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Antibiotic prescription in the outpatient paediatric population attending emergency departments in Lombardy, Italy: a retrospective database review

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ABSTRACT

Objectives This study aimed to assess the appropriateness of antibiotic prescription in children seen in emergency departments (EDs) and to compare prescription profiles in ED and primary care.

Design This is a retrospective analysis of healthcare administrative databases.

Setting The study analysed data collected in emergency departments (EDs) and primary care practices (PCPs) in Lombardy, Italy.

Participants Children and adolescents between 1 and 13 years old with an ED access and/or an antibiotic prescription in the first semester of 2012 participated in the study. Only those with an index event (ie, without ED access, hospital admissions or antibiotic prescriptions in the previous 60 days) were included.

Main outcome measures The main outcomes are percentage of subjects receiving amoxicillin (first-choice antibiotic) and percentages receiving macrolides/cephalosporins (second-choice therapies).

Results During the observation period, 133 275 children had one ED access, and 26 087 (19.6%) received an antibiotic prescription. In all, 56.1% of children seen for upper respiratory tract infections (URTIs) received an antibiotic, with a prevalence of 67.8% for otitis media and 56.4% for pharyngotonsillitis; 22.3% of children were given amoxicillin after a visit for URTIs, with no differences among infections, and 19.6% received macrolides and cephalosporins. Few differences were found when comparing the index antibiotic prescriptions in ED and PCP settings. A higher prescription of second-choice antibiotics was observed among children cared for by PCPs compared with children attending EDs (31.3% vs 23.4%, $\chi^2_{M\text{-}H}$=720, p<0.001). The place of residence was the main determinant of the qualitative profile of prescriptions.

Conclusions More must be done to improve rational use of antibiotics in the ED and PCP setting, and educational interventions including physicians in both setting are strongly needed.

What is known about the subject?

- Antibiotics are overused in outpatient children in Italy, more often than in other European countries.
- The antibiotic prescribing pattern of Italian primary care physicians is frequently inadequate.

What this study adds?

- In all, 56% of children attending an emergency department (ED) for a new episode of upper respiratory tract infections were treated with antibiotics, but only 22% received amoxicillin.
- The low prescription of amoxicillin was shared by primary care and ED physicians (24% vs 20%, respectively).
- The likelihood of receiving second-choice antibiotics was greater when the prescriber was the primary care physician.

INTRODUCTION

Antibiotics are the most frequently prescribed drugs in the paediatric population both in national and international contexts, with an overall prevalence of 47.3%, and about half the prescriptions are unnecessary.[1 2] Large qualitative and quantitative differences in the antibiotic prescription profiles for paediatric outpatients have been found between and within countries, and Italy has a high prevalence of prescriptions and frequent use of second-choice antibiotics (ie, cephalosporins and macrolides).[2] There may be several reasons for these differences: sociocultural factors, education and income, and physician's attitude seem to play major roles.[2 3]

The emergency department (ED) needs to be a target for interventions in the field of paediatric antibiotic stewardship since a large proportion of acute care outpatient visits occur in this setting.[4 5] In particular, upper respiratory tract infections (URTIs) are the most common reason for antibiotic prescriptions to children in both outpatient and ED settings.[6–8] Antibiotic prescribing patterns to children attending ED do not appear to have been widely evaluated, and studies have

mainly focused on a few countries and/or were on respiratory or urinary tract infections.[6–21]

Scant data are available concerning the profile of prescription in Italian ED, and mainly concern only small samples.[8–10]

A study in the Emilia-Romagna Region, in central Italy, reported that antibiotics were prescribed in 37.8% of 4352 visits for suspected respiratory infections (4052 performed by primary care physician (PCP) and 300 by ED physicians), most frequently for bronchitis or otitis media (69% of children with one of these diagnoses) and pharyngotonsillitis (59%). No significant difference was found in the prevalence of antibiotic prescription between primary care and ED paediatricians.[8] Antibiotics were prescribed to 81% of children with acute otitis media (AOM) in a paediatric ED in Modena, and the prevalence did not change after guidelines were introduced.[9]

A third study, in the paediatric ED of Padua, in the North East of Italy, found a prevalence of antibiotic prescription of 78% for children with AOM and 51% for those with pharyngotonsillitis. The percentages of children given antibiotics decreased to 67% and 45%, respectively, after the implementation of clinical pathways, but the percentage of amoxicillin increased, reaching 93% in children with pharyngotonsillitis.[10]

Giving the paucity of information on the antibiotic prescriptions in ED, the aim of this study was to investigate the pattern of antibiotic prescriptions in EDs in a large Italian region by analysing administrative healthcare databases, and to compare the patterns of prescriptions filled by primary care physicians and those prescribed in ED. We also evaluated the appropriateness of antibiotic prescription, in terms of choice of drugs recommended by the guidelines, in children seen in ED for URTIs, which represent one of the most common reasons for ED access, and are frequently associated with antibiotic treatment both in primary care and ED setting.[2 6–8 22]

PATIENTS AND METHODS

Data sources

Lombardy is a region in the north of Italy, with the largest population in the country (10 million inhabitants), covering 16% of the Italian paediatric population. The region is divided into eight local health units (LHUs), further divided into 27 smaller areas called ASSTs (territorial social-health units). The data sources were administrative healthcare databases of the Lombardy Region, routinely used for reimbursement reasons. Four databases were analysed, collecting:

1. Demographic information.
2. Prescriptions dispensed by retail pharmacies in the region and reimbursed by the National Health Service (NHS).
3. Characteristics of ED access.
4. Hospital discharge forms.

The organisation of the Italian NHS and the structure of the databases have already been described.[22 23]

The study included resident children and adolescents between 1 and 13 years old on 31 December 2012 (1 254 050 children). Residents of the former Cremona LHU were excluded on account of ED data quality problems. In all, data of visits performed in 82 EDs were analysed.

Databases were linked by alpha-numerical patient identification codes. All data were managed according to the current Italian law on privacy and were analysed using an anonymous subject code.

Index access

An index access was defined an ED access with the following characteristics:

- Occurring between 1 January 2012 and 30 June 2012.
- No antibiotic prescriptions, ED or hospital admission in the previous 60 days.
- No hospitalisation after the ED visit.

Index prescription

Antibiotics were defined as all drugs belonging to the J01 subgroup of the Anatomic Therapeutic Chemical classification system. An antibiotic index prescription was defined as a prescription occurring:

- Between 1 January 2012 and 30 June 2012.
- With no antibiotic prescriptions or hospital admissions in the previous 1–60 days.
- With no ED admissions in the previous 2–60 days.

In the ED, drug prescriptions can be written directly on the form for reimbursement ('red' form). In a few instances, they are written on a 'white form' that the primary care physician has to transcribe onto the red one for reimbursement. Thus, for the aim of this study, prescriptions occurring the same day or the day after the index access were attributed to ED physicians. We checked a sample of prescriptions and estimated that the potential misclassification was no more than 2%.

To assess the appropriateness of antibiotic prescription, we analysed the prescriptions associated with an ED access with diagnosis of URTI. The diagnoses were identified using the following ICD-9 (International Classification of Diseases Ninth Revision) codes:

- Pharyngotonsillitis: 034.0, 462, 463, 784.1 (pharyngitis, tonsillitis, sore throat).
- Otitis media: 381.0, 382.0, 382.9, 388.6, 388.7 (otitis, othorrea and otalgia).
- URTIs not otherwise specified: 460, 461, 465, 7862 (rhinitis, sinusitis, acute upper respiratory infections of multiple or unspecified sites, cough).

All children with an index access were included in the first part of the study (evaluation of antibiotic prescription profile in the ED), while the second part (comparison of antibiotic prescriptions in ED and in primary care) focused on all children receiving an index antibiotic prescription.

Measures

The quality of the prescriptions was evaluated using two indicators, previously applied in an analysis of antibiotic prescribing in paediatric primary care[23]:

A. Proportion of children who received amoxicillin (first-choice antibiotic for the most common paediatric infections) at the index prescription.[24–27]
B. Proportion of children who received cephalosporins or macrolides, second-line treatments in the most common URTIs of childhood.[24–27]

As previously described, the expected value for A indicator is ≥50% and for B indicator is ≤10%.[23]

The A and B indicators were compared in children receiving the index prescription in primary care and those receiving the index prescription in the ED. We compared the qualitative profile of antibiotic prescription as the percentage of children given a certain class of antibiotics in age strata: 1 year, 2–5 years, 6–9 years, 10–13 years.

Data analysis

A χ^2 test was used to compare the percentages of children receiving antibiotic prescriptions after an ED access by sex and age.

To assess appropriateness of prescription, the distribution of A and B indicators in children seen for pharyngotonsillitis was estimated in each ED. We restricted this analysis to pharyngotonsillitis, since the only causal agent that requires antibiotic therapy is Group A beta-haemolytic *Streptococcus pyogenes* (GABHS), with no known risks of antimicrobial resistance. Amoxicillin (where and when oral penicillin is not marketed, as in Italy) is the first-choice antibiotic, irrespective of the age of the child and the local epidemiological setting. For this analysis, EDs with a number of patients with index prescriptions for pharyngotonsillitis below the 25th percentile of the distribution of children by ED (10 patients) were excluded in order to have a homogeneous sample.

The Mantel-Haenszel χ^2 test was used to compare the proportions of A and B indicators at ED and PCP levels (adjusted by age). The non-parametric Spearman test was used to assess the correlation between the percentages of children receiving amoxicillin or macrolides/cephalosporins as the index prescription in ED and primary care setting by ASSTs.

Patient and public involvement

We did not involve patients or the public in our work.

RESULTS

Antibiotic prescriptions pattern in ED

During the observation period in the Lombardy Region, 133 275 children (10.6% of the paediatric population) had one index access to an ED. The most common reasons were traumatic injuries (26.1%), respiratory tract infections (RTIs) (19.9%) and gastrointestinal diseases (8.5%).

In all, 26 087 children (19.6%) received an antibiotic prescription from the ED. The prevalence of antibiotic prescription differed with age, with the largest number in preschoolers 1–5 years old (28.1%), decreasing with age (6–13 years old: 15.5%) (χ^2_t=5654.13, p<0.0001). Children with lower RTIs had the highest prevalence of antibiotic prescriptions (61.4%), followed by URTIs (56.1%) and traumatic injuries (19.9%).

Appropriateness of antibiotic prescription for URTIs in ED

In all, 23 216 children had an ED access for URTIs, 13 017 (56.1%) of whom received an antibiotic prescription. The most common diagnosis was pharyngotonsillitis (41.4%) followed by not otherwise specified URTIs (34.9%) and otitis media (23.6%). A total of 316 (2.3%) of children receiving antibiotics for URTIs returned to the ED in the week after the index access, compared with 297 (2.9%) out of 10 199 with URTIs but no antibiotic prescriptions ($\chi^2_{M\text{-}H}$=5.2 p=0.02).

The prevalence of prescriptions varied with the diagnosis: 67.8% for otitis media (3717/5480), 56.4% for pharyngotonsillitis (5427/9615) and 47.7% for other and/or not well-specified URTIs (3873/8121).

Children treated with amoxicillin after a visit for URTI amounted to 22.3%, and this decreased with age irrespective of the diagnosis (table 1).

The proportion of children receiving amoxicillin did not change among different groups of URTI, while prescriptions of second-choice antibiotics ranged between 15.8% for children with otitis and 24.6% for those with URTIs not otherwise specified.

Amoxicillin-clavulanate was the most prescribed drug for all age groups, from 53.1% to 62.8%. The proportion of children receiving macrolides increased with age, particularly for URTIs not otherwise specified, covering 30.1% of antibiotic prescriptions in children 10–13 years old.

For pharyngotonsillitis at each single ED, the percentage of amoxicillin prescriptions ranged between 0% and 81.7%, with only 6 out of 55 EDs prescribing the first-choice antibiotics to at least half the children. Second-choice treatments ranged between 0% and 50.3%.

Antibiotic prescription profiles in ED and PCP settings

During the observation period, in the Lombardy Region 335 360 children received an index prescription with a prevalence of 26.7%. As stated above, 26 087 of these prescriptions were attributable to the ED and 309 273 to the PCP. Amoxicillin-clavulanate was the most commonly prescribed antibiotic (57.9%), followed by amoxicillin (22.5%), cefpodoxime (5.1%) and clarithromycin (4.1%). Prescriptions of amoxicillin-clavulanate increased with age in the ED setting, but it were stable in primary care, while prescriptions of amoxicillin decreased with age in both settings (figure 1). Cephalosporins decreased in ED and did not change in PCP, while macrolides increased in both settings.

The percentage of amoxicillin (indicator A) was slightly higher among children treated by PCP (23.9% vs 20.1%, $\chi^2_{M\text{-}H}$=107.5, p<0.001), and a larger percentage of children in primary care received second-choice antibiotics

Table 1 Antibiotics prescribed to children in emergency departments for upper respiratory tract infections

	Amoxicillin	Amoxi-clavulanate	Cephalosporins	Macrolides	Total
Pharyngotonsillitis					
1 year	257 (31.4%)	409 (50.1%)	108 (13.2%)	42 (5.3%)	816
2–5 years	696 (24.6%)	1.648 (58.2%)	354 (12.5%)	131 (4.7%)	2829
6–9 years	272 (21.1%)	781 (60.4%)	156 (12.2%)	83 (6.3%)	1292
10–13 years	74 (15.1%)	305 (62.2%)	48 (9.8%)	63 (12.9%)	490
Overall	***1299 (23.9%)***	***3143 (57.9%)***	***666 (12.3%)***	***319 (5.9%)***	***5427***
Otitis media					
1 year	215 (32.4%)	359 (53.9%)	79 (11.9%)	12 (1.8%)	665
2–5 years	452 (21.4%)	1315 (62.2%)	310 (14.7%)	36 (1.7%)	2113
6–9 years	111 (16.0%)	473 (68.0%)	100 (14.4%)	11 (1.6%)	695
10–13 years	22 (9.0%)	189 (77.5%)	25 (10.2%)	8 (3.3%)	244
Overall	***800 (21.5%)***	***2336 (62.8%)***	***514 (13.8%)***	***67 (1.9%)***	***3717***
URTIs not otherwise specified					
1 year	344 (29.6%)	604 (52.0%)	134 (11.5%)	78 (6.6%)	1160
2–5 years	411 (20.4%)	1060 (52.4%)	305 (15.1%)	246 (12.1%)	2022
6–9 years	52 (10.7%)	285 (58.5%)	65 (13.4%)	86 (17.4%)	488
10–13 years	20 (9.8%)	106 (52.2%)	16 (7.9%)	61 (30.1%)	203
Overall	***827 (21.3%)***	***2055 (53.1%)***	***520 (13.5%)***	***471 (12.1%)***	***3873***

URTI, upper respiratory tract infection.

(31.3% vs 23.4% in ED, $\chi^2_{M\text{-}H}$=720.2, p<0.001). The likelihood of receiving a second-choice antibiotic drugs was highest among school-age children in primary care (cephalosporins and macrolides covered 34.4% of antibiotic prescriptions).

In ASSTs, the percentages of children treated with amoxicillin ranged between 11.2% and 48.7% in the primary care setting and from 6.9% to 38.4% in ED. The use of second-choice drugs ranged from 21.9% to 44.2% and from 17.3% and 34.3%, respectively.

A correlation was found between the rank distribution of A and B indicators in ASSTs in the PCP and ED (rs=0.760 and rs=0.646).

DISCUSSION

To the best of our knowledge, this is the largest study of antibiotic prescriptions to children attending ED in Italy and the first study to compare the qualitative profile of antibiotic prescribing at primary care and ED levels in Italy in the same period, by selecting index prescriptions (ie, treatment of new episodes of infections, excluding recurrences). In all, one in five children attending ED in Lombardy received an antibiotic prescription. This is similar to the rates in other international studies (eg, 16.5% in Spain).[11]

Consistent with findings from national and international studies, we found that the majority of antibiotic prescriptions were for URTIs, which were one of the most common reasons for ED access, even though they could and should be managed by PCP.

More than half of the children attending ED for an URTI received an antibiotic (56%), while international studies report a prevalence ranging from 5.1% in France to 37% in Guyana.[12 13]

The percentage of children receiving antibiotics for pharyngotonsillitis was slightly higher in our study (61%) than in another Italian study (50%)[10] but it falls within the range found in international studies, where the prevalence ranged from 28% in the UK to 87% in China.[14–16] Anyway, the proportion observed in our study is three times greater than the expected rate of pharyngotonsillitis caused by GABHS (20%) and for which antibiotics are justified.[28]

In contrast, the percentage of children receiving antibiotics for otitis in Lombardy Region (68%) was lower than in other Italian (78%–81%)[9 10] and international studies (79%–85%).[17–20] It is likely that also for AOM many children did not need an antibiotic prescription, but no information was available concerning the duration of symptoms and the severity of the disease (eg, laterality). Moreover, we cannot exclude that some children received a 'safety net prescription', and that parents were instructed to administrate the antibiotic only if symptoms did not improve within 72 hours.

The pattern of antibiotic drugs prescribed reflects previous observations in the primary care setting. Amoxicillin was underprescribed: only 23% of children with URTIs received it, with few differences among the three groups of infections.

Amoxicillin is the most commonly prescribed antibiotic in other countries. Looking at all URTIs, amoxicillin

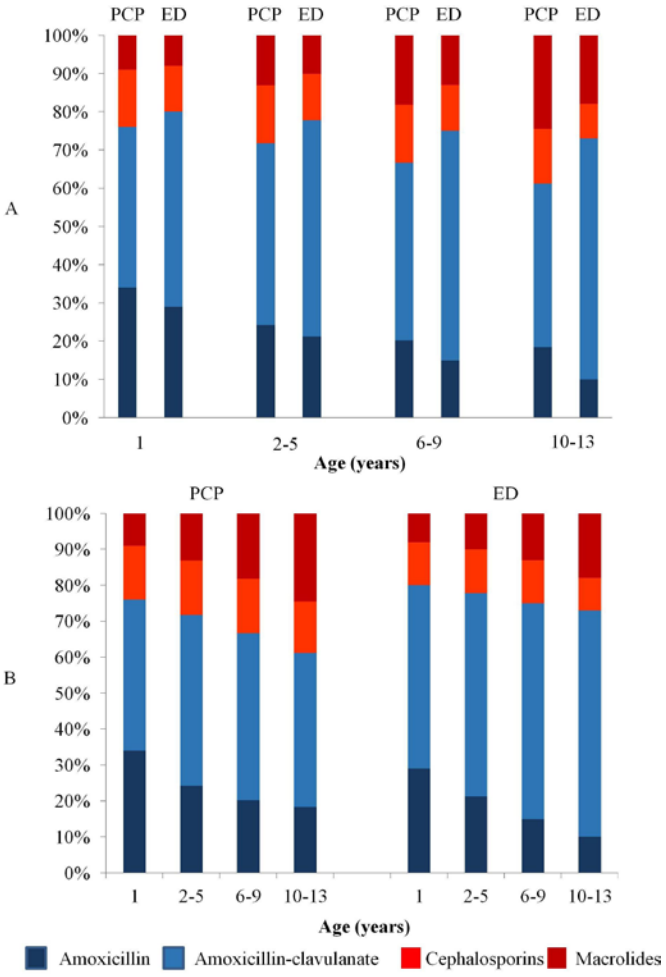

Figure 1 Distribution of antibiotics at the index prescription by age group (A) and setting (B). ED, emergency department; PCP, primary care practice.

covered from 28% to 85% of antibiotic prescriptions in EDs.[11–13 20] In children with AOM, amoxicillin was prescribed for 56% of the cases in the USA and 66% of the cases in France.[7 17] This is consistent with international guidelines.[24 25]

The treatment of pharyngotonsillitis was mostly inappropriate: only one in four children received amoxicillin, while 18% received cephalosporins or macrolides. In children 10–13 years old, the percentage treated with second-line drugs exceeded that of subjects receiving amoxicillin (23% vs 15%). Since only streptococcal pharyngotonsillitis requires antibiotic therapy, it is not clear why the prevalence of amoxicillin is age-dependent. The low use of amoxicillin for pharyngotonsillitis was shared by most of the EDs: in only 6 out of 55, more than 50% of children were given this antibiotic.

Few EDs were marked by very high inappropriateness, with amoxicillin prescriptions nearly absent and cephalosporins and macrolides covering nearly half the prescriptions. In our opinion, the finding that amoxi-clavulanic acid was the most commonly prescribed antibiotic was not reassuring, since it is less well tolerated and there are no reasons for adding a penicillinase inhibitor for GABHS pharyngotonsillitis.[25 26]

No significant differences were observed in the antibiotic qualitative profiles in ED and primary care settings: the frequency of prescriptions of amoxicillin was quite similar, but PCPs prescribed second-choice antibiotics more often than EDs.

A significant correlation was found between the PCP and ED prescription profiles at the level of place of residence, which was the main determinant of the quality of prescription.

The percentages of PCPs and EDs with adequate antibiotic prescribing were low, meaning that children were frequently given antibiotics that exposed them to a greater risk of adverse reactions and/or antimicrobial resistance.[2] Furthermore, this irrational use of antibiotics is strongly related to higher pharmaceutical expenditure.[29]

From a theoretical point of view, one might expect a wider use of second-choice antibiotics in an ED, since children attending it may have more severe infections, and physicians do not know the patients' history (eg, allergies, recurrent infections). The fact that cephalosporins and macrolides were more commonly prescribed (even if the differences are slight) by PCP is therefore surprising.

Strength and limitations

The main strengths of this study are the large population analysed: 1 254 050 children, the fact that data were collected from 82 EDs for a 6-month observation period, while previous Italian studies concerned a single or only few EDs or a limited observation period, and the possibility of comparing antibiotic prescriptions from ED and PCP settings.

No information was available concerning the use of rapid test to detect streptococcal antigens in the ED in case of pharyngotonsillitis, so we cannot see whether antibiotics were (appropriately) prescribed only to children who had pharyngitis due to GABHS. We were therefore able to assess appropriateness mainly in terms of prescription of the recommended drug. Anyway, as stated above, there is a gap between the observed and the expected prescription prevalence (60% vs 20%).[28] It cannot be excluded that children attending ED may have more severe symptoms and a more frequent occurrence of GABHS, but this threefold difference suggests that in most of the cases antibiotics were inappropriately prescribed for viral pharyngotonsillitis.

Other potential weaknesses of the study are that the diagnoses may not be accurate, and that data concerning the medical history (eg, drug allergy, severity, chronic diseases) were not available. In the first case, we are confident that taking into account URTIs, this did not have a relevant impact on the analysis since amoxicillin is the first-choice antibiotic irrespective of the diagnosis.

It is not possible to evaluate how many children had penicillin allergy and therefore required a treatment with

macrolides or cephalosporins, but it is likely that allergy affects no more than 10% of children,[23] and that the occurrence among children visited by ED physicians and PCP is not different. We expect that the choice to restrict our analysis to index prescriptions (ie, new episode of infection not preceded by major health problems in the previous 60 days) excluded frail children and subjects with recurrent infections, and increased the comparability of the group visited by PCP and the one attending ED.

We do not have the diagnoses resulting from the PCP visit, so we could not compare the appropriateness of prescription in EDs and PCPs, but only compare the profile of prescribed drugs. A previous study that examined data collected by a group of family paediatricians in Lombardy found, however, that nearly 60% of antibiotic prescriptions were for URTIs (27% for pharyngotonsillitis)[30] and we observed quite similar findings in the EDs. We can therefore hypothesise that ED and PCP mainly prescribe antibiotics for the same diseases, and that the distribution of infections in children attending PCP is not different from those attending EDs.

From this point of view, since the patterns of prescribed antibiotic drugs are similar, it would appear that in primary care too the antibiotic prescriptions are not appropriate in most cases.

In conclusion, amoxicillin is the first-line treatment for respiratory infections in children, but it is underprescribed, both in primary care and in ED. The inappropriateness of prescriptions is particularly evident in the case of pharyngotonsillitis: only one in four children received amoxicillin as antibiotic treatment, while nearly one in five children were given cephalosporins or macrolides.

More should be done to improve rational use of antibiotics in the ED and PCP, and educational interventions including physicians in both settings are strongly needed.

Finally, besides the appropriateness of antibiotic use, the evaluation of rational drug prescribing in paediatrics is an issue that deserves more research and the development and validation of adequate tools. A few instruments have been proposed (eg, POPI ('Pediatrics: Omission of Prescriptions and Inappropriate prescriptions'), but with limitations and difficulties in application in different settings.[31 32]

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Contributors All the authors contributed equally to the design of the study. FM was involved in planning the study and in data management, and drafted the initial manuscript. AC contributed in planning the data analysis and in writing the manuscript. MC carried out the statistical analyses. AC, AB, IF, LM and MB supervised the study. All authors contributed to and have approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval No ethics committee approval is required in Italy for epidemiological studies using healthcare administrative databases for research purposes and with individuals identified by an anonymous patient code.

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