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Estimating dynamic consumption of antibiotics using panel data: the shadow effect of bacterial resistance

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Abstract

To some extent, antibiotics are similar to addictive goods, since current consumption is reinforced by past use because of bacterial resistance, which represents a growing concern in many countries. The purpose of this paper is to explore how consumers adjust their current level of antibiotic consumption towards desired levels over time. We construct a balanced panel dataset (2000-2007) for 20 Italian regions and estimate a dynamic model where antibiotic consumption depends upon demographic and socioeconomic characteristics of the population, the supply of health care in the community, antibiotic price, and the “capital stock” of endogenous bacterial resistance measured by past consumption. We apply alternative dynamic estimators for short panels: the bias-corrected least squares dummy variable (LSDVC) and the system Blundell-Bond GMM estimator (GMM-BB). The estimation results are stable across different model specifications and show that antibiotic use in previous periods has a positive impact on current antimicrobial consumption (between 0.14 and 0.39). This indicates that the process of adjustment to desired levels of consumption is relatively fast (approximately 1.2-1.6 years). Weak persistence in consumption may suggest that individuals are responsive to changes in antibiotic effectiveness.

Keywords: Antibiotic consumption, bacterial resistance, dynamic model.

JEL classification: C21, C23, I1

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1 Introduction

The increasing use of antibiotics and the consequent harmful effects of bacterial resistance have become a growing concern in many countries. Evidence suggests that bacterial resistance grows with antibiotic use and may regress when antibiotic consumption is controlled (Monroe and Polk, 2000; Mera et al., 2006). It has been shown that the potential welfare loss due to bacterial resistance may account for up to 12% of total outpatient antibiotic expenditure (Filippini et al., 2009a). Although public interventions may be effective in controlling antibiotic consumption (Huttner et al., 2010), the effects of intervention policies on resistance to antimicrobial drugs cannot be assessed accurately at present. The consumption dynamics of antibiotics and its behavioural aspects are still unclear.

To some extent, antibiotics are similar to addictive goods since individuals may develop dependence or experience persistent attitudes towards consumption. Addiction is a negative side-effect of consumption where the characteristics of goods interact with the characteristics of individuals. Consumption of addictive goods is characterized by reinforcement (higher levels of consumption in the past increases the desire for present consumption) and tolerance (utility of a given level of consumption is lower when past consumption is higher) (Peper, 2004). In the case of antibiotics, current consumption may be affected by past consumption because of endogenous bacterial resistance. Past consumption increases bacterial resistance, i.e the “capital stock”, which in turn reduces the effectiveness of antibiotic use over time (Laxminarayan and Brown, 2001; Herrmann and Gaudet, 2009).

To our knowledge, the study of antibiotic consumption is limited to the investigation of cross-sectional data (Kern et al., 2006; Filippini et al., 2006). However, as suggested above, dynamic aspects of consumption may play an important role since the spread of antimicrobial resistance reduces antibiotic effectiveness on each individual as well as for other individuals in the community (external effects) and could be related to behavioural factors. From the empirical point of view, we should note that data on the “capital stock”, i.e. the level of bacterial resistance, are unfortunately not usually available.

Econometric models may incorporate the influence of consumption habits on preferences over time (Spinnewyn, 1981). To include habits or addiction aspects in models of antibiotic consumption one can drop the assumption that an increase in current consumption has just an impact on current individual’s utility and assume correlation between consumption and utility in subsequent periods. Indeed, this is the case if antibiotics are an exhaustible resource since their efficacy may be reduced by endogenous bacterial resistance.

Plausibly, individuals (and their doctors) are myopic in the sense that the effect of present antibiotic consumption on future consumption are not taken into account in their consumption choices. Past consumption is supposed to affect present consumption only through the reduced level of antibiotic effectiveness. Past antibiotic consumption can either be taken into account by means of lagged or stock variables included in empirical models of consumption. Lagged variables have been considered, for instance, in Baltagi and Levin (1986), to estimate the demand for cigarettes, and by Johnson and Oskanen (1977) to study the demand for alcohol (Bretteville-Jensen, 2006). Since, in our case, information on the “capital stock” of bacterial resistance, is not available, we follow the lagged variable approach.

The purpose of this article is to explore how consumers adjust their current level of antibiotic consumption towards desired levels over time. We propose a dynamic approach to capture the partial adjustment in consumption and the speed of the adjustment. We estimate a model of antibiotic consumption using a balanced panel of outpatient antibiotic use and several socioeconomic determinants in 20 Italian regions between 2000 and 2007. Estimations are carried out by means of two suitable approaches for short dynamic panels: the bias-corrected least squares dummy variable (LSDVC) dynamic panel estimator proposed by Kiviet (1995) to reduce the small sample bias associated to the least squares dummy variables estimator, and the generalized method of moments proposed by Blundell and Bond (1988) (GMM-BB).

Most of our findings on the impact of determinants of consumption prove consistent with previous results of static models of antibiotic use. In addition, we show that past antimicrobial use affects current consumption and that the adjustment towards desired levels of consumption is relatively fast. This may indicate that individuals are responsive to changes in antibiotic inefficacy (bacterial resistance).

The remaining of the paper is organized as follows. Section 2 provides an overview of the three main fields of the literature which are most closely related to our paper: the empirical analysis of the determinants of antibiotic consumption, the theoretical literature on optimal antibiotic consumption, and the empirical literature on addictive goods and habit formation. In Section 3 we sketch the model and discuss the estimation approach. Section 5 presents the results and Section 6 concludes.

2 The dynamics of antibiotic consumption: a review

The literature is relatively rich of studies investigating socioeconomic determinants of antibiotic consumption in outpatients within countries. Nitzan et al. (2010), for instance, analyse the use of antibiotics in outpatients by different age groups in 8 districts of Israel. Filippini et al. (2006) propose an econometric model where antibiotic use across Swiss regions varies according to the socioeconomic and demographic characteristics of the population, the incidence of infections, the local supply of health care and antibiotic price. Kern et al. (2006) investigate variations in antibiotic prescriptions across 23 areas in 16 German states in relation to age, population density, income, unemployment, and aspects of local health care supply. Finally, Matuz et al. (2005) explore regional variations in antibiotic consumption in ambulatory care in Hungary.

The above studies exploit cross-sectional data. To our knowledge, the literature lacks econometric studies on determinants of outpatient antibiotic consumption using panel data, the only exception being a recent investigation by Masiero et al. (2010) using a European panel. In a companion paper (González and Masiero, 2010), we explore variations of antibiotic use across Italian regions using panel data. The modelling approach is based on ordinary least squares with fixed effects. Spatial econometric tools are also applied to count for the fact that antibiotic consumption may be affected by antimicrobial use in neighbouring regions. However, dynamic aspects of consumption are not considered.

Static models of antibiotic consumption ignore the link between consumer's preferences in different time periods and assume that an increase in current consumption affects utility in the current period only (Bretteville-Jensen, 2006). Consequently, consumption in different periods is fully separable, which implies that individuals are assumed to instantaneously adjust to the optimal level of consumption. However, this may not be very realistic and the reasons will be carefully discussed in the following section.

The literature on dynamic aspects of consumption can be divided in two main fields (Chaloupka, 1991). The first one is represented by studies on endogenous tastes or habit formation (e.g. Gorman, 1967; Pollak, 1970, 1976; and Boyer, 1983). The second one consists of studies on rational addictive consumption (Stigler and Becker, 1977; Becker and Murphy, 1988; Becker et al, 1991, 1994). The main insights of rational addiction are theoretically derived by Becker and Murphy (1988), who show that addictive behaviour is influenced by the discount rate of future consumption, expected income and the price changes. Moreover, the long-run demand for addictive goods tend to be more elastic than the demand for non-addictive goods because their consumption at different moments of time

are complements. Many empirical studies which follow this seminal work focus on the comparison between myopic and rational addictive behaviour. Tiezzi (2005), for instance, investigates the demand for tobacco in Italy using a balanced pseudo-panel of annual data on tobacco and related products during the period 1972-2000 for the 20 Italian regions and time series data on per capita household tobacco expenditures during the period 1960-2002 by means of myopic and rational models of addiction. Similarly, Luo et al. (2003) investigate cigarette consumption in Japan using time-series data covering from 1960 to 2000.

As for antibiotics, two main aspects influence their consumption over time. First, antibiotics have the characteristics of preventive care. In this sense the use of antibiotics may contribute to reduce the spread of bacterial infections to other individuals, which may increase future benefits from consumption. Second, current antibiotic use increases the stock of bacterial resistance, which in turn reduces the effectiveness of antibiotics over time.

The literature generally models bacterial resistance as a negative externality since the risk of transmission of bacterial resistance affects the welfare of the population (Rudholm, 2002; Elbasha, 2003). This externality depends, at least partially, upon the quantity of antimicrobials consumed (Coast et al., 1998). Antibiotic resistance generates additional costs in the form of increased hospitalizations, higher mortality rates, and the diversion of resources from other medical needs into the development of new and more powerful antibiotics (Laxminarayan, 2001). Hence, the full cost of antibiotic treatment includes the monetary cost as well as the additional cost of reduced effectiveness due to past consumption. These costs should balance the expected benefits from antibiotic treatment at least in the long run when information is fully available to the consumers. However, the literature suggests that consumers (and their doctors) are rather myopic when using antibiotics. Indeed, several factors may contribute to increase antibiotic consumption, which in turn reduces antibiotic effectiveness over time.

Many theoretical studies address the issue of optimal consumption of antimicrobials. Laxminarayan and Weitzman (2002) argue that most patients in region or country are treated with the same drug for a given infectious disease, which places high selection pressure on organisms that are susceptible to that particular drug and increases the likelihood that a resistant strain will evolve and spread. As resistance to the recommended first-line drug builds up, that drug is replaced by an alternative that is used until resistance to the second drug also increases, and so on in succession. The authors concludes that this myopic strategy is not optimal and should be replaced by the simultaneous prescription of a variety of drugs.

Rudholm (2002) suggests that the use of antibiotics in one region creates a

stock of resistant bacteria which affects the welfare of consumers in other regions. Since consumers do not take this effect into account when choosing the level of antimicrobial consumption, this may result in a suboptimal allocation of resources at the global level.

Herrmann and Gaudet (2009) analyse the exploitation of an antibiotic in a market subject to open access on the part of antibiotic producers to the common pool of antibiotic efficacy. While the market equilibrium depends only on current levels of antibiotic efficacy and infection of the epidemiological system, the social optimum accounts for the dynamic externalities which relate those levels to the inter-temporal use being made of the antibiotic. They explicitly derived a demand function for the antibiotic under the assumption that individuals differ with respect to their valuation of being in good health. Furthermore, the authors show that in the open-access equilibrium, the level of antibiotic efficacy tends to a positive steady-state level in which the efficacy renews itself so as to maintain the steady state. It turns out that this steady-state level of antibiotic efficacy can be lower or higher than the level which should prevail in the socially optimal steady state.

Finally, several empirical studies support the idea that there is limited rationality in antibiotic consumption. Antibiotic prescriptions, for instance, represent a mean of shortening doctor's consultation since there is little time for clinical investigations to exclude other diagnosis. Moreover, prescribers may be concerned with the risk of losing patients and the perception of poor outcome if antibiotics are not prescribed (Sachs and Tomson, 1992; Whyte, 2002). Physicians may also fear legal consequences if they fail to secure an adequate treatment. Prescribing may then contribute to relieving doctor's anxiety. Uncertainty in the diagnosis and limitation in the follow up of patients provides an additional concern. This generates a preference for antibiotics with a broad spectrum to cover the broader range of bacteria. To conclude, the cost of diagnostic tools makes it difficult to persuade the patient that antibiotic treatment is not needed (Nordberg et al., 2005).

3 The model

In this section we sketch a dynamic model of antibiotic consumption in outpatient care where consumer's rationality is limited by poor information available on the future costs of antibiotic ineffectiveness (bacterial resistance). The model builds on previous approaches to habit formation and addictive goods. Two main aspects can be considered. First, greater past consumption of antibiotics increases the desire for present consumption. This represents the so called *reinforcement effect*

and indicates that individuals who undergone antibiotic treatment in the past are more likely to consider the use of antibiotics in the current period.¹ Second, the utility of a given amount of antibiotics (standard doses of therapy) is lower when past consumption is greater. This is because of endogenous bacterial resistance which reduces antibiotic efficacy over time. To be cured, a patient will need more antibiotics since more therapies have to be considered before finding the effective one to cure the infection.² Third, there is an optimal stock of bacterial resistance which depends on individual antibiotic consumption as well as consumption of other individuals.³

Rational individuals weigh the present benefit of antibiotic consumption against the future health consequences in terms of the risk of antibiotic inefficacy and the future costs of purchasing new pharmaceutical drugs. However, patients and their doctors are not fully aware of the future harmful consequences of current antibiotic consumption. The rationale is that the mechanism that generates antibiotic resistance from past antibiotic consumption is quite complex and the spreading process to different antimicrobial categories is not well understood. Doctors have limited information on levels of antimicrobial resistance and patients may not be able to evaluate correctly the impact of resistance on future antibiotic efficacy. Moreover, the future costs of pharmaceutical innovation are not taken into account. Patients bear a small fraction of the full cost of antibiotics directly because of social health insurance coverage. Furthermore, the decision to request an antibiotic is based on two factors: the benefit of quickly recovering from an infection and the cost of taking the medication. Patients, however, may not be aware of studies that demonstrate conclusively that prior use of antibiotics increases a person's risk of acquiring a resistance infection (Laxminarayan, 2001). Finally, current antibiotic inefficacy may also be generated by past antibiotic consumption of other individuals. This implies that the stock of bacterial resistance has an externality effect

¹This may be explained by some physical or psychological effects which persist over time. It may also reflect physician's attitude toward antibiotic prescriptions. Under uncertainty on the nature of patient's infection, antibiotic therapy may appear to have been beneficial even though patient's relief was not due to the treatment. General practitioners may prefer antibiotic therapies since they were presumably effective in the past or patients are not willing to wait for recovery.

²Under uncertainty on antibiotic effectiveness (levels of bacterial resistance), doctors usually start with the traditional therapy and then move to new antibiotic therapies when the former proves to be ineffective. This implies that the total amount of antibiotic doses will increase.

³From a biological perspective, individuals may experience a level of bacterial resistance which is positive or zero. This level depends on the individual consumption as well as the consumption of other individuals. Since the use of antibiotics generates expected benefits (infection cured) and costs (antibiotic inefficacy and monetary costs), individuals should try to optimise their level of consumption, i.e. to reach the optimal stock of bacterial resistance.

which is not considered in individual's utility maximizing choices.

We hypothesise that the utility of a representative individual in region i depends on the consumption of a composite good, $c_i(t)$, the consumption of antibiotics measured by the amount of standard defined daily doses, $a_i(t)$, and on a measure of past consumption which captures the level of inefficacy of antibiotics, i.e. the stock of bacterial resistance, $R_i(t)$. The latter measure draws from the classical SIS model used in epidemiological studies (Lindquist et al., 2010). This defines antibiotic inefficacy as $R_i(t) = I_i^R(t)/I_i(t)$, where $I_i^R(t)$ represents the number of individuals infected with a drug-resistant strain and $I_i(t)$ is the total number of infected individuals in the population. The variation in antibiotic efficacy over time, $\partial R_i(t)/\partial t$, is supposed to depend on individuals treated, n_i , and on the fitness cost of resistance, δ . The latter is a measure of the rate at which bacteria regress to the susceptibility state in the absence of antibiotic treatment. We can interpret this process as the depreciation rate of the stock of bacterial resistance. We then assume the following relationship:

$$\frac{\partial R_i(t)}{\partial t} = \beta \sum_{j=1}^{n_i} a_j(t) - \delta R_i(t). \quad (1)$$

From an economic point of view, the optimal use of antibiotics depends on whether drugs are a renewable resource. This is related to the depreciation rate of the stock of bacterial resistance, δ . If resistant bacteria were less likely to survive in the absence of antibiotics, one could consider to remove an antibiotic temporarily from active use to enable it to recover its effectiveness. On the other hand, if the resistant strain remains prevalent, then an antibiotic would fail to regain its effectiveness even if it were temporarily removed. Effectiveness would be treated as a non-renewable or exhaustible resource. This would imply higher costs for pharmaceutical innovation to replace the ineffective treatment unless the exhaustible resource was use more carefully.

Note that antibiotic inefficacy is a function of past consumption of all individuals in the region. There is a externality effect represented by the efficacy constraint generated by antibiotic consumption of other individuals in the region. However, we hypothesise that bacterial resistance cannot be transferred to individuals in other regions.⁴

⁴Bacterial resistance generated by individual consumption represents an efficacy constraint for other individuals. It is plausible to assume that bacterial resistance spreads within the region, i.e. it is a local phenomenon. However, researchers have hypothesized that bacterial resistance may have global effects (Rudholm, 2002). Spatial aspects have been considered in two previous papers using cross-sectional data (Filippini et al., 2009a, 2009b), and in a companion paper (González and Masiero, 2010) using panel data.

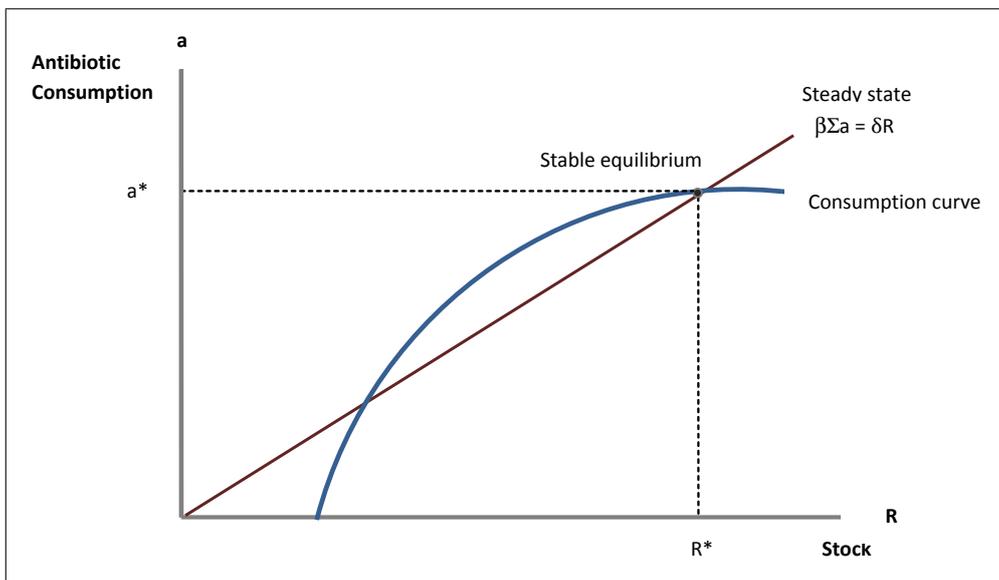


Figure 1: Model of (limited) rational antibiotic consumption. Bacterial resistance, i.e. the “capital stock”, reinforces antibiotic consumption since past antibiotic treatment increases preferences for present treatment and the efficacy from a given treatment is lower when past consumption is greater (tolerance).

Assuming that individuals in region i are identical, with a length of life equal to T and a constant rate of time preference, σ , we can write the utility function:

$$U_i(0) = \int_0^T e^{-\sigma t} u_i[c_i(t), a_i(t), R_i(t)] dt, \quad (2)$$

subject to an expenditure constraint which depends upon the price of antibiotics and other goods, earnings over time and the discount rate. Individuals maximise utility in (2) taking the expenditure constraint and the investment equation (1) into account (see Becker and Murphy, 1988, for details). A stable equilibrium is depicted in Figure 1 where a^* and R^* represent optimal levels of antibiotic consumption and stock of bacterial resistance.

As shown in Figure 1, the long-run level of antibiotic consumption is fully adjusted to its equilibrium level. At any point in time, however, current antibiotic consumption differs from the long-run equilibrium consumption. This may be imputed to the fact that consumers are not well informed about levels of bacterial resistance in their area. Nevertheless, bacterial resistance represents a constraint on antibiotic utilisation. Consequently, a link between antibiotic consumption in different periods is plausible. However, while past consumption is supposed to affect present consumption, it seems plausible to assume that individuals are

myopic when choosing antibiotic treatment and the possible effects of present consumption on future consumption are not taken into account.

Due to the fact that we are not able to observe the stock of bacterial resistance directly, our empirical approach is based on the idea that antibiotic consumption follows a partial adjustment process where the lagged dependent variable represents a fixed propensity to consumption which is carried over from period to period. The coefficient of the lagged variable can be interpreted as the speed of the adjustment to the steady state level of consumption (Tiezzi, 2005). Hence, current antibiotic use, a_t , differs from optimal use, a_t^* , because the adjustment to optimal levels is not immediate.

In this framework the relationship between current and desired levels of antibiotic consumption can be summarised as:

$$\ln a_{it} - \ln a_{it-1} = \varphi(\ln a_{it}^* - \ln a_{it-1}) + \eta_{it}, \quad (3)$$

where η_t is a random disturbance term and φ is the coefficient of adjustment indicating the rate of movement towards the desired level of consumption. It is worth pointing out that for $\varphi = 1$ the adjustment to desired levels of antibiotic consumption is instantaneous. Conversely, for $\varphi = 0$ there is no adjustment. Thus, we hypothesise that $0 < \varphi \leq 1$.

Solving (3) for the optimal level of consumption we get:

$$\ln a_{it}^* = \frac{1}{\varphi} \ln a_{it} + \left(1 - \frac{1}{\varphi}\right) \ln a_{it-1} - \frac{1}{\varphi} \eta_{it}. \quad (4)$$

Since the desired level of consumption a_{it}^* cannot be observed, equation (4) reformulates the unobserved a_{it}^* in terms of the observed levels of a_t and a_{t-1} , as well as the unobserved parameter φ and the random disturbance term η_{it} .

To empirically investigate the dynamics of antibiotic use we hypothesise that regional consumption within a country depends on socioeconomic characteristics of the population characteristics (income and age structure), the local supply of health care, the prevalence of community-acquired infections, and antibiotic price or copayment.

Let the optimal level of antibiotic use in region i at time t , measured in defined daily doses per 1000 inhabitants, be described by the following reduced form equation:

$$\begin{aligned} \ln a_{it}^* = & \beta_0 + \beta_1 \ln Y_{it} + \beta_2 P_{it} + \beta_3 DPH_{it} + \beta_4 POP_{1it} + \beta_5 POP_{2it} \\ & + \beta_6 MOR_{it} + \beta_7 DPOP_{it} + \beta_8 NORTH + \beta_9 CENTER + \varepsilon_{it}. \end{aligned} \quad (5)$$

In the hybrid log-log functional form of equation (5) P_{it} is antibiotic price/copayment, DPH_{it} is the density of physician practices, POP_{jit} is the percentage

of the population in the j age group, MOR_{it} is the mortality rate from infectious diseases, and $DPOP_{it}$ is population density. The log transformation is applied to income only since other variables are defined as percentage ratios and price/copayment is measured by integers from 0 to 4. Two dummy variables ($NORTH$ and $CENTER$) are also included to capture geographical differences between northern, southern and central regions.

Substituting the right-hand side of equation (5) for lna_{it}^* in (4) and rearranging we obtain:

$$\begin{aligned} lna_{it} = & \beta_0\varphi + (1 - \varphi)lna_{it-1} + \beta_1\varphi lnY_{it} + \beta_2\varphi P_{it} + \beta_3\varphi DPH_{it} & (6) \\ & + \beta_4\varphi POP_{1it} + \beta_5\varphi POP_{2it} + \beta_6\varphi MOR_{it} + \beta_7\varphi DPOP_{it} \\ & + \beta_8\varphi NORTH + \beta_9\varphi CENTER + v_{it}. \end{aligned}$$

where $(1 - \varphi)$ represents the speed at which individuals achieve the desired level of consumption and the composite disturbance term is $\nu_{it} = \varphi\varepsilon_{it} + \eta_{it}$. The model derived in (6) can be estimated by means of appropriate econometric techniques discussed in the following section.

4 Econometric approach and data

For the estimation of the dynamic model in (6) we have a balanced panel dataset for the 20 Italian regions. To account for unobserved heterogeneity in panel data, we could use a fixed effects (LSDV) or random effects (RE) model. However, the estimation of the dynamic panel data model (6) using LSDV or RE estimators is not appropriate. This is because the inclusion of lagged dependent variables among explanatory variables violates the strict exogeneity assumption. In fact, the lagged variable is correlated with the error term, which leads to biased and inconsistent estimates of LSDV and RE.⁵ In the literature several instrumental variable estimators have been proposed to solve this problem. Anderson and Hsiao (1982) proposed a simple instrumental variable estimator. Arellano and Bond (1991) as well as Blundell and Bond (1998) proposed two different estimators based on the general method of moments (GMM). The basic idea of these estimators is that lagged levels and/or additionally lagged differences are valid instruments for the lagged endogenous variable, that is they are uncorrelated with the transformed error term.

The Arellano and Bond estimator (GMM-AB) has the advantage of producing consistent estimates in dynamic panel regression with both endogenous right-hand side variables and measurement errors. Moreover, it is more efficient than

⁵For a discussion of this issue and for a presentation of econometric models for panel data see Baltagi (2002).

the standard Instrumental Variables (IV) estimators such as the Anderson-Hsiao estimator. Nevertheless, the method is unlikely to be suitable for small samples. It has been shown that, when T is small and the parameter of the lagged variable is close to one, then the GMM-AB estimator can be biased downward. As an alternative to the approach suggested by Arellano and Bond (1991), Blundell-Bond (1998) proposed a system GMM estimator (GMM-BB) which uses lagged first differences as instruments for equations in levels as well as the lagged variable in first-difference equations. Blundell-Bond (1998) showed that this estimator seems to be preferable to other IV and GMM estimators with small samples. A problem with this estimator is that properties hold for N large, so the estimation results can be biased in panel data with a small number of cross-sectional units.

An alternative econometric approach for small dynamic panel data set based on the correction of the bias of LSDV has been suggested by Kiviet (1995). To make the correction feasible, this procedure has to be initialized by a consistent estimator. This is because the bias approximation depends on the unknown population parameters. Three possible options to reach this purpose are the Anderson-Hsiao, the Arellano-Bond, and the Blundell-Bond estimators. Finally, the estimated asymptotic standard errors may provide poor approximations in small samples, generating unreliable t-statistics. Bootstrap methods generally provide approximations to the sampling distributions of statistics, which are at least as accurate as approximations based upon the first order asymptotic assumptions.

In a Monte Carlo analysis, Judson and Owen (1999) and Kiviet (1995) showed that in typical aggregate dynamic panels characterized by T lower or equal to 20 and N lower or equal to 50, as it is our case, the Anderson-Hsiao and the Kiviet corrected LSDV (LSDVC) estimators are better than the GMM estimator proposed by Arellano and Bond (1991). Despite having a higher average bias, the corrected LSDV estimator turns out to be more efficient than the Anderson-Hsiao. This suggests that the corrected LSDV estimator is an effective approach for small panels ($T \leq 20$), while the Anderson-Hsiao estimator is more appropriate for large panels, as the efficiency of the latter improves with T (Kiviet, 1995).

Our regional panel includes 20 regions for the period 2000 – 2007. Hence, the GMM-AB estimator may not be the most appropriate approach. Given the characteristics of our panel, we choose to estimate the dynamic model (6) using the following two estimators: the one-step system GMM estimator proposed by Blundell and Bond (1998) and the LSDVC.⁶

⁶Spatial aspects of consumption are not considered here. These aspects are addressed in studies using cross-sectional data (Filippini et al., 2009a, 2009b) and in a companion paper (González and Masiero, 2010) using panel data by means of spatial-lag and spatial error econometric ap-

The balanced panel dataset for the 20 Italian regions has been created using several sources. Data on regional outpatient antibiotic consumption were collected from annual reports prepared by the Italian National Observatory on Drugs Utilization (Osmed). Our dataset includes sales of antimicrobials, i.e. group J of the Anatomical Therapeutic Chemical Classification (ATC) of drugs. These drugs are included in class A by the Italian National Health Service (SSN), which means they require a doctor’s prescription and are supplied virtually free of charge, against small patient’s copayments. The per capita consumption is measured by the number of defined daily doses per 1000 inhabitants per day (DID). A defined daily dose represents the standard dose necessary for one day of drug treatment in adults and is defined by an independent scientific committee answering to the WHO Collaborating Center for Drug Statistics Methodology. The DID measure can be interpreted as the number of persons (out of 1000) who are taking antibiotics on a given day (Chauvin et al., 2001).

The mean level of consumption of outpatient antibiotics in Italy between 2000 and 2007 was 23.24 DID , with a peak in 2006 (23.68) and a minimum in 2000 (22.36). Antimicrobials use has been roughly stable over time but a remarkable degree of heterogeneity in consumption is observed across the regions. Generally, regions in central Italy use more antibiotics per capita (24.61 DID) than regions in the north (18.25 DID) and less than southern regions and the islands (28.36 DID). Summary statistics are reported in Table 1.

Information on the demographic structure of the population and density, per capita income, density of general practices and mortality from infectious diseases are obtained from the Italian National Institute of Statistics (Istat). Copayments are obtained from annual reports on pharmaceutical consumption and expenditure prepared by Osmed. Regional copayments vary from 0 to 4 Euros. We rescale the variable from 1 to 5 in order to avoid negative values in the log transformation. Mortality data for infectious diseases in 2004 and 2005 are not available. Since data are substantially stable before and after this period, we linearly interpolate mortality data from 2003 and 2006 to assign values to the years 2004 and 2005. We are aware that this approximation could create some bias in the estimation. We then carefully discuss the estimation results related to this covariate in section 5. Finally, it is worth noticing that covariates generally show low within variation.

proaches. In a preliminary stage of this analysis we estimated a spatial dynamic model following two approaches: the corrected 2SLS approach suggested by Beenstock and Felsenstein (2007) and the system GMM approach proposed by Kukenova and Monteiro (2009) and Bouayad-Agha and Védrine (2010). However, the results were not encouraging. This could be due to the fact that our data set is characterized by a low T and a low N .

Variable	Description	Mean value by year *									
		2000	2001	2002	2003	2004	2005	2006	2007		
<i>DID</i>	Defined daily doses per 1000 inhabitants	22.36 (4.66)	23.37 (5.28)	23.19 (5.21)	23.16 (5.09)	22.96 (5.07)	23.61 (5.28)	23.68 (5.51)	23.61 (5.21)	23.61 (5.21)	
<i>Y</i>	Income per capita (in Euro)	20327.42 (5232.20)	21259.58 (5365.84)	21913 (5509.95)	22395.24 (5632.69)	23056.71 (5860.44)	23388.35 (5826.57)	24244.20 (5934.88)	24962.70 (6034.07)	24962.70 (6034.07)	
<i>POP₁</i>	Proportion of population aged 0-14	14.01 (2.38)	13.97 (2.24)	13.93 (2.09)	13.87 (1.96)	13.81 (1.83)	13.78 (1.71)	13.71 (1.64)	13.53 (1.63)	13.53 (1.63)	
<i>POP₂</i>	Proportion of population aged 15-74	77.51 (1.29)	77.29 (1.19)	77.05 (1.11)	76.88 (1.05)	76.76 (1.00)	76.58 (0.96)	76.39 (0.93)	76.10 (1.54)	76.10 (1.54)	
<i>POP₃</i>	Proportion of population aged above 74	8.47 (1.68)	8.73 (1.70)	9.01 (1.70)	9.23 (1.69)	9.41 (1.67)	9.62 (1.64)	9.86 (1.61)	9.95 (1.75)	9.95 (1.75)	
<i>DPOP</i>	Population density	174.31 (106.25)	174.34 (106.22)	175.09 (106.65)	171.72 (99.54)	178.06 (108.55)	179.20 (109.50)	180.04 (110.32)	181.83 (111.49)	181.83 (111.49)	
<i>INF</i>	Incidence of infections per 100000 inhabitants	354.77 (235.91)	316.97 (224.02)	317.70 (152.28)	329.04 (173.01)	296.49 (177.77)	216.25 (119.66)	236.13 (144.24)	203.90 (165.14)	203.90 (165.14)	
<i>MOR</i>	Mortality rate (for infectious diseases) per 100000 inhabitants	0.64 (0.16)	0.68 (0.16)	0.74 (0.20)	1.07 (0.27)	1.12 (0.26)	1.17 (0.27)	1.21 (0.29)	1.27 (0.31)	1.27 (0.31)	
<i>DPH</i>	Density of physicians per 1000 inhabitants	0.83 (0.06)	0.83 (0.06)	0.83 (0.056)	0.83 (0.06)	0.82 (0.06)	0.82 (0.06)	0.82 (0.06)	0.82 (0.06)	0.82 (0.06)	
<i>P</i>	Copayment	1.50 (0)	0 (0)	0.83 (0.92)	0.85 (0.92)	0.95 (0.94)	0.70 (0.92)	0.65 (0.93)	0.95 (1.19)	0.95 (1.19)	

*Standard errors in parenthesis

Table 1: Descriptive statistics.

5 Results

In this section, we discuss the results obtained from the estimation of the dynamic model of antibiotic consumption defined by equation (6). The model is estimated by means of the GMM-BB and the corrected LSDV estimators. Findings are summarized in Table 2. The GMM-BB estimates are shown together with the p-value of the test statistics of serial correlation (AR1, AR2) and over identifying restrictions (Sargan). The p-values of these statistics show that in both models there is no significant second-order autocorrelation, which is the crucial aspect with respect to the validity of the instruments. Moreover, the p -value of the Sargan test statistics indicates that the null hypothesis that the population moment conditions are correct cannot be rejected.

In both models, the number of statistically significant parameter estimates is relatively low. However, the results are satisfactory as far as the coefficients of the price variables and the coefficients of the lagged variables are significant and carry the expected signs in both models. The reason is that these coefficients are used for the computation of the long-run elasticities and for the estimation of the latent impact of antibiotic resistance. The values of these coefficients are relatively different between the two models. As expected, the largest difference concerns the coefficient of the lagged dependent variable. The LSDVC approach leads to a lower coefficient estimate of the lagged variable. Finally, the significance of the lagged variable is also of relevance because it allows for the analysis of the impact of bacterial resistance on antibiotic consumption.

Generally, the results obtained using the GMM-BB estimator show that socioeconomic and demographic variables such as income and the share of elderly people, as well as variables reflecting the density of doctors and the mortality, do not seem to have a notable influence on antibiotic consumption. Only the coefficient of the population density and two coefficients of the regional dummy variables are significant. These dummy variables are plausibly linked to regional differences in terms of culture, habits and environmental conditions. The results show that antibiotic consumption is generally lower in central and northern Italian regions. Furthermore, the positive and significant coefficient of population density could be due to the likelihood of infections transmission, which is expected to be higher in populated regions compared to relatively remote regions.

The results obtained using the LSDVC estimator show that only price, income and health status coefficients are significant. Regarding the significance of the coefficients in general, it is worth noting that several variables have limited variation within regions over time. The coefficients of the explanatory variables can be imprecise if variation over time is dominated by variation across states, i.e.

the between variation (Cameron and Trivedi, 2005). Low within variation may explain the small number of significant coefficients.

Variables	LSDVC			GMM-BB		
	Coefficients	St. Err.	p-value	Coefficients	St. Err.	p-value
Constant	-	-	-	1.569453	0.959277	0.102
P	-0.015516	0.007357	0.035	-0.027835	0.009956	0.005
Y	0.257697	0.084542	0.002	0.046747	0.083528	0.576
POP ₁	0.007816	0.007191	0.277	-0.002622	0.012070	0.828
POP ₂	0.000008	0.000082	0.924	-0.000014	0.000102	0.888
DPOP	0.000006	0.000258	0.980	0.000546	0.000155	0.000
DPH	0.154433	0.128217	0.228	-0.016214	0.189424	0.932
MOR	-0.026638	0.014860	0.073	-0.000613	0.016870	0.971
NORTH	-	-	-	-0.343157	0.100239	0.001
CENTER	-	-	-	-0.162410	0.065459	0.013
a_{t-1}	0.144826	0.067315	0.031	0.392375	0.088761	0.000
Sargan test	-	-	-	-	-	0.106
Arellano-Bond (AR1) test	-	-	-	-	-	0.006
Arellano-Bond (AR2) test	-	-	-	-	-	0.968

Table 2: Parameter estimates of dynamic models of antibiotic consumption.

Since we use a log-log model specification, we can interpret the coefficients as elasticities. In the LSDVC, this implies that a 1% increase in the per capita income increases antibiotic consumption by roughly 0.15% in the short run and by 0.18% in the long run. This finding indicates that regions with a higher level of income, i.e. northern regions, use less antibiotics than regions with lower income, *ceteris paribus*. Similar results are obtained by Filippini et al. (2009a) using cross-sectional data from small geographic areas in Switzerland, and by Baye et al. (1997) using USA data. Hence, the result from our dynamic approach confirms the evidence of positive income effects.

In accordance with the economic theory, we find a statistically significant and negative association between antibiotic consumption and price/copayment in both models, even though this impact is relatively low. Using a natural experiment across Italian regions, Fiorio and Siciliani (2009) investigate the effect of copayments on drug prescriptions. They find that an increase in the copayment by one Euro reduces the per capita number of prescriptions by 4% and the per capita public pharmaceutical expenditures by 3.4%.

The dynamics of antibiotic use is captured by the coefficient of the lagged variable of consumption, a_{t-1} . In both models, this coefficient is positive, statistically significant but relatively low (0.145 and 0.392). This suggests that the time

of adjustment time is also relatively low. In fact, the gap between current and desired antibiotic consumption is almost fully offset within one year. The full adjustment occurs in approximately 1.17 years if we consider the estimation results of the LSDVC model, and 1.64 years using the GMM-BB estimation results. In other words, antibiotic consumption seems to move towards optimal levels quite fast. We can conclude that persistence in consumption appears to be relatively weak, which suggests that individuals set their level of antimicrobial use over time close to the optimal level.

6 Conclusions

Antibiotic misuse increases the threat of bacterial resistance which in turn reduces antibiotic effectiveness over time (Elbasha, 2003). The understanding of factors influencing the dynamics of antibiotic consumption may then contribute to the shaping of appropriate measures of public interventions to optimise the use of antimicrobials. The empirical literature is lacking in this respect.

In this paper, we propose a dynamic approach to investigate antibiotic use in outpatient care which hypothesises that antibiotic consumption is affected by antibiotic inefficacy, i.e. the stock of bacterial resistance to antimicrobials. The level of inefficacy represents a bad which is indirectly measurable by means of past antibiotic use. This represents the main novelty of our analysis and provides a significant contribution to the existing empirical literature on antibiotic consumption.

To some extent, antibiotics exhibit aspects which make them similar to addictive goods, such as cigarettes. Past antibiotic use decreases the marginal benefit from consumption over time, which implies that higher levels of consumption are required to maintain the same level of treatment efficacy to cure bacterial infections. Thus, consumers adjust their current levels of consumption towards optimal levels depending on the expected benefit from antibiotic treatment and the cost of bacterial resistance.

We show that individuals adjust their levels of consumption in a relatively short period. Hence, outpatient antibiotic consumption exhibits a low degree of persistence. The rationale may be that bacterial resistance represents a constraint which can hardly be ignored by consumers unless to incur in dangerous threats to their health.

Our findings may also suggest that public policies to preserve antibiotic efficacy could be improved. Efforts to restrict antibiotic use in outpatients have been much less successful than in hospitals because no central agent (such as a hospital administrator or infection control committee) can enforce an antibiotic

policy (Harbarth and Samore, 2005). Moreover, the high costs of malpractice lawsuits may induce doctors to use stronger and broader spectrum antibiotics more frequently than it would be necessary. This behaviour increases the level of resistance in the community, but the impact of each individual treatment is so small that doctor's perceived benefit from antibiotic prescriptions often outweighs the small uncertain costs associated with increased resistance (Brown and Layton, 1996). Finally, it has been asserted that policies on patent protection for antimicrobial drugs may not be optimal. Allowing for longer patent life could increase incentives for pharmaceutical firms to minimise resistance, since companies would enjoy a longer period of monopoly benefits from their antibiotic effectiveness (Herrmann, 2010). Further research is desirable to assess the impact of public policies in preserving antibiotic effectiveness.

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