Comparison of Outpatient Systemic Antibacterial Use in 2004 in the United States and 27 European Countries

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The European Surveillance of Antimicrobial Consumption (ESAC) project collects data on antibacterial use in Europe, applying the Anatomic Therapeutic Chemical classification system and defined daily dose methodology, as recommended by the World Health Organization. Comparable data for the United States have been collected from IMS Health. The IMS Health sales data, processed according to ESAC methodology, suggest that outpatient antibacterial use in the United States is high (only 3 of 27 European countries used more) and is mainly characterized by a shift towards newer antibiotics.

Antimicrobial resistance is a major global public health problem, and antibiotic consumption is increasingly recognized as the main reason for resistance [1]. The largest volumes of antibacterial agents are prescribed in primary care, and respiratory tract infections are the most common indication [1, 2]. Monitoring of antibacterial use should accompany surveillance programs on antibacterial resistance. Available data on antibacterial use will enable us to unravel the complex relationship between consumption and resistance.

Until recently, information on antibacterial consumption was limited, and the available databases use different methods for drug classification and for measuring antibacterial use. The European Surveillance of Antimicrobial Consumption (ESAC) project (granted by the European Commission) established, for the first time, a comprehensive database of internationally comparable data on antibacterial consumption in Europe by outpatients and inpatients [1, 3–10].

Data on outpatient antibacterial use, analyzed according to the ESAC methodology, have not been readily available for the United States, which hampered comparison with consumption in Europe [11–16]. In this article, we analyze outpatient antibacterial use in the United States in 2004 and compare it with ESAC data for 27 European countries.

Methods. The ESAC project collected standardized data on outpatient use of antibacterial agents for systemic use (Anatomic Therapeutic Chemical [ATC] code J01) in 2004 from 27 European countries, including 23 of the 27 European Union member states; 1 applicant country (Croatia); and Iceland, Israel, and Norway. Data on antibacterial use were reimbursement data in 9 countries and distribution or sales data in 18 countries. Available data were scored into 3 categories; only valid data and data considered valid, but with minor biases not invalidating the estimate of exposure, are included in this study. 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, 5].

Data on outpatient antibacterial use in 2004 in the United States are derived from IMS Health databases that were created using data on sales to retail outlets and to Federal Government and nongovernmental mail service pharmacies made by drug wholesalers and chain warehouses. Coverage is now 98% of their total dollar shipments. This information is projected to a national figure on a regional basis. Information is also received from ~100 manufacturers who provide direct sales to pharmacies. Nonreporting manufacturer direct sales are not estimated. Previous work indicates that this omission accounts for 0.5% of total sales. It is estimated that this audit covers 90% of the mail service market.

To compare drug use data from different regions, ESAC opted for the ATC classification system and the defined daily dose (DDD) measurement unit (developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology [3, 17]), aggregating data on drug use at the fifth level of the ATC classification. IMS Health data were delivered for the active substances in kg or IU, identified the route of administration, and allowed assignment of the ATC codes and conversion into DDD.

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To control for the size of the population, we expressed antibacterial use in number of DDDs per 1000 inhabitants per day (DID). The number of inhabitants for the European countries [18] and the United States [19] was based on the midyear population of the country.

Results. In 2004, use of 81 different antibacterial substances was recorded in the United States, compared with 153 in 27 countries in Europe. Cefdinir, cefditoren, and gemifloxacin were used substantially in the United States but not in Europe in 2004, and bacampicillin, cefixime, flucloxacillin, fosfomycin, lymecycline, pristinamycin, roxithromycin, and spiramycin were used substantially in Europe but not in the United States.

Figure 1 shows total outpatient antibacterial use in the United States, Europe, and 27 countries in Europe in 2004, expressed in DIDs. Consumption is separated in 7 major groups on the basis of the ATC classification [17]. The United States ranked fourth, compared with the European countries; consumption was only higher in Greece (33.38 DIDs), France (27.09 DIDs), and Italy (25.69 DIDs).

Table 1 depicts outpatient antibacterial use in the United States and Europe in 2004, according to ATC codes and levels, as well as our recently published classification of macrolides [8] and quinolones [9]. Table 2 compares outpatient antibacterial use (in DIDs) in 2004 at the level of the active substance (i.e., ATC-5) for substances representing ⩾1.0% of total use (i.e., 0.25 DIDs) in the United States, compared with Europe. Striking differences for other antibacterial agents, representing <1.0% of total use in the United States, were noted for quinolones (norfloxacin, 0.01 DIDs in the United States vs. 0.33 DIDs in Europe; ofloxacin, 0.04 DIDs vs. 0.14 DIDs; and gatifloxacin, 0.14 DIDs vs. no use), oral cephalosporins (cefaclor, 0.11 DIDs vs. 0.32 DIDs; cefpodoxime, 0.02 DIDs vs. 0.18 DIDs; ceftibuten, 0.01 DIDs vs. 0.09 DIDs; cefixime, no use vs. 0.25 DIDs), trimethoprim (0.03 DIDs vs. 0.18 DIDs), and fosfomycin (no use vs. 0.07 DIDs).

Discussion. Outpatient systemic antibacterial use in the United States is high, compared with Europe (only 3 of 27 European countries used more in 2004). However, the ESAC data for Spain are underestimated, because these are reimbursement data, thereby excluding over-the-counter drugs [1]. On the other hand, the data on antibacterial use for Greece are probably overestimated, because these are sales data, thereby including parallel export and hospital use [1]. Data for the United States, which are provided by IMS Health, are sales data. Because the cost of drugs is high in the United States, we do not expect an overestimation associated with parallel export to neighboring countries. In fact, increasing numbers of US citizens are buying their prescription drugs in Canada, even if it violates US law (parallel import). However, the value of these drugs was estimated to be CDN$ 507 million during the 12 months ending in June 2005, which represented <1% of the total US market, and they are mostly drugs to treat or prevent chronic illnesses, not episodic illnesses (e.g., infectious diseases) [20]. IMS Health data may also underestimate antibacterial use in the United States. Dispensing from integrated health care system pharmacies and governmental pharmacies is not included in a retail panel. According to a parallel panel, deliveries to these pharmacies are insignificant and would not influence our observations. In addition, it was suggested that a considerable number of Latinos self-medicate with antimicrobial agents obtained without a prescription from outside the United States [21]. More studies are needed to assess the magnitude

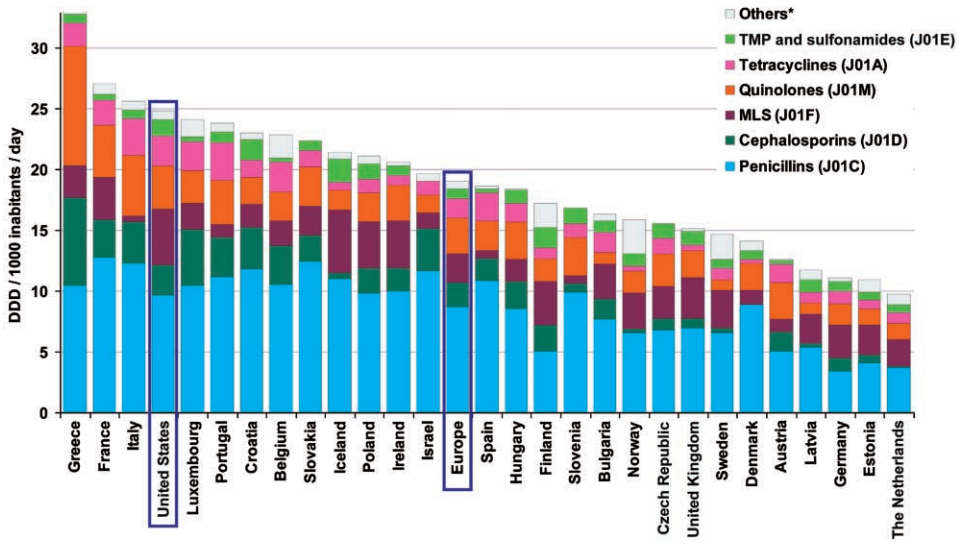

Figure 1. Total outpatient antibacterial use in the United States and 27 European countries in 2004 (total use for Greece, Iceland, and Bulgaria, 2002 data for Poland, and 2003 data for Italy). DDD, defined daily dose; MLS, macrolides, lincosamides, and streptogramins; TMP, trimethoprim. *Includes amphenicols (J01B), aminoglycosides (J01G), combinations of antibacterial agents (J01R), and other antibacterial agents (J01X).

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Table 1. Outpatient systemic use of major antibacterial classes in the United States and Europe in 2004.

ATC code	Corresponding antibacterial (sub)class	DID (%)	
		United States	Europe
J01A	Tetracyclines	4.63 (18.60)	2.37 (12.42)
J01C	Penicillins [9]	9.70 (38.93)	8.71 (45.73)
J01CE	Narrow-spectrum penicillins	0.68 (2.71)	0.75 (3.92)
J01CA	Broad-spectrum penicillins	5.68 (22.81)	4.49 (23.58)
J01CR	Combination of penicillins	3.29 (13.22)	3.20 (16.82)
J01CF	Penicillinase-resistant penicillins	0.05 (0.19)	0.27 (1.40)
J01D	Cephalosporins, monobactams, and carbapenems [10]	2.48 (9.94)	2.03 (10.65)
J01DB	First-generation cephalosporins	1.47 (5.90)	0.31 (1.62)
J01DC	Second-generation cephalosporins	0.61 (2.46)	1.12 (5.89)
J01DD	Third-generation cephalosporins	0.39 (1.57)	0.59 (3.11)
J01E	Sulfonamides and trimethoprim	1.34 (5.37)	0.77 (4.04)
J01F	Macrolides, lincosamides, and streptogramins [11]	3.52 (14.14)	2.98 (15.66)
	Short-acting macrolides	0.43 (1.73)	0.48 (2.54)
	Intermediate-acting macrolides	1.16 (4.66)	1.71 (8.96)
	Long-acting macrolides	1.68 (6.74)	0.53 (2.77)
J01FF	Lincosamides	0.25 (1.02)	0.16 (0.85)
J01FG	Streptogramins	<0.01 (0.00)	0.10 (0.55)
J01M	Quinolones [12]	2.47 (9.91)	1.58 (8.32)
	First-generation quinolones	0.01 (0.03)	0.41 (2.15)
	Second-generation quinolones	2.07 (8.30)	1.01 (5.31)
	Third-generation quinolones	0.39 (1.58)	0.16 (0.86)
J01B+G+R+X	Others	0.78 (3.11)	0.61 (3.18)
Total	…	24.92 (100.00)	19.04 (100.00)

NOTE. ATC, Anatomical Therapeutic Chemical; DID, defined daily doses per 1000 inhabitants per day.

of parallel import and over-the-counter drug use in the United States [22].

To compare data on drug use from different regions or countries, the data need to be collected and aggregated in a standardized, uniform way. ESAC opted for the ATC classification system and the DDD measurement unit [17]. Most studies on outpatient antibacterial use in the United States are based on data from the National Ambulatory Medical Care Survey, and the data are expressed in number of prescriptions per 1000 inhabitants per year [2, 12–16]. The National Ambulatory Medical Care Survey extrapolates estimates to the entire US population on the basis of 1-week period surveys of specified medical practices that are selected to be representative of medical care in the United States. Other reports are also based on sample data collected from managed care plans, expressing data in dispensings per person-year [15] or proportion of prescriptions linked to International Classification of Diseases Ninth Revision codes [23]. Only Polk et al. [11] expressed community fluoroquinolone use in DID in a 16 km (10-mile) radius surrounding 35 hospitals in the United States. Because the DDD is a technical unit, not necessarily reflecting the prescribed daily dose, other units of measurement should also be used to fully assess prescribing patterns.

The pattern of outpatient antibacterial use in the United States is characterized by a very high use of tetracyclines, macrolides, and fluoroquinolones (azithromycin and levofloxacin showed a higher use in the United States than in any country in Europe). These differences may relate to differences of treatment guidelines and marketing. In the United States, doxycycline, macrolides, and fluoroquinolones have a prominent position as first-line agents for outpatient treatment of respiratory tract infection [24]. In Europe, however, atypical infections (e.g., mycoplasma and chlamydia) are considered less clinically relevant, macrolide resistance is considered a significant clinical threat, and patients would therefore likely receive a β-lactam agent [25]. Azithromycin has been extensively marketed in the United States through direct-to-consumer advertising [26]. In Europe, however, European Union member states are still required to prohibit the advertising to the general public of medicinal products that are available by prescription only.

However, differences of use of antibacterial substances between the United States and Europe are also a result of differ-

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Table 2. Outpatient systemic use of antibacterial substances in the United States and Europe in 2004.

	DID (%)		Range of use in Europe	
Antibacterial	United States	Europe	Highest DID (country)	Lowest DID (country)
Amoxicillin	5.59 (22.4)	4.26 (22.3)	12.83 (France)	3.76 (The Netherlands)
Co-amoxiclav	3.29 (13.2)	3.16 (16.6)	7.32 (Portugal)	<0.01 (Norway)
Doxycycline	2.98 (12)	1.73 (9.1)	5.17 (Iceland)	0.31 (Italy)
Azithromycin	1.68 (6.7)	0.52 (2.7)	1.34 (Croatia)	0.04 (Sweden)
Cephalexin	1.39 (5.6)	0.17 (0.9)	1.89 (Finland)	No use (Greece)
TMP-SMX	1.31 (5.2)	0.56 (2.9)	1.62 (Croatia)	<0.01 (Denmark)
Clarithromycin	1.10 (4.4)	1.23 (6.5)	7.16 (Greece)	0.06 (Sweden)
Minocycline	1.07 (4.3)	0.24 (1.3)	1.36 (Ireland)	No use (>1 country)
Levofloxacin	1.06 (4.3)	0.24 (1.3)	1.05 (Italy)	No use (>1 country)
Ciprofloxacin	0.97 (3.9)	0.59 (3.1)	1.81 (Portugal)	0.17 (Croatia)
Phenoxymethylpenicillin	0.68 (2.7)	0.64 (3.4)	5.23 (Denmark)	No use (>1 country)
Nitrofurantoin	0.63 (2.5)	0.27 (1.4)	0.8 (The Netherlands)	No use (>1 country)
Tetracycline	0.57 (2.3)	0.08 (0.4)	1.02 (Finland)	No use (>1 country)
Erythromycin	0.43 (1.7)	0.34 (1.8)	1.72 (United Kingdom)	0.01 (Bulgaria)
Cefuroxime	0.35 (1.4)	0.70 (3.7)	3.40 (Luxembourg)	No use (Norway)
Cefdinir	0.34 (1.4)	No use	No use	No use (>1 country)
Clindamycin	0.25 (1.0)	0.14 (0.8)	0.70 (Hungary)	<0.01 (Italy)
Moxifloxacin	0.25 (1.0)	0.16 (0.9)	0.56 (Belgium)	No use (>1 country)
Total	24.91 (100)	19.04 (100)	33.37 (Greece)	9.75 (The Netherlands)

NOTE. Data are for antibacterials with ⩾1.0% of total use in the United States. DID, defined daily doses per 1000 inhabitants per day; TMP-SMX, trimethoprim-sulfamethoxazole.

ences of regulation and marketing strategies between the 2 continents. For instance, cefdinir is not marketed in Europe; also, cefixime was not available in the United States in 2004 [27], whereas flucloxacillin, fosfomycin, lymecycline, pristinamycin, roxithromycin, and spiramycin have never been approved for use in the United States [28]. Finally, differences between the United States and European countries could also be a result of differences of the health systems. For instance, the United States has no comprehensive national health plan, and there are essentially no disincentives to prescribing any given outpatient antibiotic, other than the patient's ability to pay. On the contrary, many European Union countries impose policy restrictions that prevent antibiotic prescribing in primary care, and national awareness campaigns have been organized in Belgium, France, and Spain [29].

In conclusion, this is, to our knowledge, the first study comparing outpatient antibiotic use in Europe and the United States, applying the same methodology. Our study demonstrates that in the United States, antibiotic use is higher than in most European countries, with a tendency to use new antibiotics in the United States. Benchmarking of antibacterial use by comparisons between countries is an important trigger for investigation and will inform local or national prescribing policies. Although the health care structure is more homogeneous in the United States than in Europe, important regional differences of outpatient antibiotic use in the United States can be expected. Additional studies are needed to explore the drivers of these regional differences in antibiotic prescribing and to link this variation in selection pressure with variation of resistance.

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Potential conflicts of interest. All authors: no conflicts.

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