was replaced by Greece as the highest community antibiotic user in Europe in 2003, although the continuous boost of antibiotic sales in Greece could be partially explained by the emergence of parallel exports to EU countries with higher medicine prices. On the other hand, the increasing trend was reversed in some countries. In Belgium, which dropped from the second to the seventh position in 2003, a sustainable annual reduction of outpatient antibiotic use was recorded after 2001, whereas in France a drop of antibiotic use by 9.6% was observed in 2003.[10] These changes are probably due to the nationwide campaigns to improve antibiotic use in Belgium (started in 2000) and France (started in 2002), which are the only countries in Europe that have undertaken such national campaigns.[11,12] Somewhat opposite to the rest of Europe, in the UK (only data for England presented) and Spain a period of continual decline was reversed to a steady increase since 2001 and 2002, respectively.

Many reasons have been proposed to explain these large differences in consumption of antibacterial agents among European countries including the incidence of community-acquired infections and factors which could result in differences in this incidence, culture determinants, social determinants, health care structures, resources and utilization, knowledge about antibiotics, pharmaceutical market and regulatory practices. For

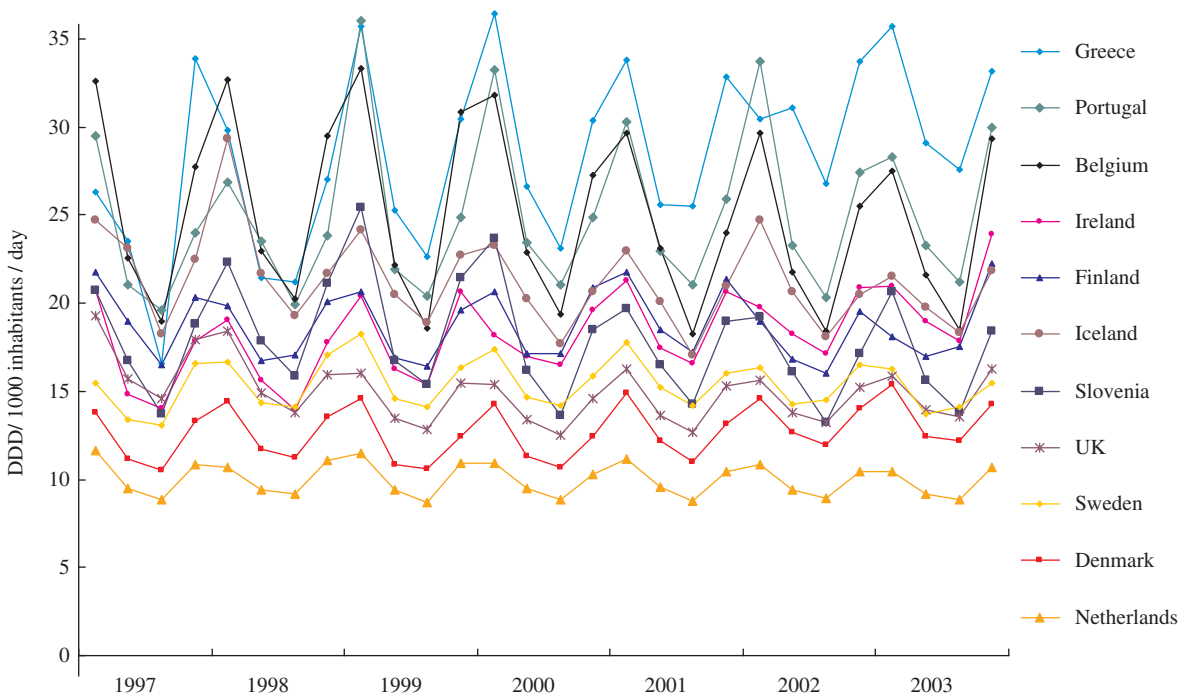

Figure 2. Seasonal variation of outpatient antibiotic use in 11 European countries with quarterly data for 1997–2003.

instance, Monnet *et al.*[13] observed a relationship between the number of trade names of oral antibacterial agents registered in the country and consumption of these agents in the outpatient setting. This relationship was observed in both high- and low-consuming countries and independently of market accessibility for copies of original agents. More studies on the determinants of antibiotic use are crucially needed to better understand the differences observed in Europe. Many of these factors are modifiable by educational activities or regulatory measures, and understanding these differences may help to design policies to reduce antibiotic use.

In all 25 European countries penicillins were the most prescribed outpatient antibiotics and further enlarged their leading position between 1997 and 2003. Likewise, use of quinolones surged, while use of another two major classes of antibiotics, tetracyclines and sulphonamides, stagnated or decreased in most European countries as newer antibiotics superseded them. Striking geographical variations were observed in the use of various antibiotic classes. For instance, the narrow-spectrum penicillins and the first-generation cephalosporins were widely prescribed for the treatment of community-acquired infections in many Nordic countries, while they almost disappeared in most Southern European countries. In the latter, we observed an increased use over time of the newer (i.e. broad-spectrum) antibiotics, such as amoxicillin/clavulanic acid, macrolides and quinolones, which will be described in detail in separate papers.[4–7]

Seasonality of outpatient antibiotic use was observed in all countries and seems to be a general phenomenon related to an increased incidence of respiratory tract infections during winter months, resulting in higher prescriptions rates for antibiotics during this period. Nevertheless, as the vast majority of respiratory tract infections are of viral origin and self-limiting, the increase of antibiotic consumption in winter months should be finite. Excessive winter consumption of antibiotics suggests their inappropriate prescribing for respiratory tract infections, such as the common cold, flu and bronchitis. High seasonal fluctuations (mean increase >30% in the first and fourth quarter compared with the second and third quarter) in high-consuming Southern and Eastern European countries, suggesting unnecessary usage for viral infections, may largely account for the differences in absolute levels of antibiotic use in Europe.

The inappropriate use of antibacterial agents may inevitably lead to emergence of antimicrobial resistance. Geographic differences in the outpatient antibiotic use correlate at ecological level with geographic variation of resistance in Europe,[2] suggesting that variation of resistance in Europe can be explained by differential selection pressure. Although the ecological relationship between resistance and the use of antimicrobials clearly exists, these correlations do not necessarily imply causality. Moreover, it is multifactorial and often confounded by a number of variables (e.g. patient compliance, time lag between use and resistance, outcome measures). However, a wealth of *in vitro* and *in vivo* studies has shown that resistance is a natural biological outcome of antibiotic use. Nevertheless, future studies should link individual patient data with group level data.

Until recently, information on outpatient antibiotic consumption was limited. In 2001, Cars *et al.*[14] published for the first time comparable outpatient antibiotic use data for 15 European countries. Their results were based on IMS data, which do not allow the classification of combinations (in particular penicillins with β-lactamase inhibitors). Also, the methods of data collection and validation presumably differed between countries but these are not described in this paper.

The European Drug Utilisation Research Group (EuroDURG) in collaboration with the WHO collaborative centre for Drug Statistics Methodology (Oslo, Norway) also aimed to collect

comparable data on antibiotic use from a sample of European countries.[15] Here the data were collected at the ATC fourth level (i.e. not at the chemical substance ATC fifth level), hindering the data management, and ATC/DDD versions varied between the countries providing data for this survey. This study emphasized the need for using a common methodological approach in order to collect comparable data and underlined the importance of collecting data at the medicinal product package level, to be able to check whether the ATC/DDD methodology is applied similarly and correctly in all countries.

The ESAC project establishes for the first time a comprehensive database of internationally comparable data on antibiotic consumption in Europe, based on cooperation between regulatory authorities, scientific societies, health insurers and professional organizations. In addition the ESAC data for the first time allow the observation of temporal trends of antibiotic use and appropriately implementing ATC/DDD methodology.[3]

Nevertheless, the distribution or reimbursement data collected within the ESAC project must be interpreted with caution and cannot be used synonymously with antibiotic exposure as their data sources vary between countries. In particular, Greek sales data may well be overestimated as the volume of parallel export could not be identified from the sales data provided by the Greek Medicine Agency. On the contrary, the ESAC antibiotic use data for Spain cover solely reimbursement data, thereby excluding drugs that were sold over-the-counter, which reportedly comprise up to 30% of Spanish antibiotic use.[16]

ESAC opted for the DDD measurement unit, defined as the assumed average maintenance dose per day for its main indication in adults. Because the DDD is a technical unit, albeit based on the use in infections of moderate severity, expressing antibiotic use data in DDDs may not adequately address differences of dosage and length of treatment for certain classes of antibiotics between countries and does not take into account children (the population of children aged 0–14 years in the ESAC participating countries ranged between 15 and 25% in 2002), in whom a significant amount of antibiotics are used.

Reporting antibiotic use data on a yearly basis could be biased by winter peaks coinciding within the same year. Indeed, there could be two epidemics of respiratory tract infections cumulated in one year, while none in the next one. This was the case in the winter of 2001–2002, when the winter peak of the first quarter of 2002 shifted to the fourth quarter of 2001 in a few countries, and thus causing a trend distortion. Therefore data related to the July–June period could provide a more accurate trend estimate than annual data.

In conclusion, further consolidation and quality enhancement of the surveillance of antibiotic consumption is crucial for better understanding of the development of antimicrobial resistance and fostering appropriate prescribing. More detailed data on antibiotic use linked to patient's age and gender, the indication and the prescriber can substantially broaden our interpretation of striking variations between European countries.[17,18] An enhanced data collection protocol to collect this kind of data will be applied in the ESAC project. In addition, information on the regimen (dosage and length of treatment) will be analysed to perform sensitivity analysis of our data collection methodology performance considering various units of measurement.

Meanwhile, the ESAC data on outpatient antibiotic use in Europe will allow countries to audit their patterns of antibiotic prescribing and position both total level of use and the share of major subclasses within the European range. Because for individual countries the demographical and epidemiological characteristics differ, one benchmark value of optimal antibiotic use cannot be given. If a range of acceptable use supported by evidence-based guidelines could be defined, countries may set their own targets and identify required interventions. Moreover ESAC could provide a valuable data source for ecological studies on the relationship between antibiotic use and resistance, for the evaluation of adherence to guidelines and policies, and for the assessment of the outcomes of national interventions.

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Transparency declarations

The authors have no interests to declare.

Supplementary data

Figures S1 and S2 are available as Online Supplementary data at http://jac.oxfordjournals.org.

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