

# Comparison of pediatric antibiotic prescribing practice between low and high prescribers for children in primary care

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## ABSTRACT

**Background.** Antibiotic prescribing is more prevalent in children. Many factors influence this practice, including the burden of outpatient visits. We aimed to compare antibiotic prescribing for children by low prescribers (LP) and high prescribers (HP) in primary care.

**Methods.** We analyzed pediatric prescriptions in primary care in İstanbul. Among the physicians randomly selected by systematic sampling, those generating  $\geq 1$  pediatric prescription/day (n=1218) were defined as LP or HP when they belonged to the lowest (n=305) or highest (n=304) quartile of prescribing, respectively. The antibiotic prescribing characteristics of these groups were compared.

**Results.** We identified that 38.5% of the prescriptions written by physicians included antibiotics, significantly higher in HPs (38.8%) than in LPs (37.2%), (p=0.04). Among antibiotic-containing prescriptions, the mean number of drugs and boxes and the percentage of prescriptions containing injectable drugs/antibiotics were significantly higher in HPs compared to that in LPs. We detected that co-amoxiclav was the most frequently prescribed antibiotic in the LP and HP groups (61.1% and 48.3%, respectively). Stratification of antibiotics by their spectra showed that 11.2% were narrow, 79.8% were broad and 0.5% were ultra-broad-spectrum drugs. LPs were significantly more likely to prescribe broad-spectrum antibiotics (82.5%) than do HPs (78.9%, p<0.001).

**Conclusions.** Antibiotic prescribing remains excessive in pediatric primary care, slightly more marked in HPs. While HPs also tend to prescribe a higher number of overall and injectable drugs/antibiotics, broad-spectrum anti-biotherapy seems to be more practiced by LPs surprisingly. Both physician groups appeared to prefer either narrow- or broad-spectrum drugs without paying enough attention to their pharmacodynamic properties.

**Key words:** antibiotics, children, co-amoxiclav, pharmacotherapy, primary care.

Despite improvements in antimicrobial treatments, infectious diseases still cause a significant health burden in the pediatric population.<sup>1</sup> The burden of disease is

undertaken by general practitioners or pediatricians at different levels of the healthcare system. In this context, more than half of the pediatric prescriptions generated by primary care physicians have been reported to contain antibiotics.<sup>2</sup> However, irrational use of these drugs continues to pose a serious global public health problem.<sup>3,4</sup> The multinational studies showed that antibiotic consumption in Turkey is at the top compared to other countries across Europe, especially for broad-spectrum

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antibiotics.<sup>5,6</sup> Moreover, it has been reported that this consumption is greater in the pediatric population.<sup>7</sup>

Apart from clinical suitability, many parameters influence antibiotic prescribing behavior.<sup>8,9</sup> This includes patient- and physician-related factors like demographic characteristics and/or knowledge level, clinical interaction between the patient and physician, the socio-economic characteristics of the area where the healthcare institution is located, and the availability of healthcare professionals in the region.<sup>5,8,10</sup> In addition, it was reported that physicians who encountered more patients prescribed antibiotics at a higher rate.<sup>11</sup>

Huge evidence of base indicates that half of the antibiotics prescribed to children in primary care are for suspicious/unnecessary indications.<sup>4</sup> For antibiotic use, children require special attention not only in terms of posology but also in terms of indication and safety.<sup>12</sup> It is important to evaluate the consumption of antibiotics from a large perspective in a group like children in which drug use should be more careful. On the other hand, to the best of our knowledge no comprehensive study has been encountered in the literature, which examines pediatric antibiotic prescriptions in primary care and correlates the prescribing pattern with the number of patients served by the physician. We aimed to compare antibiotic prescribing for children between the physicians with either low vs. high pediatric practice in primary care.

## Material and Methods

### Study design and population

We performed a cross-sectional study that included electronic prescriptions of primary care physicians in Istanbul. Among all these (n=4293) working in Istanbul in 2016, we selected 1431 physicians by systematic sampling. We analyzed all prescriptions generated for the pediatric population (<18 years of age), excluding those

of 35 physicians who did not prescribe for children during the study period, with a final sample of prescriptions by 1396 physicians. To compare prescribing performances of the physician groups, 1218 physicians who wrote an average of at least 1 prescription per day for the pediatric population in 2016 were ranked from high to low according to the total number of prescriptions. Physicians in the lowest quartile of the ranking (n = 305) were defined as low prescribers (LP), and in the highest quartile (n = 304) as high prescribers (HP), (Fig. 1). The data set was accessed after the institutional approval. The study was approved by the Ethics Committee for Non-interventional Studies of Istanbul Medipol University (Approval No: 25.06.2020-527).

### Study parameters

Prescriptions were examined in terms of descriptive characteristics such as age group (0-2 years, 3-11 years, 12-17 years), gender, and calendar year quartiles. Prescriptions were also analyzed in terms of rational use of medicine indicators such as total number of drugs/boxes/diagnoses, number of drugs/boxes/diagnoses per prescription and percentage of prescriptions containing antibiotics and injectable drugs. The "Anatomical Therapeutic Chemical (ATC)" classification system was used for the examination of the drugs in the prescriptions, and the diagnosis codes "International Statistical Classification of Diseases (ICD)" were used for the analysis of the diagnoses. The distribution of all antibiotics (ATC-3 and ATC-5 level) in the prescriptions as well as injectable antibiotics at ATC-5 level was examined.

The spectrum of antibiotics was evaluated in three groups as narrow (J01CA-penicillins with extended spectrum, J01CE01-benzyl penicillin, J01DB-first-generation cephalosporins, and J01DC-second generation cephalosporins), broad (J01CR-penicillins with beta-lactamase inhibitors, J01DD-third generation cephalosporins, J01EE01-sulfamet

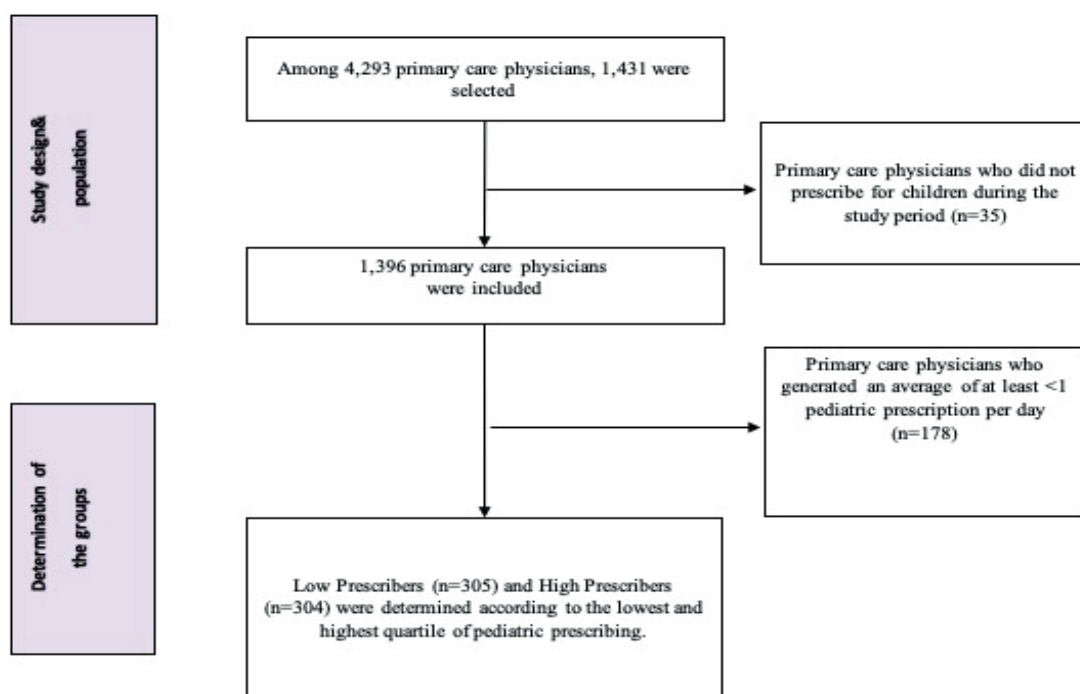


Fig. 1. Selection flowchart of the prescriber groups; high and low prescribers represented at the highest and lowest quartile of primary care physicians according to total number of prescriptions.

trimethoprim, J01FA-macrolides, and J01FF-lincosamides) and ultra-broad (J01AA-tetracyclines, J01BA01-chloramphenicol, J01DH-carbapenems, J01M-quinolones, J01XX01-fosfomycin, J01XX08-linezolid)13 Distribution of the most frequent 10 diagnoses for which antibiotics in these three spectrums was also analyzed.

### Statistical analysis

Statistical analysis was performed via SPSS 24.0 program. Descriptive data were presented as frequencies and percentages for categorical variables and mean and standard deviation for continuous variables. Independent samples t-test was used for comparison of continuous variables, and the chi-square test was used for comparison of categorical variables. Type 1 error level below 5% was accepted as statistical significance.

### Results

We found that 52.1% of the pediatric prescriptions were written to boys and the most prescribed age group was 3-11 (52.8%). In prescriptions containing antibiotics, the same age group had 60.2% of the prescriptions. These prescriptions were mostly prescribed to children in autumn (36.3%) and least in summer (16.2%).

We determined that 38.5% of the prescriptions contained antibiotics, which was significantly higher in HPs (38.8%) than LPs (37.2%) ( $p=0.04$ , Table I). In these antibiotic-containing prescriptions, the number of drugs and boxes per prescription and the percentage of prescriptions containing injectable drugs and antibiotics were significantly higher in HPs compared to LPs ( $p<0.05$  for all comparisons, Table II).

**Table I.** Comparison of descriptive characteristics of all prescriptions generated by low prescribers (n= 305) vs. high prescribers (n=304).

| All prescriptions                                      | Prescriptions of all physicians (n=1,258,688) | Prescriptions of low prescribers (n=63,469) | Prescriptions of high prescribers (n=635,798) | p-value |
|--|---|---|---|---------|
| Number of drugs per prescription                       | 2.36±0.90                                     | 2.26±0.80                                   | 2.38±0.92                                     | 0.01    |
| Number of boxes per prescription                       | 3.57±2.52                                     | 3.78±2.78                                   | 3.49±1.71                                     | <0.001  |
| Total number of drugs                                  | 2,972,351                                     | 143,632                                     | 1,511,224                                     | -       |
| Total number of boxes                                  | 4,489,753                                     | 239,713                                     | 2,216,575                                     | -       |
| Number of diagnoses per prescription                   | 1.39±0.33                                     | 1.36±0.28                                   | 1.38±0.45                                     | 0.05    |
| Total number of diagnoses                              | 1,748,032                                     | 86,356                                      | 878,109                                       | -       |
| Percentage of prescriptions containing injectable drug | 4.1   | 4.0   | 4.1   | 0.23    |
| Percentage of prescriptions containing antibiotic      | 38.5  | 37.2  | 38.8  | <0.001  |

**Table II.** Comparison of descriptive characteristics of antibiotic-containing prescriptions generated by low prescribers (n= 305) vs. high prescribers (n=304).

| All prescriptions  | Prescriptions of all physicians (n=480,136) | Prescriptions of low prescribers (n=23,614) | Prescriptions of high prescribers (n=246,373) | p-value |
|--|---|---|---|---------|
| Number of drugs per prescription                             | 2.91±1.01                                   | 2.80±0.72                                   | 2.92±0.98                                     | 0.02    |
| Number of boxes per prescription                             | 3.35±2.10                                   | 3.23±1.25                                   | 3.36±2.03                                     | <0.001  |
| Total number of drugs  | 1,395,829                                   | 66,147                                      | 718,856                                       | -       |
| Total number of boxes  | 1,608,034                                   | 76,369                                      | 828,242                                       | -       |
| Number of diagnoses per prescription                         | 1.38±0.24                                   | 1.34±0.52                                   | 1.37±0.54                                     | 0.04    |
| Total number of diagnoses                                    | 662,421                                     | 31,563                                      | 338,056                                       | -       |
| Percentage of prescriptions containing injectable drug       | 5.5   | 4.2   | 6.1   | <0.001  |
| Percentage of prescriptions containing injectable antibiotic | 4.1   | 2.9   | 4.6   | <0.001  |
| Percentage of prescriptions containing only antibiotic       | 11.1  | 13.6  | 10.5  | <0.001  |
| Percentage of prescriptions containing single diagnoses      | 71.5  | 74.8  | 71.9  | <0.001  |

Three of the most frequently prescribed ten drug groups were antibiotics: "J01C-penicillins" (21.7%), "J01D-other beta-lactam antibiotics" (6.5%) and "J01F- macrolides, lincosamides and streptogramins" (5.3%), (Fig. 2). This ranking was also similar in HP and LP groups. The most frequently prescribed ten antibiotics in

prescriptions consisted of 89.1% of all antibiotics. Four of them were cephalosporin (14.4%) and two of them were macrolide (14.8%). It was determined that amoxicillin+clavulanate was the most frequently prescribed antibiotic in the both HP and LP groups (48.3% and 61.1%, respectively), as well as the prescriptions of

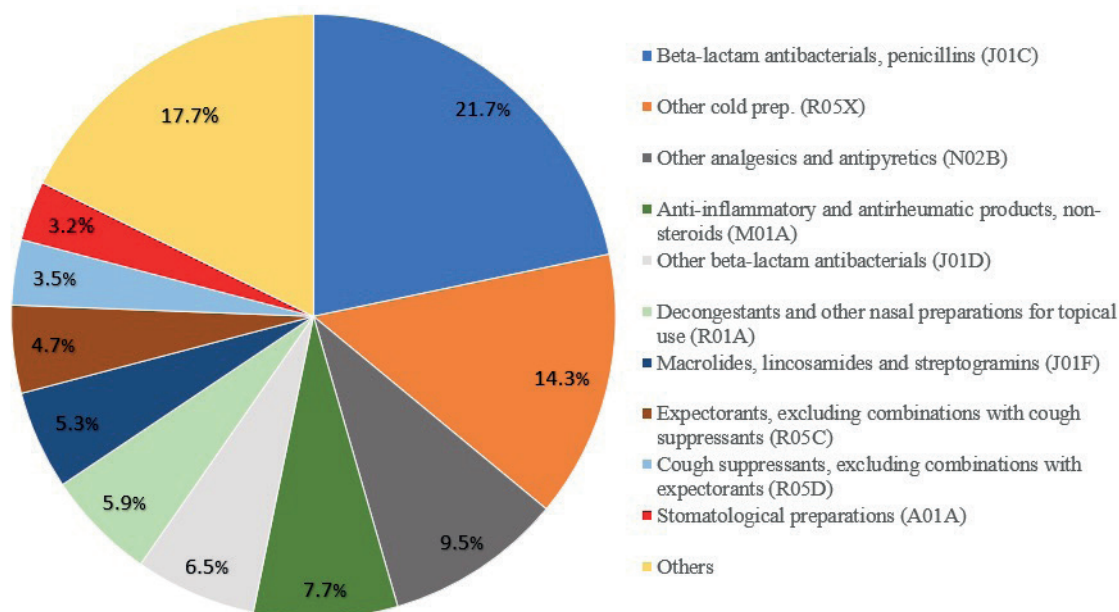


Fig. 2. Distribution of the antibiotics at ATC-3 level.

Table III. Distribution of the top ten frequently prescribed antibiotics in LP and HP groups.

| Name of drugs<br>(ATC-5)                     | All physicians  |      | Low prescriber<br>(LP) |      | High prescriber<br>(HP) |      |
|--|-----------------|------|------------------------|------|-------------------------|------|
|  | n (%)           | %*   | n (%)                  | %*   | n (%)                   | %*   |
| Amoxicillin + clavulanic acid (J01CR02)      | 250,064 (50.9)  | 17.9 | 14,770 (61.1)          | 22.3 | 121,963 (48.3)          | 17.0 |
| Clarithromycin (J01FA09)                     | 56,855 (11.6)   | 4.1  | 2,401 (9.9)            | 3.6  | 30,614 (12.1)           | 4.3  |
| Cefixime (J01DD08)                           | 27,439 (5.6)    | 2.0  | 839 (3.5)              | 1.3  | 15,730 (6.2)            | 2.2  |
| Amoxicillin (J01CA04)                        | 20,028 (4.1)    | 1.4  | 755 (3.1)              | 1.1  | 10,377 (4.1)            | 1.4  |
| Cefuroxime (J01DC02)                         | 18,179 (3.7)    | 1.3  | 960 (4.0)              | 1.5  | 8,937 (3.5)             | 1.2  |
| Azithromycin (J01FA10)                       | 15,681 (3.2)    | 1.1  | 731 (3.0)              | 1.1  | 7,727 (3.1)             | 1.1  |
| Benzathine phenoxymethylpenicillin (J01CE10) | 15,141 (3.1)    | 1.1  | 929 (3.8)              | 1.4  | 7,395 (2.9)             | 1.0  |
| Cefpodoxime (J01DD13)                        | 12,867 (2.6)    | 0.9  | 221 (0.9)              | 0.3  | 6,972 (2.8)             | 1.0  |
| Cefalexin (J01DB01)                          | 12,232 (2.5)    | 0.9  | 180 (0.7)              | 0.3  | 7,822 (3.1)             | 1.1  |
| Metronidazole (J01XD01)                      | 9,467 (1.9)     | 0.7  | 264 (1.1)              | 0.4  | 5,341 (2.1)             | 0.7  |
| Subtotal                                     | 437,953 (89.1)  | 31.4 | 22,050 (91.2)          | 33.3 | 222,878 (88.3)          | 31.0 |
| Others                                       | 53,509 (10.9)   | 3.8  | 2,134 (8.8)            | 3.2  | 29,499 (11.7)           | 4.1  |
| Total  | 491,462 (100.0) | 35.2 | 24,184 (100.0)         | 36.6 | 252,377 (100.0)         | 35.1 |

\* Percentage of drugs in prescriptions containing antibiotics.

all physicians for children (50.9%), (Table III). Tetracycline was found in 0.2% of prescriptions and quinolones were found in 0.1%. Overall, the most frequently prescribed drugs after amoxicillin+clavulanate were “R05X-Others

cold comb.” (14.3%), paracetamol (9.0%), and ibuprofen (7.0%).

Injectable antibiotics were prescribed in 4.1% of the prescriptions. Ceftriaxone was the most frequently prescribed injectable preparation

by all physicians in the HP and LP groups (39.1%, 33.9%, and 34.6%, respectively), (Fig. 3). Besides, although HP and LP groups were similar (2.4% and 2.2%,  $p=0.057$ ), 2.3% of all prescriptions were found to consist of multiple antibiotics (97.8% of combinations included dual antibiotherapy).

When antibiotics were examined in terms of their spectrum, it was found that 11.2% of them were narrow-spectrum, 79.8% of them were broad-spectrum, and 0.5% of them were ultra-broad-spectrum. This distribution was also preserved overall in HP and LP groups for narrow- (12.4% and 9.1%, respectively) and broad-spectrum (78.9% and 82.5%, respectively) with a significant difference ( $p<0.001$ ).

Most of the diagnoses in prescriptions containing antibiotics belonged to infectious diseases (74.3%), especially upper respiratory

tract infections (RTI). Noninfectious indications among the ten most frequent diagnoses were “vasomotor and allergic rhinitis” (3.1%) and “general examination” (2.4%). “Acute upper respiratory tract infections” was the diagnosis in which both narrow- (16.4%) and broad-spectrum (17.5%) antibiotics were most frequently prescribed. We detected that ultra-spectrum antibiotics were most frequently prescribed for diagnoses related to the urinary system (“Other disorders of the urinary system” 30.1% and “cystitis” 26.9%), (Table IV). In the narrow-spectrum group, amoxicillin (35.9%); in the broad-spectrum groups, amoxicillin+clavulanate (66.1%); and in the ultra-spectrum groups; fosfomycin (52.3%) were the most frequently prescribed antibiotics. The distribution of narrow and broad-spectrum antibiotics in single-diagnosis prescriptions was also similar in the HP and LP groups.

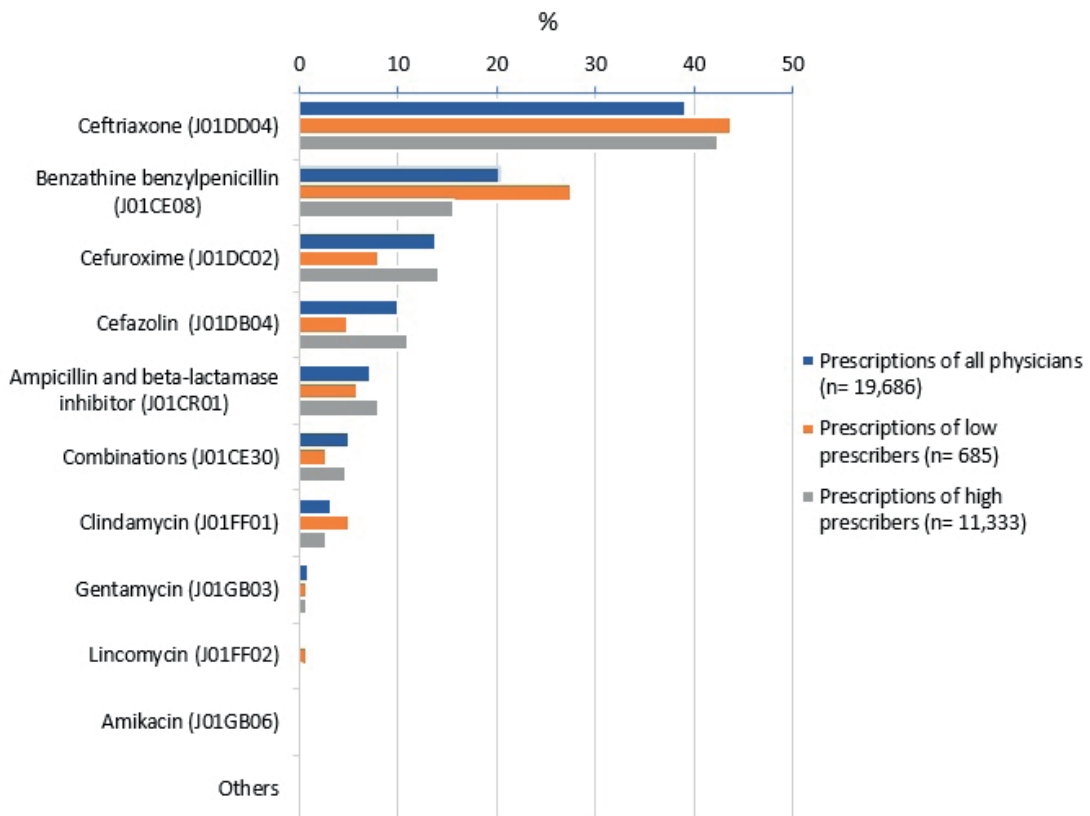


Fig. 3. Distribution of injectable antibiotics in injectable antibiotic-containing prescriptions.

**Table IV.** Distribution of diagnoses in single-diagnosis prescriptions by antibiotic spectrum.

| Diagnoses (ICD)  | Narrow |       |  | Broad   |       |  | Ultra-broad |       |                 |
|--|--------|-------|--|---------|-------|--|-------------|-------|-----------------|
|  | n      | %     | Diagnoses (ICD)  | n       | %     | Diagnoses (ICD)  | n           | %     | Diagnoses (ICD) |
| Acute upper respiratory infections of multiple and unspecified sites (J06) | 6,872  | 16.4  | Acute upper respiratory infections of multiple and unspecified sites (J06) | 49,302  | 17.5  | Other disorders of urinary system (N39)  | 490         | 30.1  |                 |
| Acute tonsillitis (J03)  | 6,540  | 15.6  | Acute tonsillitis (J03)  | 39,158  | 13.9  | Cystitis (N30)   | 438         | 26.9  |                 |
| Other diseases of upper respiratory tract (J39)                            | 5,216  | 12.5  | Other diseases of upper respiratory tract (J39)                            | 30,905  | 11.0  | Acne (L70)   | 263         | 16.2  |                 |
| Acute sinusitis (J01)  | 4,228  | 10.1  | Acute bronchitis (J20)   | 28,884  | 10.3  | Other and unspecified noninfective gastroenteritis and colitis (K52)                       | 41          | 2.5   |                 |
| Acute pharyngitis (J02)  | 4,120  | 9.8   | Acute sinusitis (J01)  | 25,742  | 9.2   | Other and unspecified dermatitis (L30)   | 27          | 1.7   |                 |
| Acute bronchitis (J20)   | 3,017  | 7.2   | Acute pharyngitis (J02)  | 24,674  | 8.8   | Acute upper respiratory infections of multiple and unspecified sites (J06)                 | 22          | 1.4   |                 |
| Unspecified acute lower respiratory infection (J22)                        | 1,692  | 4.0   | Unspecified acute lower respiratory infection (J22)                        | 16,883  | 6.0   | Acute nasopharyngitis [common cold] (J00)  | 20          | 1.2   |                 |
| Suppurative and unspecified otitis media (H66)                             | 1,403  | 3.4   | Suppurative and unspecified otitis media (H66)                             | 9,534   | 3.4   | Cutaneous abscess, furuncle and carbuncle (L02)  | 17          | 1.1   |                 |
| Acute nasopharyngitis [common cold] (J00)                                  | 958    | 2.3   | Acute nasopharyngitis [common cold] (J00)                                  | 4,875   | 1.7   | Other local infections of skin and subcutaneous tissue (L08)                               | 16          | 1.0   |                 |
| Other disorders of urinary system (N39)                                    | 631    | 1.5   | Otitis externa (H60)   | 4,463   | 1.6   | Encounter for general examination without complaint, suspected or reported diagnosis (Z00) | 14          | 0.9   |                 |
| Subtotal   | 34,677 | 82.8  |  | 234,420 | 83.4  |  | 1,348       | 82.9  |                 |
| Others   | 7,194  | 17.2  |  | 47,400  | 16.6  |  | 276         | 17.1  |                 |
| Total  | 41,871 | 100.0 |  | 281,020 | 100.0 |  | 1,626       | 100.0 |                 |

## Discussion

Inappropriate use of antibiotics is a common negative practice in primary care.<sup>2</sup> This irrational pharmacotherapy becomes more crucial in the pediatric population, which needs extra attention to promote the safety of medicines in children.<sup>12</sup> We showed that near 40% of pediatric prescriptions contain antibiotics, more marked by those physicians who were in the upper quartile of pediatric visits. While these physicians also tend to prescribe a higher number of overall or injectable drugs and antibiotics, broad-spectrum antibiotherapy seems to be more practiced by the physicians in the lower quartile.

The number of drugs per prescription and the percentage of antibiotic-containing prescriptions are well-established indicators of the World Health Organization to evaluate the rational use of medicine.<sup>3</sup> In primary care, 29.5% of all prescriptions were reported to contain antibiotic(s) in Turkey in 2016.<sup>14</sup> We observed a near 10% upward deviation of antibiotic prescribing prevalence in children (38.5%), which may not be unexpected considering the frequent use of antibiotics in children and positive correlation of antibiotic utilization with children density in a given population.<sup>4,7,15</sup> Nevertheless, it can still be considered higher than antibiotic prescribing reported from the large primary care databases in the Netherlands (18%), the US (28%), and the UK (36%).<sup>16,17</sup> In addition, it is known that many factors change the prescribing attitudes of physicians.<sup>7,9,11</sup> For instance, a study performed in Italy with 1164 pediatricians caring for almost 425,000 children reported that the quality of antibiotic prescribing was 4-fold worse among high antibiotic prescribers.<sup>18</sup> While we focused on primary care physicians, those who were visited more by pediatric patients, i.e., HPs, were more likely to escalate already-high antibiotic use (38.8%) compared to LPs (37.2%). The clinical implication of such difference needs designation of further studies beyond poor antibiotic-prescribing performances of both physician groups. In fact, general practitioners with

higher consultation rates were also reported to have increased antibiotic prescribing, especially for respiratory tract infections.<sup>19</sup> In addition, the presence of common cold combinations, paracetamol, and ibuprofen in prescriptions containing antibiotics suggests that physicians necessarily add an additional symptomatic agent to prescriptions containing antibiotics, increasing the number of drugs per prescription. This was also higher in HPs and further increased among the antibiotic-containing prescriptions, re-appraising the role of pediatric primary care a potential area for promoting rational use of antibiotics. The last decade has witnessed substantial efforts to address evidence-based targets and reduce pediatric antibiotic prescribing, from clinician-directed strategies to community-based campaigns.<sup>20-24</sup> A meta-analysis in 2013 reported a 6-21% reduction in pediatric antibiotic prescribing with combined parent education and clinician behavior modification with no benefit with passive waiting room education materials.<sup>20</sup> On the other hand, a recent randomized study reported no effect of electronically delivered prescribing feedback in reducing antibiotic prescribing in <15-year-old children, unlike adults.<sup>24</sup> These suggest the need for developing and implementing well-structured and multi-faceted interventions to improve rational antibiotic prescribing in children. Even modest improvements may have a higher impact in terms of rational antibiotic use in such countries like Turkey, with a comparably younger population and excessive antibiotic use.<sup>5,14</sup> Narrow-spectrum antibiotics are the first-line treatment option for many indications that often require antibiotics for children.<sup>25</sup> However, previous studies have shown that broad-spectrum antibiotics, especially co-amoxiclav, are frequently used in children.<sup>9,26-28</sup> In our study, 80% of the antibiotics were of broad spectrum and one of every two antibiotics prescribed by physicians was co-amoxiclav. The predominance of co-amoxiclav in our practice was previously reported in the literature<sup>7</sup>, which suggested the persistence of this inappropriate prescribing also in primary care compared to



that reported in the Netherlands (10%), the UK (4%), and in Italy (23%).<sup>17,29</sup> In fact, these figures were significantly higher in LPs in our study, including the preference for broad-spectrum drugs (83% vs. 79%). A US study evaluating almost 400,000 acute primary care visits in children showed the broad-spectrum antibiotic utilization as 42%<sup>16</sup>, nearly halving our findings. Another study performed in three European countries reported the ratio of broad-to-narrow-spectrum antibiotics as 0.3 for the UK, 3.2 for the Netherlands, and 74.7 for Italy.<sup>17</sup> Our findings indicated this ratio to be around 7, with a higher level in LPs, emphasizing the need for improving the quality of antibiotic prescribing. Our sample did not include pediatricians or specialists working in secondary/tertiary care, among which the preference for broad-spectrum antibiotics could be regarded as rather more reasonable. In fact, the literature showed that physicians with a low level of knowledge were more likely to prescribe broad-spectrum antibiotics.<sup>9</sup> This indicates that physicians' level of knowledge may be more determinant in rational prescribing, apart from the burden of prescribing. From this aspect, the training to be given by the authorities can improve the rational drug prescribing practice of physicians, focusing on primary care.

One-third of the prescriptions containing antibiotics for children indicated the diagnoses as upper respiratory tract infections.<sup>25</sup> In our study, we also observed a predominance of upper respiratory tract infections with similar frequency for both narrow- and broad-spectrum antibiotic prescriptions. This overall high rate of antibiotic prescribing might be regarded as unnecessary considering that the vast majority of these conditions have viral etiology.<sup>30</sup> Furthermore, a similar distribution of the same diagnoses for narrow- and broad-spectrum drugs may suggest an arbitrary selection of antibiotics, irrespective of HP or LP status. In fact, the preference of broad- over narrow-spectrum antibiotherapy was reported to be associated with higher rates of adverse events and decreased quality of life in children with

upper respiratory tract infections.<sup>31</sup> Though our study design did not allow us to follow patients, our findings could likely represent an inappropriate practice. On the other hand, the predominance of urinary system disorders and cystitis for ultra-broad-spectrum antibiotics may suggest that physicians tend to reserve this group for urinary tract infections. Within this group, tetracyclines and quinolones antibiotics are unfavorable antibiotics because of their safety issues in children.<sup>32,33</sup> Previous studies showed that quinolone use had a higher trend in Turkey compared to that of European countries.<sup>5</sup> Relatively low prescribing (0.3%) of tetracyclines and quinolones might indicate a rational behavior of the physicians in terms of antibiotics that have critical safety issues in children in our study.

Limited use of injectable forms of drugs is another indicator of rational use of medicines.<sup>3</sup> Overall injectable drug prescribing (4.1%) in our study appeared lower than that of the general population in Turkey (8.1%), indicating a lower preference for injectable drugs in children.<sup>14</sup> While this was similar between HPs and LPs, it is noteworthy that the rate increased by almost 50% (6.1%) among HPs compared to %5 increase (4.2%) in LPs for the antibiotic-containing prescriptions. This might be attributed to the difference between the use of injectable antibiotics in HPs (4.6%) vs. LPs (2.9%). It was reported that the prescription of antibiotics raised the likelihood of injectable medicine use<sup>34</sup>, consistent with our findings, especially for HPs. In addition, primary care physicians with a high practice activity were reported to be more liberal in antibiotic prescribing.<sup>19</sup> This may partly explain the higher use of injectable forms in HPs in our study as they represented the upper quartile of pediatric practice. This is further supported by a primary care study reporting the association of overuse of injections in younger populations.<sup>35</sup> Another remarkable finding of the study is that ceftriaxone, a broad-spectrum antibiotic, is the most frequently used injectable antibiotic in prescriptions. A previous study in primary care

showed the most common injectable form was ceftriaxone in infants, which was replaced by benzathine benzylpenicillin in older age groups of children.<sup>36</sup> Considering the relationship between the use of broad-spectrum antibiotics and antibiotic resistance<sup>37</sup>, the fact that almost 40% of injectable antibiotics are ceftriaxone can be considered an irrational choice.

Our findings need to be interpreted with the consideration of the study's limitations. Since we had no data for regional distribution of HPs and LPs at the districts level, we could not control for confounding factors that may influence their prescribing behaviors such as demographic or socioeconomic factors. As we also had no data on their age, gender, duration of occupation etc. that may have affected their practice, we could not overcome such limitation by using a generalized estimating equation or mixed models for correlated data. Besides, stratification of high or low prescribing status was based on the percentage of pediatric visits. The volume of adult visits and the experience with this population could have had an impact on their antibiotic prescribing in children. In addition, our data was based on the solo indications and their drugs on prescriptions. The diagnoses established by the physicians were accepted as correct and possible diagnostic errors could not be taken into account. Nevertheless, extensive coverage of all diagnoses with no particular focus on groups of indications (e.g., respiratory tract infections), or particular infections (e.g., sinusitis or acute otitis media) helped us to eliminate potential coding bias for a better evaluation of antibiotic prescribing practice.<sup>38</sup> Finally, as the study protocol and permissions only allowed for retrieval and collection of 2016 data, we did not have data after the year 2016. While it would be interesting to compare recent data (at latest 2019 because of the very likely confounding effect of the healthcare access-related issues of COVID-19 pandemic), we would not expect any major change between these years (i.e., 2016-2019) regarding pediatric antibiotic use. Nevertheless, temporal change may be expected due to short- and mid-term

impact of the restrictions on public access to nonprescribed antibiotic use (applicable as of the year 2013), whose outcomes indicate the need for designation of further quantitative and qualitative studies.

In conclusion, we showed that almost 40% of the prescriptions generated for children contained antibiotics, and 80% were of broad-spectrum. Physicians who had a higher population of pediatric cases were also more likely to prescribe a higher number of any drugs, injectable forms, and antibiotics whereas those who were visited by a lower number of children were more likely to prefer broad-spectrum antibiotics. Both physician groups appeared to prefer either narrow- or broad-spectrum drugs regardless of their antibiotherapy spectrums, mostly for respiratory tract infections. Available findings suggest that irrational antibiotic prescribing for children is still a problem in primary care, which warrants further large-sized studies that would probe clinicians' characteristics and contribute to the development of well-structured interventions to improve antibiotic use in children.

### Ethical approval

The study was approved by Ethics Committee for Non-interventional Studies of Istanbul Medipol University (Approval No: 25.06.2020-527). This retrospective database study did not require informed consent either from child and family.

### Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NIK, OA, NA, AA; data collection: NIK, OA, VA, AA; analysis and interpretation of results: NIK, OA, VA, AA; draft manuscript preparation: NIK, VA, OA, NA, AA. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare that the study received no funding.

## Conflict of interest

The authors declare that there is no conflict of interest.

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