

Title: Antibiotic Prescribing Patterns for Childhood infections in Ambulatory Settings in Jordan

Running head title: Antibiotic Prescribing Patterns in Pediatrics

Key words: Antibiotics; Prescribing pattern; Drug utilization; Pediatrics; Outpatients

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Title: Antibiotic Prescribing Patterns for Childhood infections in Ambulatory Settings

Abstract

Background: Antibiotics' rational prescribing is a major goal of the World Health Organization's (WHO) global action-plan to tackle antimicrobial resistance. Evaluation of antibiotic prescribing patterns is necessary to guide simple, globally applicable stewardship interventions. The impact of antimicrobial resistance is devastating, especially in low-income countries. We aimed to introduce ambulatory data on patterns of pediatric antibiotic prescribing in Jordan, which could be used to guide local stewardship interventions.

Methods: A cross-sectional retrospective study was conducted by selecting a random sample of pediatric patients, who attended ambulatory settings in 2018. Records of outpatients (age ≤ 18 years) receiving at least one antibiotic were included. The WHO's model of drug utilization was applied, and all prescribing indicators were included. Multiple linear regression was performed to examine factors influencing the ratio of prescribed antibiotics to overall medications per encounter.

Results: A total of 20,494 prescriptions, containing 45,241 prescribed drugs, were obtained. Average number of prescribed drugs per prescription was (2.21 ± 0.98) . 77.5% of overall ambulatory prescriptions accounted for antimicrobials. Only 0.6% of total prescriptions were for injectables. All antimicrobials (100%) were prescribed by generic-names and from essential drug list. Antibiotics were most commonly prescribed for respiratory tract infections. Age, gender, season, and facility type were significant predictors of prescribed antibiotics to overall medications ratio.

Conclusions: This is the first study of antibiotic prescribing patterns among outpatient pediatrics that covers wide regions in Jordan. Results indicate high rates of antibiotics use among outpatient pediatrics. Such findings necessitate more focused efforts and regulations that support rational utilization of drugs.

Key words: antibiotics, prescribing pattern, drug utilization, pediatrics, Outpatients, Jordan

1 **What's already known about this topic?**

2 In low income countries there is a general trend of antibiotics overuse, especially among pediatrics

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4 Antibiotics resistance rate is increasing dramatically in Jordan

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6 Considerable morbidity and mortality, and increased cost burden on healthcare resources, especially in
7 low- and middle-income countries, significantly challenge the provision of healthcare

8

9 **What does this article add?**

10

11 High rates of antibiotics use and elevated number of drugs per prescription among outpatient pediatrics
12 was evident

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14 Patterns of antibiotics' overuse among pediatrics might reflect a more significant problem within our
15 population

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17 Highlight the alarming needs for more focused efforts and regulations that support rational utilization of
18 drugs in general and antibiotics in particular

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1 INTRODUCTION

2 Childhood infections are common and pose considerable burden to pediatrics and
3 healthcare systems (1) (2). Compared to other age groups, and despite resilient immune system,
4 children have propensity to develop infectious diseases due to multiple risk factors (3). To
5 mention a few; daycare attendance, environmental pollutants (including exposure to tobacco),
6 crowded habitats, and poor hygienic practices are among common risk factors (1). The most
7 commonly reported infections among pediatric population include: acute otitis media, sinusitis,
8 pharyngitis, pneumonia, gastroenteritis, and urinary tract infections (4).

9 Antibiotics are mainstay in treating broad array of bacterial infections; however,
10 presumed efficacy and safety led to widespread use of antimicrobials. Such antibiotic misuse
11 can fuel the development of antibiotic resistance, which is an inevitable consequence of
12 antibiotic use (5) (6). Antibiotic overuse is common practice in caring for pediatric population
13 worldwide (7) (8) (6). As part of the developing world and due to the widespread access to
14 antibiotics, an alarmingly high rate of antibiotic authorization was reported in Jordan; with an
15 estimated prescription rate of 60% alongside equivalent percentage echoed with the use of
16 broader spectrum antibiotics in treating childhood infections (9, 10). Such imprudent use of
17 antimicrobials is associated with highlighted societal risk (11), considerable morbidity and
18 mortality, and increased cost burden on healthcare resources, especially in low- and middle-
19 income countries (12, 13).

20 Local resistance patterns are usually influenced by local prescribing patterns, where there
21 is a proportional relationship between both rates; antibiotic prescription and resistance
22 development (6, 8). In regards to drug utilization patterns, including those pertaining to
23 antibiotics, drug use indicators as aligned by World Health Organization (WHO) could serve as

valuable tool to accomplish such assessment in various settings (14). The aim of this study was to assess antibiotic prescribing patterns in treating childhood infections at multiple outpatient care settings in Jordan, using the WHO core drug use indicators. In addition, factors influencing the ratio of encounters with prescribed antibiotics were evaluated.

Materials and Methods

Study Design and Setting

A cross-sectional retrospective study was conducted using medical records of pediatric patients attending outpatient facilities attached to Royal Medical Services (RMS) and Ministry of Health (MOH) in 2018. The model of drug utilization recommended by the WHO was applied (14), where the following basic drug prescribing indicators were assessed: (i) Average number of drugs per encounter, (ii) Percentage of encounters with prescribed antibiotics, (iii) Percentage of encounters with an injection prescribed, (iv) Percentage of drugs prescribed by generic name, and (v) Percentage of drugs prescribed from formulary or essential drugs list.

Ethical approvals were obtained from Research Ethics Committees in different institutions, including: Jordan University of Science and Technology, Ministry of Health, and Royal Medical Services.

Data Collection

One-year prescription data were obtained, as per WHO recommendations, using Hakeem Program® (Amman, Jordan); the national Electronic Health Record (EHR) system in Jordan. The

study population included pediatric patients younger than 18 years who visited an outpatient healthcare institution within 124 public healthcare centers in 2018 (inclusive of 75 primary healthcare centers, 25 comprehensive healthcare centers, and 24 hospital outpatient clinics). The obtained data included: patient related variables and bio-demographics (age, gender, weight (if documented), height), institution related variables (facility name and type, governorate location, prescriber related factors), and prescription related variables (diagnosis, number of prescribed medications, dosage forms, and route of administration).

Statistical Analysis

Retrieved dataset was analyzed using both STATA version 14 (Stata Corporation, College Station, TX, USA) and Statistical Package for Social Sciences (SPSS) version 23 software (IBM Corporation, Armonk, NY, USA). Results were expressed as means, total numbers (number of drugs and number of antimicrobials per prescription), frequencies and percentages. T-test and ANOVA were used to compare means of continuous variables between different categories. Multivariate linear regression model was performed to identify predictors influencing the ratio of encounters with prescribed antibiotics.

RESULTS

Demographic Characteristics

A total of 20,494 prescriptions containing antimicrobial medications related to pediatric patients within outpatient healthcare settings were obtained from the EHS records. These prescriptions contained a total of 45,241 medications. Mean age of the study sample was (6.1± 4.9) years, with male-to-female ratio of 1.18:1.00. In the present study, and according to FDA classification (15), patients were further classified into different age groups, including: neonates

1 (≤ 1 month), infants (>1 month - ≤ 2 years), children (>2 years - ≤ 11 years), and adolescents ($>$
2 11 years - ≤ 18 years). These age groups accounted for 0.17%, 20.47%, 58.23%, and 21.13% of
3 the study sample, respectively. According to the map of coverage of EHS (as related to the
4 implementation of Hakeem program) within public healthcare sectors in Jordan, results were
5 fairly representative, covering the main cities. The majority of target pediatric patients presented
6 to public outpatient facilities from the most populated central region of Jordan (54.52%).
7 Descriptive details related to demographic characteristics are summarized in Table (1). This
8 study delineated the main facilities in public healthcare sector. Both MoH and RMS facilities
9 represented 48.8% and 51.2% of study records. The highest pediatric patients' visiting rate
10 (67.5%) was observed for outpatient clinics (within hospital settings), followed by primary
11 clinics (19.6%), comprehensive healthcare centers (6.7%), and comprehensive clinics (6.2%).

12 *Indications of Antibiotic Prescriptions*

13 Respiratory tract infections (20.97%) were the most common diagnosis among pediatrics
14 receiving antibiotic prescriptions at public outpatient care facilities during the study period.
15 Blood-related diseases and infections (17.41%) ranked second, while congenital problems and
16 related complications ranked third (17.34%) in the same aspect.

17 *WHO Prescribing Indicators*

18 Mean cumulative number of prescribed drugs per prescription was (2.21 ± 0.98) (as
19 depicted in figure 1). A breakdown of the total number across the main healthcare sectors
20 indicated a mean number of (2.35 ± 0.89) prescribed medications per encounter with a range of
21 (1 – 7) within MoH facilities, and a mean number of (2.07 ± 1.09) with a range of (1 – 10) within
22 RMS facilities. Average number of antimicrobials per encounter was (1.04 ± 0.21) within a

range of (1 – 5) (as depicted in figure 2). In addition, the ratio of antimicrobials to overall prescribed medications per encounter was fairly similar for both sectors, (0.5 ± 0.23) and (0.63 ± 0.27) at MoH and RMS, respectively.

The percentage of encounters with prescribed antimicrobials among the population of outpatient pediatrics in 2018 was calculated and found to be 77.5% of the overall encounters. Furthermore, antimicrobials represented 35% of the overall prescribed medications among the targeted population in this study. Narrow spectrum antibiotics represented 51.7% of total prescriptions, while broad spectrum antibiotics represented 40.9%, only. All prescribed antimicrobials (100%) were from the essential drug formulary list for the public healthcare sector. In addition, all antibiotic prescriptions (100%) in the study sample used the drug's generic names rather than brand names.

The majority of the prescribed drugs were for oral administration (85.2%) followed by topical route of administration (9.1 %), while injections accounted for only 0.6% of the total prescriptions. Among the most commonly prescribed dosage forms, suspensions accounted for 69.4% of the prescribed medications. More descriptive statistics related to prescribed medications included in this study are presented in Table (2).

Using ANOVA test, a comparison of the means of number of total prescribed medications and mean ratio of prescribed antibiotics to total drugs among the main age groups of pediatric patients within our study sample showed statistical significance ($P < 0.001$). Further, dataset was split based on antibiotic issue date, for which higher ratio of antibiotic to total prescribed drugs was significantly associated with colder months in winter season ($P < 0.001$). According to adjusted linear regression model (Table 3), Patients' age group, gender, season of

encounter (winter vs. other), and facility settings (clinics vs. hospital) were found to significantly predict the ratio of prescribed antibiotics to total prescribed drugs.

DISCUSSION

The current study assessed pediatric antibiotic prescribing in outpatient settings as reflected by WHO drug use indicators. The study revealed modest deviation from standard values aligned by WHO with a reported high rate of antibiotic prescription rate per encounter, elevated number of drugs per prescription, acceptable low percentage of encounters with an injection prescribed, ideal percentage of drugs prescribed by generic name, and perfect adherence with formulary list.

In the present study, the most common indication for antibiotic prescription was respiratory tract infections, followed by blood-related infections, and congenital-related diseases. This result is consistent with similar studies conducted in a number of developed and developing countries, where respiratory tract infections were the diagnoses more frequently associated with antibiotic prescription (16-20). This finding defines an important stewardship initiative where intensified training is needed to enhance prescribers' basic knowledge related to childhood respiratory infectious diseases; the predominant etiologic agents in such infective episodes are viruses rather than bacteria which renders antibiotics ineffective in such episodes (21). Additionally, winter season was identified as an independent predictor of higher antibiotic prescribing rates. Exposure to cold climate is a well-defined factor in the development of both upper and lower respiratory tract infections (22). However, seasonality of viral respiratory infections has been recognized for years rendering the accuracy of antibiotic prescribing for such infective episodes questionable (23).

According to WHO drug utilization indicators, the reported average number of drugs per prescription of 2.21 was high compared to the WHO standard ideal of (1.6-1.8). Similar number (2.4) was reported in a local study that evaluated drug use indicators in pediatrics visiting emergency departments (24). A number of close studies in developing countries showed comparable high mean numbers of drugs per prescription in Nigeria (3.8) (25), India (5.6) (26), and Sudan (2.0) (27). Such high number of drugs authorized per prescription can be attributed to heavy physician workloads, constrained physician-patient interaction time, and time restraints which limit physicians' ability to brush-up on their knowledge and skills needed to master therapeutic equivalency aspects. Hence, the general trend is to prescribe a drug for each symptom reported by patients, following a quick glimpse of symptoms, in order to keep patients' queue line moving fast (28, 29). In this regard, it is very important to reflect on overworked physicians and associated risks of malpractice that can jeopardize patient's safety and impact healthcare outcomes (30).

Furthermore, antibiotic prescribing rate was alarmingly high with 77.5% percentage of prescriptions containing antibiotics. Such ratio exceeded the WHO standard of (20%-26.8%) for the same indicator. Similarly, high antibiotic prescribing rates were also reported in other developing countries, like India (81.1%) (31) and Sudan (81.3%)(32). However, promising lower prescribing rates were reported in Saudi Arabia (18.5%) and United Arab Emirates (44.6%) (33, 34).

Regarding predictors of higher antibiotic prescribing rates, younger age was identified as composite in higher rates. Such finding can be explained by the higher propensity of younger ages to catch childhood infectious diseases given lower maturity of immune system (35). Moreover, a prescription issued by ambulatory hospital setting had higher rates of antibiotic

1 prescribing compared to clinic based ambulatory care services. This represents a potential
2 initiative for antibiotic prescribing antimicrobial stewardship program at hospitals to stress the
3 viral etiological nature of vast majority of such infections. Such finding was congruently
4 highlighted in a study conducted by van den Broek et al. where antibiotics accounted for 79%
5 prescriptions (36).

6 Narrow-spectrum antibiotics were more frequently prescribed as compared to broad
7 spectrum antibiotics. This finding is consistent with recommendations of treating childhood
8 infections using narrow spectrum antibiotics; as such approach would essentially improve
9 treatment outcomes and control antimicrobial resistance (16, 37). Noteworthy, 62.5% of broad-
10 spectrum antibiotics were prescribed for the treatment of respiratory tract infections. Such
11 finding contradicts the updated recommendations of treating pediatric patients with respiratory
12 infections using narrow-spectrum antibiotics (16). Such trend in prescribing should be
13 highlighted for further investigation in order to enhance rational prescribing of antibiotics in
14 Jordan. Accordingly, we insist on the impulsive needs of efforts to improve physicians'
15 knowledge and awareness about irrational prescribing of antibiotics and the emergence of
16 antimicrobial resistance.

17 Additionally, the index of injection prescribing for pediatric outpatients within public
18 healthcare sectors in Jordan was 0.6%, which is extremely low as compared to the WHO
19 standard value of (13.4% - 24.1%). Such small value is expected given the nature of outpatient
20 care settings where pediatric patients present mostly for scheduled appointments and are usually
21 prescribed enteral rather than parenteral medications to treat simple implicated infections. Such
22 assumption could be further articulated by the reported percentage of dispensed dosage forms,
23 with two-thirds of all prescribed antibiotics being suspensions. The reported low number of

1 injections prescribing in the current study was different from higher number reported by Al-
2 azayzih et al, who conducted a study in five teaching hospitals, only (38).

3 In regard to generic drug indicator, the percentage of drugs prescribed by generic name
4 was ideal (100%) compared to WHO standards. Moreover, adherence to formulary list was
5 optimal with a reported adherence of 100%. Such flawless measurements can be attributed in
6 part to the settings of study conduction; the current study was limited to public healthcare
7 sectors, where prescribers restricted to closed formulary systems. Commonly in Jordan, in cases
8 where brand medications are preferred, patients have the option to fill an authorized prescription
9 from a detached community pharmacy, on their own expenses. Additionally, only electronic
10 prescriptions were reviewed in the current study; electronic prescribing may force prescribers to
11 choose from available generics in public healthcare facilities. It is important to keep in mind that
12 such perfect numerical values can't be assessed apart from other indicators; rather, a true
13 reflection of drug prescribing behavior can be elucidated when values of all other indicators are
14 pieced together. Further, the enforced regulatory systems and national health policy implemented
15 within the public healthcare sector in Jordan might have an influential positive impact on drug
16 utilization practices.

17 As we can figure, the current study covered a broad geographical area across the country,
18 which can add to the generalizability of reported findings to different outpatient care settings.
19 Additionally, the large number of included encounters further adds to the strengths of the present
20 study. Likewise, we need to report potential limitations. Firstly, the retrospective design confers
21 risk of incomplete data. Further, a high percentage of encounters missed patients' weight which
22 is an important factor for dosage calculation in pediatric population. Such issue precluded the
23 confirmation of accuracy of prescribed antibiotic doses. Finally, pertinent data were collected

from electronic system and didn't include direct data collection from prescribers, so causal relationships to different practices couldn't be established.

In conclusion, the current study highlighted the irrational antibiotic prescribing patterns in pediatric outpatient care settings in Jordan. Such practices included: polypharmacy, high rate of antibiotic prescription, prolonged duration of antibiotic therapy, and the use of broader-spectrum antibiotics. Multifaceted interventions are encouraged to contain antibiotic dispensing and curb the development of evolving resistant bacterial strains. Structured discussions about judicious antibiotic use among healthcare delivery systems' leadership and prescribers must be facilitated. Moreover, determinants of cost-effective dispensing practices should be adopted nationwide.

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