

Antibiotic and anti-asthmatic drug prescriptions in Italy: geographic patterns and socio-economic determinants at the district level

Daniele Piovani · Antonio Clavenna · Massimo Cartabia ·
Maurizio Bonati · on behalf of the Interregional Italian
Drug Utilisation Group

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Abstract

Purpose To analyse the prevalence rate of antibiotics and anti-asthmatics in children and adolescents at the healthcare district level.

Methods Data sources were three regional prescription databases. A total of 175 healthcare districts (3.3 million children/adolescents) participated in the study, providing data for the year 2008. Prevalence rate was standardised by age. The ANOVA test was used to compare prevalence rates of districts in the three regions. The standardised prevalence ratio (SPR) was calculated for each district and a map of the index was elaborated. The correlation among latitude, average annual income per inhabitant, hospitalisation rate, number of paediatricians per 1,000 resident children and prevalence rate was evaluated by district (Spearman's test).

Results The antibiotic prevalence rate was, on average, 47.9 % (34.0 to 67.9 % between districts), while the anti-asthmatic prevalence was 21.4 % (11.7–35.6 %). The prevalence was higher in districts from the southern regions (antibiotics $F=92.1$, anti-asthmatics $F=107.5$; $p<0.001$). There was a significant correlation between the prevalence of antibiotics and anti-asthmatics ($r_s=0.77$ $p<0.001$), and the prevalence of both was inversely related to latitude (respectively $r_s=-0.71$, -0.72 ; $p<0.001$) and

average income ($r_s=-0.77$, -0.73 ; $p<0.001$). Children/adolescents living in districts in the lower quintile of average income were more exposed to antibiotic (OR=1.75; 1.74–1.77) and anti-asthmatic (OR 1.56, 1.55–1.57) prescriptions.

Conclusions A lower income at the district level is related to higher antibiotic and anti-asthmatic drug prescription rates. Local socio-economic inequities can concur in prescribing distribution and must be considered when planning educational interventions to reduce over-prescription.

Keywords Anti-asthmatic agents · Anti-microbial agents · Prescription · Drug utilisation · Children · Adolescent

Introduction

Drug prescription rates in Italian children are among the highest in Europe and the most frequently prescribed classes are antibiotics and anti-asthmatics [1].

Large differences in antibiotic exposure between countries have been found. An Italian child has, on average, a fourfold higher risk of being exposed to antibacterial drugs than an English child and a threefold higher risk than a Dutch child [2]. Cephalosporins, a second-line treatment in most paediatric infections, are widely prescribed in Italy (39 % of paediatric antibiotic prescriptions), while in the Netherlands and Denmark this class is hardly ever prescribed [2].

Wide differences have also been observed in exposure of children to anti-asthmatics between different countries: prevalence rates (percentage of children receiving at least one prescription in a year) range from 6.2 % in Norway to 19 % in Italy [3]. β_2 -mimetics and inhaled steroids are the most frequently prescribed anti-asthmatics in Italy and their use is, threefold and fourfold higher than in UK and in the Netherlands respectively [4]. In Italy the prevalence of anti-asthmatic

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Interregional Italian Drug Utilisation Group:
Lombardy Region: Angela Bortolotti, Ida Fortino, Luca Merlino
Lazio Region: Marina Davoli, Ursula Kirchmayer
Puglia Region: Ambrogio Aquilino, Francesco Bux
Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud: Antonio D'Ettore, Vito Lepore

D. Piovani (✉) · A. Clavenna · M. Cartabia · M. Bonati
Department of Public Health, Laboratory for Mother and Child
Health, IRCCS—Istituto di Ricerche Farmacologiche “Mario
Negri”, Via Giuseppe La Masa 19, 20156 Milan, Italy
e-mail: daniele.piovani@marionegri.it

drugs is much higher than the prevalence of disease, indicating that anti-asthmatics are over-prescribed [4, 5].

Prescribing differences also exist within countries. In Italy the prevalence rate for all drugs prescribed to children and adolescents is 57.3 % in the North, while it is 68.3 % in the South [1]. The prescription profile of antibiotics has been extensively described at the regional level. The highest prevalence rate is found in southern regions and differences at the LHU level range from 35.6 % to 68.5 % [6]. Under-use of recommended drugs, such as amoxicillin, is an issue, especially in the southern part of the country, with excessive exposure to second-choice treatment (i.e. oral and parenteral cephalosporins) [6]. Notable differences have also been demonstrated within regions, as is the case in the Lombardy region, where the prevalence rate for all drugs ranged from 38.4 % in Milan's local health unit (LHU) to 54.8 % in Brescia's LHU in 2006 [7]. The anti-asthmatic prescription patterns within Italy have not been investigated in depth; however, it is known that beclometasone (which is often related to inappropriate or unlicensed use in Italian children) is the most frequently used anti-asthmatic drug and is most frequently used in the South [8, 9].

In this context a comparison of the two most frequently used drug classes (which are characterised by high inappropriateness of use in Italy) was made at a district level. Three prominent regions were included: Lombardy, Lazio, and Puglia. The aim of this study was to evaluate the antibiotic and anti-asthmatic drug prevalence rate at the district level as well as the influence of the territorial setting, including a few socio-economic determinants, on an Italian child and adolescent outpatient population.

Materials and methods

The Italian national health system

Italian healthcare is provided free or at a nominal charge through a network of LHUs. Each LHU consists of a number of healthcare districts, which are population-based territorial entities that aggregate different municipalities. Every Italian resident is registered with a family (paediatric or general) practitioner. Children are assigned to a paediatrician until they are 6 years old; afterwards, the parents can choose to register a child with a general practitioner. All adolescents >13 years old are assigned to a general practitioner. A national formulary is available, in which drugs are categorised in two classes: class A includes essential drugs that patients do not have to pay for and class C contains drugs not covered by the national health system (NHS). Most antibiotics and anti-asthmatics are free of charge.

Data source

Data sources were regional databases routinely updated for administrative and reimbursement reasons. The databases

stored all community prescriptions reimbursed by the NHS. The study population was composed of 3,301,096 children and adolescents <18 years old (32.5 % of the population <18 years old), living in three large Italian regions: Lombardy (1,616,268 resident children), Lazio (926,015) and Puglia (758,813), from North to South. The observation period was from 1 January to 31 December 2008 for all regions. Overall, 193 healthcare districts (45 in Puglia, 55 in Lazio and 93 in the Lombardy region), participated in the study. The cities of Rome and Milan were considered as a whole and not as "composed of districts", because data at such an aggregation level were not available. Two districts from the Lombardy region were excluded from the analyses because their paediatric population size was under the first percentile of the distribution of the population by district. The average number of resident children/adolescents in each district was 16,932 (ranging from 16,237 in Lazio to 17,375 in Lombardy region).

All drugs were classified according to the ATC system (Anatomical Therapeutic Chemical classification system). In this study antibiotics were considered to include every drug belonging to the J01 sub-group and anti-asthmatics every drug belonging to the R03 sub-group.

Measures

In order to describe the prescription profile the prevalence rate for antibiotics and anti-asthmatics was calculated at the district level. The prevalence rate was the number of individuals who received at least one prescription in 1 year, divided by the number of children/adolescents.

The all-cause hospitalisation rate and hospitalisation rate for asthma as the primary or secondary diagnosis were calculated by district, expressed as the number of patients admitted to the hospital at least once in 1 year (ordinary admissions) divided by 1,000 resident children/adolescents. Data were retrieved from hospital discharge records, which include information on primary diagnoses and up to five co-existing conditions such as secondary diagnoses, procedures performed, date of admission, discharge, and in-hospital death. Asthma diagnoses were classified according to ICD9 (International Statistical Classification of Diseases and Related Health Problems) code 493. The number of paediatricians per 1,000 resident children under 12 years old was calculated by district.

It was not possible to use statistical methods such as logistic regression analysis because aggregated and anonymous data were provided. Demographic distribution among the three age strata (0–5, 6–11 and 12–17 years old) was heterogeneous across the districts, possibly influencing prevalence rates. In order to adjust prevalence rates by age a standardisation method was applied. A logistic regression analysis, using the Lombardy Region database to evaluate the association between drug prescription and age, was performed [7]. The adjusted odds ratios (see reference for details)

were used as “weight” in the standardisation and were calculated for three age strata: ≤ 5 years old ($OR=1.77$), 6 to 11 years old ($OR=1$), and 12 to 17 years old ($OR=0.70$). By using the age-specific weight and prevalence, the age-corrected prevalence rates for each district for antibiotic and anti-asthmatic drugs were obtained [10, 11]. All data analyses were performed using the age-corrected prevalence rates.

An indirect standardisation method was also applied to prevalence rates for antibiotics and anti-asthmatics in all districts in order to calculate the standardised prevalence ratio (SPR). The indirect standardisation uses age-specific prevalence rates from the overall population to derive the numbers of expected cases in the region’s population (i.e. district). SPR indicates whether the prevalence rate observed at a district level is significantly higher or lower than what is observed in the standard population. Confidence intervals were calculated using a shortcut method [12]. Districts with an SPR that is significantly lower than 1 will be referred to as “lower than expected” and those having a SPR significantly higher than 1 as “higher than expected”.

SPR	$T_{obs}/T_{exp} = T_{obs} / [\sum_{age\ groups} (P_{as} N_{as})]$
SPR	Standardised prevalence ratio
T_{obs}	number of treated children (district).
T_{exp}	number of expected treated children (district)
P_{as}	age-specific prevalence rate (standard population).
N_{as}	number of people in the age-specific group (district).

A choropleth map of SPR for antibiotics and anti-asthmatics was elaborated at the district level [13]. The map was created using the software Arcmap 10.1. The non-parametric Spearman test was used to evaluate the correlation between antibiotic and anti-asthmatic prevalence rates and some determinants including: average annual income per inhabitant, latitude, number of paediatricians per 1,000 resident children, and hospitalisation rate for all causes and for asthma. The ANOVA test and the Bonferroni post-hoc test were used to compare the prevalence rate by districts in the three regions. The odds ratios (OR) and 95 % confidence intervals (CI) were used to calculate the likelihood of receiving an antibiotic or anti-asthmatic prescription for children resident in districts with a lower average annual income per inhabitants (lowest quintile) versus a higher average annual income (highest quintile). The coefficient of variation (CV) was used to assess the variability of district prevalence among LHUs.

Results

Regional prescription profile

During 2008, 1,861,425 children and adolescents (56.4 % of the study population) received at least one drug prescription.

The antibiotic prevalence rate was, on average, 47.9 %, ranging from 44.1 % in the Lombardy region to 57.5 % in the Puglia region. The anti-asthmatic prevalence rate was, on average, 21.4 %, ranging from 16.9 % in Lombardy to 27.0 % in Puglia. The male/female odds ratio for the prevalence rate for antibiotics was, on average, 1.05 (95 % CI 1.05–1.06), with no significant differences among regions, while for anti-asthmatics it was 1.21 (1.20–1.21) with a slightly higher ratio in Lombardy (1.24; CI 1.23–1.25) than in Lazio and Puglia (1.18; CI 1.17–1.19).

Prescription profile at the district level

The age-corrected prevalence rate for all drugs ranged from 41.0 % to 74.7 %, from 34.0 % to 67.9 % for antibiotics and from 11.7 % to 35.6 % for anti-asthmatics. The age-corrected and crude prevalence rates differed significantly only in a few districts that had a small population size. The ANOVA and Bonferroni tests showed a significant difference in the prevalence rates of antibiotic and anti-asthmatic drugs in districts across the three regions (Table 1; $p < 0.0001$), with the exception of anti-asthmatic prevalence in Lazio and Puglia ($p = 0.19$).

SPR ranged from 0.70 to 1.44 for antibiotic drugs and from 0.54 to 1.72 for anti-asthmatic drugs, Fig. 1. In Lombardy 69 % of the districts (66/95) had a SPR lower than expected for both anti-asthmatics and antibiotics. On the contrary, in Puglia, none of the districts had an SPR lower than expected and in 82 % of them (37/45) the SPR was higher than expected. Large differences were observed in the variability of district prevalence within each LHU: CV ranged from 0.01 to 0.15 for antibiotics and from 0.03 to 0.22 for anti-asthmatics.

The median average annual income per inhabitant was 7,187 € (interquartile range, IQR=6,440–8,262 €) in the high-prevalence districts (districts having both antibiotic and anti-asthmatic drug prevalence over the mean plus 1 SD), while it was 15,360 € (IQR=13,358–16,837 €) in the low-prevalence districts (prevalence under the mean minus 1 SD).

Determinants

Spearman’s test scored a significant positive correlation between antibiotic and anti-asthmatic prevalence rates at the district level ($r_s=0.77$ $p < 0.0001$). The within-region correlation was significant, but less strong, especially in Lombardy ($r_s=0.57$) and Puglia ($r_s=0.50$).

There was a significant inverse correlation between average annual income per resident and the prevalence rate of both antibiotics ($r_s=-0.77$ $p < 0.0001$) and anti-asthmatics ($r_s=-0.73$ $p < 0.0001$). Children resident in districts in the lowest quintile of annual income per resident had a higher chance (highest vs lowest quintile) of receiving an antibiotic (OR 1.75, 95 % CI 1.74–1.77) or anti-asthmatic drug (OR 1.56, 95 % CI 1.55–1.57; Table 2).

Table 1 Average district prevalence (%) and ANOVA test on the prevalence rates grouped by region

	Antibiotic drug prevalence (%)		Anti-asthmatic drug prevalence (%)	
	Range	Mean $\pm$ SD	Range	Mean $\pm$ SD
Lombardy	34.0–55.1	44.1 $\pm$ 4.1	11.7–26.0	17.8 $\pm$ 3.3
Lazio	35.6–66.7	49.8 $\pm$ 6.7	17.3–32.4	25.1 $\pm$ 3.6
Puglia	48.0–67.9	57.5 $\pm$ 4.9	17.4–35.5	26.5 $\pm$ 4.6
ANOVA test	$F=105.26$	$p<0.0001$	$F=112.30$	$p<0.0001$

The correlations between prevalence rate of antibiotic and anti-asthmatic drugs toward other determinants are reported in Table 3.

Discussion

This is the first Italian study evaluating antibiotic and anti-asthmatic prescriptions at the district level in three large Italian

regions. The result concerning antibiotics was similar to what was observed, at the LHU level, in a previous study [6], although prevalence rate ranges at the district level were wider than those found in the previous study (e.g. in Lombardy the range was 34.0–55.1 % at the district level, while it was 36.3–50.6 % at the LHU level). In particular, this study underlines the fact that, even in settings characterised by low prevalence rates (i.e. Lombardy), there are districts with a higher prevalence than expected and that variability is often very high even

Fig. 1 Choropleth map of the standardised prevalence ratio (SPR) at the district level for antibiotics and anti-asthmatics. The SPR indicates whether the prevalence observed in each district is significantly higher (SPR>1) or lower (SPR<1) than expected by using a standard population as a reference (the overall study population)

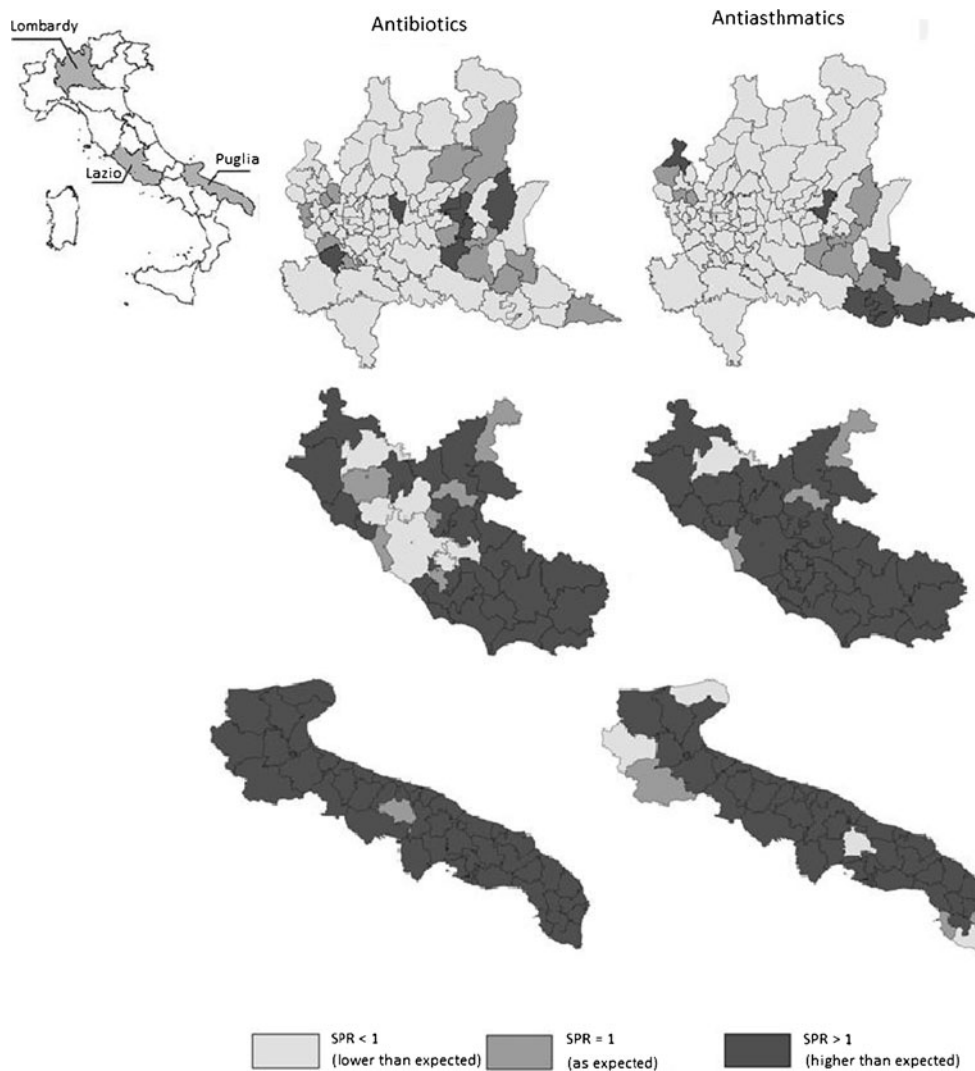


Table 2 Analysis of the correlation between antibiotic (J01) and anti-asthmatic (R03) prevalence rates versus average annual income per resident at the district level, numbers in parentheses are confidence intervals

Prevalence rate	Average annual income per resident	
	Overall rS	Lowest vs highest quintile OR
Lombardy		
Antibiotics	−0.27	1.23 (1.22–1.24)
Anti-asthmatics	−0.46	1.25 (1.24–1.27)
Lazio		
Antibiotics	−0.55	1.31 (1.30–1.33)
Anti-asthmatics	−0.38	1.16 (1.15–1.18)
Puglia		
Antibiotics	−0.34	1.29 (1.27–1.30)
Anti-asthmatics	−0.02*	1.03 (1.02–1.05)
Total		
Antibiotics	−0.77	1.75 (1.74–1.77)
Anti-asthmatics	−0.73	1.56 (1.55–1.57)

*Non-significant *p* value (>0.05)

among districts within the same LHU. The use of anti-asthmatics was found to be higher than in a previous study in children (same age group) in the North [5], while it was similar to what was observed in another Italian paediatric population [14].

The current study shows that the use of anti-asthmatics, as well as antibiotics, is higher in the South and that there is a correlation between anti-asthmatic and antibiotic use at the district level. In particular, the SPR (for both antibiotics and anti-asthmatics) increases from North to South. Another study already showed that Italian children living in the South have a greater chance of receiving a prescription of any drug

Table 3 Correlation between the prevalence rate of antibiotic and anti-asthmatic drugs vs other determinants at the district level

Prevalence rate vs	rS	<i>p</i> value
Latitude (South to North)		
Antibiotics	−0.71	<0.0001
Anti-asthmatics	−0.72	<0.0001
Hospital admission rate		
Antibiotics ^a	0.33	<0.001
Anti-asthmatics ^b	0.03	0.65
Paediatricians per 1,000 inhabitants		
Antibiotics	−0.19	0.01
Anti-asthmatics	−0.02	0.80

^a All-cause hospitalisation rate

^b Hospitalisation rate for asthma

compared with their counterparts living in the rest of the country [8]. Since antibiotics and anti-asthmatics are the most commonly prescribed drugs in Italy this finding is in part expected and may mean that the geographical differences observed may not be linked to a particular class of drugs, but to other, independent factors.

The association between asthma and antibiotic use in children has already been shown in the literature [15–17]. The relationship between anti-asthmatics and antibiotics use, however, is a quite different phenomenon. In fact, particularly in Italy, anti-asthmatic drug consumption in an outpatient setting is not a good disease indicator, since the inappropriate use of this drug class is very high [4]. The unreliability of anti-asthmatic consumption as a disease indicator in this setting is evident if one looks at its association with hospitalisations for asthma: they are unrelated. For this reason the correlation of the use of these two drug classes is probably thought to be due to a generally inappropriate use of drugs and not to the anti-asthma–antibiotic use link.

Concerning income, children living in low income districts have a higher chance of receiving a prescription of an antibiotic or an anti-asthmatic. This trend persists within regions/areas characterised by different prescribing volumes. The finding that there is a twofold absolute difference in the average annual income per inhabitant between the high and the low prevalence districts is striking. Similar findings have been recently found in Germany [18] and in Switzerland as well [19]. In these countries, as in Italy, the cost of antibiotic and anti-asthmatic drugs is, at least partially, reimbursed. In these cases, given the methodology used, the confounding role of out-of-pocket drug use cannot be excluded [8].

Concerning latitude, the prevalence is higher in southern Italy, but this is not true in Germany, where antibiotic use is higher near the upper-western border and the far north, suggesting that latitude and other related factors (such as climate) cannot explain these data. The inverse correlation between latitude and antibiotic/anti-asthmatic drug prescription is valid in Italy, where the North–South socio-economic polarisation is well known, but not necessarily in other countries. Another study on antibiotic prescriptions found that in Lombardy there is a West–East geographic trend rather than a North–South one [13]. In this study, latitude and average annual income were both related to prevalence of antibiotics and anti-asthmatics (the two indicators are collinear), but the hypothesis is that income is a more relevant variable, because, when looking at prescriptions within regions of different income levels, the same association persists.

A plethora of other factors possibly associated with drug prescription to children (mainly antibiotics) have been considered in a number of international and Italian studies [20–26]. Education and income level are factors known to indirectly affect individual health. Various studies agree in demonstrating that poor and less educated people have inadequate access

both to primary prevention and to early diagnosis [27]. These facts could also reflect a lower quality of children's healthcare. A lower educational level could also affect the understanding of the therapy's importance and, indirectly, how much the prescriber perceives the parental expectation of a prescription, the latter of which is a known factor influencing the physician's decision [25]. It has been demonstrated that parents of children receiving many antibiotics use more medicines themselves [28]. These data reinforce the hypothesis that area income deprivation is only a proxy of other linked deprivations, which are probably more relevant or more directly affect the amount of prescriptions in children. In particular, educational deprivation, which is very often related to income deprivation [29], may play, at least in part, a causal role in the amount of medicines prescribed to children. The role of the prescriber is also particularly important: in Lombardy, in the highest prevalence areas, a higher number of paediatricians classified as high prescribers was found [13].

Ultimately, the current study shows that prescribing distribution at a micro-level is associated with socio-economic disparities, even if the Italian NHS fully reimburses antibiotics and anti-asthmatics. A recent study in the same setting (Lombardy region) showed that a local educational intervention in paediatricians was able to improve the prescription profile [30]. If education (of families and physicians) is one of the most important factors affecting prescribing, policy makers should take into account the differences highlighted in order to plan educational interventions to reduce prescription and implement more rational drug use.

Finally, as a methodological issue, this study also underlines the importance of the evaluation of epidemiological outcomes in small census areas. The prescription profile of a region cannot be representative of the national pattern. On the other hand, the profiles observed at the national and regional levels are not applicable at the district level. From this point of view, the local context influences drug prescriptions and its role should be investigated as part of the monitoring of drug utilisation.

This study is able to provide more robust data on the association between income and prescription of reimbursed drugs to children by including an analysis of data at the district level. The entire child/adolescent population of three regions, representative of different geographical and economic settings, was included, avoiding selection bias (e.g. different social or educational backgrounds). The prevalence rate by age, which is the most important factor associated with higher drug prescription in children, was standardised in this study. However, some limitations must be considered.

Since reimbursement data were analysed, it was not possible to ascertain adherence to prescribed treatments. This is a limitation because other studies on adult patients reported low adherence rates in primary care [31], even if in paediatric patients the phenomenon may be limited. The use of aggregated data precluded the application of more appropriate

statistical methods such as logistic regression analysis. Furthermore, data on out-of-pocket drug use were not available for antibiotics and anti-asthmatics (although they are fully reimbursed). Out-of-pocket drug use could potentially bias the relationship between higher anti-asthmatic and antibiotic drug consumption and lower income as described elsewhere [8]. However, it is likely that the phenomenon is limited for reimbursed drugs.

Conclusions

The current study highlights anti-asthmatic and antibiotic prescription differences at the district level showing wide local differences and specificities that were not demonstrable in other studies. Anti-asthmatic and antibiotic drug prescribing are related and their use is higher in the south of Italy. The data also confirm the presence of an inverse association between annual income and the prevalence rate of antibiotic and anti-asthmatic drugs at the district level. Local socio-economic inequities can concur in prescribing distribution and must be considered when planning educational interventions to reduce prescription and increase rational drug use.

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Conflict of interest The authors declare that they have no conflict of interest.

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