Antibiotic prescribing in paediatric populations: a comparison between Viareggio, Italy and Funen, Denmark

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Background: High rates of antibiotic prescribing in paediatric populations represent a major issue because of the problem of antibiotic resistance. North European countries reported an appropriate use of antibiotics in general population; few studies on this issue have been conducted until now, especially in Italy. Therefore a comparison concerning paediatric antibiotic prescribing rates between an Italian administrative area in Tuscany (Viareggio) and the county of Funen (Denmark) was conducted.

Methods: Reimbursement data from 2003 were gathered from the Tuscany Health Authority database and from the database containing pharmacy dispensing data from the Danish Medicines Agency. All data were converted to Defined Daily Doses (DDD) per 1000 inhabitants per day (DDD/TID). Data were broken down by age, identifying four age groups: 0–4, 5–9, 10–14, 15–19 years. Results: The overall prescription of antibiotics to paediatric patients from 0 to 19 years of age was higher in Viareggio (67 DDD/TID) than in Funen (35 DDD/TID). In Viareggio amoxicillin and amoxicillin plus enzyme inhibitors ranked in the first two places as the most frequently prescribed antibiotics in the whole population. Cephalosporins were also heavily used in Viareggio with cefaclor being the third most frequently prescribed antibiotic, especially in the 0–4 and 5- to 9-year-old age groups. In Funen, phenoxymethylpenicillin was the most commonly used antibiotic in all age groups, representing almost one-third of prescriptions, followed by amoxicillin. Conclusions: The paediatric antibiotic prescription rate is substantially higher in Viareggio compared with Funen. These data confirm possible overuse and misuse of antibiotics in the Italian paediatric population.

Keywords: antibiotic prescription, drug utilization, paediatric population.

Introduction

In the past decades most infective microorganisms have shown increasing resistance to standard available therapies; it is suggested that this worldwide phenomenon is due to the overuse and misuse of antibiotics. Antibiotics are often prescribed by physicians more often than what is suggested by guidelines for a variety of reasons: market advertisements, pressure from the patients, inappropriate use (e.g. for viral infections). The high quantity of antibiotic prescriptions has probably favoured the development and spread of antibiotic-resistant microorganisms. Paediatric antibiotic prescription is a major concern in terms of public health, since infections are the most frequent cause of childhood disease and systemic antibiotics account for one-third of all prescriptions in pre-school children. Approximately 70% of all antibiotics in children are prescribed for upper respiratory tract infections (RTI) and it is widely known that the spread of antibiotic resistance in Streptococcus pneumoniae is enhanced in younger people.

In the USA every year a considerable proportion of all antibiotics prescribed are given to children and 50% of those seem to be unnecessary. In Canada, 74% of pre-school children, seeking care for respiratory infections, were prescribed an antibiotic; in 85% of these cases such prescriptions were inappropriate. Increasing resistance to antibiotics has prompted many countries to investigate their policies on antimicrobial consumption with the aim of developing common guidelines for appropriate use of these drugs among paediatric patients. Cross-national studies have already recorded a marked variability in prescription of antimicrobials, especially in primary care, with higher consumption in southern than in northern European countries. For instance, misuse of beta-lactams and macrolides is responsible for a high proportion of resistance to Streptococcus pneumoniae, a well-known cause of serious community-acquired infections among adults and children. In Italy, surveillance data show that the prevalence of macrolide resistance to Streptococcus pyogenes and S. pneumoniae is >30%; penicillin-resistant S. pneumoniae strains are still not as widespread as in Spain or France, but their frequency is increasing. A recent study by Resi et al. showed that macrolides were prescribed most often in children over 6 years of age.

The number of resistant microorganisms is proportionate to per capita antibiotic usage rates. France and Spain have high rates of penicillin-resistant pneumococci, while use of narrow spectrum antibiotics in Denmark is associated with low resistance rates. The same findings have been recently confirmed by Marra et al. who compared antibiotic use in children in Canada and Denmark, finding that Denmark is a country with one of the lowest antibiotic prescription rates in Europe. Although several cross-national studies have already been conducted in this field, only Vaccheri et al.
performed this kind of analysis in Italy: a comparative study between Italy and Denmark revealed a lower profile of appropriate antibiotic use, especially of broad-spectrum antimicrobials by Italian General Practitioners (GPs) compared with their Danish colleagues. Although their study did not focus on antibiotic consumption in a paediatric population, it still reports on major concerns influencing the efficacy of a public health system.

The aim of the present study was to compare the use of antimicrobials in primary healthcare among children stratified by age (0–4, 5–9, 10–14, 15–19 years) in two different European populations, one in the county of Funen (Denmark) and the other in the administrative area of Viareggio (Tuscany, Italy).

**Methods**

**Data source**

All prescription data referring to 2003 were retrieved from the database containing pharmacy dispensing data from Denmark, through the DMA (Danish Medicines Agency), and from the Tuscany Health Authority database, through the ARS (Azienda Regionale Sanità, Regional Health Agency) of Florence. The assembled data in both databases was derived from community pharmacies: each prescription filled by pharmacies, whether prescribed by GPs or paediatricians, was included in the database. Table 1 shows the main features of the areas of Viareggio (Italy) and Funen (Denmark). In Denmark all individuals contact the GP directly, independently of their age. The GP is the gatekeeper for all patients (adults and children) in the primary health care system. Instead in Italy individuals < 14 years of age are generally looked after by a paediatrician, and around 15 years of age by a general practitioner.

In both Italian and Danish databases the patient code allows for reconstruction of each individual’s drug history. The following information for each reimbursement prescription was gathered: identification of the product dispensed according to the Anatomical Therapeutic Chemical (ATC) classification system, number of Defined Daily Doses (DDDs) dispensed, anonymous code of the prescribing GP or prescribing paediatrician, and the date of the prescription.

**Data analysis**

Antibiotic consumption was expressed not in number of prescriptions or purchased boxes, but in DDDs: the DDD is the average maintenance dose consumed per day of a drug for its main indication in adults. Therefore, in order to make comparison more manageable, all data were converted to DDDs per 1000 inhabitants (DDD/TID) as indicated by the WHO Collaborating Centre for Drug Statistics Methodology (Oslo-Norway release 2003), limiting the data collection to antibiotics for systemic use (ATC class J01). Antifungals and topical antibiotics were excluded. Data were broken down by age and divided into four age categories: 0–4, 5–9, 10–14, 15–19 years. We chose the DDD/TID approach in order to disregard occasional prescriptions. In the analysis of the aggregated data, the antibiotic consumption was expressed as prevalence of use (number of subjects with at least one prescription/1000 inhabitants)

**Results**

In the year studied (2003), the overall antibiotic prescription to paediatric patients from 0 to 19 years of age was higher in Viareggio (67 DDD/TID) than in Funen (35 DDD/TID). As shown in Figure 1, the annual use prevalence was also higher in the Italian (512 exposed subjects/1000 inhabitants/year) than in the Danish sample (328 exposed subjects/1000 inhabitants/year). In terms of the DU90%, prescriptions in Viareggio encompassed a greater number of compounds, with amoxicillin plus enzyme inhibitors (ATC code: J01CR02) and amoxicillin (J01CA04) ranking in the first two places as the most frequently prescribed product in the population we studied (Table 2).

On the other hand, in Funen, phenoxymethylpenicillin (J01CE02) was the most commonly used antibiotic in all age groups, representing almost one-third of prescriptions, followed by amoxicillin (J01CA04). Tetracycline (J01AA07), erythromycin (J01FA01) and clarithromycin (J01FA13) were
only used in the 15–19 age group. No fluoroquinolones were used (Table 3).

Cephalosporins (J01DA) were used only in Viareggio: cefaclor (J01DA08), a second-generation cephalosporin, was the third most frequently prescribed antibiotic, especially in the 0–4 and 5–9 years age groups, whereas macrolides such as clarithromycin (J01FA09) were the fourth most frequently prescribed drugs. A relevant use of fluoroquinolones such as ciprofloxacin (J01MA02) was shown in the 15–19 year age group. A small proportion of children received treatment with \( b \)-lactamase-sensitive penicillin (J01CE).

The only categories of antibiotics prescribed in both countries were broad-spectrum penicillin (J01CA) and macrolides (J01FA).

No injectable drugs appeared on the Funen list; the only route of administration for systemic antibiotics was oral. In contrast, ceftiraxone (J01DA13), a parenteral antibiotic, was present in the Viareggio sample and mainly used in the 0–4 year age group.

Discussion

To our knowledge few population-based studies on antibiotic prescribing in paediatric patients have been performed until now, especially in Italy.\(^\text{25}\) Only Vaccheri \textit{et al.} have demonstrated a marked difference in antibiotic prescribing between the province of Ravenna (Italy) and the county of Funen (Denmark);\(^\text{26}\) although that analysis did not focus only on the paediatric population, a striking difference was highlighted for children aged from 0 to 9 years.

In this context our study has confirmed marked differences in antibiotic paediatric prescribing in two European settings, the administrative area of Viareggio (Italy) and the county of Funen (Denmark). The selection of antibiotics by Viareggio physicians was significantly different from that reported in Funen: Italian patients received more cephalosporins, broad-spectrum penicillin, including combinations with beta-lactamase inhibitors, and macrolides. A negligible use of narrow-spectrum penicillin was observed in the Italian sample compared with the Danish one; in Viareggio those antibiotics were not even included among the 10 most frequently prescribed drugs. In Funen narrow spectrum penicillin (penicillin V) was the most commonly prescribed antibiotic in all age groups, but it is noteworthy that the majority (almost a half) of prescriptions for children younger than 4 years were broad-spectrum penicillins. This finding was surprising, since Danes are considered to be the lowest users of this kind of antimicrobial. This result may help to explain why \textit{S. pneumoniae} and \textit{H. influenzae} strains resistant to narrow spectrum penicillin, have been more frequently isolated in EU countries.\(^\text{14}\) In areas with a high prevalence of penicillin non-susceptible pneumococci (PNSP) amoxicillin is a better alternative, due to better absorption, longer half-life and less protein-binding. Penicillin V is quite effective, especially in Nordic countries, but its efficacy depends on a low resistance rate in pneumococci. Additionally, vaccination is effective against invasive diseases but not against all common infections such as acute otitis media and pneumonia.\(^\text{27-30}\)

On the other hand, cephalosporins were more frequently used in Viareggio even though there is no evidence indicating that cephalosporins are first choice drugs in these age groups.

### Table 2

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<th>Rank</th>
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<th>Antibiotic</th>
<th>DDD/TID</th>
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<tr>
<td>1</td>
<td>J01CR02</td>
<td>Amoxicillin plus enzyme inhibitor</td>
<td>23.08</td>
</tr>
<tr>
<td>2</td>
<td>J01CA04</td>
<td>Amoxicillin</td>
<td>14.06</td>
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<td>3</td>
<td>J01DA08</td>
<td>Cefaclor</td>
<td>7.03</td>
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<td>4</td>
<td>J01FA09</td>
<td>Clarithromycin</td>
<td>3.98</td>
</tr>
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<td>5</td>
<td>J01DA13</td>
<td>Ceftriaxone</td>
<td>3.31</td>
</tr>
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<td>6</td>
<td>J01EE01</td>
<td>Sulfamethoxazole and trimethoprim</td>
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<td>7</td>
<td>J01DA39</td>
<td>Ceftibuten</td>
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<td>Cefixime</td>
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<td>9</td>
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<td>Ciprofloxacin</td>
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<th>10–14</th>
<th>15–19</th>
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<td>( N = 5314 )</td>
<td>( N = 5545 )</td>
<td>( N = 5822 )</td>
<td>( N = 5788 )</td>
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### Table 3

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<td>J01CE02</td>
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<td>J01CA04</td>
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<td>J01AA07</td>
<td>Tetracycline</td>
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<table>
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<th>Overall</th>
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<th>15–19</th>
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<td>( N = 5107 )</td>
<td>( N = 5989 )</td>
<td>( N = 6263 )</td>
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<td>J01CA04</td>
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<td>3</td>
<td>J01FA01</td>
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<tr>
<td>4</td>
<td>J01AA07</td>
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In fact international guidelines generally consider them as second- or even third-choice antibiotics.

In Denmark, drugs such as oral cephalosporins and tetracyclines are not subsidized by the National Health Service and this factor could explain some of the difference. The relevance of these drugs is negligible: cephalosporins accounted for only 0.2% of the total DDDs of antibiotics sold in Denmark during 1996, and tetracyclines are not recommended for children <8–12 years of age. The Danish Guidelines recommend narrow spectrum penicillin (penicillin V) as the first choice drug in RTIs in all age groups.

The proportion of subjects exposed to antibiotics in Viareggio was higher than in Funen for both DDD and prevalence comparisons. The use of DDD as the referent measure could help to explain this difference, even if it might not adequately address differences in dosage and length of treatment for special classes of antibiotics. Nevertheless, the prescription rates in Viareggio appeared higher than those reported by Italian National Statistics, and these findings are in agreement with the broad variations observed among Italian regions in which Southern regions report higher antibiotic consumption in comparison with northern regions.

The higher amount of antibiotics prescribed in Viareggio than in Funen is difficult to explain: it is no doubt due to multiple factors. It is unlikely that there are major differences in the prevalence of infectious diseases between these two places, at least in primary health care. The presence of specialized paediatricians for paediatric patients in Italy might explain some of our unexpected results. The prescribing availability (1 paediatrician for 645 children in Viareggio) might favour the prescribing behaviour. Nevertheless, at least in Italy, no study has demonstrated that paediatricians possess better capabilities to treat young patients with antibiotics when compared with GPs.

The striking differences we observed between Italy and Denmark were quite expected. One recent survey has indicated that the level of misconceptions regarding antibiotic use was higher in southern than in northern EU countries, and Denmark is one of the countries with the lowest antibiotic use in outpatients. In contrast Italy ranked sixth in antibiotic use, after France, Spain, Portugal, Belgium and Luxembourg, the countries with the highest sales of antibiotics. These differences may not reflect actual therapeutic needs but rather lack of awareness of antibiotic resistance. Italian physicians may be more influenced by market and patient pressures than by public health emergencies, and antibiotics might also be misused because of the self-medication phenomenon. Physicians’ and patients’ attitudes towards antibiotics, historical backgrounds, cultural and social factors, and disparities in healthcare systems are also probably important factors in determining prescribing patterns. A recent study of cultural differences in coping with upper RTIs show differences related to diagnostic labelling of RTI. Dutch family practitioners (a country with low antibiotic consumption and low ‘winter peaks’) labelled most of these episodes of upper respiratory tract infection as common cold or flu, whereas Flemish family practitioners (in a country with the highest antibiotic consumption) labelled most of their episodes as bronchitis and prescribed more antibiotics. It is worth mentioning that amoxicillin was the molecule most frequently used (46.5% in 1999) by Dutch practitioners who prescribe the least antibiotic prescriptions in Europe and have one of the slowest developments of resistance.

In conclusion, the high consumption of amoxicillin (in terms of dosages), cephalosporins and macrolides might influence high rates of resistance among pneumococci as well as Haemophilus influenzae.

**Limitations**

Compliance with the ATC/DDD classification is a major issue in this analysis; for some older antibiotics (e.g. benzathine benzylpenicillin) and antibiotic combinations (e.g. sulpha-methoxazole plus trimethoprim), no official DDD was initially assigned by the WHO Collaborating Centre in Oslo. We were able to aggregate the national consumption of antibiotics since we retrieved the DDD list in terms of the ATC Classification for each marketed medicinal product package from the DURG-Italy.

The lack of information about length of treatment and the indication the drugs were prescribed for, (prescribing appropriateness) was not available; so we did not know if the use of antibiotics was appropriate, or whether the patient completed their prescribed course of antibiotic. This issue could lead to overestimation of antibiotic use because no indication was available about the conclusion or not of an already started antibiotic course. As a consequence any possible association with antibiotic resistance could be biased.

Finally, this study is based only on reimbursement data, and this could lead to an underestimation of real exposure to antibiotics, because some prescriptions are made by private physicians; some patients may purchase drugs while they are away from their home region or country, or even obtain them ‘over the counter’ (illegal both in Italy and Denmark) and possibly self-administer them.

**Conclusions**

This study demonstrates that surveillance programmes on antibiotic resistance should be accompanied by analyses of drug utilization data which can aid in the creation of valid cross-national studies on antibiotic usage and resistance, in order to motivate improvements in prescribing, and guideline-directed antibiotic prescribing in Italian children.

On the basis of the results reported here, the prescribing of antibiotic drugs in Italian children may not always be appropriate. Not only were broad-spectrum antibiotics prescribed more frequently than in Denmark (and also in comparison with other northern countries), but at a higher prevalence among children during the year of our study.

As a consequence, a big effort should be made to change the approach of Italian health care providers when coping with childhood disease and to better educate parents about antibiotic use, with the explicit aim of decreasing unnecessary prescribing.

To this end an aetiological rapid test (e.g. Strep A test) might target therapy in some cases. Herein empirical antibiotic therapy and prophylactic measures must be based on accurate knowledge of bacterial prevalence and antibiotic susceptibility testing.

**Acknowledgements**

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**Conflicts of interest:** None declared.
Key points

- The paediatric antibiotic prescription rate is substantially higher in Viareggio (Italy) compared with Funen (Denmark).
- Cross-national evaluations are fundamental in order to obtain a clear map of the use of antibiotics in human medicine in relation to resistance patterns.

References


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