

Outpatient antibiotic use in Europe and association with resistance: a cross-national database study

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Summary

Background Resistance to antibiotics is a major public-health problem and antibiotic use is being increasingly recognised as the main selective pressure driving this resistance. Our aim was to assess outpatient use of antibiotics and the association with resistance.

Methods We investigated outpatient antibiotic use in 26 countries in Europe that provided internationally comparable distribution or reimbursement data, between Jan 1, 1997, and Dec 31, 2002, by calculating the number of defined daily doses (DDD) per 1000 inhabitants per day, according to WHO anatomic therapeutic chemical classification and DDD measurement methodology. We assessed the ecological association between antibiotic use and antibiotic resistance rates using Spearman's correlation coefficients.

Findings Prescription of antibiotics in primary care in Europe varied greatly; the highest rate was in France (32·2 DDD per 1000 inhabitants daily) and the lowest was in the Netherlands (10·0 DDD per 1000 inhabitants daily). We noted a shift from the old narrow-spectrum antibiotics to the new broad-spectrum antibiotics. We also recorded striking seasonal fluctuations with heightened winter peaks in countries with high yearly use of antibiotics. We showed higher rates of antibiotic resistance in high consuming countries, probably related to the higher consumption in southern and eastern Europe than in northern Europe.

Interpretation These data might provide a useful method for assessing public-health strategies that aim to reduce antibiotic use and resistance levels.

Introduction

Antibiotic resistance is a major public-health problem worldwide, and international efforts are needed to counteract its emergence. There is much information on the prevalence of resistance in human pathogens, and these data show that there are substantial geographic differences in the proportion of resistance to various classes of antibiotics in Europe.¹ Although rates of antibiotic resistance remain low in northern European countries, these rates are reaching alarming levels in southern and central Europe. Antibiotic consumption is increasingly being recognised as the main cause of this emerging resistance, and differential selection pressure of antibiotics could be responsible for some of these differences.²

The highest rates of antibiotic prescriptions for systemic use are in primary care, and respiratory tract infection is the most common indication. Monitoring antibiotic use should accompany surveillance programmes on antibiotic resistance. However, data for their use are scarce and not freely available, and the factors that determine differences in use are not fully understood. Moreover, national databases use different methods for drug classification and for measuring antibiotic use. However, temporal trends and regional differences are important triggers for action and investigation, and benchmarking by comparisons between countries should be an important stimulus to quality improvement. Additionally, development, implementation, and assessment of guidelines need

information about practice of antibiotic prescribing, which will inform local or national prescribing policies.

On Nov 15, 2001, a European Union (EU) Council recommendation³ stated that specific strategies should continue to gather data for antibiotic use. The European Surveillance of Antimicrobial Consumption (ESAC) project, granted by the European Commission, is an international network of surveillance systems aiming to obtain comparable and reliable data about antibiotic use in Europe. Here, we present the first results of the ESAC project for outpatient antibiotic use and we relate these consumption data to existing resistance data.

Methods

Data collection

32 countries joined the ESAC project, including all 15 original EU countries, nine of the ten most recent member states (but not Cyprus), four applicant countries (Bulgaria, Croatia, Romania, and Turkey), two of the three European free trade association/European economic area countries (Iceland and Norway, but not Liechtenstein), Russia, and Switzerland. We obtained data for use of systemic antibiotics in ambulatory care grouped according to active substance in the drug, for 1997–2002, in accordance with the anatomic therapeutic chemical (ATC) classification and defined daily dose (DDD) measurement unit (WHO, version 2003).⁴ Antibiotic use for ATC class J01 (ie, antibacterials for systemic use, excluding antifungals; antibacterials for

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tuberculosis; and topical antibiotics) is based on either distribution or reimbursement data. We obtained information from the ESAC national representatives about the characteristics of the data sources and data providers. Validity of the data collection process was assessed with a checklist consisting of: coverage bias in census data, sampling bias in sample data, bias by unaccounted over-the-counter sales in reimbursement data, parallel trade or inadequate registration of non-reimbursed antibiotics, and bias by shifts in the mix of antibiotic use between ambulatory and hospital care. The number of inhabitants in the European countries was based on the mid-year population of the country, which was obtained from the WHO European health for all database,⁵ enabling us to control for the size of the population by expressing data in DDD per 1000 inhabitants daily (DID).

Data for outpatient antibiotic use from 26 of the 32 countries was suitable for further analysis. Ambulatory care data were obtained from 24 countries, whereas Iceland and Bulgaria were able to provide only total use (ie, inpatient and outpatient) data in groups (data from these two countries were, however, also included because use of antibiotics in ambulatory care represented 90–94% of the total use data for the countries providing separate data). For the UK, data from England only were used, which covers 83·6% of the UK population. Data for antibiotic use were reimbursement data in 12 countries and distribution or sales data in 14. Reimbursement data were gathered by the third-party payer on the basis of financial claims from legitimate beneficiaries, prescribers, or dispensing pharmacies. Distribution or sales data were based on reports from pharmaceutical companies, wholesalers, pharmacies, or market research companies. In 24 countries, census data were provided covering at least 90% of the population. In two countries, sample data were obtained and extrapolated to 100%—Poland (60% coverage of data) and the Netherlands (83% coverage of data). 14 countries were able to deliver valid data for all 6 years (1997–2002), ten of which provided data on a quarterly basis. A complete description of the data providers, details of the methodology used and the associated problems, and discussion of the validity of the data has been published elsewhere.⁶

Antibiotic use and resistance

We used an analytical multiple-group study design to assess the ecological association between antibiotic (total and ATC groups) use and antibiotic resistance rates according to the biological mechanism of resistance. Such ecological studies use the average exposure of a population (ie, antibiotic use) and compare it with some measure of outcome in that population (ie, antibiotic resistance rates). We searched surveillance studies from countries for which antibiotic resistance rates of *Streptococcus pneumoniae*, *S pyogenes*, and *Escherichia coli*

were available. We used a time gap of 1–2 years between antibiotic use and collection of isolates, in accordance with other ecological studies.^{7,8}

We obtained β -lactam resistance data for *S pneumoniae* from the European Antimicrobial Resistance Surveillance System (EARSS) project, which surveyed the antimicrobial susceptibility among invasive (from blood and cerebrospinal fluid) pneumococcal isolates.⁹ EARSS is a continuing initiative and gathers comparable and validated antimicrobial susceptibility test results from most European countries according to standard protocols. Non-susceptibility to penicillin included both intermediate-level and high-level resistance. Macrolide resistance data on 4202 isolates of *S pneumoniae* and 4179 isolates of *S pyogenes* were obtained from the telithromycin surveillance project on antimicrobial resistance among isolates from respiratory tract specimens.¹⁰ Susceptibility of erythromycin was determined by testing the minimum inhibitory concentration, according to National Committee for Clinical Laboratory Standards guidelines. Resistance in *E coli* isolates was obtained from a pan-European project surveying the antimicrobial susceptibility of urine pathogens from women aged 18–65 years with clinical symptoms of acute uncomplicated urinary tract infections.¹¹ Details of these surveillance procedures have been reported previously.^{9–11} We calculated correlations between antibiotic resistance and use using two-tailed Spearman's coefficient (r) for non-parametric correlations. A p value of less than 0·05 was regarded as significant.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Outpatient antibiotic use differed significantly in Europe, varying by a factor of 3·2 between the country with the highest rate (32·2 DID in France) and the country with the lowest rate (10·0 DID in the Netherlands) (figure 1). We noted significant differences across Europe, with antibiotic use being low in northern, moderate in eastern, and high in southern regions. Figure 2 shows the seasonal fluctuation of outpatient antibiotic use in the ten European countries that provided quarterly data. Seasonal fluctuations were high (mean increase was $\geq 30\%$ in the first and fourth quarters compared with the second and third quarters) in southern and eastern European countries, whereas in northern European countries the increase in antibiotic use during winter was less than 25%.

Total outpatient penicillin (ATC group J01C) use in 2002 varied by a factor of 4·2 between the country with the highest (16·3 DID in France) and the country with

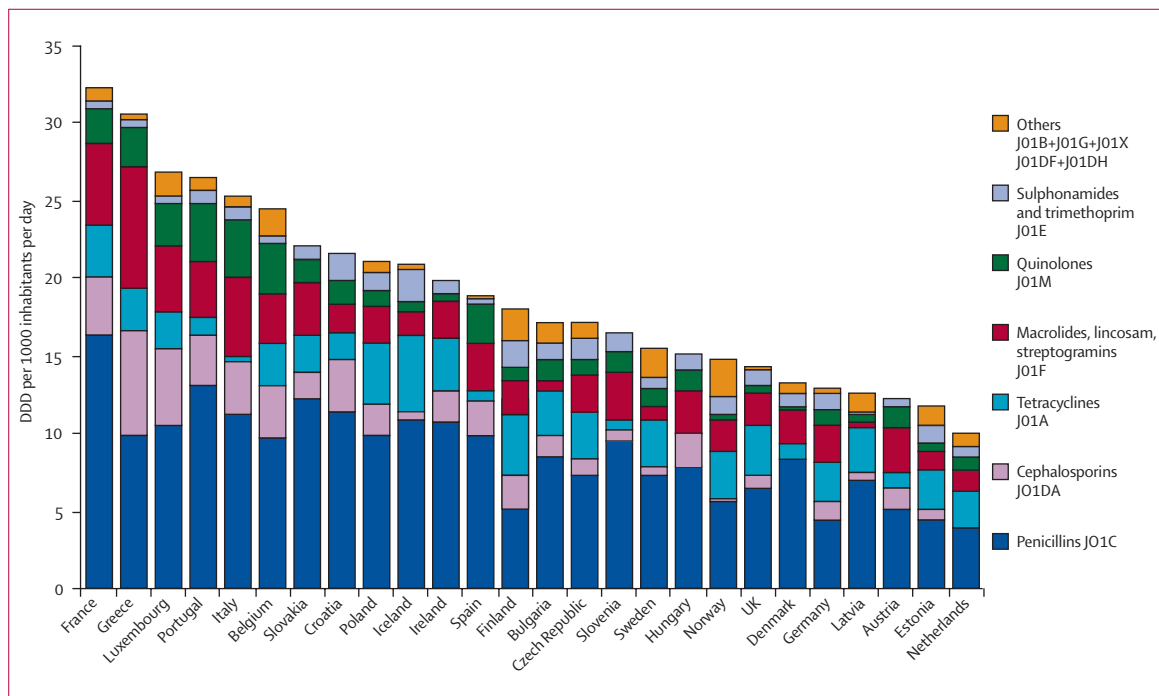


Figure 1: Total outpatient antibiotic use in 26 European countries in 2002

the lowest (3.9 DID in the Netherlands) penicillin use (figure 1). Figure 3 shows the proportion of use of the four different types of penicillins according to the ATC classification for 2002.

Total outpatient cephalosporin (ATC group J01DA) use in 2002 varied by a factor of 256.2 between the

country with the highest (6.7 DID in Greece) and the country with the lowest (0.03 DID in Denmark) use (data not shown). In France and Italy, we noted high consumption of cephalosporins as shown by the very high use of third-generation cephalosporins, which represent about a third of cephalosporins use in these

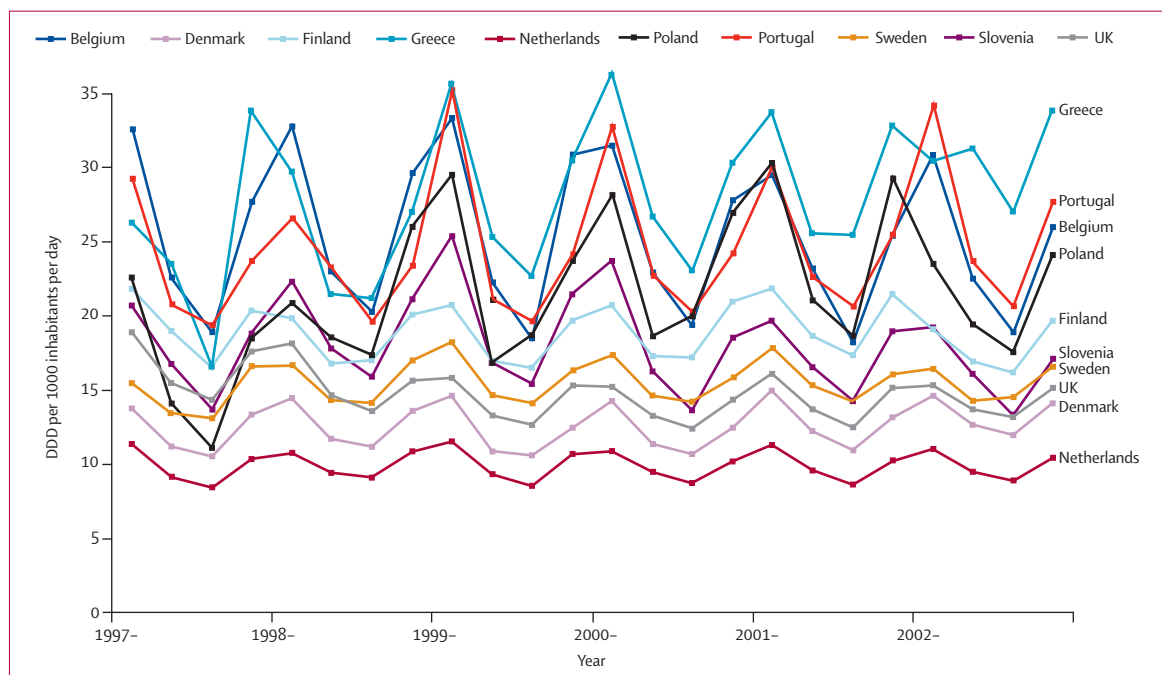


Figure 2: Seasonal variation of total outpatient antibiotic use in ten European countries between 1997 and 2002

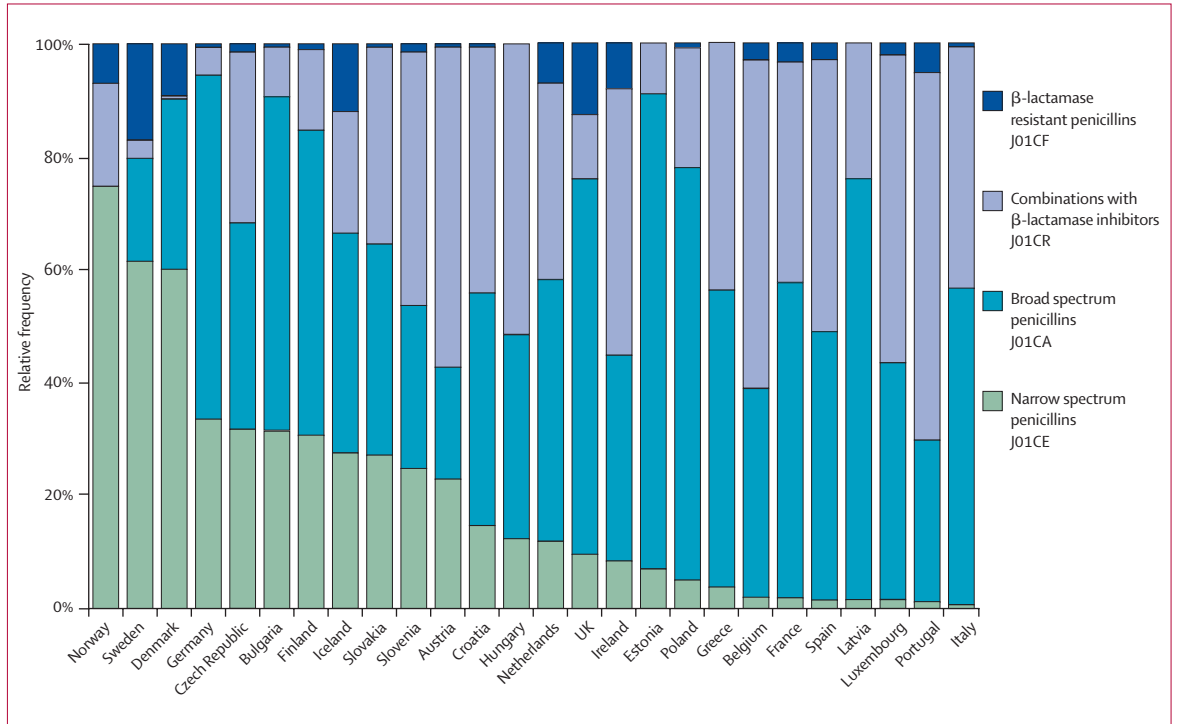


Figure 3: Outpatient use of penicillins (JOIC) in 26 European countries in 2002 in descending order of narrow spectrum penicillins

countries—ie, of the injectable (ceftriaxone in Italy) and oral (ceftibuten and cefixime in Italy; cefpodoxime and cefixime in France) cephalosporins. The old first-

generation cephalosporins still represented more than 50% of the total outpatient cephalosporin use in eight countries (Norway, 100% of cephalosporin use; Finland,

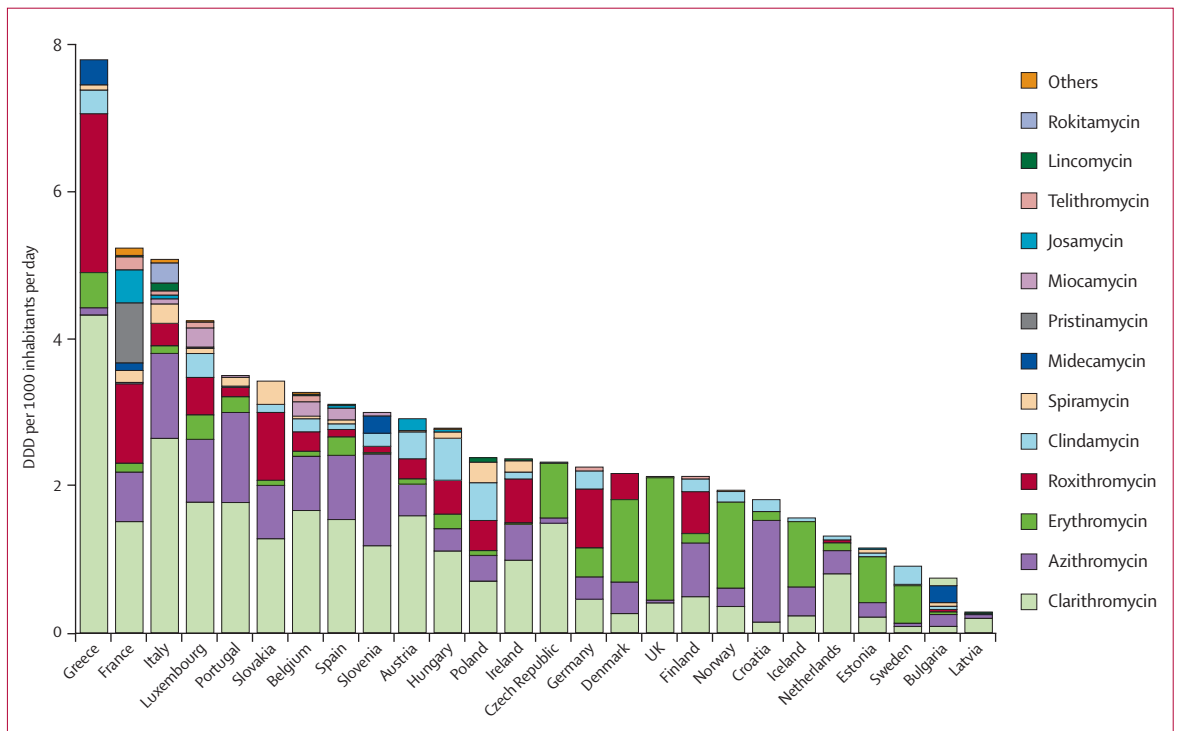


Figure 4: Outpatient use of macrolides, lincosamides, and streptogramins (JOIF) in 26 European countries in 2002

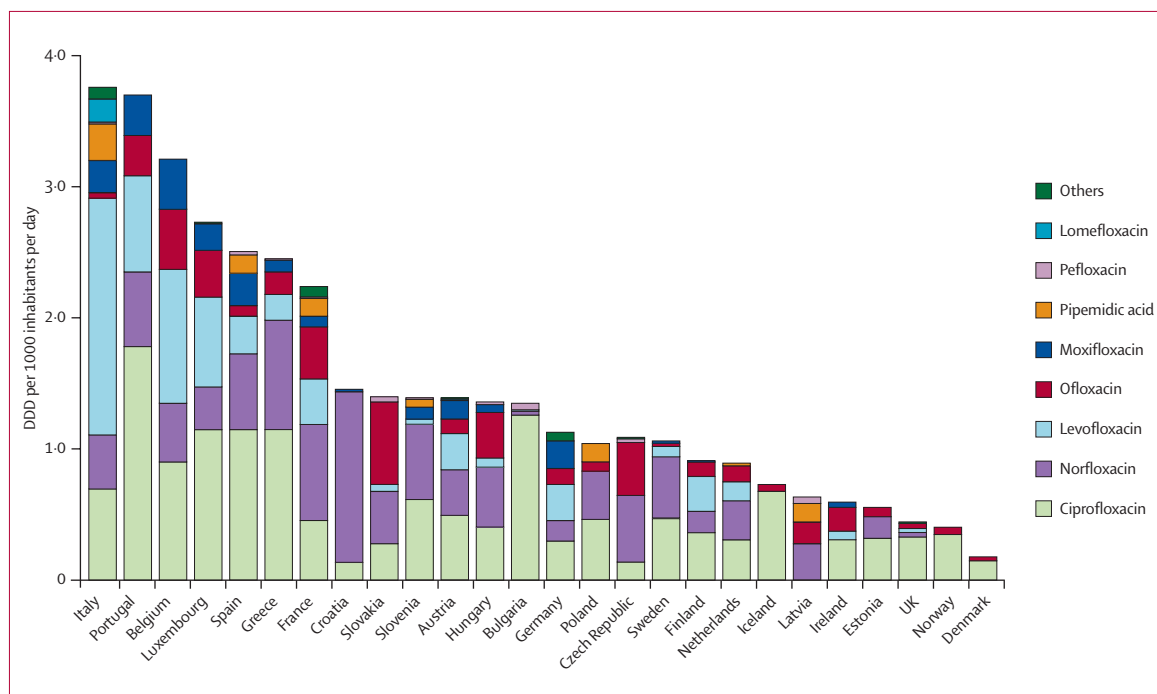


Figure 5: Outpatient use of quinolones (J01M) in 26 European countries in 2002

91.7%; Latvia, 81.8%; Sweden, 73.7%; UK, 70.9%; Bulgaria, 62.0%, Croatia, 55.4%, and Estonia, 53.8%.

Total outpatient use of macrolides (J01FA), lincosamides (J01FF), and streptogramins (J01FG) in 2002 varied by a factor of 26.9 between the country with the highest rate (7.8 DID in Greece) and the country with the lowest rate (0.3 DID in Latvia). Figure 4 shows the outpatient use of this group of antibiotics at the fifth level of active substance according to the ATC classification. Total outpatient quinolone (ATC group J01M) use in 2002 varied by a factor of 21.2 between the country with the highest (3.76 DID in Italy) and the country with the lowest (0.17 DID in Denmark) quinolone use. Figure 5 shows the outpatient use of these quinolones at the fifth level of active substance according to the ATC classification. Total outpatient use of sulfonamides and trimethoprim (ATC group J01E) in 2002 varied by a factor of 19.5 between the country with the highest (2.0 DID in Iceland) and the country with the lowest (0.1 DID in Latvia) sulfonamide and trimethoprim use (data not shown).

The table shows the Spearman correlations between antibiotic use and resistance. A significant correlation was recorded for all combinations, especially for antibiotic resistance and use combinations of *S pneumoniae*. The correlations show that resistance to microorganisms increased with consumption of antibiotics (figure 6). Differences in selection pressure accounted for geographic variation of resistance; higher rates of antibiotic resistance exist in countries of southern and eastern Europe where generally more antibiotics are consumed than countries in northern Europe.

Discussion

We identified significant variation in outpatient antibiotic use in Europe. Seasonal fluctuations were high in southern and eastern European countries, whereas in northern European countries the increase in antibiotic use during winter was less than 25%. We also showed a correlation between antibiotic resistance and outpatient antibiotic use in Europe.

	Antibiotic resistance	Antibiotic use, ATC group (year of data)	Number of countries	Spearman correlation (95% CI)	p
<i>S pneumoniae</i> 1999/2000 ¹⁰	Erythromycin	Macrolides, J01FA (1998)	16	0.83 (0.67–0.94)	0.0008
<i>S pneumoniae</i> 2001 ⁹	Penicillin	Penicillins, J01C (2000)	19	0.84 (0.62–0.94)	<0.0001
		Cephalosporins, J01DA (2000)		0.68 (0.33–0.87)	0.0014
<i>S pyogenes</i> 1999/2000 ¹⁰	Erythromycin	Macrolides, J01FA and lincosamides, J01FF (1998)	21	0.65 (0.25–0.86)	0.0015
<i>E coli</i> 1999/2000 ¹¹	Ciprofloxacin	Quinolones, J01M (1999)	14	0.74 (0.35–0.91)	0.0023
	Co-trimoxazole	Co-trimoxazole, J01EE01 (1999)		0.71 (0.29–0.90)	0.0048

Table: Correlation between antibiotic use and resistance, by organism and year of isolation

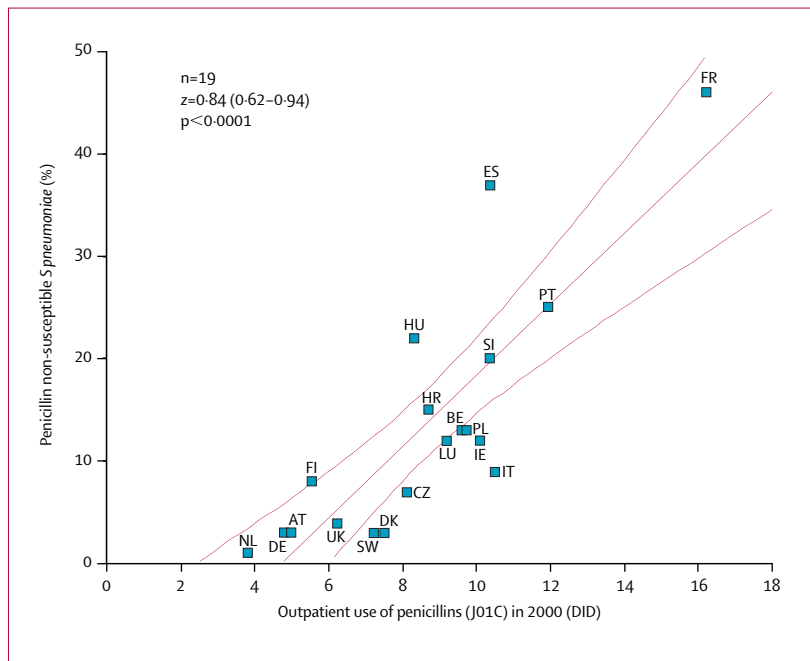


Figure 6: Correlation between penicillin use and prevalence of penicillin non-susceptible *S pneumoniae*
 AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only.

Data for outpatient antibiotic use have been reported with various units of measurement, but to compare data from different regions or countries, data should be gathered and aggregated in a standardised uniform way. ESAC chose the ATC classification system and the DDD measurement unit, developed by the WHO collaborating centre for drug statistics methodology.⁴ Outpatient antibiotic use in all age-groups (children and adults) was converted to DDDs. The DDD is the assumed average maintenance dose per day for the drug's main indication in adults and is assigned by the WHO collaborating centre. Because the DDD is a technical unit, albeit based on use in infections of moderate severity, expression of data for antibiotic use in DDDs might not adequately address differences in dosage and length of treatment for specific classes of antibiotics between countries. For instance, there is substantial variation in the dose regimen for the combination of penicillins with β -lactamase inhibitors (J01CR) in Europe. Also, DDDs do not take into account different doses for children (the population of children aged 0 to 14 years in ESAC participating countries ranged between 15% and 25%). Hence, the use of DDDs for adults to express children's consumption might lead to underrepresentation of this segment of users in the total. Nevertheless, Monnet and colleagues¹² showed that the number of DDDs correctly indicate the number of antimicrobial prescriptions for outpatients at the national level. Thus the number of DDDs is an acceptable measurement unit to express

outpatient antimicrobial use and to benchmark countries for their level of antimicrobial consumption.

A striking finding was the pronounced differences in antibiotic prescribing in primary care in Europe, which Cars and colleagues¹³ also noted. In general, antibiotic use was highest in southern and eastern Europe, and lowest in northern Europe. However, the ESAC antibiotic use data for Spain (21.4 DDD, in 1997) differ significantly from those of Cars and co-workers (32.4, in 1997).¹³ Our study covers reimbursement data for Spain, thereby excluding drugs that were sold over-the-counter, which were included in Cars and colleagues' sales data. However, these sales data could also be biased because they include antibiotics exported to other countries (parallel export). Nevertheless, we could estimate that the over-the-counter use in Spain stands at around 30% (ie, difference between sales and reimbursement data), which confirms the results of Orero and colleagues¹⁴ who showed that only two-thirds of antibiotic packages in Spanish households were prescribed by a physician.

In most countries, we noted a growing use of the newer (ie, broad-spectrum) antibiotics, such as combination of amoxicillin and clavulanic acid, the new macrolides, and quinolones (results not shown) to the detriment of the older (narrow-spectrum) penicillins and cephalosporins. However, the narrow-spectrum penicillins and the first-generation cephalosporins are still widely prescribed for the treatment of community-acquired infections in certain northern European countries. The high winter peaks of antibiotic use in countries with high annual levels of antibiotic use might be related to diagnostic labelling of respiratory tract infections. In a recent study of cultural differences in the lay perspective on coping with upper respiratory tract infections and using antibiotics, Dutch family practitioners (country with low antibiotic consumption and low winter peaks) labelled most of these episodes of upper respiratory tract infection as common cold or influenza, whereas Flemish family practitioners (country with high antibiotic consumption and winter high peaks) labelled most of their episodes as bronchitis and prescribed more antibiotics.¹⁵ In a similar study of Canadian family practitioners, Hutchinson and colleagues¹⁶ showed that low prescribers and high prescribers of antibiotics diagnosed urinary tract infections and skin and soft-tissue infections at similar rates, but differed greatly in their rates of diagnoses of respiratory tract infections; high prescribers diagnosed significantly more bacterial infections than low prescribers.

In all but one country (Portugal) we recorded no seasonal variation of ciprofloxacin use (data not shown), suggesting that this drug was used mainly for treatment of urinary tract infections. Fluctuations in prescriptions for ciprofloxacin in Portugal are consistent with it being given as a treatment for adults with winter seasonal

infections, especially those of the respiratory tract. Ciprofloxacin has little activity against streptococci, and the general belief is that this drug should not be used for treatment of patients with respiratory tract infections.¹⁷ We suggest that a low seasonal fluctuation of the early fluoroquinolones, such as ciprofloxacin, is a good marker of restrained use. Levofloxacin and moxifloxacin have better activities against pneumococci than do the early agents,¹⁷ and their introduction in Europe was generally very successful in countries with high antibiotic use and resistance rates. When sounding the alarm about the problem of rising antibiotic resistance, we could be inadvertently promoting inappropriate use of these new quinolones. This inappropriate use will inevitably lead to emergence of not only resistant pneumococci, but also of a host of resistant gram-negative organisms.¹⁸

In France, use of cephalosporin has been rising for treatment of uncomplicated respiratory tract infection despite no recommendation for cephalosporin use in such circumstances.¹⁹ This high cephalosporin use was due to the strikingly high use of oral third-generation cephalosporins—ie, cefpodoxime and cefixime.

Differences in antibiotic use between countries might be explained by variations in incidence of community-acquired infections, culture and education, and differences in drug regulations and in the structure of the national pharmaceutical market. Pharmaceutical marketing activities in the Netherlands, relating to 11 therapeutic markets, make doctors less sensitive to costs and quality of prescribing drugs, and to reduce their choice of competing drugs.²⁰ This finding might explain the growing use of newer (broad spectrum) antibiotics. In a survey, pharmaceutical advertisements for antibiotics in four major journals between 1984 and 2002, and targeted at family practitioners showed a strong increase of advertisements promoting fluoroquinolone.²¹ Incentive-based formularies could be used as an instrument to curb the rising use and costs of prescribing drugs. Financial incentives (ie, reduced copayments) might encourage physicians to prescribe antibiotics that exert less ecological pressure and are more cost-effective than alternative antibiotics. In Denmark, delisting—ie, removal of subsidisation—of both tetracyclines and fluoroquinolones resulted in a rapid drop in the consumption of these antibiotics.²²

Geographic differences in the proportion of resistance can be explained by differential selection pressure for resistance or the dissemination of certain resistant clones in some countries but not in others. The ESAC antibiotic use data were correlated with published data for resistance in *S pneumoniae*, *S pyogenes*, and *E coli*; three pathogens that cause massive antibiotic prescribing in primary care. Various ecological studies, which used different models in the statistical analysis, have also shown an association between outpatient antibiotic use and the prevalence of resistance estimated

at different time-points or locations.^{2,7,8,23,24} In an ecological study²⁵ that combined aggregate, environmental, and global measures, antibiotic use seemed to be the only force behind resistance patterns in different geographic areas in Spain. But ecological studies have to be interpreted cautiously and have several limitations. Antibiotic distribution or reimbursement data cannot be used synonymously with antibiotic exposure, sampling bias could have affected the results of this link study, and we have no good data about the time lag between antibiotic use and possible changes in antibiotic resistance. With a mathematical transmission model, McCormick and colleagues²⁶ showed that the variation in resistance of *S pneumoniae* to β lactams and macrolides in the USA was best explained by geographic variation in selection pressure for resistance, rather than by clonal dynamics. Thus our study lends support to the hypothesis that differences in selection pressure account for geographic variation of resistance in Europe.

With population genetics methods and epidemiological observations, Austin and co-workers²⁷ showed that the time scale for emergence of resistance under constant selective pressure is much shorter than the decay time after cessation or decline in the level of drug use. Enne and others²⁸ showed that a huge decrease in sulphonamide prescribing in the UK did not have an effect on the prevalence of resistance to this drug in *E coli* within a useful time. Therefore, there is a need for early intervention once resistance is detected. Finally, Nasrin and colleagues,²⁹ investigating the effect of β -lactam antibiotic use in children on pneumococcal resistance to penicillin, showed that reduction of antibiotic use could result in a more rapid drop of resistance rates than commonly appreciated (about 6 months). That antibiotic resistance is not only the effect but also a cause of consumption of antibiotics (resistant organisms require high doses or alternative antibiotics to be eradicated) is noteworthy.

We were not able to investigate whether restrictive use of antibiotics in most northern European countries was associated with a raised frequency of illness and death from complications. Van Zuijlen and co-workers³⁰ have shown that the incidence rate of acute mastoiditis in countries with low antibiotic use was higher than countries with high antibiotic use. However, the potential increase is only two extra cases per 100 000 children per year, and must be weighed against potential adverse effects (such as allergic reactions, gastric upset, emergence of bacterial resistance, and unfavourable changes in nasopharyngeal bacterial flora).³¹ Another retrospective study³² showed that there was a potential link between reduction of antibiotic prescribing and increased community-acquired pneumonia mortality in the UK. However, the association was weak and there are serious methodological flaws in that study. In future studies, outpatient antibiotic use and interventions to

reduce prescribing should be prospectively correlated with incidence of serious complications of respiratory tract infections.

The ESAC data allow ecological studies on the relation between antibiotic use and resistance, audit of patterns of antibiotic prescribing, educational and other interventions, assessment of guidelines and policies, and monitoring of the outcomes of the interventions. Our study indicates a tendency to use new antibiotics, which fail to offer substantial improvements over other available drugs. We also show that the variation in resistance between different European countries can be explained by variation in selection pressure for resistance. Comparisons of individual linked data with group level data are needed to clarify relations between antibiotic use, antibiotic resistance, and outcome that could be obscured by group level ecological studies. Population-based studies are needed to determine the motivations, expectations, and incentives that lead individuals to use or not use antibiotics. The ethics of promoting antibiotics in clinical situations in which they are unnecessary should be given serious consideration. In view of the emergence of bacterial resistance and the decline in the rate of development of novel antibiotics, effective professional and public strategies to encourage appropriate prescribing of antibiotics should be studied and implemented. If not, we will lose the miracle drugs of the 20th century.

Contributors

H Goossens wrote the ESAC project proposal and is the ESAC project leader, he was responsible for the analysis and interpretation of the data and prepared the initial, revised, and re-revised draft of the manuscript; M Elseviers, M Ferech, and R Vander Stichele were responsible for collation, validation, and analysis of the use data; M Elseviers and M Ferech provided statistical advice and analysis; and all authors contributed to the final version of the manuscript. The members of the ESAC project group collected the data and critically reviewed the manuscript.

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Conflict of interest statement

We declare that we have no conflict of interest.

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