A spatial-dynamic approach to the demand for outpatient antibiotics

M. Filippini [*] G. Masiero [†] K. Moschetti [‡]

January 2009

Abstract

We model demand for different classes of antibiotics used for respiratory infections in outpatient care in Switzerland using a spatial version of the linear approximate almost ideal demand system model. This takes spatial dependency into account by mean of spatial lags of antibiotic budget shares. We control for patients' health status and the potential harmful effects of antibiotic use, i.e. levels of bacterial resistance. We compute elasticities to socioeconomic determinants of consumption and own- and cross-price elasticities between different groups of antibiotics. Significant cross-price elasticities are found between newer/more expensive generations and older/less expensive generations of antibiotics.

JEL classification: I0; C3; C43

Keywords: Antibiotic use; Demand equations; Demand elasticities; Almost Ideal Model; Bacterial esistance.

[*]Department of Economics, University of Lugano; Swiss Federal Institute of Technology, Zurich, Switzerland. Support from the Swiss National Science Foundation is acknowledged. We are grateful to Dr. Enos Bernasconi and Dr. Marco Bissig from the Cantonal Hospital of Lugano for invaluable advice on the selection of antibiotic categories. Any mistake is clearly our fault.

[†]Department of Economics and Technology Management, University of Bergamo, Italy; Department of Economics, University of Lugano, Switzerland.

[‡]Department of Economics, University of Lugano; IMS, University of Lausanne, Switzerland.

1 Introduction

Antibiotics differ from other pharmaceutical products in many peculiar aspects (Ellison and Hellerstein, 1999). Because of their pharmacological characteristics, they are generally prescribed by doctors. Consequently, patients' preferences for specific therapeutical components may be of little relevance. On the other hand, such aspects as the price may play an important role if consumers bear directly a substantial share of the cost of drugs.

In primary care, doctors may face a first tradeoff between prescribing or delaying an antibiotic therapy under uncertainty on the nature of patient's infection (viral or bacterial). Although the antibiotic therapy is not effective against common viral infections, expected cost savings (time and troubles) in the case of bacterial infections may overcome the expected social loss from bacterial resistance. From the economic point of view, bacterial resistance accounts for relevant external effects. First, several antibiotic therapies can be prescribed before finding the effective one, hence leading to income loss or even premature deaths. Second, the reduced effectiveness of drugs increase social costs to produce new generations of pharmaceutical components.

A second tradeoff is observed between prescribing broad spectrum or narrow spectrum antibiotics. Although the intensive use of broad spectrum components reduces uncertainty in the outcome of the treatment, this may generate higher levels of bacterial resistance. It has been argued that the persistent use of one type of antibiotics may be sub-optimal for the society. The literature suggests that the negative externality of resistance can be reduced by changing the type of antibiotic used (Ellison and Hellerstein 1999; Laxminarayan and Weitzman, 2002; Rowthorn and Brown, 2003), since the same type of bacteria may be susceptible to more than one antibiotic component.[1]

[1] Increasing rates of Streptococcus pneumonie strains resistant to penicillin has led to the use of macrolides. However, the clinical effectiveness of the latter category has began to decrease as well (Alvarez-Elcoros and Enzler, 1999). The analysis by Ednie et al. (1996) suggests that in areas where penicillin-resistant strains are common, the empirical antibiotherapy using macrolides should then be changed.

Regional heterogeneity in the mix of antibiotics used has been recently observed within countries (Filippini et al., 2006; Kern et al., 2006). This may indicate that some antibiotic components are preferred by local physicians and patients, which raises the issue of optimal use at local level. The increase of resistant organisms force physicians to face an effectiveness constraint in substituting away some types of antibiotics with newer and more effective ones.[2] However, substantial local differences in the mix of antibiotics can hardly be explained only by levels of bacterial resistance and, consequently, the internalization in doctors' and patients' decisions. There is no evidence that bacterial resistance significantly varies at local level but the availability of detailed information on its impact and the spread of local guidelines is quite poor. Plausibly, doctors differ in attitudes towards the same type of antibiotics and their strategies can be influenced by patients' characteristics, antibiotic price and economic incentives.

The current paper focuses on factors affecting the local mix of main antibiotics categories in Switzerland. The analysis suggests that policy instruments, such as locally differentiated taxes on antibacterials affected by resistance problems, may induce a better use of antibiotics.

The demand for specific antibiotic groups has been investigated in studies by Ellison et al. (1997) and Chaudhuri et al. (2003). The focus is on the structure of the demand for two segments of the market: cephalosporins and quinolones. Demand is modelled in two stages: a substance is firstly chosen among a set of substances and a brand/generic version of the product is chosen afterwards. The approach is suitable for the analysis of specific categories of antibiotics since substances constitute close therapeutic substitutes and may be similar in tems of the impact of bacterial resistance. The models relies on the hypothesis that physicians' decisions within a given antibiotic category do not depend on the availability of alternative categories and are firstly based on specific names of substances. We argue, however, that this scenario may not reflect the patient's and doctor's view correctly. Indeed, doctors an

[2]The resistance-induced antibiotic substitution has been recently addressed by Howard (2004) among others.

patients tend to be concerned with the effectiveness of broad categories of antibiotics, each of them including a set of active ingredients with similar characteristics and, for this reason, likely to be differently affected by bacterial resistance. Individuals may then choose among a limited set of antibiotic types clustered according to common practice and shared beliefs regarding their effectiveness.

We intend to investigate the structure of the demand for antibiotics used for respiratory infections by modelling the decision process of rationale patients. We are interested in price and income sensibility of different antibiotic categories. Similarly to Ellison et al. (1997) and Chaudhuri et al. (2003), we model antibiotic demand as a multistage budgeting problem but consider a wider set of substances, those that can be prescribed for common respiratory infections in outpatient care. Outpatient antibiotics are then aggregated in four groups (*classic* penicillins, penicillins amoxi/clav plus 1^{st} and 2^{nd} generations of cephalosporins, 3^{rd} generation of cephalosporins and quinolones, macrolides), according to what are plausible alternatives in the treatment of respiratory infections.[3]

The allocation of antibiotic expenditure across antibiotic groups is analysed using the Almost Ideal Demand System (AIDS) specification proposed by Deaton and Muellbauer (1980) and extended to take spatial dependency in antibiotic use into account.[4] The AIDS model is commonly used to estimate price and income elasticities of the demand for goods when expenditure share data are available.[5] We compute own- and cross-price elasticities between old and new generations of antibiotics and between antibiotics differently affected by bacterial resistance using data from small

[3] Most of the antibiotics used in outpatient care are for the treatment of respiratory infections (Blasi et al., 2006; Gonzalves et al., 2001). We focus on this category and exclude antibiotics mainly used for other types of infections. Hence, our categories include all plausible therapeutic substitutes.

[4] Spatial dependency in AIDS models has been applied, for instance, by Paraguas et al. (2006) to investigate fish expenditure in the Philippines. The model, however, does not include socio-economic factors as determinants of consumption.

[5] Ma and al. (2004) estimated the share equations of animal product consumption for Chinese households. Combining the AIDS model and the two-stage Heckman procedure, Lazaridis (2004) focused on the factors affecting the demand for different types of oils and fats in Greece. Boetel and Liu (2003) estimated a meat demand system and investigated the effect of food information on the meat shares consumed.

geographic areas in Switzerland. We also estimate conditional expenditure elasticities and marginal expenditures shares for each group of antibiotics.

The structure of the article is as follows. In section 2 we sketch the application of the linear approximate AIDS model to the demand of antibiotics and discuss some testable hypothesis. In section 3 we present the data and summarize the variables used in the model. Section 4 gives some results and section 5 concludes.

2 The model

To sketch the demand for antibiotics in outpatient care we build on the AIDS model. We hypothesize that the individual utility derived from the use of antibiotics is weakly separable from quantities of all other types of goods consumed. Consequently, consumers follow a multistage process to allocate their budget to antibacterial products. In the first stage, the total spending is allocated to broad categories of goods, such as health care versus other types of goods or services. The health care spending is then separated in subgroups, such as pharmaceuticals, diagnostic tests and inpatient care. Given the nature of the infection, the budget share for pharmaceuticals is assigned to antibiotics and other types of drugs. Finally, the choice is between different categories of antibiotics according to their therapeutical attributes, the risks of bacterial resistance and the cost of treatment.

The individual expenditure function derived from the consumer theory is aggregated across individuals to obtain the antibiotic expenditure in the local market area.[6] Muellbauer (1975, 1976) showed that exact aggregation is possible within a specific family of preferences. These preferences are known as the price independent generalized logarithmic (PIGLOG) class of preferences. The PIGLOG class can be denoted by the following expenditure function, which is the minimum expenditure necessary

[6] Aggregation theory provides the necessary conditions under which the aggregate demand, i.e. the representation of market demand, can be treated as if it was the outcome of the decisions of a rational representative consumer. See Muellbauer (1975) and Cornes (1992) for a general discussion.

to achieve a certain level of utility at any given price

$$\log c(u,p) = (1-u)\log a(p) + u \log b(p), \tag{1}$$

where u is the level of utility, $a(p)$ and $b(p)$ represent functions of a price vector p. Following Deaton and Muellbauer (1980) we assume

$$\log a(p) = \alpha_0 + \sum_i \alpha_i \log p_i + \frac{1}{2}\sum_i \sum_j \lambda_{ij} \log p_i \log p_j \tag{2}$$

and

$$\log b(p) = \log a(p) + \beta_0 \prod_i p_i^{\beta_i}, \tag{3}$$

where $\alpha_0, \alpha_i, \beta_0, \beta_i$ and λ_{ij} are constants, and i and j are indexes representing different antibiotic categories.
Substituting for $\log a(p)$ and $\log b(p)$ in (1) we can write the cost function as

$$\log c(u,p) = \alpha_0 + \sum_i \alpha_i \log p_i + \frac{1}{2}\sum_i \sum_j \lambda_{ij} \log p_i \log p_j + \beta_0 u \prod_i p_i^{\beta_i}, \tag{4}$$

which is linearly homogeneous in prices, provided that the following restrictions on the parameters hold

$$\sum_i \alpha_i = 1,\ \sum_i \lambda_{ij} = \sum_j \lambda_{ij} = 0,\ \sum_i \beta_i = 0. \tag{5}$$

By applying the Shephard's lemma[7] and substituing afterwards the indirect utility function[8] derived from (2) we then obtain the expenditure share of the i^{th} group of anbitiotic substances

$$w_i = \alpha_i + \sum_j \gamma_{ij} \log p_j + \beta_i \log(x/P), \tag{6}$$

[7] Demand functions in budget share form are derived from a natural logarithmic differentiation of the expenditure function with respect to prices.

[8] Total expenditure x is equal to $c(u,p)$ for a utility maximising consumer. Hence, $c(u,p)$ can be inverted to give $u(p,x)$, the indirect utility function.

where x is the total expenditure for antibiotics in outpatient care[9], P is a price index defined by

$$\log P = \alpha_0 + \sum_i \alpha_i \log p_i + \frac{1}{2} \sum_i \sum_j \gamma_{ij} \log p_i \log p_j \tag{7}$$

and

$$\gamma_{ij} = \frac{1}{2}(\lambda_{ij} + \lambda_{ji}). \tag{8}$$

The following restrictions are implied by (5) and (8)

$$\sum_i \gamma_{ij} = \sum_j \gamma_{ij} = 0, \; \gamma_{ij} = \gamma_{ji} \; \forall \; i, j \; (i \neq j). \tag{9}$$

Provided that (5), (8) and (9) hold, the equation (6) defines a system of demand functions. These are homogeneous of degree zero in prices and total expenditure and satisfy the Slutsky symmetry. The total expenditure is then given by $\sum w_i = 1$.

The interpretation of the demand share summarized by (6) is straightforward. Without any change in relative prices and expenditures, i.e. the second and the third terms of the right-hand side of the equation, the budget shares of different groups of antibiotics are constant. Changes in relative prices affect the demand share through the terms γ_{ij}. These capture the effect on the i^{th} budget share from a one percent increase in the price of the j^{th} category of goods, with x/P held constant. Changes in real expenditure are taken into account by the parameter β_i, which is assumed equal to zero.

The share equation also underlines some basic properties of the demand function. Other things being equal, the expenditure share of each group of commodities is inversely associated with its own price and is positively related to the price of other goods. The expected sign of γ_{ii} is then negative. On the other side, γ_{ij} should exhibit a positive sign for any $i \neq j$ if goods are close substitutes.

[9] We define $x = \sum_i p_i q_i$ as the total expenditure on antibiotics for respiratory infections in outpatient care, where p_i and q_i represent the price and the quantity for the i^{th} group of antibiotics by the representative consumer.

2.1 Spatial dependency and other determinants

The demand for antibiotics may also be affected by variables other than price that account for expenditure shifts. For instance, the incidence of infections may imply seasonal trends in the per capita consumption. Socioeconomic characteristics of the population and aspects of health care supply may also affect antibiotic use. These aspects may be of little relevance in the demand share of different classes of antibiotics, unless they shape preferences for specific antibiotic categories.

It has been suggested that patients' age significantly affects the route of administration of antibiotics for lower respiratory tract infections (Mazzaglia et al., 1999) and the type of antibiotic used (Pendergrast and Marrie, 1999). Moreover, physicians may have an incentive to prescribe the newer and more expensive antibiotics, i.e. those with a broader spectrum of activity which apparently reduce risks for patients. Our model can be easily modified to account for expenditure shifts determined by the structure of the population and cultural differences.[10]

Following Ray (1980) and Pollack and Wales (1992), we include the additional determinants in the model by a log-linear scaling procedure. Cultural differences across regions are taken into account by dummy variables.

From (6) the AIDS model can then be extended to analyse aggregate data on antibiotic consumption across small geographic areas. Assuming separability in quantities consumed for different types of goods, we can write

$$\begin{aligned} w_i &= \theta_i M w_i + \sum_j \gamma_{ij} \log p_j + \beta_i \log(x/P) + \sum_{k=1}^{S} \nu_{ik} \log V_k + \psi_i \log H + \\ &\quad + \phi_i \log R_i + \sum_{t=1}^{T} \rho_{it} DT_t + u_i, \qquad (10) \end{aligned}$$

where θ_i, ν_{ik}, ψ_i, ϕ_i and ρ_{it} are new parameters. The index $i = 1, 2, 3, 4$ denotes four groups of antibiotic substances discussed later on in section 3 and summarized

[10] Socioeconomic determinats of outpatient antibiotic use in Switzerland have been investigated in previous studies by Filippini et al. (2006, 2009). The authors apply multivariate parametric approaches to the aggregate demand of antibiotics but fail to investigate determinants of different antibiotic groups.

in table 1. The constant term α_i has been substituted with the spatial lags of consumption, $\theta_i M w_i$, by means of the spatial weight matrix M.[11] The consumption of antibiotic group i in one area is assumed to be affected by the level of consumption in neighbouring areas. Indeed, spatially adjacent areas may exhibit similar behaviour in terms of antibiotic utilization due to inherent common spatial influences. V_k is a set of variables that capture demographic and cultural characteristics of the population, H is a proxy for the health status of the population represented by the incidence of main bacterial infections at the cantonal level, and R_i are indicators of bacterial resistance. The magnitude of bacterial resistance contry-wide is known to doctors and patients, but such a figure is not broken down for small areas. We operate on the assumption that bacterial resistance varies across main regions rather than across local areas. Doctors and patients may differ in their attitudes towards available information on bacterial resistance and may also differ in the perception of the implications of bacterial resistance. Finally, DT_t $(t = 1, .., 3)$ are time dummies, and the random term u_i is normally and identically distributed with variance σ_ε^2.

The expenditure share function is linearly homogeneous in all the explanatory variables provided that the new parameters satisfy the following condition

$$\sum_i \theta_i = \sum_i \nu_{ik} = \sum_i \psi_i = \sum_i \phi_i = \sum_i \rho_{it} = 0, \tag{11}$$

and P is approximated by the Stone's geometric price index

$$\log P = \sum_i w_i \log(p_i). \tag{12}$$

To avoid simultaneity problems we use the median values of the expenditure shares to calculate the Stone price index. Note, however, that this may not be sufficient since price differences across the areas are due to variations in consumption shares of

[11] The modified version of the AIDS model using spatial lags is built upon the structure of dynamic almost ideal demand systems. The way to introduce dynamic elements into the demand system analysis is discussed, for instance, by Garcia et al. (1998) and Shukur (2002). The spatial lag can be thought as an "inertia lag" in the sense that consumers slowly adjust their consumption behaviour to neighbouring areas. Consequently, spatial dependency can be introduced by mean of an autoregressive specification that modifies the intercept term in the demand system equations.

different antibiotic groups rather than in the price of the same antibiotic substance. To reduce the risk of endogeneity between quantities and prices we then use lagged values for prices.

2.2 Expenditure and price elasticities

Since we are interested in studying the response of the demand for different antibiotic groups to changes in price and expenditure, we calculate elasticities at the sample mean of expenditure shares. Using (10) and (12) we derive the uncompensated (Marshallian) own-price elasticities (ε_{ii}) and cross-price elasticities (ε_{ij}) as[12]

$$\varepsilon_{ii} = -1 + \frac{\gamma_{ii}}{w_i} - \beta_i, \tag{13}$$

$$\varepsilon_{ij} = \frac{\gamma_{ij}}{w_i} - \beta_i \frac{w_j}{w_i}, \; i \neq j. \tag{14}$$

Using the Slutsky equation, we then obtain the expenditure elasticity for the i^{th} antibiotic category given by

$$\eta_i = 1 + \frac{\beta_i}{w_i}. \tag{15}$$

A positive value suggests that good i is normal.

The income compensated or net (Hicksian) own-price elasticities (δ_{ii}) and cross-price elasticities (δ_{ij}) are obtained by applying the Slutsky decomposition to (15) and using the price index in (12). These can be written as

$$\delta_{ii} = -1 + \frac{\gamma_{ii}}{w_i} + w_i, \tag{16}$$

$$\delta_{ij} = \frac{\gamma_{ij}}{w_i} + w_j, \; i \neq j. \tag{17}$$

Consumer theory suggests that compensated own-price elasticities are negative for normal goods. Moreover, if (14) and (17) are positive the two groups of antibiotics are cross substitutes, otherwise they are complements.

[12] See Alston et al. (1994) and Chalfant (1987) for details.

Using again the Slutsky equation, it is possible to derive a relationship between the compensated cross-price elasticities and expenditure elasticities: $\varepsilon_{ij} = w_j\sigma_{ij} - w_j\eta_i$, where σ_{ij} are the partial elasticities of substitution, known also as the Allen elasticities of substitution

$$\sigma_{ij} = 1 + \frac{\gamma_{ij}}{w_i w_j} \; i \neq j \tag{18}$$

The sign of σ_{ij} determines whether the goods i and j are complements or substitutes. If σ_{ij} is positive (negative) the two goods are substitutes (complements).

3 Data and variables

Our data cover 240 contiguous market areas representing the whole Swiss territory. The areas exhibit a good degree of internal homogeneity in terms of population density and providers of health care. Aggregate data on outpatient antibiotic sales of different classes of antibiotics were provided by IHA-IMS Health Market Research[13]. The dataset is detailed at product/brand name and data are available quarterly for 2002. Since we focus on respiratory infections, we limited our analysis to the antibiotics mainly used in the treatment of these diseases. We aggregated active substances according to the antibiotic class and the generation. Consequently, we kept 66% of the original dataset in terms of sales. We excluded antibiotics with a parenteral route of administration. Four antibiotic groups were identified (*classic* penicillins, penicillins amoxi/clav plus 1^{st} and 2^{nd} generation of cephalosporins, 3^{rd} generation of cephalosporins and quinolones, macrolides) using the relevant literature on antibiotic treatments and suggestions by experts. These groups are summarized in table 1.

[13] Data on antibiotic sales derive from transactions between wholesalers and pharmacies and physicians. Clearly, we are aware that the quantity of antibiotics sold and the quantity actually consumed may differ. In this study we assume that patient non-compliance with doctor's prescription, if any, is a negligible factor. Finally, the potential mismatch between wholesale records and prescribing data due to seasonal fluctuations of retailers' stocks is assumed to have only a limited temporary effect and is likewise ignored.

	Antibiotic group	Description of main active ingredients
1	Penicillins (classic)	Penicillin V, amoxicillin, ampicillin
2	Penicillins (amoxi/clav) and $1^{st} - 2^{nd}$ generation cephalosporins	Clavucanic acid/amoxicillin, cefaclor, cefixime, cefadroxil, cefetamet pivoxil, cefprozil, cefuroxime axetil
3	3^{rd} generation cephalosporins and quinolones	Ceftibuten, cefpodoxime proxetil, moxifloxacin, levofloxacin
4	Macrolides	Erytromycin, clarithromycin, roxithromycin, azithromycin

Table 1: Antibiotic groups used in the treatment of respiratory infections.

Penicillins are among the first discovered antibiotics and have been largely used against streptococcus pneumoniae pathogens, which are a primary cause of respiratory tract infections (Schito et al., 2000). In particular, *classic* penicillins (penicillins V, ampicillin, amoxicillin) are commonly utilized to treat angina from streptococci and only rarely for other types of respiratory infections. The rate of penicillin-resistance streptococcus pneumoniae has substantially increased since the mid-1980s (CDC, 1994).

Newer penicillins (amoxi/clav) can be combined with some cephalosporins since they belong to the same broad classification (beta-lactams). The spectrum of amoxi/clav and 2^{nd} generation of cephalosporins are very similar. Observed cross-resistance between cephalosporins and penicillins may imply that patients infected by penicillin-resistant bacteria may be resistant to cephalosporins as well. The 1^{st} generation of cephalosporins is currently of very little use.

The 3^{rd} generation of cephalosporins has a broader activity spectrum compared to previous generations, which implies that it can be used against a larger variety of bacteria. Consequently, it is suitable for more severe infections. Nevertheless, it is generally used as an alternative to the 2^{nd} generation. Practices may significantly vary across the areas since some doctors are more likely than others to preserve the 3^{rd} generation for more resistant bacteria.

Similarly, quinolones have a large range of antibacterial activity, which includes multidrug resistant strains responsible for respiratory tract infections. Since this category should also be used with caution and better preserved for more severe cases, we considered it in a group together with the 3^{rd} generation of cephalosporins. When the nature of the infection is uncertain and doctors are quite risk averse, 3^{rd} generation of cephalosporins and quinolones may be preferred to penicillins and other cephalosporins.

Finally, macrolides are generally known as an alternative to beta-lactams. In some cases, bacterial resistance is more severe than for penicillins. Resistance to macrolides has increased over time among penicillin-resistant pneumococci and penicillin-susceptible strains. The preference for either penicillins or macrolides may then depend upon established local practices and patients preferences.

Average prices of each antibiotic group have been imputed using expenditure data and quantities. Quantities are measured in days of treatment (DOT) and prices are consequently defined in currency units per one day of treatment. A daily dose is standardised by the WHO.

	Min	Mean	SD	Max
Expenditure share				
Group 1	0.018	0.093	0.029	0.233
Group 2	0.149	0.463	0.069	0.704
Group 3	0	0.141	0.056	0.430
Group 4	0.154	0.303	0.073	0.787
Price				
Group 1	0.974	1.589	0.212	2.639
Group 2	2.331	3.340	0.220	4.018
Group 3	4.974	5.935	0.291	7.451
Group 4	3.614	4.787	0.344	6.086

Table 2: Summary statistics of budget shares and prices for the four groups of antibiotics.

Table 2 gives some summary statistics of expenditure shares and prices for the four groups of antibiotics. Penicillins (amoxi/clav) and early generations of cephalosporins and macrolides represent the largest shares of the expenditure. Note, however, that strong differences are observed across the areas. These categories may account for 15% only of the total expenditure. On the other hand, in some areas they are largely used and may reach a share of more than 70%.

Information on the other variables included in the model (see table 3) are mainly obtained from IHA-IMS . Demographic variables include the share of the population classified in 5 ranges of age. Note, for instance, that individuals under 26 represent less than 1% of the total population in some areas and more than 20% in others. Similarly, the proportion of people between 60 and 74 largely varies across areas, from 9.5% to almost 25%. French and Italian speaking areas represent 43.7% of all areas and are generally characterized by a more intensive use of antibiotic per capita. We defined a dummy variable that takes value equal to 1 if the area has a Latin culture (French and Italian) and 0 otherwise.

Variable	Description	Min	Mean	Max
x/P	Income per capita defined in CHF	15422	23465	51446
POP_1	Population under 14/total population	0.088	0.166	0.218
POP_2	Population between 15 and 25/total population	0.069	0.125	0.185
POP_3	Population between 26 and 59/total population	0.423	0.495	0.638
POP_4	Population between 60 and 74/total population	0.095	0.136	0.249
POP_5	Population over 74/total population	0.034	0.077	0.139
INF	Incidence of common gastrointestinal infections (Salmonella and Campylobacter) in 100,000 inhab.	91.9	114.7	187.7
$INF2$	Incidence of common respiratory infections (Streptococcus) in 100,000 inhabitants	2	64.98	144
$DLAT$	Areas with a Latin culture	-	0.437	-
RES	Resistance indicator (pneumococcal susceptibility)	West	Mid	East
	Group 1	76	90.4	93.2
	Gourp 2	76	100	96.1
	Group 3	83	90.9	87.6
	Group 4	100	97.7	69.5

Table 3: Variables notation and summary statistics.

Data on bacterial infections are based on information on the incidence of common gastrointestinal and respiratory diseases. As an indicator, we use the incidence of Campylobacter and Salmonella infections, the leading cause of gastrointestinal infections. In alternative regressions we also test the incidence of Streptococcus pneumoniae infections which represent the most common airborne bacterial infections among the population. Although, in most cases, patients recover from these infections without any medical treatment, patients, especially children and elderly patients, may be prescribed an antibiotic when symptoms are particularly severe. Data on gastrointestinal infections are generally more reliable than those for airborne bacterial infections. Our information comes from yearly publications of the Swiss Federal Statistical Office at the cantonal level.

Finally, the magnitude of bacterial resistance is calculated for the three main Swiss regions. There is a lack of resistance indicators for outpatient antibiotics covering the whole Swiss territory. A systematic collection of data has not started until recently. However, main hospital guidelines include a summary of susceptibility tests performed by local laboratories for several antibiotic substaces. Guidelines are generally prepared every two years and are available to general practitioners. We use information from guidelines published between 1999 and 2003 by hospitals in the west of the country (Geneva), mid (Bern) and east (Lugano and Zurich). The separation into three main areas reflects the current clusters defined by the Sentinel Surveillance of Antibiotic Resistance in Switzerland. In our regressions, we test four resistance indicators: susceptibility to Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli and Campylobacter jejeuni. In table 3 we report the susceptibility of different antibiotic groups to the Streptococcus pneumoniae which is used as an indicator in the basic specification of the model. The reason is that streptococcus pneumonie may be more accurately related to respiratory infections than other bacteria. Note that the ranking between antibiotic groups in terms of bacterial susceptibility is not straightfoward, as expected. For this reason, an ordered probit model may not be a good alternative to our approach.

4 Estimation results

The spatial AIDS model defined by equation (10) is used to investigate the expenditure shares of different groups of antibiotics. Explanatory variables include the price of antibiotics, population characteristics (age structure and income, cultural aspects), the incidence of community-acquired infections, and seasonal dummies. In addition, the share of different antibiotic groups can be influenced by the level of bacterial resistance and antibiotic consumption in adjacent areas.

We estimate the model through the Zellner's Iterative Seemingly Unrelated Regression (SUR) procedure with the software STATA. The set of restrictions leads to a singular residual variance/covariance matrix. Consequently, we drop one share equation from the system. This is the first groups, *classic* penicillins, which represents the smallest budget share on average across the four groups. Using the estimated parameters of the share equations of the other three groups and the restrictions applied above, we then obtained the parameters for the dropped group.

The estimation results are reported in table 4. Each equation is estimated with 720 observations, since data for 240 areas are quarterly available, and one quarter is excluded to allow for the use of lagged values for prices. The adjusted R^2 suggests that selected variables explain approximately 36%, 40% and 48% of cross-area variations in the use of antibiotics, respectively for group 2 (penicillins amoxi/clav and early generations of cephalosporins), group 3 (3^{rd} generation of cephaloporines and quinolones) and group 4 (macrolides).

The estimated spatial autoregressive parameter associated with the lag term DID_{-i} is significant and positive[14]

The impact of consumer expenditure on the demand share of group 2 is negligible, and it is negative for groups 3 and 4. Note, however, that the coefficients are never significant. As detailed in table 5 below, income elasticities are all positive, which suggests that different outpatient antibiotic groups are normal goods.

Most price coefficients are significant at less than 1% with few exceptions, but the demand for group 3 and group 4 seems to be positively related to their own prices

[14]The result suggests the evidence of consumption externalities across the areas. Higher consumption of one group of antibiotics in one area is significantly associated with higher consumption of that group in adjacent areas. A plausible explanation for this result is related to doctors and patients perceptions on which antibiotic group is the most appropriate for the treatment of common respiratory infections. Preferences may be affected by practice styles in adjacent areas.

	Penicillins (amoxi/clav) and 1^{st} - 2^{nd} generations cephalosporins		3^{rd} generation cephalosporins and quinolones		Macrolides	
Obs.	720		720		720	
R^2	0.358		0.402		0.479	
	Coeff.	S.E.	Coeff.	S.E.	Coeff.	S.E.
Constant	0.229**	0.089	0.155**	0.068	0.079	0.111
DID_{-i}	0.661****	0.035	0.605****	0.042	0.594****	0.037
P_1	0.000	0.011	0.052****	0.010	-0.051****	0.010
P_2	0.151****	0.028	-0.085****	0.021	-0.066***	0.021
P_3	-0.085****	0.021	0.020	0.025	0.013	0.019
P_4	-0.066***	0.021	0.013	0.019	0.105****	0.025
x/P	0.000	0.004	-0.002	0.003	-0.004	0.004
POP_1	-0.005	0.028	0.006	0.023	0.017	0.025
POP_2	0.034	0.027	0.000	0.022	-0.037	0.024
POP_4	0.000	0.018	-0.001	0.014	0.022	0.015
POP_5	0.014	0.010	0.014*	0.008	-0.038****	0.008
INF	0.011**	0.004	-0.007	0.004	-0.004	0.004
$DLAT$	-0.004	0.007	0.012**	0.005	-0.015**	0.007
RES	0.000	0.000	0.000**	0.000	-0.001	0.001
DT_2	-0.001	0.005	0.004	0.004	-0.014***	0.005
DT_3	0.013**	0.005	-0.002	0.004	-0.020****	0.005

* significant at 10%, ** significant at 5%, *** significant at 1%, **** significant at 0.1%

Table 4: Parameter estimates for the restricted linear approximate AIDS model of antibiotic groups.

and negatively related to the price of other groups. Price elasticities will be analysed later on in section 4.1 to investigate complementary and substitution effects between antibiotic groups.

The impact of demographic variables and cultural aspects on the demand share of all of the four antibiotic groups is plausible but coefficients are not highly significant. The age class 26-59 (POP_3) is the baseline category. The proportion of individuals over 74 years of age (POP_5) reflects some health considerations. The coeffcient is positive and significant at less than 10% for antibiotic group 3, whereas it is negative and significant at less than 1% for antibiotic group 4. This may suggest that elderly people are more exposed to the risk of severe infections in the community compared to other individuals, or that they are more concerned with the implications of bacterial resistance. Indeed, antibiotic group 3 (3^{rd} generation of cephalosporins and quinolones) are generally used for severe cases and are generally less affected by bacterial resistance. The literature on the determinants of health care expenditure indicates that the increasing prevalence of chronic health problems associated with aging may cause an increase in the utilization of health care services (Di Matteo and Di Matteo, 1998; Di Matteo and Grootendorst, 2002). We argue that the share of antibiotics for more severe infections may increase with the proportion of elderly patients in the community. Our result is also in accordance with findings by Mazzaglia et al. (1999), who suggested that cephalosporins are the antibiotics most frequently prescribed for lower respiratory tract infections in adults, while macrolides are the less prescribed.

We did not find clear evidence that a higher proportion of children (POP_1) negatively affects the share of antibiotic group 1 (penicillins) and positively affects the share of macrolides. According to Otters et al. (2004), there has been a decrease in the proportion of narrow-spectrum antibiotics prescribed for children between 1987 and 2001 in the Netherlands. By contrast, the proportion of macrolides increased from 8% to 16%. Similarly, Schindler et al. (2004) showed that macrolides were the most frequently prescribed antibiotics (48.1%) for respiratory infections among children aged between 0 and 6 in Germany.

Areas with a French/Italian culture exhibit a significantly lower consumption of macrolides (group 4) and a higher consumption of 3^{rd} generation cephalosporins and quinolones (group 3) compared to areas with a German culture. Similar differences are observed at a larger scale across European countries. France and Italy, for instance, use a relatively larger amount of 3^{rd}generation cephalosporins compared to other European countries (Coenen et al. 2006).

The coefficient of the incidence of infections significanlty increases with the share of antibiotics in group 2 and negatively affects antibiotics in group 3. The result hypothesizes that epidemiological differences are relevant in explaining variations in the use of different types of antibiotics in the community. An increase in the spread of community-acquired infections raises the share of narrow-spectrum antibiotics rather than the share of the latest generation of antibiotics more suitable for severe cases.

The study of the impact of bacterial resistance on the utilization of different antibiotic groups may add some insights to the analysis of epidemiological aspects. We did not find evidence that the share of different antibiotic groups is affected by the degree of bacterial susceptibility in the area. There are some plausible explanations for this result. First, since data are available for macro regions through hospital guidelines, they may only partially reflect the level of bacterial resistance locally. Second, guidelins may not easily reach general practitioners and patients. Finally, each resistance indicator may capture the susceptibility of one antibiotic group rather than suceptibility for all antibiotic categories.

Finally, we find remarkable seasonal effects seasonal effects on antibiotic shares. The basesline season is represented by the fourth quarter, i.e. the autumn dummy (October, November, December). The consumption of more expensive antibiotics (group 3 and 4) is higher in winter (1^{st} quarter) and lower during the summer (3^{rd} quarter). This may connote higher doctors' and patients' risk aversion in periods when the incidence of infections in general and severe infections occur more frequently. Accordingly, patients' willingness to pay for drugs may raise with the perceived risk of infection. By contrast, less expensive antibiotics, such as penicillins and early generations of cephalosporins, are used less often during the 1^{st} quarter and more often in the summer quarter.

4.1 Elasticities

Using the estimation results from table 4 and applying the definitions derived in section 2.2, we calculate the own-price, cross-price and expenditure elasticities of the demand for different antibiotic groups. The figures are summarized in tables 5 and 6. Some important implications can be straightfowardly derived.

Expenditure elasticitities are positive for all antibiotic groups. The result may suggest that antibiotics are normal goods and is in accordance with Baye et al. (1997), who estimated that anti-infectives have positive income elasticity (around 1.3). More

	Uncompensated price elasticities	Compensated price elasticities	Expenditure elasticities
Classic penicillins	-1.005	-0.903	1.049
Penicillins (amoxi/clav) and 1^{st} - 2^{nd} generation cephalosporins	-0.682	-0.208	1
3^{rd} generation cephalosporins and quinolones	-1	-0.863	1
Macrolides	-0.641	-0.349	1

Table 5: Price elasticities and expenditure elasticities evaluated at the sample mean.

specifically, Chaudhuri et al. (2003) observed positive expenditure elasticities for different types of quinolones, ranging from 0.3 to 2.20. Since our expenditure elasticities are very close to one, the consumption share of each group of antibiotics remains constant as the amount spent on other groups changes. The evidence then indicates that antibiotics in outpatient care can be denoted as necessities. As income raises, the need for additional consumption of antibiotics is negligible, *ceteris paribus.*

Grootendorst and Levine (2006) showed that pharmaceutical demand elasticities depend on whether patients receive social assistance, or if non-eligible patients have private health insurance. Health insurance in Switzerland is mandatory for residents and the same basic contract is offered by competing private insurance companies The insurance premium varies according to a limited menu of deductibles. Individuals' income and health status at least partially affect the selected level of deductible.

All uncompensated own-price elasticities have the expected negative sign and vary substantially from -0.641 to -1.005. The comparison with the existing literature is not straightforward, although some similarities may be pointed out. Focusing on anti-infectives, Baye et al. (1997) estimated uncompensated own-price elasticity equal to -0.916. Ellison et al. (1997) found significant and negative uncompensated own-price elasticities for the four types of cephalosporins analysed. Looking at quinolones only, Chaudhuri et al (2003) calculated a relatively high uncompensated own-price elasticity, equal to -2.5 on average and ranging from -0.45 to -5.5.

	Classic penicillins	Penicillins (amoxi/clav) and 1^{st}- 2^{nd} gen. cephalosporins	3^{rd} generation cephalosporins and quinolones	Macrolides
Classic penicillins	-	1	4.914	-0.809
Penicillins (amoxi/clav) and 1^{st}- 2^{nd} gen. cephalosporins	-	-	-0.304	0.521
3^{rd} generation cephalosporins and quinolones	-	-	-	1

Table 6: Allen elasticity of substitution between two groups of antibiotics.

Our estimates indicate that the demand for 3^{rd} generation cephalosporins and quinolones (group 3) and the demand for classic penicillins (group 1) are more price elastic than the demand for penicillins amoxi/clav and 1^{st} and 2^{nd} generation cephalosporins (group 2) and the demand for macrolides (group 4). It is worth noticing that the highest own-price elasticities are found for the most expensive antibiotic category (group 3) and the traditional and less frequently used antibiotics (classic penicillins). The rationale may be that doctors and patients are more likely to increase or reduce the consumption of the latest generation of cephalosporins and quinolones when their price changes, since this category of antibiotics is at least partially used to reduce uncertainty on the severity of the infection and the risks of bacterial resistance. On the other hand, they are less likely to leave commonly used antibiotic therapies such as previous generations of cephalosporins, penicillins and macrolides. Classic penicillins represent a traditional antibiotic therapy whose comparative advantage has been substantially undermined by better alternatives. Consequently, they may be quite sensitive to variations in relative prices.

As expected, the Hicksian own-price elasticities are smaller in magnitude compared to the Marshallian elasticitites. This indicates that the pure effect of substitution is only partially compensated by the income effect.

Substitution and complementary relationships among antibiotic groups are captured by the Allen elasticities summarized in table 6. Positive values denote that the two groups are substitutes. In our case, narrow spectrum antibiotics such as penicillins amoxi/clav and early generations of cephalosporins (group 2) do not appear to be good substitutes for antibiotics with a larger spectrum such as new cephalosporins and quinolones (group 3). The rationale may be that old generations of cephalosporins are not perceived to be effective against severe infections. Moreover, newer generations are generally taken into account to overcome specific problems of bacterial resistance encountered in the use of previous generations.

When the price of group 1 (classic penicillins) and 4 (macrolides) increases, doctors may prefer to switch to penicillins amoxi/clav and cephalosporins (group 2) rather than to more effective antibiotics such as newer generations of cephalosporins and quinolones (group 3). Elasticities of substitution between group 1 and 4 and groups 2 and 3 are positive.

The Allen's elasticity of substitution confirms that the demand for classic penicillins follows the demand for macrolides when the price of the latter category changes. The result may be associated to a certain degree of persistency in patients' tastes. For instance, doctors argue that children have a preference for macrolides rather than penicillins. This could imply that an increase in the price of macrolides is likely to induce a higher consumption of cephalosporins or newer antibiotic components, rather than driving the utilization of classic penicillins upward, *ceteris paribus*.

5 Conclusion

Antibiotic misuse and the cost of bacterial resistance are major threats undermining efficient treatment practices agaist community-acquired respiratory infections. The demand for antibiotics has been investigated in studies by Ellison et al. (1997) and Chaudhuri (2003). The focus is on specific market segments where antibiotic substances constitute very close theraperutic substitutes and are similar in terms of the impact of bacterial resistance. There are, however, arguments for considering a more extendend set of drugs. The major contribution of this study is the investigation of sources of local variations in the use of different types of antibiotics in the community.

We extended the linear approximate demand system model to account for spatial dependency in antibiotic consumption across small areas and added determinants of antibiotic demand other than price, such as demographic and cultural characteristics of the population and patients' health status. Therapeutic components are aggregated in four groups suitable to define, at the best of our knowledge, doctor's and patient's choice set in the treatment of community-acquired respiratory infections in Switzerland. Estimations are carried out on 2002 quarterly data of defined daily doses per 1000 inhabitants (DID) available for 240 small areas.

The results lead us to the conclusion that the highest demand elasticities are observed for the 3^{rd} generation cephalosporins and quinolones, the newer and more expensive antibiotic category, and classic penicillins, the most traditional and cheapest category. We found complementary effects between antibiotics with a relative narrow spectrum (penicillins amoxi/clav and cephalosporins $1^{st}/2^{nd}$ generations) and antibiotics with a relative large spectrum (3^{rd} generation cephalosporins and quinolones), and between classic penicillins and macrolides. On the other hand, demand elasticity suggests a good degree of substitution between the other groups, for instance between penicillins amoxi/clav and cephalosporins $1^{st}/2^{nd}$ generations (group 2) and macrolides (group 4).

Looking at the impact of population characteristics, we observed that an increasing proportion of elderly people positively affects the proportion of new cephalosporins/quinolones (group 3) and reduces the proportion of macrolides used. The rationale may be that elderly people are more exposed to severe infections and to the risk of bacterial resistance. Italian- and French-speaking regions are associated with a more substantial use of newer and more expensive antibiotics (group 3) and a lower proportion of macrolides (group 4).

Because different groups of antibiotics are associated with different degrees of bacterial resistance, variations in physicians' practice styles and patients' attitudes are probably related to attitudes towards the risk of bacterial resistance. If bacterial resistance is developed for certain class of antibiotics, no amount of cross elasticity between this class and another class may persuade patients to purchase or doctors to prescribe the ineffective class. Our analysis addresses consumer's willingness to trade off a lower level of bacterial resistance to a relatively higher price since we tested the impact of available information on bacterial resistance. The lack of evidence either suggests that information on bacterial resistance is poorly shared by general practitioners and patients or that antibacterial resistance indicators currently available only partially reflect the effectiveness of antibiotic groups. Indeed, accurate data on the incidence of bacterial resistance at local level are not available yet. To promote the regular collection of this information would be advisable

Despite limitations, the analysis helps to enlighten the impact of determinants of variations in the use of different types of antibiotics in the community. Our findings point out that health care policy makers may improve efficiency in antibiotic use by taking economic incentives into account. More effective dissemination of information on prices and the impact of bacterial resistance to physicians and patients may be one example.

References

Alston JM, Foster KA and Green RD, “Estimating elasticities with the Linear Approximate Almost Ideal Demand System: some Monte Carlo results”, *The review of Economics and Statistics*, 76, 2, 351-356, 1994.

Alvarez-Elcoros S and Enzler MJ, “The macrolides: Erythromycin, clarithromycin, and azithromycin”, *Mayo Clinic Proceedings*, 74, 6, 613-634, 1999.

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.

Blasi F, Tarsia p, Aliberti S, Santus P and Allegra L, “Highlights on the appropriate use of fluoroquinolones in respiratory tract infections”, *Pulmonary Pharmacology and Therapeutics*, 19, 11-19, 2006.

Boetel BL and Liu DJ, “Evaluating the effect of generic advertising and food health information within a meat demand system”, *Agribusiness*, 19, 3, 345-354, 2003.

Centers for Disease Control and Prevention (CDC), “Prevalence of penicillin-resistant streptococcus pneumoniae – Connecticut, 1992-1993”, *Morbidity and mortality weekly report* 43, 12; 216-217, 1994.

Chalfant J, “A global Flexible, Almost Ideal Demand System”, *Journal of Business and Economic Statistics*, 5, 233-242, 1987.

Chaudhuri S, Goldberg PK and Jia P, “Estimating the effects of global patient protection in pharmaceuticals: a case study of quinolones in India”, *Working paper 10159*, National Bureau of Economics Research, 2003.

Coenen S, Ferech M, Dvorakova K, Hendrickx E, Suetens C and Goossens H, “European Surveillance of Antimicrobial Consumption (ESAC): outpatient cephalosporin use in Europe”, *Journal of Antimicrobial Chemotherapy*, 58, 413-417, 2006.

Cornes R, “*Duality and Modern Economics*”, Cambridge: Cambridge University Press, 1992.

Dalhoff K, “Worldwide guidelines for respiratory tract infections: community-acquired pneumonia”, *International Journal of Antimicrobial Agents*, 18, S39-S44, 2001.

Deaton A and Muellbauer J, “An almost ideal demand system”, *American Economics*

Review, 70, 312–326, 1980.

Di Matteo L and Di Matteo R. "Evidence on the determinants of Canadian provincial government health expenditures: 1965-1991", *Journal of Health Economics*, 17, 211-228, 1998.

Di Matteo L and Grootendorst P, "Federal patent extension, provincial policies, and drug expenditures, 1975-2000", *Canadian Tax Journal*, 50, 6, 1913-1948, 2002.

Ednie LM, Visalli MA, Jacobs MR, and Appelbaum PC, "Comparative activities of clarithromycin, erythromycin, and azithromycin against penicillin-susceptible and penicillin-resistant pneumococci", *Antimicrobial Agents and Chemotherapy*, December, 40, 8, 1950–1952, 1996.

Ellison SF and Hellerstein JK, "The economics of antibiotics: an exploratory study", In: Triplett J, ed., *Measuring the prices of medical treatments*, Washington, DC: Brookings Institution Press, 118–43, 1999.

Ellison SF, Cockburn I, Griliches Z and Hausman J, "Characteristics of demand for pharmaceutical products: an examination of four cephalosporins", *Rand Journal of Economics*, 28, 3, 426-446, 1997.

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

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

Garcia-Rey C, Fenoll A, Aguilar L and Casal J, "Effect of social and climatological factors on antimicrobial use and Streptococcus pneumoniae resistance in different provinces in Spain", *Journal of Antimicrobial Chemotherapy*, 54, 465-471, 2004.

Gonzalves R, Bartlett JG, Besser RE, Cooper RJ, Hickner MJ, Hoffman JR, and Sande MA, "Principles of Appropriate Antibiotic Use for Treatment of Acute Respiratory Tract Infections in Adults: Background, Specific Aims, and Methods", Annals of internal medicine, 134, 6, 479-486, 2001.

Lazaridis P, "Olive Oil Consumption in Greece: A Microeconometric Analysis", *Journal of Family and Economic Issues*, 25, 3, 411-430, 2004.

Laxminarayan R and Weitzman ML "On the implications of endogenous resistance to medications", *Journal of Health Economics*, 21, 4, 709-18, 2002.

Ma H, Rae A, Huang J and Rozelle S, "Chinese animal product consumption in the 1990s", *The Australian Journal of Agricultural and Resource Economics*, 48, 4, 569-560, 2004.

Mazzaglia G, Arcoraci V, Greco S, Cucinotta G, Cazzola M and Caputi AP, "Prescribing habits of general practitioners in choosing an empirical antibiotic regimen for lower respiratory tract infections in adults in Sicily", *Pharmacological Research*, 40, 1, 47-52, 1999.

Muellbauer J, "Aggregation, income distribution and consumer Demand", *The Review of economic studies*, 62, 525-43, 1975.

Muellbauer J, "Community preferences and the representative consumer", *Econometrica*, 44, 976-99, 1976.

Otters HB, van der Wouden JC, Schellevis FG, van Suijlekom-Smit LW and Koes BW, "Trends in prescribing antibiotics for children in Dutch general practice", *Journal of Antimicrobial Chemotherapy*, 53, 361–366, 2004.

Paraguas FJ, Dey MM and Kamil AA, "Spatial linear approximate to almost ideal demand system", *Advances and Applications in Statistics*, 6, 3, 361-375, 2006.

Pendergrast J and Marrie T, "Reasons for choice of antibiotic for the empirical treatment of community acquired pneumonia by Canadian infectious disease physicians", *Canadian Journal of Infectious Disease*, 10, 4, 337-345, 1999.

Pollak RA and Wales TJ, "*Demand sytem specification and estimation*", New York: Oxford University Press, 1992.

Ray R, "Analysis of a time series of household expenditure surveys for India", *The Review of Economics and Statistics*, 62, 4, 595-602, 1980.

Rowthorn R and Brown GM. "Using antibiotics when resistance is renewable", in *Battling resistance to antibiotics and pesticides*, Laxminarayan R, ed., RFF press, 2003.

Schindler C, Krappweis J, Morgenstern I and Kirch W, "Prescriptions of systemic antibiotics for children in Germany aged between 0 and 6 years", *Pharmacoepidemiology*

and drug safety, 12, 113–120, 2003.
Schito GC, Debbia EA and Marchese A. "The evolving threat of antibiotic resistance in Europe: new data from the Alexander Project", *Journal of Antimicrobial Chemotherapy*, 46, 3-9, 2000.
Shukur G, "Dynamic specification and misspecification in systems of demand equations: a testing strategy for model selection", *Applied Economics*, 34, 709-725, 2002.