Socioeconomic determinants of regional differences in outpatient antibiotic consumption: Evidence from Switzerland

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Abstract

This paper investigates the determinants of regional variations in outpatient antibiotic consumption using Swiss data. The analysis contributes to the debate on appropriate antibiotic use by improving the understanding of its determinants, and may help to define more effective health care policies to reduce the resistance phenomenon. Findings suggest that Switzerland exhibits relatively low levels of consumption among European countries. There are significant differences between cantons both in the per capita antibiotic sales and defined daily doses per 1000 inhabitants (DID). Econometric estimations suggest that DID are significantly related to per capita income, antibiotic price, the density of medical practices, demographic, cultural and educational factors. The incidence of bacterial infections is also relevant. Appropriate policies affecting antibiotic consumption in the community can be designed by looking at crucial determinants in the model and their related impact.
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1. Introduction

The consumption of antibiotics has rapidly increased during the past 50 years. Antibiotics have significantly contributed to the reduction in the likelihood of dying from infectious diseases worldwide [1,2]. However, researchers suggest that almost one-third of drug prescriptions are questionable [3,4].

Between 1980 and 1991 most European countries experienced an increase in the number of antibiotic prescriptions. The growth rate of consumption was about 45% for England, 65% for France and almost 80% for Germany. According to Davey et al. [5] a partial explanation is represented by the increasing use of antibiotics for respiratory symptoms. Antibiotic prescriptions have slightly decreased during the 1990s but prescribing practices still vary widely across countries [6]. For instance, the percentage of antibiotic prescriptions for colds and tonsillopharyngitis between 1980 and 1991 were, respectively, 48.7% and 94.6% in France versus 7.7% and 69.6% in Germany [7]. During the same period the French consumption of antibiotics for respiratory infections with presumed viral origin increased by around 115% for children and 86% for

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adults [8]. Mousquès et al. [9] suggested that a change in physicians' behavior may at least partially explain the large amount of prescriptions for acute rhinopharyngeal infections: there is a tendency to prescribe the most recent and the most costly antibiotics, such as cephalosporins.

In the USA the use of broad spectrum antibiotics and prescriptions of antibiotics for common viral diseases, such as upper respiratory tract infections, increased during the 1990s [10]. Antibiotic prescription rates, respectively, for people with colds, URIs and acute bronchitis was 46%, 47% and 60% in 1996 [11]. McCaig et al. [12] showed that on average 45% of the population received antibiotics in 2000. The analysis of Cantrell et al. suggests that around 11 million of prescriptions in the USA are inappropriate and estimates a waste of health care resources up to US$ 281 millions.

Antibiotic consumption may not be optimal because of multiple market imperfections. First, patients may not face the marginal cost of drugs when making their consumption choices. Consumers have an incentive to purchase more drugs than they would if insurance was not available [13]. Second, the individual production function of health is characterized by uncertainty. Although antibiotics are not effective in treatments of viral diseases, patients' lack of knowledge and experience may increase inappropriate consumption. Indeed, studies have shown that doctors decisions to prescribe antimicrobials are related to patients' expectations. Under time pressure, doctors tend to satisfy their patients and to avoid follow up visits [14]. Third, marginal social benefits from consumption may not reflect marginal private benefits. Marginal private benefits from consumption may not internalize external benefits derived from one's treatment with antibiotics which reduces the probability of infection spreading to other individuals [15]. Finally, overconsumption of antibiotics may contribute to the selection of resistant bacteria, and hence, reduce their effectiveness [16]. Marginal social costs of antibiotic usage may then not reflect marginal private costs since the latter do not consider the costs of reduced antibiotic effectiveness due to bacterial resistance [17,18]. Because of resistance, antibiotics become a scarce resource and it is in the interest of the society as a whole to preserve their effectiveness [19–21].

The investigation of regional variations in antibiotic consumption may contribute to the debate on appropriate antibiotic use by improving the understanding of its determinants. Moreover, the analysis may help to define more effective health care policies to reduce the resistance phenomenon.

Differences between geographical areas may be explained by demographic, cultural and socioeconomic factors. However, it is hard to believe that physicians and/or patients in different areas will not vary in their preferred treatment practices for health conditions where alternative treatments are available and where the nature of the infection exhibits substantial uncertainty. Researchers suggest that the investigation of small geographical areas may bring out the role of health care supply organizational factors compared to demand variables [22].

The literature lacks empirical investigation of within country variations in antibiotic use. Moreover, studies focusing on international comparisons between countries use a descriptive statistics approach rather than applying econometric techniques to explain the determinants of cross-country variations [23].

The paper intends to investigate regional variations in outpatient antibiotic use in Switzerland, to estimate the cantonal demand for antibiotics and study the impact of critical factors. In Section 2 we compare outpatient antibiotic sales in Switzerland with other European countries and investigate cantonal differences within the country. In Section 3 we estimate the cantonal demand for outpatient antibiotics and discuss its determinants. Section 4 concludes.

2. Variations in antibiotic consumption

2.1. Outpatient antibiotic use in Switzerland

In this section, we investigate outpatient antibiotic utilization in Switzerland and compare it with use in other European countries. We consider both total use in terms of defined daily doses per 1000 inhabitants per day (DID)[1] and sales per capita. Swiss sales data were provided by IHA-IMS Health. Defined daily doses per

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[1] The defined daily dose (DDD) measurement unit is based upon the WHO version 2003.

1000 inhabitants daily and sales per capita were calculated using additional demographic information and WHO standard doses (we refer the reader to Section 3.2 for further details on data).

Fig. 1 is constructed by using data from the European Surveillance of Antimicrobial Consumption (ESAC I) project and by including new data from Switzerland. The ESAC project collected either reimbursement data or distribution/sales data depending on the method for measuring antibiotic use employed by each national database. Antibiotic sales, prescribing and consumption are then used interchangeably in the European study although concepts are not exactly the same. Patients may systematically lack compliance either because they badly tolerate the treatment or because symptoms have resolved. Moreover, as suggested by Cizman [24], physicians may overprescribe antibiotics to meet patient's expectations or to reduce misdiagnosis of bacterial infections. As a result prescribing data may overestimate antibiotic consumption. As for wholesales to dispensing pharmacies, doctors and drugstores, these may not match prescribing data if drugs can also be purchased without any prescription. However, this is unlikely to happen for antibiotics. A mismatch between wholesales and prescribing data may derive instead from seasonal fluctuations of retailers' stocks of drugs due, for instance, to unexpected variations in the incidence of infections. In our analysis we will also ignore the possible mismatches between antibiotic sales and antibiotic consumption and use either one term or the other interchangeably.

Large differences in outpatient antibiotic consumption are observed across European countries [25,6]. Relatively high consumption defined in daily doses per 1000 inhabitants per day is observed in France, Greece, Luxembourg, Portugal and Italy, among others. On the contrary, Austria, Estonia, Germany, Latvia and the Netherlands, for instance, exhibit significantly lower values. Median European consumption of antibiotics in ambulatory care in 2002 is 18.8 DID. The greatest consumption (32 DID) is attained by France. Outpatient antibiotic use in Switzerland measured in DDDs per 1000 inhabitants daily is 9 DID, below the Dutch level of 9.8 DID.

The ranking obtained by ordering European countries as with respect to DDDs per 1000 inhabitants per day in 2002 suggests that Switzerland is indeed the country with the lowest antibiotic consumption in the community.

Not surprisingly, this is in accordance with the 2003 OECD statistics [57] suggesting that Switzerland is among countries with low consumption rates of pharmaceuticals. Among possible explanations is the combination of organizational aspects of the health care system based upon private health insurances and physicians' and patients' attitude towards the use of drugs. The combination of deductible and direct payments may contribute to the prevention of moral hazard behavior. Swiss physicians and patients may either be more aware of the implications of antibiotic consumption, such as bacterial resistance, and face tighter financial incentives. The health economics literature
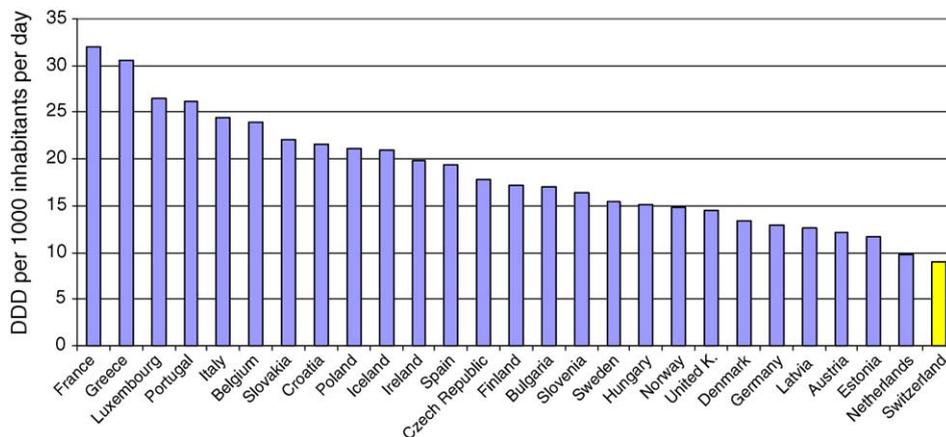

Fig. 1. Outpatient antibiotic use per country including Switzerland (2002). *Sources*: ESAC and IHA-IMS.
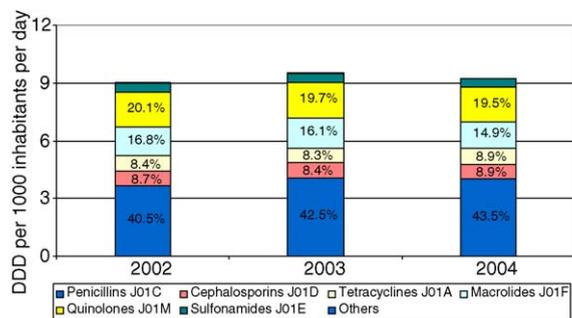
Fig. 2. Structure of outpatient antibiotic consumption in Switzerland (2002–2004).

Fig. 3. Penicillins composition in Switzerland (2002).

suggests that pure fee-for-service payment schemes, akin to the Swiss one, may increase the volume of services provided compared to capitation regimes. However, the incentive to reduce workload by increasing prescriptions may be lower (see Ref. [26]).

As shown in Fig. 2, total antibiotic consumption in ambulatory care in Switzerland has been roughly stable over the 3 years considered. Consumption has slightly increased in 2003 (9.5 DID) but decreased in 2004 (9.3 DID).

Looking at the consumption structure, the literature suggests that there is wide variation in the proportion of different classes of antibiotics between countries [27,24]. The Swiss share of quinolones is 20.1% of total consumption in 2002. Although the Swiss use of quinolones is not far from the European average (1.8 DID against 1.4 DID), Switzerland uses this category of antibiotics in the community in much higher proportions (the European average share of quinolones without Switzerland is 7.3%). This implies that Switzerland uses relatively lower proportions of others classes of antibiotics compared to European countries.

The use of penicillins has slightly increased over time (from 40.5% in 2002 to 43.5% in 2004). The Swiss consumption of penicillins is below the European average both in terms of DID and the share on total consumption (3.7 DID and 40.5% compared to 8.7 DID and 46.4%). Looking at penicillins in more details, we observe that combinations with β-lactamase inhibitors represent 63% of total consumption of penicillins (Fig. 3). This proportion is similar to the proportion used in Belgium and Portugal, for instance, and above the European average.
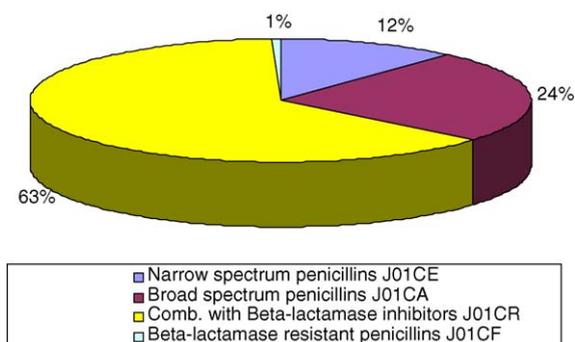
Similar figures can be observed for cephalosporins and macrolides. The Swiss consumption for the former category is 0.8 DID (8.7%) whereas the European average is 1.9 DID (10.2%). In the latter category Switzerland consumes 1.5 DID (16.8%) compared to the European average of 2.7 DID (14.3%).

The ranking of Switzerland between European countries in terms of per capita consumption for different classes of antibiotics can then vary. Switzerland is 18th out of 27 European countries for the consumption of cephalosporins, and the 5th least consuming country for macrolides. On the other side, Switzerland is the eighth larger consumer of quinolones.

It is worth noticing that the comparison of Swiss consumption data with those of other European countries as well as between the European countries of the ESAC study requires a bit of carefulness. There may be differences related to the collection of data since not all of the countries derive data from the same source. These may either come from the distributional channel or the reimbursement registrations which may not perfectly match. Moreover, outpatient antibiotic consumption may either include or exclude antibiotic used in nursing homes. Nursing homes are generally counted in outpatient antibiotic consumption of most European countries although for few of them they are included in the hospital consumption.

2.2. Cantonal differences

Switzerland is a federal state made of 26 cantons. Cantons generally differ not only with respect to geographical characteristics, but also for cultural and socioeconomic aspects of the population and the
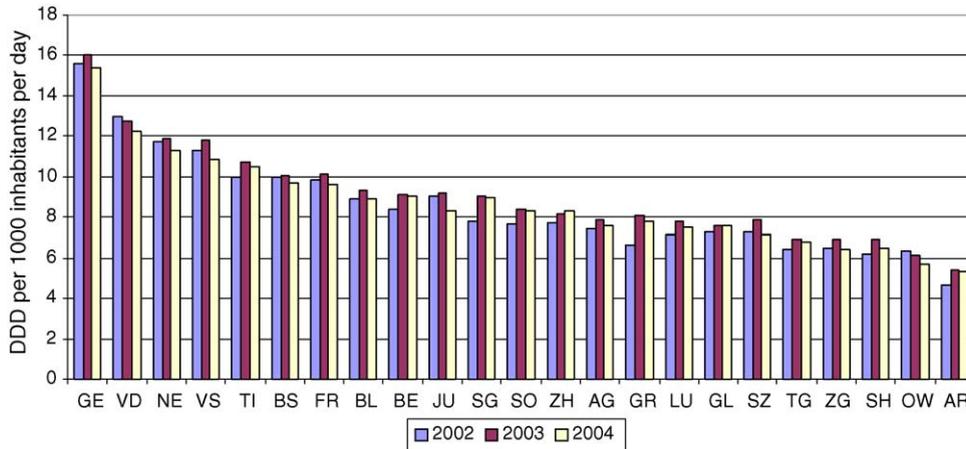
Fig. 4. Outpatient antibiotic use per canton.

organization of the health care system. The analysis of cantonal differences in antibiotic consumption may then reflect these aspects besides epidemiological ones. We investigate cantonal antibiotic use in terms of sales (in CHF) per capita and DDDs per 1000 inhabitants daily using yearly data from 2002 to 2004.[2]

The average cantonal expenditure in 2002 was around CHF 12 per capita with a standard deviation of 3.72. The expenditure varies from a minimum of CHF 6.44 to a maximum of CHF 22.63. Average per capita expenditure has increased between 2002 and 2003 by 3.2% and decreased afterwards by 4.5%. Differences between cantons appear to be significantly large all over the 3 years.

In terms of DDDs per 1000 inhabitants per day, the average cantonal outpatient antibiotic consumption was 9 DID in 2002 (Fig. 4). Average antibiotic use has slightly increased in 2003 and then reduced to 9.3 DID in 2004. Hence, average individual consumption daily has been roughly stable over the 3 years. Note, however, the wide differences between cantons. These can be summarized by the variation coefficient[3]: 29 in 2002, 26 in 2003 and 26 in 2004. Given a minimum cantonal consumption of 4.7 DID in 2002 (AR: Appenzell Rhodes), the highest consumption is more than three times greater (15.6 DID for GE:

Geneva). Similar figures are observed for 2003 (Min. 5.3 DID–Max. 16 DID) and 2004 (Min. 5.3 DID–Max. 15.4 DID). Median values were 7.7 DID in 2002 (ZH: Zurich), 8.3 DID in 2003 and 2004 (SO: Solothurn and Zurich).

Although there are substantial cantonal differences in all of the 3 years observed, the variation coefficient indicates that differences has slightly reduced over time. In 2003 the big majority of cantons have increased antibiotic use expressed in DDDs per 1000 inhabitants daily but two cantons (VD: Vaud and OW: Obwalden) have reduced consumption. On average, consumption has increased by 5.6%. However, cantons, such as St. Gall (SG) and Grisons (GR), exhibit more substantial growth. The *t*-test on the mean equality between 2002 and 2003 confirms that cantonal consumption has significantly increased. In 2004 average outpatient antibiotic consumption expressed in DID has decreased by 2.7% compared to 2003. The reduction characterizes all cantons with the exception of Zurich.

Looking more carefully at Fig. 4, we note that cantons with the highest consumption (such as Geneva, Vaud, Neuchatel and Valais) are generally located in the South-West part of Switzerland. Conversely, cantons with the lowest consumption are located North-East in the country.

Cantonal antibiotic consumption can be disaggregated by main antibiotic classes (Fig. 2). We summarize the following six categories as previously done for the whole Switzerland: penicillins, cephalosporins, tetracyclines, macrolides, quinolones and sulfonamides.

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[2] In the analysis which follows five small cantons have been aggregated into two bigger regions (see Section 3.2 for further details).

[3] The variation coefficient is the ratio between the standard deviation and the mean multiplied by 100.
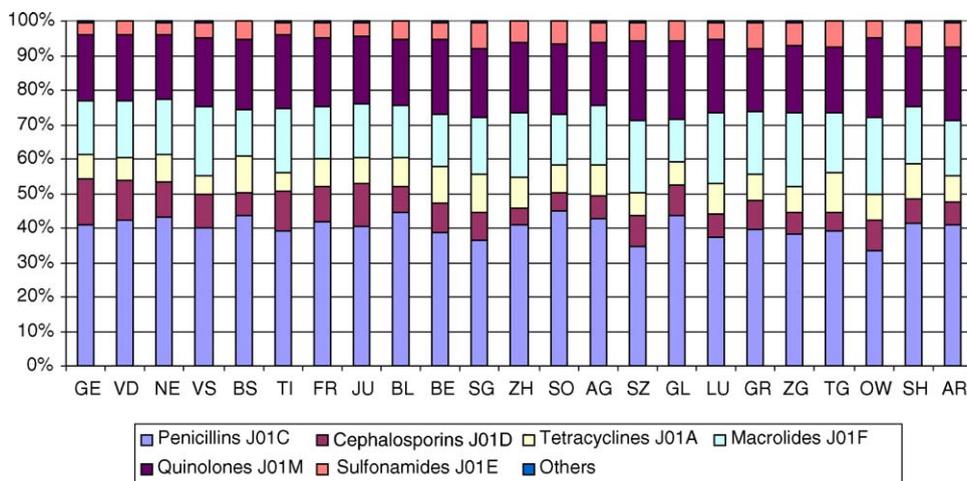
Fig. 5. Structure of antibiotic consumption in the community per canton.

Cantonal differences can be observed in the structure of total consumption (Fig. 5). The proportion of penicillins use is between a minimum of 33.5% in Obwalden and a maximum of 44.8% in Solothurn. Macrolides range from 12.7% to 22.1% whereas quinolones vary from 17.2% to 23.1%. Although there are clearly differences in the cantonal consumption structure, figures suggest that within country variations are less substantial compared to those observed across European countries (see Ref. [6]). Cantonal differences in terms of the proportion of each antibiotic category on total consumption may be related to local variables, such as the prevalence of infections, patients' and doctors' preferences, pharmaceutical marketing strategies, cantonal regulation and the incidence of bacterial resistance.

3. Explaining variations

Regional variations in antibiotic consumption may be explained by a variety of factors. Several authors have suggested that doctors' decision to prescribe and patients' use of antibiotics are explained not only by clinical factors and by differences in bacterial infections across regions. Difference in bacterial infection can hardly explain variation in morbidity as large as four fold among industrialized countries. The literature has suggested the lack of education, physicians and patients' expectations, uncertainty, cultural and social

behavior, and differences in regulatory practice, among other factors [28,29].

Previous studies focusing on the determinants of antibiotic consumption have been conducted either in the form of trials or questionnaire surveys. Mecfarlane et al. [30] investigated the impact of patient's information. Their experiment showed that the distribution of information leaflets to patients not in need for antimicrobials effectively reduced their use without affecting the doctor–patient relationship. Using a questionnaire survey on 22 Australian non-randomly selected general practitioners and 336 patients, Cockburn and Pit [31] showed that patients expecting a medication were nearly three times more likely to receive it compared to other patients. Moreover, patients were 10 times more likely to receive a medication if practitioners perceived a patient's expectation on prescribing. Doctors' perception and patients' expectations were significantly associated to each other. Webb and Lloyd [32] suggested that older people are more likely to be prescribed a medication, although this result is not confirmed by Cockburn and Pit's study. Harbarth et al. [33] suggested that large differences in antibiotic consumption between France and Germany are at least partially related to differences in the concentration of child care facilities and the use of breast feeding between the two countries. Finally, Unsworth and Walley [34] showed that antibiotic prescribing is related to practice characteristics in the British NHS. Deprived and single-handed practices tend to prescribe more but cheap antibiotics,

while dispensers and trainers, with low level of deprivation and early wave fundholders have lower rate of prescriptions.

An alternative approach to investigate the determinants of antibiotic consumption is to use regional consumption data and regress them against a set of variables suggested by the literature as plausible causal factors of the demand for drugs. This approach is applied, for instance, by Di Matteo [35] to investigate the macro determinants of health expenditure in the United States and Canada. We apply a similar approach to regional outpatient antibiotic consumption in Switzerland and discuss it in the following section.

3.1. An econometric approach

From the economic point of view, antibiotics are an input of the health care and the health production process. Therefore, following the Grossman's tradition it is possible to derive the demand for antibiotics directly from the demand for health care. In this framework, the demand for antibiotics is a demand derived from the demand for healthy days and can be specified using the basic framework of household production theory.[4] In this framework, a household combines drugs, health care, time, exercise, education and capital equipment to produce healthy days.

Inspired by this approach and given the restriction of aggregate data,[5] it is possible to specify an ad hoc demand function for the cantonal per capita outpatient antibiotic consumption, where the demand for antibiotics depends on the individual's stock of health care (H), income (Y), prices of antibiotics and prices of other health care services, the incidence of infectious diseases and other socioeconomic variables, such as age, nationality and education.[6] These socioeconomic variables are usually included in the model as prox-

ies for the individual stock of health care, which is difficult to measure. Moreover, under a pure fee-for-service reimbursement scheme, there may be incentives to induce the demand for physicians' services.[7] Thus, the demand for antibiotics could also depend on some characteristics of the supply of health care services as physicians' density.

Taking into account the availability and the quality of data for the Swiss cantons, we first specify the following parsimonious empirical model (*Model 1*) for the per capita demand of outpatient antibiotics:

$$\mathrm{DID}_{it} = f(Y_i, P_{it}, \mathrm{DPH}_i, \mathrm{UNDER20}_i, \mathrm{OVER65}_i,$$
$$\mathrm{FO}_i, \mathrm{EDU}_i, \mathrm{INF}_i, \mathrm{DLATIN}, \mathrm{DT}_t), \qquad (1)$$

where DID_{it} are per capita antibiotic sales in canton i and quarter t, measured in defined daily doses, Y_i the cantonal per capita income, P_{it} the price of a defined daily dose, DPH_i the cantonal physicians' density, $\mathrm{OVER65}_i$ indicates the percentage of the population older than 65 years, $\mathrm{UNDER20}_i$ the percentage of the population below 20 years, FO_i the share of foreigners on total population and EDU_i is the percentage of individuals without post-mandatory education. The incidence of infections (INF_i) is taken into account by the number of campylobacter infections per 100,000 inhabitants per year. As stressed by Ledergerber et al. [38], campylobacter is a major cause of foodborne bacterial gastrointestinal human infections in Switzerland.[8] A "cultural" dummy (DLATIN) that takes into account similarities with adjacent countries and cultural differences across Switzerland is also included. Lecomte and Paris [40] suggested that sociocultural factors which are hard to measure might explain differences in consumption patterns between European countries. For instance, they underline the relevance of the medical training since German students are more likely to learn homeopathic principles whereas UK students are more likely to recognize the importance of primary care. We divided cantons in

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[4] For a precise presentation of the household production theory, see Becker [36]. See also Grossman [37] for an application of household production theory to health care.

[5] An alternative approach would be to use more disaggregated data even at individual level. However, such a dataset was not available.

[6] Of course, we are aware that the use of aggregated data to explain individual antibiotics consumption implies the assumption that the hypothesized relationship between the economic variables in question is homogeneous across all individuals. Therefore, using this aggregate data set at the cantonal level we could encounter an aggregation bias.

[7] For a summary reading of the supply-induced demand theory see McGuire [39].

[8] Streptococcus pneumonie was also an important bacteria responsible for the large majority of respiratory tract infections and a good candidate as an indicator of the incidence of infections. Since data on campylobacter infections appear to be more reliable than data on streptococcus infections we used the former as an explanatory variable in our models.

two groups: "Latin", "non-Latin". The "Latin" group includes French and Italian speaking cantons (GE, VD, NE, FR, VS, TI, JU) whereas "non-Latin" includes German speaking cantons (BS, BL, BE, SG, ZH, SO, AG, SZ, GL, LU, GR, ZG, TG, OW, SH, AR).[9] Finally, DT_t is a dummy variable to control for seasonal effects of antibiotic use. This takes value equal to 1 for period t ($t = 1$–4); otherwise is 0.

Estimation of Eq. (1) requires the specification of a functional form. Several alternative forms could be considered since the theory of demand is quite ambiguous regarding this issue. The log–log specification offers an appropriate functional form for investigating the responsiveness of antibiotic sales to changes in a number of explanatory variables. The major advantage is that the estimated coefficients can be interpreted as elasticities,[10] which are, therefore, assumed to be constant. By applying the log–log functional form, the model (*Model 1*) can be written as:

$$\ln DID_{it} = \beta_0 + \beta_1 \ln Y_i + \beta_2 \ln P_{it} + \beta_3 \ln DPH_i$$
$$+ \beta_4 \ln UNDER20_i + \beta_5 \ln OVER65_i$$
$$+ \beta_6 \ln FO_i + \beta_7 \ln EDU_i + \beta_8 \ln INF_i$$
$$+ \beta_9 DLATIN + \beta_{10} DT_1 + \beta_{11} DT_2$$
$$+ \beta_{12} DT_3 + \varepsilon_{it}, \tag{2}$$

where ln( ) is a natural logarithm applied to the variable.

However, since prices and the number of infections are plausibly endogenous, the estimation of Eq. (2) may lead to biased results. To tackle this problem we consider two alternative approaches: the inclusion of lagged values (*Model 2*) and the instrumental variable method (*Model 3*). In *Model 2* instead of P_{it} we use P_{it-1}—the lagged price of a defined daily dose—and instead of INF_i we use $MEANINF_i$—the average number of infections calculated over the years 1999–2001. The estimation of *Model 1* and *Model 2* was carried out by using an OLS estimation procedure and a GLS

estimation procedure for pooled time-series and cross-sectional data suggested by Kmenta [41].[11]

If the spread of a disease is a dynamic process an instrumental variable may be preferred. Thus, we specify a model (*Model 3*) by instrumenting the number of campylobacter infections (INF_i) with the average number of infections over the past 3 years ($MEANINF_i$) and three additional variables: the density of the population ($DPOP_i$), the mortality rate amenable to health care (MOR_i),[12] and the poverty rate (POV_i).[13] In this case, a two-stage least squares approach is applied. Since data on most explanatory variables are limited to four quarters, the inclusion of lagged prices will restrict the number of observations available for the estimation. *Model 2* and *Model 3* are then estimated by using antibiotic sales for only three quarters.

3.2. The data

The data for the estimation of Eq. (2) were obtained from three sources. Information on the per capita income, physicians' density, demographic structure of the population, the share of foreign people, the level of education, the number of campylobacter infections and the poverty rate were extracted from yearly publications by the Swiss Federal Statistical Office. Mortality amenable to health care was obtained from the Department of Health of the Canton Ticino. Data on antibiotic

[9] Looking at the values of the partial correlation coefficient between the explanatory variables and the dependent variable we observe some variables with a negative sign, Y (−0.14), P (−0.27) and UNDER20 (−0.33) and some variables with a positive sign, OVER65 (0.13), DPH (0.62), EDU (0.08), FO (0.54), INF (0.13) and DLATIN (0.7).

[10] This means that coefficients represent the percentage change in the value of the explained variable corresponding to a 1% variation in the value of the explanatory variable.

[11] From the econometric point of view, we should consider that our panel dataset is characterized by a relatively small number of time periods, a limited number of cross-sectional units and a zero within variation for most of the explanatory variables. The only two variables that are changing over time are the outpatient per capita consumption and the price of an antibiotic daily dose. Hence, the least squares dummy variable model and the error components model are not appropriate. For this reason we use the Kmenta approach. For a general presentation of this econometric procedure see Kmenta [41] and Greene [42]. The estimation has been performed using the econometric software "STATA8".

[12] The rate is defined as the proportion of "untimely and unnecessary" deaths in the total population from diseases for which effective health care is available [43]. The rate for Swiss cantons is derived by the Department of Health of the Canton Ticino following the method applied by Nolte and McKee [44].

[13] The poverty rate indicates the proportion of individuals below the "poverty threshold" over the population of residents. The "poverty threshold" is defined by a level of total income according to the rules of the Conférence suisse des institutions d'action sociale (CSIAS). Its current amount is CHF 1800 (€1161) for a household of only one individual.

sales and prices were provided by IHA-IMS Health. The dataset includes aggregate outpatient antibiotic expenditure and quantities of different classes of antibiotics for Switzerland. Quarterly data were available for 3 years (2002–2004) and detailed at cantonal level. For privacy reasons five small cantons have been aggregated to obtain two "macro" cantons in the dataset so that the total number of cantons was reduced to 23 instead of 26.[14]

Data on antibiotic sales derive from transactions between wholesalers and pharmacies and physicians in Switzerland. Since the retailers' stock of drugs is roughly constant over time, wholesales data provide a good estimation of outpatient antibiotic consumption in the country. However, our data may slightly underestimate total sales for three main reasons. First, data collected for ambulatory care at least partially exclude drugs delivered in nursing home facilities.[15] Second, errors in data collection measurements may account for approximately 5% of the data which are missing. Third, since the aim of our analysis is to focus on ambulatory care, few antibiotic classes mainly related to hospital care (representing less than 2% of the data) were excluded from the purchased dataset.

The dataset is also detailed at product/brand and eventually package levels. Pharmaceutical companies generally provide drug packages standardized for the whole federal territory.[16]

The data were available on a specific software, "ORACLE Sales Analyser", having a multidimensional cube structure: the product, the region, the time period, the channel of sales and measures of consumption. The dataset was partially exported into MS Excel and STATA8 formats to perform the analysis.

The Anatomical Classification (AC-system) provided by the European Pharmaceutical Market Research Association (EphMRA) classifies drugs into 16 groups at three or four levels with an alpha-numeric coding structure. All antibacterial agents (antibiotics) are identified by the alpha-numeric code J01. Antibiotics were disaggregated into different classes (for example, J01F macrolides) to investigate the consumption structure in Section 2. Because the classification system of EphMRA does not perfectly match the international one, we rearranged some of the classes to obtain the standard antibiotic classes commonly used in international studies.[17] In particular, according to the EphMRA classification, broad spectrum penicillins (coded J01C) and medium and narrow spectrum penicillins (coded J01H) define two separate groups but have been grouped together in the ATC classification (J01C penicillins). Quinolones are included in class M in the ATC international classification, whereas they fill class G for EphMRA. We finally summarized seven different classes: J01A tetracyclines, J01C penicillins, J01D cephalosporins, J01F macrolides, J01M quinolones, J01E sulfonamides and others.

Antibiotic sales are measured in terms of currency units (CHF) and the number of sold packages. Furthermore, the dataset provides a third measure named counting units (CU). CU are defined in terms of milligrams and days of treatment (DOT). DOT are derived from milligrams using the total number of sold packages, the milligrams per package and the defined daily dosage (DDD) as DOT = (number of packages) (mg per package)/DDD. The latter measure, according to the WHO,[18] is the assumed average maintenance dose per day for a drug used for its main indication in (by) adults. For some products like penicillins, the standard counting unit is not the milligrams but the International Unit (IU) established by the UK National Institute for Medical Research. Hence, we

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[14] The dataset could not provide detailed information for areas with less than five pharmacies and/or drugstores. Hence, some small cantons were merged. Uri, Obvalden and Nidwalden were grouped together and included in Obwalden (OW), whereas Appenzell Outer-Rhodes and Appenzell Inner-Rhodes were included in Appenzell Rhodes (AR).

[15] In Switzerland around 50% of nursing homes have an internal pharmacy unit. Antibiotics delivered by the internal pharmacy are not included in the dataset and counted as hospital consumption.

[16] However, since different types of packages could also be sold in different proportions among geographical areas, we randomly compared the shares of packages sales for main categories of products across cantons by means of the coefficient of variation. The value was fairly low and very close to zero for most types of packages.

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[17] The ATC classification used in international studies is an extension of the EphMRA classification suggested by Norwegian researchers in the 1970s. Since 1996, the use of the ATC and, more generally, of the ATC/DDD system is recognized by the WHO as the international standard.

[18] This is a constant for each active pharmaceutical ingredient. As the WHO emphasized, the DDD is a unit of measurement and does not necessarily reflect the recommended or the prescribed daily dose. For example, doses may depend on individual characteristics, such as age and weight.

adapted the above expression to consider IU instead of milligrams.

In addition to the original variables we calculated total per capita sales and days of treatment per 1000 inhabitants per day using demographic data at cantonal level. The latter measure constitutes the explained variable in all the three econometric models defined above. Since daily doses are standardized, our variable assumes that cantonal variations may be related to two main sources: the number of antibiotic treatments per 1000 inhabitants per period and the average dosage schedule for each treatment.

Since many explanatory variables were available for 2002 only, we estimated Eq. (2) by using four quarters. Because of the inclusion of lagged prices, *Model 2* and *Model 3* are instead estimated by using three quarters. As an exception, the level of education (EDU) refers to year 2000. Table 1 gives summary statistics of variables included in the models.

3.3. Estimation results

The parameter estimates of the three model specifications are summarized in Table 2. All of the models give satisfactory and stable results. In the first model (*Model 1*) price and infections endogeneity is not addressed. *Model 2* includes lags of prices and the number of infections although observations are restricted to three quarters. The results are presented for both OLS and GLS estimation procedures. Moreover, we estimated the model by using OLS and report

the Huber/White standard errors. Finally, *Model 3* is estimated by using two-stage least squares. However, according to the Hausman test the null hypothesis of exogeneity cannot be rejected ($p = 0.85$).

The majority of the coefficients are significantly different from zero and carry the expected sign in all the models. Each model accounts for more than 80% of observed cantonal variations in outpatient antibiotic DID. As for the interpretation of the results, some common points across the alternative specifications can be summarized.

The income coefficient is always very significant and shows a negative sign. This suggests that richer cantons generally spend less on outpatient antibiotics compared to lower income cantons. Since per capita antibiotic sales and regressors are in logarithm form, the coefficients can be interpreted as elasticities. The responsiveness of the outpatient antibiotic DID to a change in the average cantonal income, *ceteris paribus*, is around 0.5 in all of the specifications. This result suggests that anti-infectives may not be as strongly normal goods as argued by Baye et al. [45], whose calculated income elasticity was 1.331. Differences may be related at least to three main reasons: the population under study, the time period considered and the source of data. First, our analysis focuses on Swiss outpatient antibiotic expenditure whereas Baye et al. use USA data. The results may then suggest that the Swiss population is more keen on substituting antibiotics with alternative treatments when income increases. Findings may also imply that the Swiss population is more

Table 1
Variables notation and summary statistics

Variables	Unit of measurement	Minimum	Medium	Maximum
Outpatient antibiotic consumption (DID)	DDDs per 1000 inhabitants per day	4.28	7.89	18.49
Income per capita (Y)	Income (CHF)/population	35952	45746	77583
Price of a daily dose (P)	Sales (CHF)/DDDs	3.40	3.72	4.32
Physicians' density (DPH)	Physicians per 100,000 inhabitants	118	160	353
Population under 20 years (UNDER20)	Under 20 years/population	0.17	0.24	0.26
Population age over 65 years (OVER65)	Over 65 years/population	0.12	0.15	0.21
Share of foreign population (FO)	Foreign people/population	0.09	0.19	0.38
Percentage of people without post-mandatory education (EDU)	Basic education/population	0.19	0.24	0.32
Incidence of campylobacter infections (INF)	Number per 100,000 inhabitants	92	115	187.7
Density of population (DPOP)	Inhabitants/km^2	27	218	5149
Poverty rate (POV)	Proportion of population below wealth threshold	0.001	0.170	0.237
Mortality rate (MOR)	Mortality rate amenable to health care	22.39	29.81	34.807

Table 2
Parameter estimates for the three models

| | Model 1 (observations 92, adjusted R^2 0.887) | | | | Model 2 (observations 69, adjusted R^2 0.90) | | | | Model 3 (observations 69, adjusted R^2 0.894) | |
| | OLS | | GLS | | OLS | | GLS | | 2SLS | |
	Coefficient	Robust S.E.	Coefficient	S.E.	Coefficient	Robust S.E.	Coefficient	S.E.	Coefficient	S.E.
Constant	0.383	1.394	2.636[b]	1.160	1.146	1.191	2.404[c]	0.770	1.644	1.381
Y	−0.509[d]	0.108	−0.515[d]	0.098	−0.477[d]	0.100	−0.490[d]	0.071	−0.519[d]	0.114
P_t	−0.595[a]	0.326	−0.561[c]	0.198	–	–	–	–	–	–
P_{t-1}	–	–	–	–	−0.606[a]	0.331	−0.570[d]	0.178	−0.564[a]	0.295
DPH	0.680[d]	0.111	0.543[d]	0.100	0.629[d]	0.116	0.613[d]	0.073	0.650[d]	0.110
UNDER20	−0.372	0.261	−0.054	0.246	−0.350	0.281	−0.004	0.181	−0.257	0.275
OVER65	−1.027[d]	0.220	−0.691[d]	0.211	−0.885[d]	0.212	−0.667[d]	0.136	−0.864[d]	0.179
FO	0.186[c]	0.064	0.246[d]	0.057	0.194[d]	0.057	0.264[d]	0.041	0.221[b]	0.060
EDU	0.442[c]	0.165	0.168	0.143	0.318[b]	0.162	0.317[c]	0.101	0.350[b]	0.133
INF	0.201[c]	0.084	0.312[d]	0.066	–	–	–	–	0.157[b]	0.078
MEANINF	–	–	–	–	0.172[b]	0.085	0.164[d]	0.045	–	–
DLATIN	0.173[d]	0.042	0.220[d]	0.043	0.171[d]	0.045	0.153[d]	0.031	0.154[c]	0.049
DT_1	0.077[b]	0.037	0.073[d]	0.014	–	–	–	–	–	–
DT_2	−0.205[d]	0.027	−0.206[d]	0.014	−0.171[d]	0.029	−0.176[d]	0.015	−0.173[d]	0.028
DT_3	−0.178[d]	0.027	−0.184[d]	0.011	−0.166[d]	0.027	−0.180[d]	0.013	−0.166[d]	0.026

[a] Significant at 10%.
[b] Significant at 5%.
[c] Significant at 1%.
[d] Significant at 0.1%.

aware of the perverse effects of antibiotic consumption induced by bacterial resistance. This explanation can be supported by the relatively low per capita antibiotic consumption in Switzerland compared to other countries. Second, Baye et al.'s study is based upon 1984–1990 data. The raising concern over the impact of antibiotic resistance over the 1990s may have reduced the income elasticity of outpatient antibiotic expenditure over time thus leading to our lower elasticity value. Finally, Baye et al. use retailing prescription data collected through surveys of a sample of pharmacies. Instead, we use total outpatient antibiotic wholesales to pharmacies, drugstores and medical practices. Our data may not capture the effect of retailing strategies associated with income because they are not directly related to the final consumer.

The level of education is negatively related to the per capita outpatient antibiotic expenditure defined in DID. The coefficient is significant at less than 0.05 in all the regressions and shows that an increase in the percentage of people without post-mandatory education increases the per capita antibiotic expenditure

defined in DID. Education elasticities range from 0.317 to 0.442. To our knowledge there are not comparable multivariate studies on the impact of education on the use of outpatient antibiotics. A comparison with the literature on medical care utilization, such as physician office visits or hospital services, suggests that antibiotics are quite peculiar, as expected. Hunt-McCool et al. [46] found positive education elasticity to physician office visits and hospital care, although the impact is not very significant. The same kind of impact may not be expected for outpatient antibiotic use where the association between increasing consumption and the reduced effectiveness due to resistance may induce more informed individuals to restrain from antibiotic utilization. Lleras-Muney and Lichtenberg [47] found that highly educated people are generally more likely to use drugs more recently approved by the Food and Drug Administration, with the exception of some disease categories, such as infectious diseases where antibiotics are generally consumed.

In terms of the investment in health function in the Grossman model the results suggest that relatively rich

and highly educated people either use health care inputs (antibiotics) more efficiently or have higher initial health stocks. Higher levels of productivity imply that the same amount of health investment can be obtained by a lower amount of health care services. Also, higher initial health stocks imply that lower investment in health, and hence in health care inputs, are required for any given level of optimal health stocks, *ceteris paribus*.

As expected the price of a daily dose has a negative and slightly significant impact on antibiotic sales. Price elasticities range from −0.561 (GLS of *Model 1*) to −0.606 in the lagged model (*Model 2*). Swiss consumers directly bear only a small fraction of the total cost of drugs because of compulsory health insurance purchasing. However, antibiotic sales may be affected by price changes because of standardized deductibles and copayments. On the other hand, the demand for antibiotics may be more inelastic compared to other types of drugs since antibiotics are generally purchased under doctor's prescription. Our estimates are slightly lower than those of Baye et al. [45] who found negative compensated (−0.785) and uncompensated (−0.916) own-price effects for anti-infectives. Still, they may support their argument that anti-infectives have the largest own-price elasticities among all major pharmaceutical classes. Focusing on the demand for one antibiotic class, the cephalosporins, Ellison et al. [48] calculated own-price elasticities for different brand/generic names unconditional on drug expenditure and using US wholesale data from 1985 to 1991. Their estimates range from −0.38 to −4.34. Our results could also be compared to the ones found in Rudholm [49] who derives own-price elasticities for three Swedish pharmaceuticals submarkets during the years 1989–1996. The prescription drug market for beta-receptor blocking agents is maybe the closest to our outpatient antibiotic market, although not exactly the same. Mean own-price elasticities calculated by Rudholm are also negative and significant at 5% level ranging between −0.12 and −3.43. A shorter range (from −1.62 to −2.13) is covered by elasticities estimated by Rizzo [50] using wholesales data from the US antihypertensive drug market.

An increase in the number of physicians at cantonal level causes an increase in the cantonal per capita antibiotic DID. The coefficients of physicians' density are positive and highly significant. Estimated elastici-ties are also very stable across different model specifications ranging from 0.543 to 0.680. This result may suggest some evidence of supply-induced demand in the Swiss market for outpatient anti-infectives.[19] Note that antibiotics should only be purchased under physician's prescription. Under the assumption that the mismatching between wholesale figures and physicians' prescriptions can be ignored, our findings may support the hypothesis that physicians do not act as perfect agents for consumers.[20] This is also in accordance with the health economics literature suggesting that in systems where physicians are paid under a fee-for-service scheme, akin to the Swiss one, over-consumption of drugs is more likely. Given that daily doses are standardized, our result suggests that cantonal variations in physician's practices may either take the form of differences in the number of antibiotic treatments per person or differences in daily dosage schedule. A different result to ours is obtained by Di Matteo and Grootendorst [51] who estimate the socioeconomic and demographic determinants of real per capita Canadian provincial government drug expenditure. In their study the per capita number of prescribing physicians is found to be a negative, although not a significant, determinant of the Canadian drug expenditure. However, it is important to point out that the health care system under investigation exhibits substantial differences compared to the Swiss one.

To capture the effects of demography on antibiotic sales we included as covariates the proportions of the population aged below 20 years and over 65 years. One might expect a drug expenditure decline during the first few years of life followed by an increase as the population ages. The literature on the determinants of health care expenditure generally suggests that the increasing prevalence of chronic health problems as people grow older may determine an increase in the utilization of health care services. For instance, Di Matteo and Di Matteo [52] investigated the determinants of the real per capital provincial government health expenditure in Canada using a log–log functional form. They

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[19] For an exhaustive discussion on the supplier induced demand theory see McGuire [39].

[20] This means that physicians may not choose the same doses or type of antibiotic as the patient would if he/she was as much informed as the physician.

calculated a 0.81 elasticity of the proportion of the population aged over 65 years. In a similar study Di Matteo and Grootendorst found a slightly significant increase in drug expenditure as the population ages until 64. Between 64 and 74 the effect is still positive although this result is not confirmed by the more recent study by Di Matteo [35]. We argue, however, that the consumption of anti-infectives in the community may be quite different from other health care services and consequently does not follow the same trend over the lifetime. First, doctors and patients might be more concerned about the potential harmful effect of prescribing antibiotics to very young and elderly individuals. Antibiotic treatment is more likely to be delayed for these individual categories to avoid resistance implications. Second, the antibiotic therapy may sometimes be conceived as a time-saving choice and hence more likely to be adopted by individuals belonging to the labor forces. These hypotheses are in accordance with the results of a French study conducted on a panel of general practitioners and focusing on antibiotic prescriptions for rhynopharingeal infections [9]. Antibiotics are less likely to be prescribed to the population class aged below 16 years compared to the 40–64 population class. On the other hand, individuals over 64 years are less likely to get an antibiotic prescription. Similarly, we obtained negative and significant coefficients of the proportion of individuals over 65 years (from -0.667 to -1.027). We also found a negative impact of the proportion of the population aged under 20 years on the per capita antibiotic DID. However, this result is not significant.

Another important factor that may be related to differences in outpatient antibiotic expenditure across Swiss cantons are the cultural and linguistic variations. One can argue that cantons adjacent to countries, such as France, Germany and Italy, could share similar cultural attitudes for at least two reasons. First, the public perception of the need for antibiotics may be influenced by the perception of neighboring populations. Second, cantonal "medical attitudes" to prescribing may be influenced by "medical attitudes" in neighboring countries. These hypotheses are worth testing also in the light of differences observed in antibiotic consumption between adjacent countries [6]. Both cultural covariates introduced in our models exhibit significant coefficients. The share of foreign people on the total population increases the cantonal per capita outpatient antibi-

otic expenditure. This result was expected because of the lower Swiss antibiotic consumption compared to adjacent countries. The "Latin" dummy suggests that antibiotic expenditure is higher in French and Italian speaking cantons compared to German speaking cantons, which is also in accordance with the hypothesis above.

The number of infections is significant at less than 5% level both in the lagged and in the two-stage least squares specifications. Coefficients exhibit the expected positive sign and suggest that outpatient antibiotic expenditure is not much elastic to the impact of epidemiological factors. Looking at the pharmaceutical consumption for cardiovascular disease and stroke, Dickson and Jacobzone [53] found that drug use may be strongly related to indicators of the burden of disease for more effective and inexpensive types of drugs only. It is important to point out that the lack of quarterly data on the prevalence of bacterial infections in our dataset may dilute the seasonal impact on antibiotic consumption. Seasonal effects are then captured by time dummies.

Time dummies clearly suggest that there are some seasonal effects in antibiotic consumption in ambulatory care. The baseline season is represented by the third quarter, i.e. the *autumn* dummy (October, November, December). Per capita outpatient antibiotic DID are expected to be higher during the fourth quarter, *winter* (January, February, March), and lower in the first and the second quarter of the year, as pointed out by Goossens et al. Accordingly, the estimated coefficients of DT_2 and DT_3 are both negative and highly significant in all the three models. The *winter* dummy appears in *Model 1*. This is positive and significant at less than 5% level.

4. Conclusions

The investigation of regional variations in outpatient antibiotic use may help to understand the determinants of the demand for antibiotics and contribute to the discussion on the reduction of antibiotic resistance. There is a lack of empirical evidence in the analysis of within country variations in outpatient antibiotic consumption. Wide differences in the utilization of drugs were observed, for instance, between three major urban areas in Sweden [54].

We analysed cantonal outpatient antibiotic sales in Switzerland. We showed that the country uses relatively low volumes of antibiotics in ambulatory care compared to other European countries. In terms of consumption structure, Switzerland is characterized by high proportions of quinolones.

Antibiotic use in ambulatory care significantly increased in terms of defined daily doses per 1000 inhabitants daily and sales per capita between 2002 and 2003 in most Swiss cantons. Conversely, consumption generally decreased in 2004.

The investigation of cantonal differences showed that there are wide variations across cantons. These can hardly be explained by epidemiological factors only. Econometric estimations on quarterly data for 2002 suggested that per capita income, price, demographic factors, including the proportion of foreign residents, the density of medical practices, and cultural and educational differences may contribute to explain regional variations in ambulatory antibiotic use.

More effective policies to improve the efficient use of antibiotics in the community may be driven by these findings. Appropriate incentives affecting antibiotic consumption and, consequently, levels of bacterial resistance can be designed by looking at crucial determinants suggested in the model and their relative impact. A number of studies suggest, for instance, that inappropriate individual consumption is associated with the lack of awareness of the danger of antibiotic use [55,56]. We showed that higher level of education may account for lower antibiotic use in the community. Cantonal educational efforts are then needed if the consumption of antibiotics is to be reduced. Moreover, local guidelines could represent a valid tool given the evidence that per capita antibiotic consumption is associated with the density of general practices. The cantonal public health authorities should then promote local guidelines with adequate incentives for doctors and effective information campaigns for appropriate antibiotic use.

Econometric models using data at local level and the application of multiple-choice models to selected categories of antibiotics should be explored to further explain small area variations in outpatient antibiotic use. Additional suspicious determinants like bacterial resistance and prescribing practices should also be considered.

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