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Abstract

This paper investigates socioeconomic determinants of outpatient antibiotic consumption in Europe. Comparable data on antibiotic use measured in the defined daily doses per 1000 inhabitants (DID) are currently provided by the ESAC project. Results from applied econometric estimations for panel data reveal a link between antibiotic use and the per capita income, the demographic structure of the population, the level of education and cultural aspects. Supply-side factors, such as the density of providers and their remuneration methods, are also considered. We provide the first estimate of the impact of bacterial resistance on consumption when the effect of other determinants is simultaneously taken into account.

JEL classification: I0; C3

Keywords: Antibiotic use. Cross-country variations. Bacterial resistance. Supply-induced demand

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1 Introduction

Antibiotics have significantly contributed to the reduction in the likelihood of dying from infectious diseases worldwide (WHO, 2000; 2001). However, researchers have suggested that almost one third of drug prescriptions are questionable (Wise et al., 1998; Homer et al., 2000). Indeed, multiple imperfections characterize the market for antibiotic treatment. First, consumers may have the incentive to purchase more drugs than they would if insurance coverage was not available (Newhouse, 1993). Studies have shown that under time pressure doctors tend to satisfy their patients and to avoid follow up visits by prescribing more antibiotics (Butler et al., 1998). Second, the inappropriate use of antibiotics may be due to patients' lack of information. The individual's marginal benefit from consumption does not consider the external benefit derived from one's treatment with antibiotics which reduces the probability of infection spreading to other individuals (Elbasha, 2003). Finally, the misuse of antibiotics may contribute to the selection of resistant bacteria. This leads to the production of newer and more effective generations of drugs, thus raising the costs for society (Coast et al., 1998; McGowan, 2001; Levy, 1998).

During the 80s most European countries experienced a remarkable increase in the number of antibiotic prescriptions. According to Davey (1996) a partial explanation is represented by the increasing use of antibiotics for respiratory symptoms. Although antibiotic prescriptions have slightly decreased during the 90s and been roughly stable in recent years, prescribing practices still vary widely across countries (Elseviers et al. 2007). Consequently, the investigation of cross-country differences may contribute to the debate on appropriate antibiotic use through the understanding of determinants of consumption.

The European Surveillance of Antimicrobial Consumption (ESAC) project has been collecting comparable data on outpatient antibiotic use across European countries since 1997. Preliminary investigations have shown the presence of clusters of consumption across Europe and an association with bacterial resistance (Goossens et al. 2005). To our knowledge there are no rigorous multifactorial analysis of determinants of antibiotic use. Previous studies on socioeconomic determinants have rather focused on regional variations within a country (Filippini et al., 2006; Bremon et al., 2000).

Differences in antibiotic use across geographical areas may be explained by demographic, cultural, and economic factors capturing consumer's behaviour. Moreover, supply-side factors such as the density of doctors and their remuneration system may also have an impact on consumption. This paper proposes an approach to the study of determinants of outpatient antibiotic use in Europe based on multivariate econometric techniques. The interaction between determinants of consumption is taken into account and the impact of each single determinant is assessed. This allows for a more precise investigation of the association between bacterial resistance and consumption compared to previous studies.

The paper is organized as follows. In section 2 we summarize data on cross-country variations in outpatient antibiotic use in Europe. In section 3 we discuss potential determinants and present some summary statistics. A simple econometric model of antibiotic use is sketched in section 4. Estimation results are analysed in section 5. Section 6 concludes.

2 Variations across Europe

Outpatient antibiotic utilization across European countries can be compared in terms of defined daily doses (DDD) per 1000 inhabitants per day (DID)[1]. The European Surveillance of Antimicrobial Consumption (ESAC) project collected data on antibiotic use from national databases using either reimbursement or distribution/sales data. Antibiotic sales, prescribing and consumption are sometimes used interchangeably in the European study although concepts are not exactly the same. Patients may systematically lack compliance either because they badly tolerate the treatment or because symptoms have resolved. Moreover, as suggested by Cizman (2003), physicians may overprescribe antibiotics to meet patient's expectations or to reduce misdiagnosis of bacterial infections. On the other hand, prescribing data may also underestimate consumption since antibiotics purchased over the counter are not included. As for wholesales to dispensing pharmacies, doctors and drugstores, these may not match prescribing data if drugs can also be purchased without any prescription. This is illegal in the EU, but happens in southern Europe. A mismatch between wholesales and prescribing data may also derive from seasonal fluctuations of retailers' stocks of drugs due, for instance, to unexpected variations in the incidence of infections. We hypothesize that possible mismatches between antibiotic sales and antibiotic prescribing can be ignored and, consequently, we use either one term or the other interchangeably.

[1] The defined daily dose (DDD) is based upon the WHO version 2004.

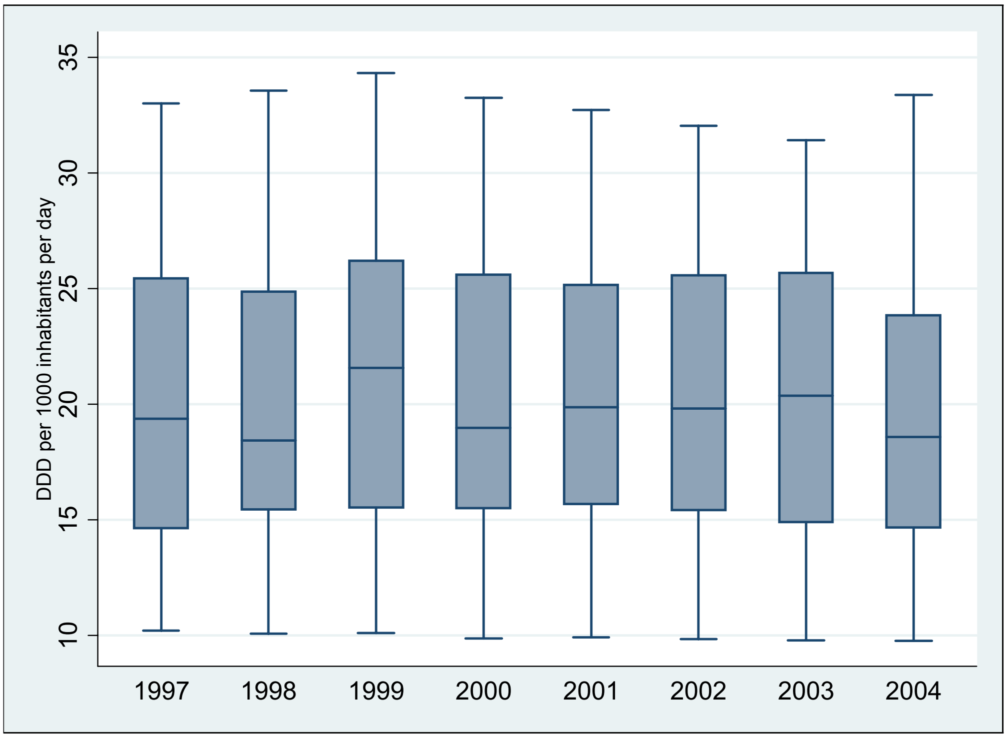

Figure 1: Variations in outpatient antibiotic use across Europe by year.

We summarize outpatient antibiotic use for 21 European countries participating in the ESAC project and able to provide comparable and reliable data for at least 7 years since 1997. As shown in figure 1 use has been roughly stable between 1997 and 2004. However, large differences are observed across countries (Ferech et al., 2006). Relatively high use is registered in France, Greece, and Spain, among others (figure 2). On the other hand, Austria, Denmark, and the Netherlands, for instance, exhibit significantly lower values. The mean consumption between 1997 and 2004 has been 20.34 DID with a peak in 1999 (21.15 DID) and a minimum in 2004 (19.43 DID).

Elseviers et al. (2007) showed that there are substantial regional differences in use when European countries are clustered into 3 main groups (East, North and South).

In table 1 we consider a more detailed clustering and classify countries in 4 groups (East, North, South and West). Countries in the western group (19.97 DID) generally consume more antibiotics than northern countries (16.86 DID) and less than eastern countries (20.96 DID). These differences could suggest that cultural aspects/patients' preferences can at least partially explain variations in antibiotic use across European countries. Nevertheless, the effect of these aspects can only be ascertained when supply-side factors are simultaneusly taken into account.

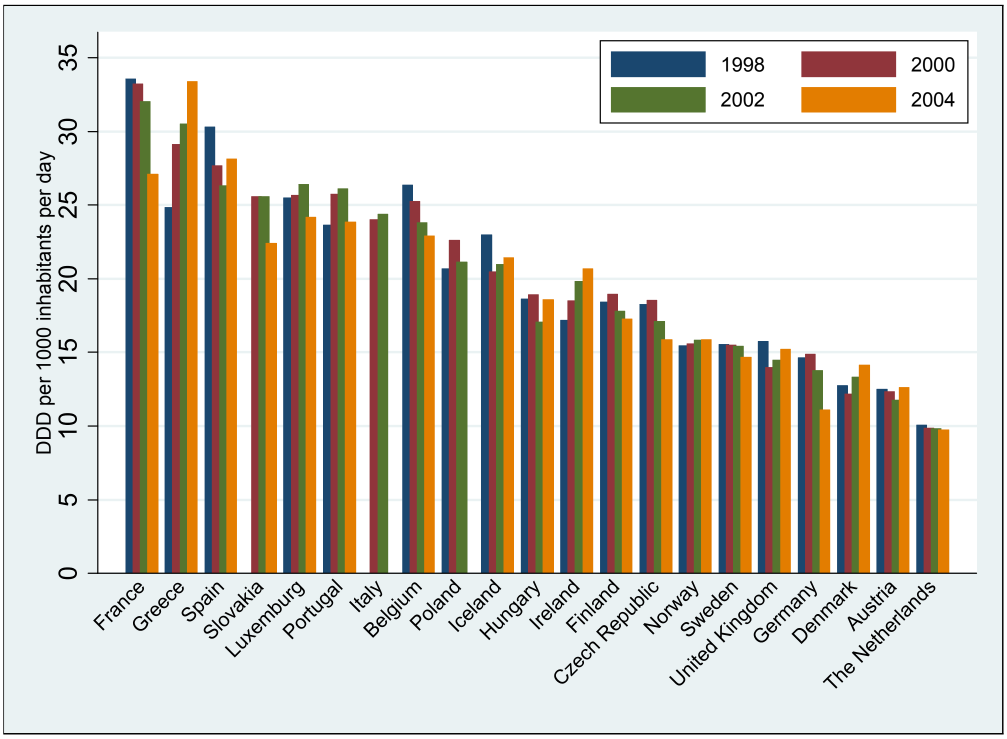

Figure 2: Outpatient antibiotic use in Europe by country and year.

3 Determinants

Cross-country variations in antibiotic consumption in the community can be explained by a variety of factors. Harbarth et al. (2002) suggested that large differences in antibiotic consumption between France and Germany may be partially associated to risk factors in the incidence of infections., i.e. differences in the concentration of child care facilities and in the breast feeding practices between the two countries. However, the difference in the incidence of bacterial infections can hardly explain variations in the use of antibiotics as large as three fold among European countries. The literature has mentioned the lack of education, physicians and patients' expectations, uncertainty, cultural and social behavior, and differences in regulatory practices, among other factors (Belongia and Schwatz, 1998; Finch et al. 2004). Hence, patients' preferences and doctors' incentives to prescribe may play an important role in explaining the use of antibiotics across Europe.

Country	Mean DID (1997-2004)	Country	Mean DID (1997-2004)
Austria	12.39	Denmark	12.89
Luxemburg	25.96	Finland	18.59
The Netherlands	9.94	Iceland	21.28
Belgium	24.74	Ireland	19.12
Germany	13.95	Norway	15.66
France	31.87	Sweden	15.28
		United Kingdom	15.02
West	19.97	North	16.86
Czech Republic	17.65	Greece	29.04
Hungary	19.40	Italy	24.75
Poland	21.30	Portugal	24.94
Slovakia	26.22	Spain	28.32
East	20.96	South	26.97

Table 1: European outpatient antibiotic use by country and regions.

Previous studies focusing on specific determinants of antibiotic use have been conducted either in the form of trials or questionnaire surveys. Macfarlane et al. (2002), for instance, investigated the impact of patient's information and showed that the distribution of information leaflets may effectively reduce the use of antibiotics without affecting the doctor-patient relationship. This advocates the role played by supply-side factors, such as doctors' attitudes towards antibiotic prescriptions, when patients lack information. Unsworth and Walley (2001) revealed that antibiotic prescribing is related to practice characteristics in the British NHS. Deprived and single-handed practices tend to prescribe more but cheaper antibiotics, while dispensers and trainers with low level of deprivation and early wave fundholders have lower rate of prescriptions. The result indicates that doctors are sensitive to economic incentives. Consequently, under imperfect information a higher concentration of practices may result in a higher number of prescriptions per capita if doctors are profit maximizers. The effect may be even stronger under a fee-for-service payment system, since marginal gains are directly related to the amount of services provided. Conversely, under a capitation contract, doctors' remuneration is based upon the number of patients cured and the link with the number of prescriptions may be less important.

Patients' preferences may also play a significant role. Cockburn and Pit (1997) assert that doctors may be prone to pleasing patients. Patients expecting a medication are nearly three times more likely to receive it compared to other patients. Moreover, patients are ten times more likely to receive a medication if practitioners perceive a patient's expectation on prescribing.

Antibiotic prescribing are expected to be related to the demographic structure of the population. Resi et al. (2003) found that the percentage of children receiving antibiotics decreases as they grow up. Focusing on provincial governments in Canada, Di Matteo and Grootendorst (2002) have shown that drug expenditure increases as the population ages.

Finally, differences in levels of bacterial resistance across countries may affect the use of antibiotics. The knowledge of overall levels of bacterial resistance within a country is likely to be shared by health care providers after some time. Therefore, prescribing strategies are expected to change and to include more recent generations of antibiotics. In that sense, antibiotic resistance will drive prescribing of new, broad-spectrum antibiotics. Although resistance is primarily caused by increasing antibiotic use, the following increase in broad spectrum antibiotics is a secondary and perhaps relevant effect. A positive correlation between antibiotic use and bacterial resistance in Europe has been recently alleged by Goossens et al. (2005). Although the correlation is evident, the impact of bacterial resistance can only be assessed when other determinants of consumption are simultaneously considered. The proposed model in section 4 will address this point.

3.1 Data

Annual data available on determinants of outpatient antibiotic use between 1997 and 2004 are summarized in table 2. These include socioeconomic characteristics of the population (income, demographic structure, education and cultural/regional clusters), supply-side factors (density of doctors and the system of remuneration) and levels of bacterial resistance.

Data were obtained from a variety of sources. Information on per capita income, density of physicians, and the level of education (attainment of ISCED 5A/6) were extracted from publications by the OECD (OECD Health Data, 2006). The demographic structure of the population was derived from Eurostat tables (Eurostat, 2006). Looking at yearly country profiles published by the European Observatory on Health Systems and Policies (2006) we collected information on the main type of payment system on hold for general practitioners (fee-for-service, capitation and salary).

As for the levels of bacterial resistance, data were obtained from the European Surveillance on Antimicrobial Resistance database (EARSS, 2006). Routine antimicrobial susceptibility tests on invasive isolates of *Streptococcus pneumoniae* are collected by participating laboratories in each country and submitted to EARSS. We neglect possible bias in the comparison of susceptibility data between countries that may be due to differences in case mix and hospital specialities or may be introduced as a result of different laboratory routines between countries.

Data for all variables were generally available for 8 years, with the exception of bacterial resistance whose systematic collection across European countries started more recently (from 1999/2000).

4 The model

Our approach to the investigation of determinants of antibiotic consumption is to use European consumption data and regress them against a set of variables suggested by the literature as plausible causal factors of the demand for drugs. This method is

Description	Variables	Mean	Std. Dev.	Min.	Max.
Outpatient antibiotic consumption	DDDs per 1000 inhab. per day (DID)	20.34	6.25	9.75	34.33
Income per capita	GDP in PPP/pop. (Y)	24800	9302	8759	63453
Demographic structure of population	Pop. under 14/pop. (POP_1)	18.02	2.25	14.1	24
	Pop. 15-24/pop. (POP_2)	13.47	1.92	10.6	17.5
	Pop. 25-64/pop. (POP_3)	53.57	1.96	47.9	57.2
	Pop. 65-79/pop. (POP_4)	11.53	1.47	8.5	14.6
	Pop. over 80/pop. (POP_5)	3.41	0.79	1.8	5.3
Attainment of high education	Pop. with ISCED 5A/6 over total pop. (EDU)	14.37	4.97	5.9	29.4
Density of doctors	Nr./1000 inhab. (DPH)	3.11	0.61	1.9	4.9
Bacterial resistance	Nr. PNSP isolates/tested isolates (RES)	11.31	11.13	0	48
GPs reimbursement	Fee-for service ($PGP_1 = 1$)				
	Capitation				
	Salary ($PGP_2 = 1$)				
Cultural aspects (regional clusters)	West				
	East ($REG_e = 1$)				
	North ($REG_n = 1$)				
	South ($REG_s = 1$)				

Table 2: Variables notation and summary statistics

applied, for instance, by Di Matteo (2005) to investigate the macro determinants of health expenditure in the United States and Canada and by Filippini et al. (2006) to study regional variations in the use of antibiotics in Switzerland.

We specify an ad-hoc demand function for antibiotics used in outpatient care in Europe. The demand for antibiotics depends on the individual's stock of health care, income, the level of bacterial resistance, and other socioeconomic variables such as age, education, and cultural attitudes towards the use of drugs.[2] Socioeconomic variables are usually included in the model as proxies for the individual stock of health care, which is difficult to measure. Moreover, the demand for antibiotics could

[2]The use of aggregated data to explain individual antibiotics consumption implies the assumption that the hypothesized relationship between the economic variables used is homogeneous across all individuals. Therefore, by using aggregate data at a national level we could encounter an aggregation bias.

also depend on some characteristics of the supply of health care services, such as physicians' density or the physicians' remuneration system. Antibiotics are usually purchased under doctors' prescriptions and fully reimbursed by the NHS or social insurances; hence, we neglect antibiotic price.

We specify the following parsimonious empirical model for the per capita demand of outpatient antibiotics:

$$DID_{it} = f(Y_{it}, DPH_{it}, POP_{jit}, EDU_{it}, PGP_{kit}, REG_{hi}, RES_{it-1}), \tag{1}$$

where DID_{it} are per capita antibiotic sales in country i and year t, measured in defined daily doses, Y_{it} is the per capita national income, DPH_i is the physicians' density, POP_{1it} .. POP_{5it} indicate the percentage of the population below 14, between 15 and 24, 25 and 64, 65 and 79, and over 80. EDU_{it} is the percentage of individuals with graduate education ($ISCED$ $5A/6$). The remuneration system for general practitioners is taken into account by two variables: PGP_{1it} and PGP_{2it}. PGP_{1it} is equal to 1 if doctors are paid a fee per service provided, and 0 otherwise. Instead, if doctors work under a salary regime PGP_{2it} is 1, otherwise 0. Consequently, the capitation contract represents the system for comparison. A "cultural" or geographical dummy (REG_{hi}) that takes into account similarities with adjacent countries and cultural differences across Europe is also included. Lecomte and Paris (1994) suggested that socio-cultural factors which are hard to measure might explain differences in consumption patterns between European countries. We divided countries into four groups: "North" ($REG_{ni} = 1$), "South" ($REG_{si} = 1$), "East" ($REG_{ei} = 1$), and "West", i.e. the reference group. Finally, RES_{it-1} measures the rate of bacterial resistance. The hypothesis that the impact of baterial resistance on antibiotic use is instantaneous is not very realistic. More plausibly, the information on levels of bacterial resistance within a country spreads among decision makers with a time lag. Prescribing strategies may be updated over time when new data are available. We assume that antibiotic consumption in the current period (t) is affected by levels of bacterial resistance established during the previous period ($t-1$).

The estimation of equation 1 requires the specification of a functional form. Several alternative forms could be considered since the theory of demand is quite ambiguous regarding this issue. Generally, the log-log specification offers an appropriate functional form for investigating the responsiveness of antibiotic sales to changes in explanatory variables. The major advantage is that the estimated coefficients can be interpreted as elasticities[3], which are, therefore, assumed to be constant. However, the log transformation has not been applied to the demographic structure of the population, education, and the level of bacterial resistance since they are defined as percentage ratios. Thus, we are using a hybrid log-log functional form. The functional specification can then be written as:

$$\ln DID_{it} = \beta_0 + \beta_1 \ln Y_{it} + \beta_2 \ln DPH_{it} + \sum_{j=3}^{6} \beta_j POP_{jit} + \beta_7 EDU_{it} + \\ + \sum_{k=8}^{9} \beta_k PGP_{kit} + \sum_{h=10}^{12} \beta_h REG_{hi} + \beta_{13} RES_{it-1} + \nu_i + \varepsilon_{it}, \qquad (2)$$

where ln() is a natural logarithm applied to the variable and ν_i and ε_{it} are error terms with standard distribution assumptions. The inclusion of lagged values for bacterial

[3]This means that coefficients represent the percentage change in the value of the explained variable corresponding to a one percent variation in the value of the explanatory variable.

resistance restricts the number of observations available for the estimation to 79.

With regard to the choice of the econometric technique, it should be noted that in the econometric literature we can find various types of models focusing on cross-sectional variation, i.e. heterogeneity across units. The three most widely used approaches are: the fixed-effects model, the random effects model and the Kmenta model.[4] In order to choose the econometric approach it is important to consider that our dataset is a panel characterized by a relatively small number of time periods as well a relatively small number of cross-sectional units. Moreover, the within variation of the majority of the variables included in the model is relatively low. In this case, as suggested by Cameron and Trivedi (2005), the use of the fixed effects model could imply a low statistical efficiency of the estimated parameters. Therefore, the following comments are based on the results obtained with a random effects model (*Model 1*) and with a Kmenta model (*Model 2*).[5] Moreover, for comparison purposes we present also the estimation results obtained using OLS.

Estimations have been carried out using the econometric software STATA (version 9). We discuss our findings in the following section.

[4] For a detailed presentation of the econometric methods that have been used to analyze panel data, see Greene (2003) and Baltagi (2001). The Kmenta approach is also technically known as the cross-sectionally heteroskedastic and timewise autoregressive model (Kmenta, 1986). This approach is attractive when N, the number of units, is lower than T, the number of periods, or when the within variation of many explanatory variables is very low.

[5] In the Kmenta model we consider the heteroschedasticity and time-wise autocorrelation of the error terms.

5 Results

The parameter estimates of the three models are summarized in table 3. The results are satisfactory and stable over the three models. The level and number of significant coefficients in the random effects model is slightly less than in the other two models. This difference could be due to the low within variation of the variables. However, no structural difference in the results is observed. Therefore, the impact of the different explanatory variables on the per capita antibiotic consumption is based on all three models.

The coefficient of income is always very significant and shows a positive sign. This suggests that richer countries generally use more outpatient antibiotics compared to lower-income countries. Since per capita antibiotic doses and regressors are in logarithmic form, the coefficients can be interpreted as elasticities. The responsiveness of the per capita outpatient antibiotic use to a 1% change in the average national income, *ceteris paribus*, is between 0.37% and 0.68%. The result conjectures that antimicrobials may not be as strongly normal goods as argued by Baye et al. (1997), whose calculated income elasticity was 1.331 and is in accordance with previous findings on regional Swiss data analysed by Filippini et al. (2006). Since Baye et al. focus on USA data, our finding may then denote that the European population is less keen on consuming antibiotics when income increases or is more likely to substitute antibiotics with alternative treatments. Also, note that Baye et al.'s study is based upon 1984-1990 data. The raising concern on the impact of antibiotic resistance over the 90s may have reduced income elasticity of outpatient antibiotic expenditure over time thus leading to lower elasticity values. Indeed, the coefficient on time trend does not show any significant increase in the use of antibiotics between 1997 and 2004.

	Model 1:	OLS	**Model 2:**	GLS AR(1)	**Model 3:**	GLS Random-effects
	Obs.	79	Obs.	79	Obs.	79
	Adj. R^2	0.9334	Wald χ^2 (14)	1364.47^{d}	Wald χ^2 (14)	163.23^{d}
			Log likelihood	113.3498	R^2(overall)	0.8867
Variables	Coeff.	Std. Err.	Coeff.	Std. Err.	Coeff.	Std. Err.
Constant	-8.234648^{d}	1.148146	-7.283572^{d}	1.03831	-2.711372	1.812378
lnY	.681311^{d}	.0789913	.5741782^{d}	.070008	.3697206^{c}	.1361809
POP_1	.0525683^{c}	.0164403	.0623434^{d}	.0162189	.0415756	.0281299
POP_2	.0688822^{c}	.0190896	.0666265^{d}	.0175879	.0043953	.02419
POP_4	.1951813^{d}	.0235587	.1934276^{d}	.01931	.0792842^{b}	.0359754
POP_5	-.1557526^{d}	.0358406	-.1476135^{d}	.0320138	-.1293506^{b}	.0582641
EDU	-.0111827^{d}	.0029492	-.0131378^{d}	.0024642	-.0142094^{c}	.0052054
REG_e	.4170515^{d}	.0678572	.4186644^{d}	.0672672	.3344426^{b}	.1361288
REG_n	.286858^{d}	.0634562	.2822059^{d}	.0608847	.2087966^{b}	.1058358
REG_s	.3172736^{d}	.0523735	.3566177^{d}	.05231	.415573^{d}	.1032227
lnDPH	.3281048^{c}	.097591	.2790845^{c}	.0818382	.3160585^{a}	.1616467
PGP_1	.1791297^{d}	.0395915	.2200967^{d}	.0299377	.2281424^{c}	.0620284
PGP_2	.127164^{d}	.0309736	.1177165^{d}	.027197	.1505106^{b}	.0620284
t	.0055566	.009082	.0189277^{c}	.0065225	.0071173	.010927
RES	.0113529^{d}	.0018655	.0101437^{d}	.001546	.0102264^{d}	.0024806
						σ_κ = .0536263
						σ_ε = .04383086
						ρ = .59950498

^{a} significant at 10%, ^{b} significant at 5%, ^{c} significant at 1%, ^{d} significant at 0.1%,

Table 3: Parameter estimates for the three models.

The level of education is negatively related to the per capita outpatient antibiotic expenditure defined in DID and is highly significant. It shows that an increase in the percentage of people with higher education reduces the individual consumption of antibiotics. Education elasticities are close to zero in all the estimations. The outcome advances that countries with a higher proportion of highly educated people use antibiotics more efficiently, *ceteris paribus*. To our knowledge, there are no comparable multivariate studies on the impact of education on the use of antibiotics. A comparison with the literature on medical care utilization, such as physician office visits or hospital services, suggests that antibiotics are quite peculiar. Hunt-McCool et al. (1994) found positive education elasticity to physician office visits and hospital care, although the impact is not very significant. In the case of antibiotics in outpatient care the possible link between increasing consumption and the reduced effectiveness due to bacterial resistance may induce more educated individuals to restrain from antibiotic utilization. Another explanation is that more educated individuals show better compliance with antibiotic treatment, hence a lower amount of antibiotic doses is required for effective care, *ceteris paribus*.

The effects of different classes of age on antibiotic sales are captured by covariates $POP_1 - POP_5$. It is worth noticing the impact of children and elderly consumers. One may expect that antibiotic use is higher for young people since doctors and patients are likely to reduce the risk of bacterial infections under uncertainty. For similar reasons, antibiotic consumption may be higher for elderly people. Accordingly, our estimations show positive and significant coefficients of the proportion of individuals below 25 in the OLS and the Kmenta models.[6] We also found a positive impact of the proportion of the population between 65 and 79 in the three models. Indeed, the literature on determinants of health care expenditure generally suggests that the increasing prevalence of chronic health problems as people grow older may determine an increase in the utilization of health care services. However, this may not hold for antibiotics in the same extent. Di Matteo and Grootendorst (1998) found a slightly significant increase in drug expenditure in the population between 64 and 74, although

[6] Note that DID measures generally underestimate antibiotic use by children. Consequently, the estimated impact of young consumers could even be stronger.

the result is not confirmed by the more recent study by Di Matteo (2005). We show that individuals above 80 seem to reduce the per capita consumption of outpatient antibiotics. Because of major health problems, one can point out that people in the last few years of life are more likely to consume antibiotics in nursing homes or hospital clinics rather than getting them prescribed in outpatient care.

Some countries share cultural characteristics that may shape their attitudes towards the use of antibiotics. Indeed, public perception of the need for antibiotics and the prescription policy may be affected by cultural identities. These hypothesis are worth testing also in the light of differences observed in antibiotic consumption across regional clusters (Goossens et al., 2005). Cultural covariates introduced in our models exhibit significant coefficients. They indicate that antibiotic use is higher in southern and eastern part of Europe ($REGs$ and $REGe$) compared to western European countries. This result should generally account for cross-country differences in the characterisitics of the demand, hence in patients' attitude towards antibiotics. However, it is hard to exclude any dependence between demand and supply, i.e. patients and doctors, when decisions about consumption are taken. The correlation between geographical dummies and the density of doctors suggests that higher per capita antibiotic use in southern countries may not derive from consumers' attitudes only.

Note that the coefficient of $REGn$ is positive and theorizes that northern countries are likely to consume more antibiotics per capita than western countries, *ceteris paribus*. This is apparently surprising if compared with the descriptive statistics above. The reason lies in the interaction with supply-side factors such as the density of physicians and the remuneration system for doctors. When the effects of supply-side variables are not taken into account, the regional dummy $REGn$ is biased and the negative impact of cultural aspects in northern countries is overestimated. The rationale for lower antibiotic use in norther countries may then be due to lower physicians' density and the remuneration to general practitioners mainly based on capitation, rather than to cultural aspects. Indeed, an increase in the density of physicians in a country causes an increase in antibiotic DID. The coefficient of physicians' density is positive and quite significant. This might put forward some evidence of supply-induced demand of antibiotic treatment in European countries, *ceteris paribus.*

Moreover, physicians' attitudes toward prescriptions may respond to financial incentives attached to reimbursement schemes. These widely vary across Europe. Relatively high levels of consumption may be more likely if physicians are paid under a fee-for-service scheme compared to a capitation one. We found evidence that countries with a fee-for-service and a salary schemes are prone to consume more antibiotics per capita compared to countries adopting a capitation reimbursement. Variables PGP_1 and PGP_2 are both positive and significant. This is in accordance with the theoretical hypothesis on financial incentives under different payment schemes for physicians. Under a fee-for-service, doctors' revenue is usually related to the amount of prescriptions. The salary scheme may have similar effects. It can be argued that salaried practitioners lack of incentives to compete for patients compared to practitioners under a capitation payment. This could imply that under a capitation scheme doctors are likely to provide better quality services, hence more appropriate antibiotic treatments.

The association with bacterial resistance (*RES*) is positive as expected and highly significant. Higher rates of bacterial resistance are associated with an increase in the per capita antibiotic use in the following period. The result is confirmed in all the models. Coefficients are around 0.01 and suggest that the elasticity of antibiotic use to the number of penicillin non-susceptible *Streptococcus pneumonie* isolates is very small. Our findings may be weakened by the use of an indicator specifically constructed for penicillins (*% PNSP*). A similar result can be obtained by means of an alternative indicator, the percentage of *MRSA* isolates. However, the robustness is reduced since fewer data are available.

6 Conclusions

Antibiotic consumption is characterized by multiple market imperfections. Above all, increasing levels of bacterial resistance represent a harmful challenge for the society (Rudholm, 2002). It has been suggested that higher levels of antibiotic use may be associated to higher rates of bacterial resistance (Goossens et al., 2005). The battle against resistance is generally fought with the adoption of additional antibiotic components, which raises concerns about optimal levels of antibiotic consumption (Laxminarayan and Weitzman, 2002). The investigation of determinants of antibiotic use may represent an important contribution to the discussion about effective government interventions to induce an efficient use of drugs.

Comparable data on outpatient antibiotic use across European countries have been recently become available thanks to the European Surveillance of Antimicrobial Consumption (ESAC) network. Also, the quality of national data on bacterial resistance has been improved by the European Antimicrobial Resistance Surveillance System (EARSS). This unveiled an opportunity for more accurate investigations of antibiotic use across Europe.

We have shown that differences in outpatient antibiotic use across countries can hardly be explained by epidemiological, demographic and cultural factors only. Supply-side factors such as the density of doctors and economic incentives attached to the remuneration system may contribute to the explanation of variations in antibiotic consumption. The impact of bacterial resistance has been assessed simultaneously with other determinants.

Econometric estimations indicate that the per capita income, the proportion of children and the elderly, and cultural attitudes in southern and eastern countries induce higher levels of antibiotic use. On the other hand, higher levels of education reduce consumption. Increasing antibiotic use is also associated with a higher density of doctors and a fee-for-service and salary remuneration. Bacterial resistance has a positive impact on antibiotic use.

From a biological perspective, antibiotic use will lead to selection and emergence of antibiotic resistance (Malhotra-Kumar et al., 2007). But vice versa, bacterial resistance will result in (i) increased antibiotic use of the more recently available antibiotics (such as the fluoroquinolones) and/or (ii) increased dosage of the old classes of antibiotics to overcome resistance against these antibiotics (such as amoxicillin and amoxicillin/clavulanic acid). The former may have less impact on volume of use because it reflects the substitution of old by new antibiotics. The latter will result in a substantial increase of the number of DDDs (but not of the number of prescriptions). Finally, the volume use of antibiotics and proportions of resistance is for the most part stable. This is not surprising since in absence of national interventions that would abruptly change the utilisation pattern for an entire country, no trend changes would be expected. Indeed, mathematical models as well as empirical data suggest that following a reduction in prescribing, the decay of resistance will typically occur on a slower time scale then the rise in resistance (Austin et al., 1999)). Likely, no decline in resistance may occur even with a significant reduction of certain antibiotic families which can be attributed to the co-selection of genetically linked resistance determinants by alternative antibiotic pressure (Enne et al., 2001).

In conclusion, our findings assert that incentives for antibiotic prescribers are indeed important sources of variations in antibiotic consumption in outpatient care across Europe. Next to guidelines on appropriate use of antibiotics and awareness campaigns, economic incentives may provide opportunities for additional policies instruments.

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References

Austin DJ, Kristinsson KG, and Anderson RM. "The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance". *Proc Natl Acad Sci USA*, 96(3), 1152-6, 1999.

Baltagi BH. *Econometric Analysis of Panel Data*, 2 edition, John Wiley & Sons, 2001.

Baye MR, Maness R, and Wiggins SN. "Demand systems and the true subindex of the cost of living for pharmaceuticals", *Applied Economics*, 29, 1179-1189, 1997.

Becker GS. "A Theory of the Allocation of Time", *Economic Journal*, 75, 493-517, 1965.

Belongia EA, and Schwartz B. "Strategies for promoting judicious use of antibiotics by doctors and patients", *BMJ*, 317, 668-671, 1998.

Bremon AR, et al. "Non-hospital consumption of antibiotics in Spain: 1987-1997", *Journal Antimicrobial Chemotherapy*, 45, 395-400, 2000.

Butler CC, et al. "Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats", *BMJ*, 317, 637-642, 1998.

Cameron AC, and Trivedi PK, *Microeconometrics*, Cambridge University Press, 2005.

Cizman M. "The use and resistance to antibiotics in the community", *International Journal of Antimicrobial Agents*, 21, 297-307, 2003.

Cockburn J, and Pit S. "Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations - a questionnaire study", *BMJ*, 315, 520-523, 1997.

Coast J, Smith RD, and Millar MR. "An economic perspective on policy to reduce antimicrobial resistance", *Social Science and Medicine*, 46(1), 29-38, 1998.

Davey PG, Bax RP, Newey J, Reeves D, Rutherford D, Slack R, Warren RE, Watt B and Wilson J. "Growth in the use of antibiotics in the community in England and Scotland in 1980-93", *British Medical Journal*, 312, 613, 1996.

Di Matteo L. "The macro determinants of health expenditure in the United States and Canada: assessing the impact of income, age distribution and time", *Health Policy*, 71, 23-42, 2005.

Di Matteo L, and Grootendorst P. "Federal patent extension, provincial policies, and drug expenditures, 1975-2000", *Canadian Tax Journal*, 50(6), 2002.

Elbasha EH. "Deadweight loss of bacterial resistance due to overtreatment", *Health Economics*, 12, 125-138, 2003.

Elseviers M, Ferech M, Vander Stichele RH, and Goossens H. "Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations", *Pharmacoepidemiology and Drug Safety*, 16, 115-123, 2007.

Enne VI, Livermore DM, Stephens P, and Hall LM. "Persistence of sulphonamide resistance in Escherichia coli in the UK despite national prescribing restriction". *The Lancet*, 357(9265), 1325-8, 2001.

European Antimicrobial Resistance Surveillance System. *http://www.rivm.nl/earss* [December 2006].

European Observatory on Health Systems and Policies. *http://www.euro.who.int/observatory* [December 2006].

Eurostat. *http://epp.eurostat.ec.europa.eu* [December 2006].

Ferech M, Coenen S, Malhotra-Kumar S, Dvorakova K, Hendrickx E, Suetens K, and Goossens H. "European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe", *Journal of Antimicrobial Chemotherapy*, 58, 401-407, 2006.

Filippini M, Measiero G, and Moschetti K. "Socioeconomic determinants of regional differences in outpatient antibiotic consumption: Evidence from Switzerland", *Health Policy*, 78, 77-92, 2006.

Finch RG, Metlay JP, Davey PG, and Baker LL. "Educational interventions to improve antibiotic use in the community: report from the International Forum on antibiotic resistance (IFAR) colloquium", *The Lancet*, 4, 44-53, 2004.

Goossens H, Ferech M, Vander Stichele R, Elseviers M, and The ESAC Project Group, "Outpatient antibiotic use in Europe and association with resistance: a cross-national database study", *The Lancet*, 365, 579-587, 2005.

Greene WH. *Econometric Analysis*, New York: Prentice Hall, 2003.

Harbarth S, Albrich W, and Brun-Buisson C. "Outpatient antibiotic use and prevalence of antibiotic-resistance pneumococci in France and Germany: a sociocultural perspective", *Emerging Infectious Diseases*, 8(12), 2002.

Homer J, et al. "Toward a dynamic theory of antibiotic resistance", *System Dynamics Review*, 16(4), 287-319, 2000.

Hunt-McCool J, Kiker BF, and Ng YC. "Estimates of the demand for medical care under different functional forms", *Journal of Applied Econometrics*, 9(2), 201-218, 1994.

Kmenta J. *Elements of Econometrics*, 2d edition. New York: Macmillan Publishing Company, 1986.

Laxminarayan R, and Weitzman ML. "On the implications of endogenous resistance to medications", *Journal of Health Economics*, 21, 709-718, 2002.

Levy SB. "The challenge of antibiotic resistance", *Scientific American*, 278(3), 46-53, 1998.

Lleras-Muney A, and Lichtenberg FR. "The effect of education on medical technology adoption: are the more educated more likely to use new drugs?", *NBER Working Paper* 9185, 2002.

Macfarlane J, et al. "Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet", *BMJ*, 315, 1211-1214, 2002.

Malhotra-Kumar S , Lammens C, Coenen S, Van Herck K, and Goossens H. "Comparative Impact of Azithromycin and Clarithomycin Therapy on Pharyngeal Carriage of Macrolide-Resistant Streptococci among Healthy Volunteers. A Double-Blind, Placebo-Controlled, Longidudinal Study". *The Lancet*, 369: 482-490, 2007.

McGowan JE. "Economic impact of antimicrobial resistance", *Emerging Infectious Diseases*, 7(2), 286-292, 2001.

Newhouse JP. *Free for all? Lessons from the Rand Health Insurance Experiment Group.* Harward University press, Cambridge, 1993.

OECD. *OECD Health Data*, 2006.

Resi D, Milandri M , Moro ML and the Emilia Romagna Study Group on the Use of Antibiotics in Children, "Antibiotic prescriptions in children", *Journal of Antimicrobial Chemotherapy*, 52, 282–286, 2003.

Rizzo JA. "Advertising and competition in the ethical pharmaceutical industry: the case of antihypertensive drugs", *Journal of Law and Economics*, 42, 89-116, 1999.

Rudholm N. "Economic implications of antibiotic resistance in global economy", *Journal of Health Economics*, 21, 1071-1083, 2002.

Unsworth L, and Walley T. "Trends in primary care antibiotics prescribing in England 1994-1998", *Pharmacoepidemiology and Drug Safety*, 10, 309-314, 2001.

WHO, "Overcoming antimicrobial resistance", *World health report on infectious diseases*, 2000.

WHO, *The WHO global strategy for containment of antimicrobial resistance*, 2001.

Wise R, et al. "Antimicrobial resistance. Is a major threat to public health", *BMJ*, 317, 609-610, 1998.

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