



UNIVERSITA' DEGLI STUDI DI BERGAMO
DIPARTIMENTO DI INGEGNERIA GESTIONALE
QUADERNI DEL DIPARTIMENTO[†]

Department of Economics and Technology Management

Working Paper

n. 03 – 2009

*Socio-economic determinants of outpatient antibiotic consumption in
Europe*

by

**Giuliano Masiero, Massimo Filippini, Matus Ferech, Herman Goossens,
The ESAC project group**

[†] Il Dipartimento ottempera agli obblighi previsti dall'art. 1 del D.L.L. 31.8.1945, n. 660 e successive modificazioni.

COMITATO DI REDAZIONE[§]

Lucio Cassia, Gianmaria Martini, Stefano Paleari, Andrea Salanti

[§] L'accesso alla Collana dei Quaderni del Dipartimento di Ingegneria Gestionale è approvato dal Comitato di Redazione. I *Working Papers* della Collana costituiscono un servizio atto a fornire la tempestiva divulgazione dei risultati dell'attività di ricerca, siano essi in forma provvisoria o definitiva.

Socio-economic determinants of outpatient antibiotic consumption in Europe

Giuliano Masiero*

Massimo Filippini[‡]

Matus Ferech[∞]

Herman Goossens[°]

The ESAC project group

June 2009

Abstract

Outpatient antibiotic consumption widely vary across Europe. The investigation of what lies behind such variation may help to identify sources of inefficiency. Comparable data on antibiotic use in 21 European countries between 1997 and 2005 are provided by the European Surveillance of Antimicrobial Consumption (ESAC). Data on determinants are available for 17 countries between 2000 and 2005. We estimate an ad-hoc econometric model to assess the impact of socio-economic determinants of antibiotic consumption and the role played by bacterial resistance knowledge. The population income, the demographic structure, the density of general practitioners and their remuneration method appear to be significant determinants of antibiotic consumption. Although countries with higher levels of bacterial resistance exhibit significantly higher levels of per capita antibiotic use, *ceteris paribus*, the responsiveness of antibiotic use to changes in bacterial resistance is relatively low (0.009-0.015). This may suggest that the dissemination of information on bacterial resistance across Europe lacks effectiveness. Next to guidelines on appropriate use of antibiotics and awareness campaigns, economic incentives to general practitioners may provide opportunities for additional policy instruments to increase efficiency in antibiotic consumption.

JEL classification: I0; C3

Keywords: Antibiotic use. Cross-country variations. Bacterial resistance.

* Department of Economics and Technology Management, University of Bergamo, Italy; correspondence address: Department of Economics, University of Lugano, via Buffi 5, 6900 Lugano, Switzerland; E-mail: giuliano.masiero@lu.unisi.ch; Tel.: +41 058 666 4731.

[‡] Department of Economics, University of Lugano; ETH, Zurich, Switzerland.

[∞] Laboratory of Microbiology, University of Antwerp, Belgium; Enterprise and Industry DG, Pharmaceuticals Unit, European Commission, Brussels.

[°] Laboratory of Microbiology, University of Antwerp, Belgium; Laboratory of Microbiology, Leiden University Medical center, Leiden, The Netherlands.

1. Introduction

The market for antibiotics is characterised by multiple imperfections. Above all, antibiotic use may contribute to the selection of resistant bacteria (Elbasha, 2003). This leads to the production of newer and more effective generations of drugs, thus raising the costs for society (McGowan, 2001).

Although antibiotic prescriptions have slightly decreased during the 90s and have been roughly stable in recent years, prescribing practices still vary widely across countries (Elseviers et al. 2007). Mean figures of defined daily doses per 1000 inhabitants (DID) for 21 European countries participating in the European Surveillance of Antimicrobial Consumption (ESAC) project and able to provide comparable and reliable data for at least 7 years between 1997 and 2005 show that France (31.55 DID), Greece (29.67 DID), and Spain (27.31 DID), among others, exhibit significantly higher values of antibiotic use than Austria (12.47 DID), Denmark (13.08 DID), and the Netherlands (10 DID) (see Figure 1).

The investigation of what lies behind such variation may help to identify sources of inefficiency in antibiotic consumption. To our knowledge there are no multifactorial analysis of socio-economic determinants of outpatient antibiotic use at European level. Previous studies have rather focused on regional variations within a country (Matuz et al., 2006). Comparable data on outpatient antibiotic use and bacterial resistance across European countries has only recently become available and the impact of information on bacterial resistance has not been previously investigated together with other factors.

The knowledge of overall levels of bacterial resistance within a country is likely to be shared by health care providers. In several countries guidelines on antibiotic treatment and information on routine tests concerning bacterial resistance are issued by hospitals or local health authorities every year or every two years. Guidelines are available to general practitioners in the area. This conveys the idea that bacterial resistance is an indicator of poor quality of treatment. If doctors are concerned about resistance externalities, higher levels of bacterial resistance would induce them to prescribe antibiotics more

carefully. On the other hand, if the quality of treatment is poor, i.e. there are relatively high levels of bacterial resistance, increasing rates of antibiotic use may be required to overcome the reduced antibiotic effectiveness.¹ Bacterial resistance can then be seen as a bad that must be produced as a joint product of the antibiotic treatment process.

This article proposes an econometric model to study the determinants of outpatient antibiotic use in Europe. Since the interaction between socio-economic determinants of consumption and information on bacterial resistance is simultaneously taken into account and the impact of each single determinant is assessed, we argue that the approach can provide an indirect assessment of the effectiveness of policies implemented across Europe between 2000 and 2005 to control antibiotic use and, consequently, to reduce the social impact of endogenous bacterial resistance.

The article is organised as follows. In Section 2 we present the econometric specification and discuss the data. Estimation results are analysed in Section 3. Finally, section 4 concludes.

2. Methods

Our approach to the investigation of determinants of antibiotic consumption in Europe is to specify an econometric model using a set of covariates suggested by the literature.² This method is 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. (2009) to study small area variations in the use of antibiotics in Switzerland.

¹ Antibiotic resistance may drive prescribing of new, broad-spectrum antibiotics (Austin et al., 1999; Albrich et al., 2004). Moreover, bacterial resistance may result in an increased volume of antibiotics if retreatment is necessary after traditional treatment failure. Although resistance is primarily caused by an increasing use of antibiotics, the subsequent increase in broad spectrum antibiotics is a secondary and perhaps relevant effect (Woodhead, 2005).

² Among possible determinants, the literature mentions the level of education, physicians and patients' expectations, cultural aspects, regulatory practices, and antibiotic prices (Belongia and Schwatz, 1998; Finch et al. 2004).

We define an ad-hoc demand function for antibiotics used in outpatient care in Europe which depends upon the individuals' health status, patients' attitudes towards the use of drugs, antibiotic price and the characteristics of health care supply, such as physicians' density, physicians' remuneration scheme and information on the quality of antibiotic treatment, i.e. levels of bacterial resistance. Socio-economic variables are usually included in the model as proxies for the individuals' stock of health, which is difficult to measure. We also include mortality for infectious diseases.

The per capita demand of outpatient antibiotics can then be specified by the following parsimonious model:

$$DID_{it} = f(Y_{it}, DPH_{it}, POP_{1it}, EDU_{it}, PGP_{kit}, P_{it}, REG_{hi}, INF_{it}, RES_{it}) \quad (1)$$

where DID_{it} is the per capita antibiotic use in country i and year t , Y_{it} is the per capita national income, DPH_{it} 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 (25-64) with at least upper secondary education.

The type of remuneration system for general practitioners is taken into account by means of dummy variables. 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. P_{it} is a price index for a defined daily dose of antibiotics.

A "cultural" or geographical dummy (REG_{hi}) that takes into account similarities with adjacent countries and cultural differences across Europe is also included. We divide countries into four groups: "North" ($REG_{ni}=1$), "South" ($REG_{si}=1$), "East" ($REG_{ei}=1$), and "West", i.e. the reference group.

Finally, INF_{it} and RES_{it} capture the impact of infections and the rate of bacterial resistance. We use mortality rates for infectious diseases as a proxy for the incidence of bacterial infections since other

indicators are less exhaustive and less reliable. The level of bacterial resistance can be seen as an indicator of (bad) quality of care since it reduces antibiotic effectiveness. Since the impact of infectious diseases and bacterial resistance may be endogenous, the estimation procedure of equation 1 will address this problem later on.

The estimation of equation 1 requires the specification of a functional form. Several alternative forms can 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 use 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 dummy variables. Thus, we use a hybrid log-log functional form.

The functional specification can then be written as:

$$\begin{aligned} \ln DID_{it} = & \beta_0 + \beta_1 \ln Y_{it} + \beta_2 \ln DPH_{it} + \sum_{j=3}^6 \beta_j \ln POP_{jit} + \beta_7 \ln EDU_{it} + \sum_{k=8}^9 \beta_k PGP_{kit} + \beta_{10} P_{it} \\ & + \sum_{h=11}^{12} \beta_h REG_{hi} + \beta_{13} INF_{it} + \beta_{14} RES_{it} + v_i + \varepsilon_{it}, \end{aligned} \quad (2)$$

where $\ln()$ is a natural logarithm applied to the variable and v_i and ε_{it} are error terms with standard distribution assumptions. Only 17 countries out of 21 are considered for regressions with the STATA software since resistance and mortality data are not always available.⁴

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 variations over time, i.e.

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.

⁴ Belgium, Poland, Slovakia and Greece are excluded from the analysis.

heterogeneity across units and periods. The most widely used approaches are the fixed-effects model and the random-effects model.⁵

In order to choose the econometric approach it is important to consider that our dataset is a panel characterised by a relatively small number of time periods as well as 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, we focus on random-effects GLS regressions (*Model 1*).

However, since bacterial infections and resistance are plausibly endogenous, the estimation of equation 2 may lead to biased results. To tackle this problem we consider two alternative approaches: the inclusion of lagged values (*Model 2*) and the instrumental variable method (*Model 3*). In *Model 2* instead of INF_{it} we use INF_{it-1} - the lagged mortality rate for infectious diseases, and instead of RES_{it} we use RES_{it-1} - the lagged rate of bacterial resistance.

For the instrumental variables approach we considered some variables related to the spread process of infections. The density of the population and the size of a country may plausibly contribute to the spread of infections. Levels of bacterial resistance may be related to the extensive use of antibiotics in agriculture and in animal breeding.⁶ Thus, we specify a model (*Model 3*) by instrumenting the rate of bacterial resistance and the mortality from infectious diseases with the density of the population (POP_{DEN}_{it}), the country area ($AREA_{it}$), the production of milk ($MILK_{it}$) and pigs (PIG_{it}). In this case, a two-stage least technique with random effects is applied.

⁵ For a detailed presentation of the econometric methods used to analyse panel data, see Greene (2003) and Baltagi (2005).

⁶ As an example, *Campylobacter* is the most-frequently reported zoonotic pathogen causing human illnesses and resistant bacteria tend to be harboured in the meat produced (Swiss National Science Foundation, 2007). The common practice of using milk produced during antibiotic treatment for feeding calves and pigs causes a marked selection for resistant bacterial strains (i.e. enterococci) which may enter the food chain.

Annual data available on determinants of outpatient antibiotic use between 1997 and 2005 are summarised in Table 1. These include socio-economic characteristics of the population (income, demographic structure, education and cultural/regional clusters), supply-side factors (density of doctors and the system of remuneration), the incidence of bacterial infections (mortality rates), price, and levels of bacterial resistance.

Data are obtained from a variety of sources. Information on per capita income (measured in US dollars in purchasing power parity), density of physicians, the level of education and the incidence of infections are extracted from publications by the OECD (OECD Health Data, 2007). The demographic structure of the population is derived from Eurostat tables (Eurostat, 2007). Looking at yearly country profiles published by the European Observatory on Health Systems and Policies (2007), we collect information on the main type of payment system on hold for general practitioners (fee-for-service, capitation and salary).

We derive price levels for antibiotics during 2000-2005 by combining information from two indicators: the comparative price level index (PLI) and the harmonized annual average price index (HICP) for pharmaceutical products.⁷

As for the levels of bacterial resistance, data are obtained from the European Surveillance on Antimicrobial Resistance database (EARSS, 2007). 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. Available data on bacterial resistance reduces the time span for the analysis since the systematic collection of bacterial resistance across European countries has not started until recently (from 1999/2000).

⁷ The PLI indicates the price level of each country compared to the average price level of the 25 EU countries in 2005. The HICP includes information on price trends for pharmaceuticals for each country during 2000 and 2005, where 2005=100. These indices are provided by Eurostat

3. Results

The parameter estimates of the three models are summarised in Table 2. The results are satisfactory and stable and no structural difference is observed across the models.

The coefficient of income suggests that richer countries use more outpatient antibiotics compared to lower-income countries. The responsiveness of the per capita outpatient antibiotic use to a 1% change in the average national income, *ceteris paribus*, is between 0.71% and 0.85%. The result conjectures that antimicrobials are normal goods, as argued by Baye et al. (1997), whose calculated income elasticity was 1.33, but contrasts with findings on regional Swiss data (-0.5) analyzed by Filippini et al. (2006).

The level of education is highly significant only in model 2 and is very close to zero. 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 indicates that antibiotics are quite peculiar. Hunt-McCool et al. (1994) find positive education elasticity to physician office visits and hospital care, although the impact is not very significant. In the case of antibiotics, educated individuals may restrain from using antibiotics if they are aware of the potential implications of bacterial resistance.

Our estimations show positive and significant coefficients for the proportion of individuals between 14 and 25. The impact of individuals below 14 is also positive, although not highly significant. Finally, we find a positive and significant effect of the proportion of the population between 65 and 79 in the three models. 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. Di Matteo and Grootendorst (2002) observe a slightly significant increase in drug expenditure in the population between 64 and 74, although the result is not confirmed by the more recent study by Di Matteo (2005). 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 to get them prescribed in outpatient care. Indeed, we observe that individuals over 80 seem to reduce the *per capita* consumption of outpatient antibiotics.

Some countries share cultural characteristics that may shape their attitudes towards the use of antibiotics. The impact of regional covariates introduced in our models is unclear. They indicate that antibiotic use is higher in southern and eastern Europe compared to western Europe, although not significantly.

The physicians' density has a positive and significant effect in all of the three estimations. This might put forward some evidence of supply-induced demand. Moreover, variables PGP_1 and PGP_2 are both positive and significant, which is in accordance with the hypothesis on financial incentives under different payment schemes for physicians. Under a fee-for-service, doctors' revenue is usually related to the number and the time of consultations. This may imply a positive relationship with the amount of prescriptions, though not straightforwardly. Doctors may then be prone to meet patients' preferences for antibiotic treatment since the risk of losing disappointed patients immediately after a consultation is higher compared to the capitation scheme. Conversely, under a capitation scheme doctors may have less incentives to prescribe antibiotics. This is because the quality of treatment is not directly related to the quantity of antibiotics prescribed but may improve with doctor's ability to induce patient's compliance and to reduce inappropriate antibiotic use. Similarly to the fee-for-service, salaried practitioners may lack incentives to restrain from prescribing antibiotics.

Individuals' health status is significant at less than 5% level in the two-stage least squares specification.⁸

The coefficients exhibit the expected positive sign and suggest that outpatient antibiotic expenditure is not very elastic to the impact of epidemiological factors. Looking at the pharmaceutical consumption for

⁸ Similar results are obtained by using mortality for pneumonia and influenza instead of mortality for infectious diseases. Data available for the former variable are fewer and reduce the number of observations in our estimations.

cardiovascular disease and stroke, Dickson and Jacobzone (2003) find that drug use is strongly related to indicators of the burden of disease only for more effective and inexpensive types of drugs.

Generally, antibiotics are perceived as necessary in the case of presumed bacterial infections. Since antibiotics are purchased under doctor's prescription, their demand may be less elastic to price compared to other types of drugs. In our estimations, price elasticity has the expected negative sign in all the three models, with a 5% significance level in model 1 and model 3. Looking at prices for anti-infectives, Baye et al. (1997) find negative compensated (-0.785) and uncompensated (-0.916) own-price effects. Focusing on the demand for one antibiotic class - the cephalosporins - Ellison et al. (1996) calculate own-price elasticities for different brand/generic names unconditional on drug expenditure using US wholesale data from 1985 to 1991. Their estimates range from -0.38 to -4.34 and are very close to our results (-0.437 in *model 1* and -0.403 in *model 3*).

The association between antibiotic use and bacterial resistance is positive and highly significant in all the three model specifications. A 1% increase in the level of bacterial resistance induces an increase in antibiotic consumption between 0.009% and 0.015%.⁹ The higher values of estimated elasticities are obtained when endogeneity of bacterial resistance is taken into account. Consequently, the role of bacterial resistance may be underestimated when endogeneity is not addressed.

4. Conclusion

The investigation of socio-economic determinants of antibiotic use may contribute to the discussion about effective government interventions to induce an efficient use of drugs. Using an econometric

⁹ Since general indicators for bacterial resistance are not available we used specific indicators such as the proportion of penicillin non-susceptible *Streptococcus pneumoniae* isolates (PNSP). Clearly, these indicators can only be partially associated to total antibiotic use but still represents a valid information for the overall magnitude of bacterial resistance in a country. Our results are generally confirmed with alternative indicators, for instance the percentage of MRSA (methicillin-resistant *Staphylococcus aureus*) isolates.

approach, 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 appear to play an important role. Indeed, higher levels of antibiotic use per capita are associated with higher density of doctors and a fee-for-service remuneration scheme.

Increasing levels of bacterial resistance represent a harmful challenge for the society (Rudholm, 2002). Several studies show that changes in antimicrobial use may be followed by changes in antimicrobial resistance (Bergman et al., 2004; Stephenson, 1996). Moreover, bacterial resistance may result in (i) an increased antibiotic use of the more recently available antibiotics (such as the fluoroquinolones) and/or (ii) an increased dosage of the old classes of antibiotics to overcome resistance against these antibiotics (such as amoxicillin and amoxicillin/clavulanic acid) (Woodhead, 2005). The former effect may have a minor impact on the volume of use if it reflects the substitution of old by new antibiotics only. The latter may result in a substantial increase of the number of doses. In both cases the number of doses may increase through the number of prescriptions if there are more treatment failures associated with resistance and the need for retreatment, possibly with increased dosage or alternative antibiotics. Conversely, the awareness of resistance externalities by doctors, patients and policy makers should result in lower rates of antibiotic use to reduce the social costs of lower antibiotic effectiveness.

We estimated that bacterial resistance has a positive and significant impact on antibiotic use although the responsiveness is relatively low. This may suggest doctors' and patients' perceptions of the social implications of bacterial resistance are not very strong or that the dissemination of information on bacterial resistance is not very satisfactory. Next to guidelines on appropriate use of antibiotics and awareness campaigns, economic incentives to general practitioners may provide opportunities for additional policy instruments to increase efficiency in antibiotic consumption.

Acknowledgments

The ESAC Project Group members are Helmut Mittermayer, Sigrid Metz (Austria); Herman Goossens (Belgium); Boyka Markova (Bulgaria); Arjana Andrasevic, Igor Francetic (Croatia); Despo Bagatzouni (Cyprus); Jiri Vlcek (Czech Republic); Dominique L. Monnet, Annemette Anker Nielsen (Denmark); Ly Rootslane (Estonia); Pentti Huovinen, Pirkko Paakkari (Finland); Philippe Cavalié, Didier Guillemot (France); Winfried Kern, Helmut Schroeder (Germany); Helen Giamarellou, Anastasia Antoniadou (Greece); Gabor Ternak (Hungary); Karl Kristinsson (Iceland); Robert Cunney, Ajay Oza (Ireland); Raul Raz (Israel); Giuseppe Cornaglia (Italy); Sandra Berzina (Latvia); Rolanda Valenteliene (Lithuania); Robert Hemmer, Marcel Bruch (Luxembourg); Michael Borg, Peter Zarb (Malta); Robert Janknegt, Margreet Filius (the Netherlands); Hege Salvesen Blix (Norway); Waleria Hryniewicz, Pawel Grzesiowski (Poland); Luis Caldeira (Portugal); Irina Codita (Romania); Leonid Stratchounski (deceased June 7, 2005), Svetlana Ratchina (Russia); Viliam Foltan, Tomas Tesar (Slovakia); Milan Cizman (Slovenia); José Campos (Spain); Otto Cars, Gunilla Skoog, Sigvard Mölsted (Sweden); Giuliano Masiero (Switzerland); Serhat Unal (Turkey); Peter Davey (UK).

References

- Albrich, W., Monnet, D., Harbarth, S., 2004. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerging Infectious Diseases* 10 (3), 514-517.
- Austin, D.J., Kristinsson, K.G., Anderson, R.M., 1999. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proceedings of the National Academy of Sciences of the United States of America* 96 (3), 1152-1156.
- Baltagi, B.H., 2005. *Econometric analysis of panel data*, 3rd edition, John Wiley & Sons.
- Baye, M.R., Maness, R., Wiggins, S.N., 1997. Demand systems and the true subindex of the cost of living for pharmaceuticals. *Applied Economics* 29 (9), 1179-1189.
- Belongia, E.A., Schwartz, B., 1998. Strategies for promoting judicious use of antibiotics by doctors and patients. *British Medical Journal* 317 (7159), 668-671.
- Bergman, M., Huikko, S., Pihlajama, M., Laippala, P., Palva, E., Huovinen, P., Seppa, H., the Finnish study group for antimicrobial resistance, 2004. Effect of macrolide consumption on erythromycin resistance in *Streptococcus pyogenes* in Finland in 1997--2001. *Clinical Infectious Diseases* 38 (9), 1251-1256.
- Cameron, A.C., Trivedi, P.K., 2005. *Microeconometrics*. Cambridge University Press.
- Cockburn, J., Pit, S., 1997. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations - a questionnaire study, *British Medical Journal*, 315, 520-523.
- Dickson, M., Jacobzone, S., 2003. Pharmaceutical use and expenditure for cardiovascular disease and stroke: a study of 12 OECD countries, *OECD Health Working Papers*.
- Di Matteo, L., 2005. The macro determinants of health expenditure in the United States and Canada: assessing the impact of income, age distribution and time. *Health Policy* 71 (1), 23-42.
- Di Matteo, L., Grootendorst, P., 2002. Federal patent extension, provincial policies, and drug expenditures, 1975-2000. *Canadian Tax Journal* 50 (6), 1913-1948.
- Elbasha, E.H., 2003. Deadweight loss of bacterial resistance due to overtreatment. *Health Economics* 12 (2), 125-138.
- Ellison, S.F., Cockburn, I., Griliches, Z., Hausman, J., 1996. Characteristics of demand for pharmaceutical products: an examination of four cephalosporins. *Rand Journal of Economics* 28 (3), 426-446.
- Elsevier, M., Ferech, M., Vander Stichele, R.H., Goossens, H., 2007. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. *Pharmacoepidemiology and Drug Safety* 16 (1), 115-123.
- European Antimicrobial Resistance Surveillance System, <http://www.rivm.nl/earss> [December 2007].

European Observatory on Health Systems and Policies, <http://www.euro.who.int/observatory> [December 2007].

Eurostat, <http://epp.eurostat.ec.europa.eu> [December 2007].

Filippini, M., Masiero, G., Moschetti, K., 2006. Socioeconomic determinants of regional differences in outpatient antibiotic consumption: Evidence from Switzerland. *Health Policy* 78 (1), 77-92.

Filippini M., Masiero G., Moschetti K., 2009. Small area variations and welfare loss in the use of outpatient antibiotics. *Health Economics, Policy and Law* 4 (1), 55-77.

Finch, R.G., Metlay, J.P., Davey, P.G., Baker, L.L., 2004. Educational interventions to improve antibiotic use in the community: report from the International Forum on antibiotic resistance (IFAR) colloquium. *The Lancet* 4 (1), 44-53.

Goossens, H., Ferech, M., Vander Stichele, R., Elseviers, M., the ESAC project group, 2005. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *The Lancet* 365 (9459), 579-587.

Greene, W.H., 2003. *Econometric Analysis*. Prentice Hall, New York.

Hunt-McCool, J., Kiker, B.F., Ng, Y.C., 1994. Estimates of the demand for medical care under different functional forms. *Journal of Applied Econometrics* 9 (2), 201-218.

Matuz, M., Benko, R., Doro, P., Haidu, E., Nagy, G., Nagy, E., Monnet, D.L., Soos, G., 2006. Regional variations in community consumption of antibiotics in Hungary, 1996-2003, *British Journal of Clinical Pharmacology* 61 (1), 96-100.

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

OECD, 2007. *OECD Health Data*.

Rudholm, N., 2002. Economic implications of antibiotic resistance in a global economy", *Journal of Health Economics* 21 (6), 1071-1083.

Stephenson, J., 1996. Icelandic researchers are showing the way to bring down rates of antibiotic-resistant bacteria. *JAMA* 275 (3), 175.

Swiss National Science Foundation, 2007. *National Research Programme NRP 49: Antibiotic Resistance, Final Report*.

Woodhead, M., Blasi, F., Ewig, S., Huchon, G., Leven, M., Ortqvist, A., Schaberg, T., Torres, A., van der Heijden, G., Verheij, T.J.M., 2005. Guidelines for the management of adult lower respiratory tract infections. *European Respiratory Journal* 26 (6), 1138-1180.

Description	Variables	Mean	Std. Dev.	Min.	Max.
Outpatient antibiotic consumption	DDDs per 1000 inhab. per day (DID)	20.30	6.18	9.75	34.72
Income per capita	GDP in PPP/pop. (Y)	25926	9747	8898	70600
Population density	Population/km ²	130.34	98.89	2.62	392.64
Demographic structure of population	Pop. under 14/pop. (POP ₁)	17.90	2.27	14.1	24
	Pop. 15-24/pop. (POP ₂)	13.41	1.89	10.4	17.5
	Pop. 25-64/pop. (POP ₃)	53.67	1.94	47.9	57.7
	Pop. 65-79/pop. (POP ₄)	11.53	1.49	8.5	14.7
	Pop. over 80/pop. (POP ₅)	3.45	0.80	1.8	5.4
Attainment of high education	Pop. with upper secondary education/total pop. (EDU)	66.18	16.91	17.8	89.9
Density of doctors	Nr./1000 inhab. (DPH)	3.14	0.61	1.9	4.9
Bacterial resistance	Nr. PNSP isolates/tested isolates (RES)	11.25	10.99	0	48
Infections	Mortality rate for infectious diseases	6.70	3.64	2	20.1
Country area	km ²	203067.5	170135	2586	551500
Animal production	Cow's milk (1000 t)	7091.39	7801.24	113	28723.9
	Number of pigs (1000)	7045.43	7615.61	3.51	26989.1
		Number of countries			
		1997-2000	2001-2005		
GPs reimbursement	Capitation	10	10		
	Fee-for service (PGP ₁ = 1)	4	5		
	Salary (PGP ₂ = 1)	7	6		
Price	Comparative price levels for pharmaceutical products	21	21		
Cultural aspects (regional clusters)	West	6	6		
	East (REG _e = 1)	4	4		
	North (REG _n = 1)	7	7		
	South (REG _s = 1)	4	4		

Table 1: Variables notation and summary statistics.

	Model 1		Model 2		Model 3	
	Random-effects GLS		Random-effects GLS		Random-effects 2SLS	
Obs.	81		Obs.	83	Obs.	81
Wald $\chi^2(16)$	639.57 ^d		Wald $\chi^2(16)$	708.51 ^d	Wald $\chi^2(17)$	630.54 ^d
R ² (overall)	0.9090		R ² (overall)	0.9148	R ² (overall)	0.9074
Variables	Coeff.	Std. Err.	Coeff.	Std. Err.	Coeff.	Std. Err.
Constant	-6.627295 ^d	1.749882	-6.851335 ^d	1.455432	-7.220176 ^d	1.812758
lnY	.7798388 ^d	.1433832	.7121763 ^d	.1025463	.8518591 ^d	.1531678
POP ₁	.0262406	.0348197	.0054376	.0215031	.0193611	.0354117
POP ₂	.0688448 ^c	.0239373	.1095265 ^d	.0212367	.0552193 ^b	.0254125
POP ₄	.2060824 ^d	.0345925	.1929409 ^d	.0296339	.1980966 ^d	.0351922
POP ₅	-.2369182 ^d	.0617537	-.1207789 ^b	.0559627	-.2525716 ^d	.0637246
EDU	-.0029463	.0038377	-.0084978 ^c	.0027534	-.0022773	.0039009
REG _e	.1030227	.1633479	.2736013 ^b	.1303155	.1714670	.1698326
REG _n	.3148661 ^c	.1045596	.2218048 ^c	.0843911	.3786041 ^c	.1150470
REG _s	.076417	.1974833	-.0833759	.130632	.0812201	.1994036
DPH	.1708393 ^c	.0601477	.1317017 ^c	.050695	.1918101 ^c	.0629893
PGP ₁	.1961537 ^b	.0764034	.3088698 ^d	.0677188	.1301179	.0877345
PGP ₂	.140456 ^c	.0442585	.1942793 ^d	.0401293	.1170945 ^b	.0477875
P _t	-.437112 ^b	.1904187	-.1834193	.1681948	-.4033169 ^b	.1934067
INF _t	-.0042152	.0075902	-	-	.0005976	.0089142
INF _{t-1}	-	-	-.0185863 ^c	.0065809	-	-
RES _t	.0122405 ^d	.0025871	-	-	.0150385 ^d	.0030539
RES _{t-1}	-	-	.0092705 ^d	.0022712	-	-
t	-.0021771	.0148391	-.0074614	.0111756	-.0093010	.0156017
σ_{κ}		0		0		.0000001
σ_{ε}		.04187606		.06126256		.0443676
ρ		0		0		0

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

Table 2: Parameter estimates for the three models.

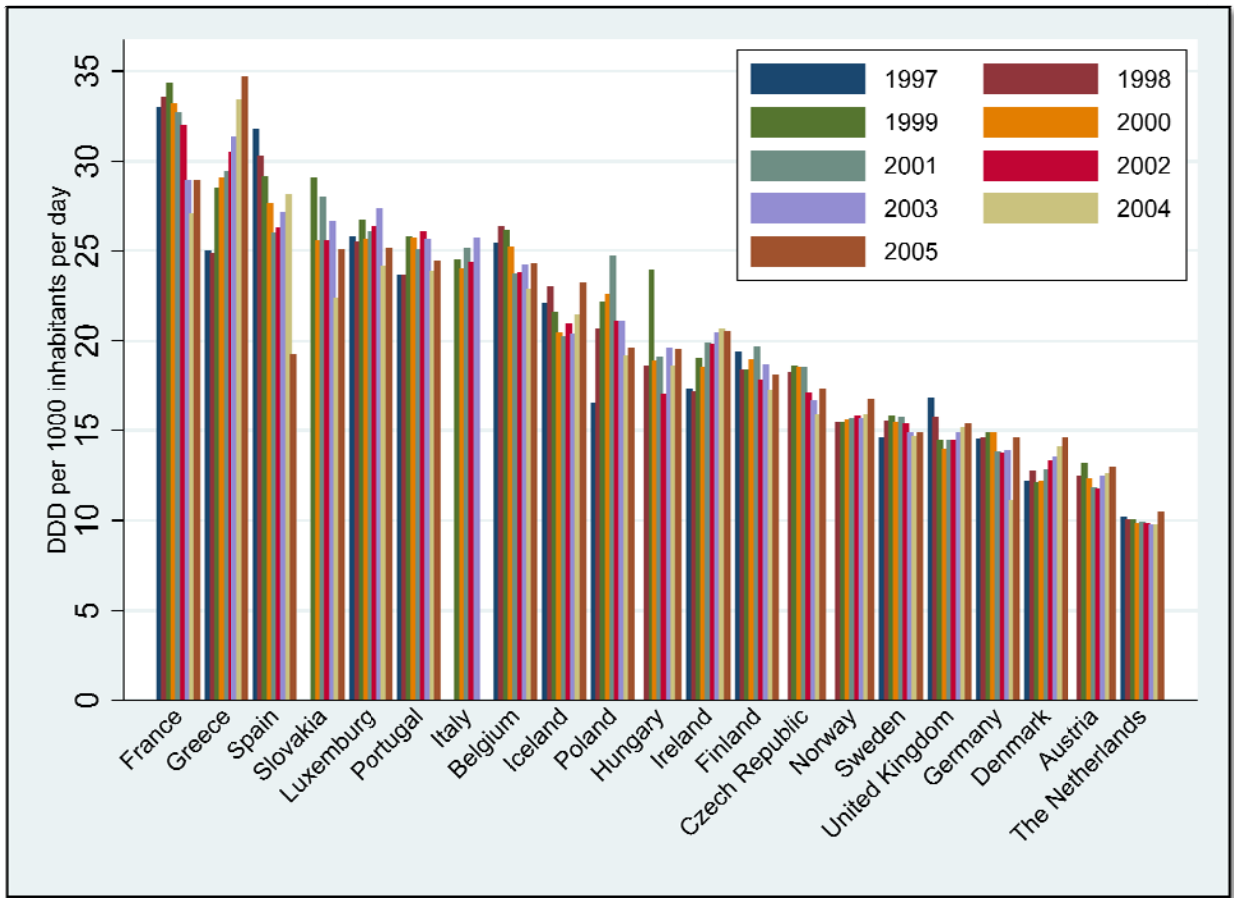


Figure 1: Outpatient antibiotic use in Europe by country and year.