Determinants of the drug utilization profile in the paediatric population in Italy's Lombardy Region

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drug utilization studies performed in the Italian paediatric population have found a prescription profile that appears to be specific to Italy.
- Quantitative and qualitative differences with other European countries have been found.
- The prevalence of drug prescription is higher in southern Italy compared with northern Italy.

WHAT THIS STUDY ADDS

- This is the first study to evaluate the geographical differences in the pattern of drug prescribing to children and adolescents in a large Italian region.
- Large differences in the prescription prevalence rate were found between local health units.
- Living in the eastern part of the Lombardy region is associated with the highest risk of drug exposure.

AIMS

To evaluate the intraregional differences in drug prescribing to children and adolescents.

METHODS

Prescriptions reimbursed by the National Health System, involving 1543 203 children and adolescents <18 years old and dispensed during 2005 by the retail pharmacies of 15 local health units (LHU) in the Lombardy Region, were analysed. Logistic regression analysis was performed to evaluate the association between drug prescription and age, gender, prescriber, and setting.

RESULTS

A total of 747 790 youths (48%) received at least one drug prescription. The prescription prevalence rate was highest in children 1–5 years old (65%), decreased with increasing age to 38% in adolescents, and was slightly higher in boys than in girls. Antibiotics and anti-asthmatics were the most prescribed therapeutic classes. Amoxicillin + clavulanic acid was the most prescribed drug (18% of children; 20% of packages). Large differences were found in the drug prescription prevalence rate between the different LHUs. The rate ranged between 38.4 and 54.8%, and was not correlated to hospitalization rate in the paediatric population. Being 1–5 years old [odds ratio (OR) 4.51, 95% confidence interval (CI) 4.43, 4.58] and living in the eastern part of the region (OR 2.06, 95% CI 1.99, 2.13) were the factors associated with the highest risk of drug exposure.

CONCLUSIONS

The results resemble the profiles observed in other Italian contexts, in particular concerning the wide use of antibiotics and anti-asthmatics. However, large differences were found between LHUs, highlighting the need for more detailed investigations on therapeutic needs, drug use, and related variables in different geographic contexts.

Introduction

Pharmacoepidemiology can be a useful tool for evaluating the appropriateness of drug prescriptions and for estimating therapeutic needs [1]. In particular, pharmacoepidemiology can be valuable in the paediatric setting, which is characterized by the availability of only limited information on the safety and effectiveness of drug use [2, 3].

Drug utilization studies performed in the Italian paediatric population have found a prescription profile that appears to be specific to Italy [4–9], especially concerning antibiotics, in which both quantitative and qualitative differences with other European countries were found. The prescription prevalence was three- to fourfold higher than in the Netherlands or the UK, with a wide use of second-choice antibiotics such as cephalosporins [10]. Moreover, wide, irrational use of anti-asthmatics, in particular inhaled steroids, has been observed [8, 9].

The results of a study performed using a multiregional prescription database also highlighted that differences in the prevalence rate between regions exist [11]. In particular, the prescription prevalence was lower in northern Italy (57.3%) and higher in southern Italy (68.3%). Differences in drug consumption at the regional level were found also in the general population [12].

Few studies analysing the differences between geographical areas belonging to the same Italian region are available, however. Differences in the prevalence rate in the overall population between the four local health units (LHU) belonging to Umbria, a small region in central Italy, were found [13].

In this regard, an in-depth analysis of the determinants of drug prescribing to children and adolescents was performed using the administrative prescription database of the Lombardy Region (the Italian region with the largest population size and the highest economic index), with particular interest in the evaluation of the differences between LHUs.

Methods

The analysis involved all paediatric prescriptions reimbursed by the Health Service and dispensed by the retail pharmacies of 15 LHUs in the Lombardy Region, in northern Italy, between 1 January and 31 December 2005.

The source of data was a database routinely updated for administrative and reimbursement reasons. The database stores all community (i.e. outside hospital) prescriptions, reimbursed by the National Health Service (NHS), issued to individuals living in the Lombardy Region. The structure of the database has been described in detail elsewhere [14].

Data were managed and analysed using an anonymous patient code, after obtaining each LHU director's authorization.

The study population was composed of 1543 203 children and adolescents <18 years old, male/female ratio 1.06, living in the Lombardy Region. The study sample represented 15% of the Italian paediatric population. The number of youths <18 years old by LHU varied between 15 790 and 189 238.

During 2005 in the Lombardy region there were 1165 primary care paediatricians and 6791 general practitioners. In Italy, children are assigned to a paediatrician until they are 6 years old; afterwards, parents can choose to register a child with a general practitioner. All adolescents >14 years old are assigned to a general practitioner.

Prescribed drugs were classified according to the International Anatomic Therapeutic Chemical Classification system (ATC).

In order to evaluate pharmaceutical consumption, the number of packages of medications (boxes) was used as an indicator of the whole drug exposure during the considered period. In fact, it can be related to the same medicine prescribed repeatedly or to different medicines.

Prevalence data by sex and age were calculated by dividing the number of drug users by the total number of male and female residents in each age group.

In addition, a Mantel–Haentzel χ^2 test was performed in order to compare the drug prescription prevalence in boys and girls.

The area under the prevalence–time curve (AUC) from time 0 to 18 years (data plotted at mid-time interval) were calculated according to the linear trapezoidal rule.

The relationship between the prevalence rates of the most prescribed therapeutic classes and between the prevalence rates in the paediatric and adult populations by local health unit was investigated using the nonparametric Spearman rank correlation test. The rate of hospitalization was estimated considering hospital discharge forms.

The relationship between the prevalence and hospitalization rates by local health unit was investigated using the nonparametric Spearman rank correlation test.

Logistic regression analysis was performed to evaluate the association between drug prescription and age, gender, LHU of residence, kind of physician in charge of the patient (paediatrician, general practitioner) and physician gender. Statistical analysis was performed using SAS software, version 9.1 (SAS Inc., Cary, NC, USA). A *P*-value <0.05 was considered to be statistically significant.

Results

Prescribing pattern during 2005

During 2005, 747 790 children and adolescents (48.5% of the population) received at least one drug prescription. The highest prevalence was observed in the 1–5 years age range (average value 65%), and then decreased to 38% in the 12–17 years range (Figure 1).

The prevalence was slightly higher in boys than in girls for all ages ($\chi^2 = 641$; $P < 0.001$) with the exception of 16- and 17-year-old adolescents. The trend for gender was similar up to 14 years of age, after which the prevalence increased in girls.

The AUC₀₋₁₈ male/female ratio was 1.04.

In all, 1165 paediatricians prescribed drugs to 65% of the children, whereas 6791 general practitioners prescribed drugs to 35% of the children. Each paediatrician prescribed drugs to a median of 437 children, whereas general practitioners prescribed them to a median of 29 children or adolescents.

A total of 2177 469 prescriptions were dispensed, corresponding to 3122 745 medication packages. Each treated child received an average of 2.9 prescriptions (median 2) and 4.2 packages (median 2). Boys received a greater average number of prescriptions (2.9 vs. 2.7) and packages (4.3 vs. 3.9) compared with girls. The highest number of prescriptions/treated child was observed in children 1–5 years old (3.3; median 3).

Figure 1

Prescription prevalence rate by gender and age. ♀ (—△—); ♂ (—▲—)

Table 1

The 10 most prescribed drugs by age group

<1 year Drug	%	1–5 years Drug	%	6–11 years Drug	%	12–17 years Drug	%	0–17 years Drug	%
Amoxicillin	10.7	Co-Amoxiclav	29.7	Co-Amoxiclav	16.8	Co-Amoxiclav	10.4	Co-Amoxiclav	17.9
Beclometasone	9.5	Amoxicillin	23.1	Amoxicillin	11.1	Amoxicillin	7.0	Amoxicillin	13.1
Co-Amoxiclav	7.7	Beclometasone	16.3	Beclometasone	7.8	Clarithromycin	5.1	Beclometasone	9.1
Salbutamol	6.7	Cefaclor	11.5	Clarithromycin	7.2	Azithromycin	4.4	Clarithromycin	7.0
Cefaclor	3.3	Salbutamol	11.2	Azithromycin	5.3	Beclometasone	4.0	Salbutamol	6.1
Flunisolide	2.3	Clarithromycin	9.9	Salbutamol	5.2	Cefixime	2.6	Cefaclor	5.3
Clarithromycin	1.9	Azithromycin	7.0	Cefaclor	4.7	Salbutamol	2.5	Azithromycin	5.2
Salbutamol + others	1.1	Cefixime	5.6	Cefixime	3.8	Cetirizine	2.2	Cefixime	3.8
Ceftibuten	1.0	Ceftibuten	4.5	Cetirizine	2.7	Desloratadine	1.1	Ceftibuten	2.3
Cefixime	1.0	Flunisolide	3.3	Ceftibuten	2.0	Levocetirizine	0.9	Cetirizine	2.2
% of packages*	79		78		65		42		64
N. Drugs	266		649		672		719		757

*% of packages covered by the 10 most prescribed drugs.

In all, 25% of treated children received one package only, whereas 20% received more than six packages. The rate of children receiving six or more packages was higher in boys than in girls (21 vs. 19%; $\chi^2 = 758$; $P < 0.001$), and in children 1–5 years old (25%) compared with those <1 year (9%) and 6–11 years old (18%) ($P < 0.001$).

Antibiotics were the most prescribed therapeutic class (41% of the population), followed by anti-asthmatics (15%) and antihistamines (5%). Altogether, these three therapeutic classes comprised 81% of the prescribed packages.

In all, 65% of treated children received drugs belonging to one therapeutic class only, whereas 28% received drugs belonging to two classes (mainly antibiotics and anti-asthmatics, prescribed to 24% of treated children), and 7% belonging to three or more classes (3% received antibiotics, anti-asthmatics, and antihistamines).

The trend for antibiotics was similar to the overall prevalence trend, while the highest value of anti-asthmatic prevalence was observed at 1 year (29%). The prevalence of anti-asthmatics reached a second age-dependent peak at 4 years (26%). The prevalence of antihistamines increased with increasing age, reaching a maximum of 6% at 16 years.

The AUC₀₋₁₈ male/female ratio was 1.03 for antibiotics, 1.21 for anti-asthmatics and 1.32 for antihistamines.

In all, 757 drugs were prescribed. Amoxicillin + clavulanic acid was the most prescribed drug (18% of children), followed by amoxicillin (13%) and inhaled beclometasone (9%) (Table 1). The 10 most prescribed drugs, seven of which were antibiotics, represented 64% of the prescribed packages.

A total of 70 drugs, belonging to 22 main therapeutic groups of the ATC classification, comprised 90% of the prescribed packages. In particular, 23 were antibiotics, 13 were anti-asthmatics and six were antihistamines. Seven second- and third-generation cephalosporins (out of 20 prescribed) were among these 70 drugs.

Amoxicillin was the most prescribed drug in children <1 year old, whereas amoxicillin + clavulanic acid was the leading drug in children ≥1 year old. Although the prevalence rates differed across ages, six of the 10 most prescribed drugs were the same in all ages.

Salbutamol in fixed combination with other anti-asthmatics ranked among the top 10 drugs only in children <1 year old and flunisolide in those ≤6 years old. Azithromycin was among the 10 most prescribed drugs in children ≥1 year old, cetirizine in children ≥6 years old and desloratadine and levocetirizine in adolescents ≥12 years old (Table 1).

In all, 253 drugs of the total 757 (33%) were prescribed to children of all age groups, whereas 538 drugs (71%) were prescribed in children ≥1 year old.

In all, 49% of treated children received one drug, 25% two, 13% three, and 13% four or more different drugs. The proportion of children receiving four or more drugs was higher in boys compared with girls (14 vs. 12%; $\chi^2 = 748$; $P < 0.001$) and in children 1–5 years old (19%) compared with those <1 year (9%) and ≥6 years old (9%) ($P < 0.001$).

Distribution of prevalence by local health unit

Large differences were found in prevalence rates between different LHUs, ranging between 38.4% in Milan to 54.8% in Brescia (Figure 2). The mean prevalence rate was 49.1% (median 49.2%). The distribution of the prescription rates (mean number of prescriptions by treated child) was similar, ranging from 2.65 in Milan to 3.31 in Brescia.

The prevalence of antibiotics ranged between 32.2% in Milan and 49.0% in Brescia, that of anti-asthmatics ranged between 10.1% in Milan and 20.1% in Mantova and that of antihistamines ranged between 3.3% in Milan and 6.0% in Sondrio.

A statistically significant correlation between rank distributions at LHU level of the overall prevalence rate and antibiotic and anti-asthmatic prevalence was found. In contrast, no statistically significant rank correlation was found between overall and antihistamine prevalence.

In the adult population (18–64 years) the prevalence ranged between 47.8% in Milan and 58.6% in Valle Camonica. A statistically significant correlation between

Figure 2

Distribution of the prevalence rate by local health unit

Table 2

The 10 most prescribed drugs in the Milan and Brescia local health units

Milan Drug	%	Brescia Drug	%
Co-Amoxiclav	15.2	Co-Amoxiclav	24.8
Amoxicillin	11.9	Amoxicillin	11.0
Beclometasone	6.5	Beclometasone	11.0
Clarithromycin	5.3	Cefaclor	8.4
Salbutamol	4.9	Clarithromycin	8.4
Azithromycin	3.1	Salbutamol	7.5
Cefaclor	2.6	Azithromycin	5.8
Cefixime	1.9	Cefixime	4.7
Cetirizine	1.6	Ceftibuten	3.4
Flunisolide	1.1	Cefuroxime	2.5
% of packages*	66	% of packages*	64
N. Drugs	513	N. Drugs	526

*% of packages covered by the 10 most prescribed drugs.

rank distributions at LHU level of the paediatric and adult prescription prevalence rates was found.

In contrast, no correlation was found between rank distribution at LHU level of the prevalence rate and hospitalization rate in the paediatric population. The hospitalization rate ranged between 7.1% in Mantova and 9.8% in Milan-1 (one of the three LHUs of the province of Milan). In this regard, the rates in Milan and Brescia were similar (8.7 and 8.9%, respectively), despite the fact that they ranked as opposites in prescription prevalence rates.

The total number of drugs prescribed to the paediatric population in each LHU ranged between 294 and 593. Only 204 drugs were prescribed in all the 15 LHUs, and eight were among the 10 leading drugs in all the LHUs (amoxi-clavulanic, amoxicillin, beclometasone, clarithromycin, azithromycin, salbutamol, cefixime, cefaclor). Of these, cefixime was the one with the greatest ratio between the highest and lowest LHU prevalence (4.2), followed by cefaclor (3.2), and azithromycin (3.1). Amoxi-clavulanic acid, the drug with the lowest ratio (1.8), was the most prescribed drug in 13 LHUs, whereas amoxicillin was the leading drug in the other two (Valle Camonica and Milan-3).

A total of 14 drugs were among the top 10 in all the 15 LHUs.

Table 2 compares the prevalences of the 10 most prescribed drugs in Brescia and Milan, which are the LHUs at the opposite ends of the prevalence rate range, even if eight of the 10 most prescribed drugs were the same and a strong rank correlation was found ($r_s = 0.89$).

Multivariate analysis

Table 3 summarizes the results of the multivariate analysis. The age and residence of the child were the main determinants of drug exposure. In particular, being 1–5 years old [odds ratio (OR) 4.51, 95% confidence interval (CI) 4.43, 4.58] and living in Brescia (OR 2.08, 95% CI 2.06, 2.11) were the factors associated with the highest risk of drug exposure.

Table 3

Results of the multivariate analysis

Variables		Adjusted OR (95% CI)
Age group (years)	<1	Reference
	1–5	4.51 (4.43, 4.58)
	6–11	2.11 (2.08, 2.14)
	12–17	1.41 (1.39, 1.43)
Gender	F	Reference
	M	1.09 (1.08, 1.10)
LHU	Milano	Reference
	Brescia	2.08 (2.06, 2.11)
	Valle Camonica	2.06 (1.99, 2.13)
	Mantova	1.88 (1.85, 1.92)
	Cremona	1.76 (1.72, 1.80)
	Lodi	1.80 (1.76, 1.85)
	Milano-1	1.71 (1.68, 1.73)
	Pavia	1.66 (1.63, 1.69)
	Como	1.67 (1.64, 1.70)
	Bergamo	1.63 (1.61, 1.65)
	Milano-3	1.57 (1.55, 1.59)
	Lecco	1.55 (1.52, 1.58)
	Varese	1.57 (1.54, 1.59)
Prescriber	Paediatrician	Reference
	General practitioner	1.06 (1.05, 1.07)
Prescriber gender	F	Reference
	M	0.92 (0.91, 0.93)

Male gender and having a female general practitioner also slightly increased the probability of receiving a drug prescription.

Discussion

This is the first study to evaluate the geographical differences in the pattern of drug prescribing to children and adolescents in a large Italian region. Moreover, it is the first Italian drug utilization study performed in the entire paediatric population (up to 17 years old), and has also taken into consideration other potential determinants.

However, one limitation of the study is that it considered only prescribed drugs. Another limit is that the findings apply to the Lombardy Region, the top Italian region according to the socio-demographic and economic national profile, and may thus be not fully representative of other Italian settings.

Data collected by the National Drug Utilization Monitoring Centre of the Italian Drug Agency show, in fact, that Lombardy is among the Italian regions with the lowest drug consumption: 776.8 defined daily doses per 1000 inhabitants vs. a mean of 880.5 (and a maximum of 1019.3) [15]. However, the general prescribing profile is similar to that observed in other Italian studies, in particular in Northern Italy [4–9, 11].

Furthermore, this study has confirmed that a plethora of drugs is prescribed. In all, 757 drugs were prescribed,

although only 70 (9%), most of which were antibiotics, antiasthmatics and antihistamines, comprised 90% of the packages and only 14 drugs were sufficient to cover the more common diseases independently of age and geographical setting.

The profile observed in adolescents is strongly indicative of this plethora of too many drugs, since among the 10 leading drugs prescribed in this age group there were three antihistamines: cetirizine, its enantiomer levocetirizine, and desloratadine.

Only 253 drugs were prescribed to children of all age groups. If infants are excluded from the analysis, however, this number increases to 538. In contrast, analysis of the licences of medications marketed in Italy found that a paediatric indication was reported for only 80 drugs, whereas for 124 a paediatric dosage schedule was reported.

Amoxi-clavulanic acid was the most prescribed antibiotic, despite the fact that amoxicillin is considered the antibiotic of choice for the most common infections in the paediatric age group [16–18] and is the most prescribed antibiotic in other countries [10].

In 2005 in the Netherlands, the prevalence of antibiotic prescriptions was 18% [19] vs. 41% in Lombardy and 32% in Milan, the LHU with the lowest value. Amoxicillin was the most prescribed antibiotic in the Netherlands and represented >40% of antibiotic prescriptions, whereas amoxi-clavulanic acid comprised 10%; in contrast, in Lombardy amoxi-clavulanic acid comprised 32% and amoxicillin 22% of antibiotic prescriptions.

A wide use of inhaled steroids, in particular nebulized beclometasone and nebulized flunisolide, was also observed. These drugs in Italy are mainly prescribed for upper respiratory tract infections, despite lack of evidence of efficacy [20].

Concerning flunisolide, this drug is the sixth in order of prevalence in children <1 year old, even if it is licensed only for children ≥ 4 years old.

The most interesting findings of this study relate to the differences between LHUs. Despite the fact that the Lombardy region is a quite homogeneous region, wide geographical differences were found. A child living in Brescia or Valle Camonica (nearby LHU) has a twofold higher risk of receiving a drug prescription than a child living in Milan, independent of age and gender.

The rank distribution of prevalence in children and adolescents correlates with that in adults; in contrast, no correlation was found in hospitalization rate, which could be considered a proxy of disease prevalence (at least of severe cases).

It could therefore be hypothesized that the quantitative and qualitative differences between LHUs are not due to a different epidemiology of the diseases, but to different prescribing habits between physicians. This hypothesis is also supported by other findings. First, only 204 of the 757 drugs (27%) were prescribed in all 15 LHUs. Moreover, for some of

the leading drugs (cefixime, cefaclor, azithromycin) three- or fourfold differences in prevalence were found.

Concerning antibiotics, amoxi-clavulanic acid was the drug for which the smallest difference in prevalence was found and was the most prescribed drug in 13 of the 15 LHUs.

In this regard, it is interesting to note that Valle Camonica is one of the two LHUs in which amoxicillin was the most prescribed antibiotic, despite the fact that it is also one of the LHUs with the highest prevalence rate. A high prevalence is not synonymous with inappropriateness in all cases, and vice versa. In Milan, despite the lowest prevalence, amoxi-clavulanic acid was the most prescribed antibiotic. Moreover, the prevalence of nebulized beclometasone was not different from that reported in Valle Camonica.

In conclusion, these findings support the fact that pharmacoepidemiology is a valuable tool for monitoring the appropriateness of drug prescribing. The differences observed between LHUs suggest that educational interventions for healthcare professionals and parents could be effective in improving rational drug use. However, more effort is needed also in certain contexts characterized by a low prevalence rate, but also by sometimes inappropriate drug use.

Competing interests

None declared.

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