Overview of Availability, Cost, and Affordability of Antibiotics for Adults in Jordan: an AWaRe Classification Perspective

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Article

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Abstract: Antimicrobial resistance (AMR) poses a global public health threat, with rates directly linked with consumption. The World Health Organization (WHO) AWaRe-classification aims to guide antibiotic use, which is influenced by drug availability, affordability, and economic policies. In Jordan, a high proportion of consumed antibiotics belong to the 'Watch' category. Data from the WHO-AWaRe classification, the Essential Medicines List, and the Jordan Food and Drug Administration were analyzed. Antibiotics for adults were classified and their cost per Defined Daily Dose (DDD) was determined, then affordability was assessed. In 2023, 43 injectable and 43 oral antibiotics for adults were registered in Jordan. 'Watch' antibiotics were the most common. 'Access' antibiotics had the lowest cost/DDD. 'Reserve' antibiotics were the most expensive with few generics. Injectable antibiotics had a negative correlation between cost and the number of alternatives. Affordability was higher for oral antibiotics compared to injectable ones. 'Reserve' antibiotics were generally unaffordable. This study highlights the need to promote 'Access' antibiotics over other categories by encouraging registration of missing 'Access' antibiotics and adjusting 'Watch' and 'Reserve' antibiotic prices. Competition among generics can lead to lower prices, increasing affordability and accessibility. We emphasize the importance of the AWaRe-classification in guiding antibiotic use in Jordan.

Keywords: antibiotic; AWaRe classification; affordability; cost per DDD; access; watch; reserve; MAH; Jordan

1. Introduction

Antimicrobial resistance (AMR), as a seriously identified global public health problem, is becoming an urgent demanding issue [1–3]. It is well-proved that rates of AMR have been directly related to rates of antimicrobial consumption. The frequent and irrational use of broad-spectrum antibiotics is a main cause of this problem. In addition to its burden on health, AMR exerts an economic pressure that requires searching for new expensive antibiotics to treat resistant bacterial infections [2].

The World Health Organization (WHO) experts had created a classification of antibiotics that is expected to slow-down the resistance rates against available antibiotics. This classification is based on listing antibiotics into three groups, i.e. 'Access', 'Watch', and 'Reserve' antibiotics (AWaRe). By considering AWaRe classification in antibiotics prescribing practice and antimicrobial stewardship efforts, this tool can help in selecting antibiotics properly with low participation possibility of causing antibiotic resistance. In other words, considering AWaRe classification of antibiotics may rationalize antibiotic consumption [4,5]. The WHO had put a target that at least 60% of antibiotic consumption

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being from agents belonging to 'Access' group [4,6], however, 70.5% of the prescribed antibiotics in Jordanian hospitals belonged to the 'Watch' category [7].

Antimicrobial stewardship, including all related dimensions can provide solutions to fight against AMR [3]. However, there are different other factors which may affect the quality of prescribing antibiotics. One of the factors that may lead to increased prescribing of broad-spectrum antibiotics is the shortage in primary healthcare settings [8]. On the other hand, economic policies such as implementing income-based pharmaceutical co-payment were found to reduce consumption of antibiotics in general [9,10]. At the same time, low public prices of antibiotics can enhance their affordability and consumption [11].

During the nineties till 2010, development of new antibiotics was seriously abandoned by big pharmaceutical companies. In fact, the number of companies researching antibiotics dropped from 18 to 4. At the same time, the number of newly approved antibiotics had been affected to reach a low number while warning levels of resistance to available antibiotics were reached [12]. Many guidelines recommend the use of old antibiotics whenever appropriate. Regardless of their safety and efficacy, the availability of the older antibiotics is a challenge from commercial point of view [13].

Affordability of a drug or treatment can be defined as a measurement of the easiness or feasibility of the society members to pay for a drug. It is correlated with drug prices, insurance coverage, a family's financial status, and sometimes, the indication of the drug [14]. In 2008, the WHO and Health Action International (HAI) defined treatment affordability based on the daily wage of the lowest-paid unskilled government worker [15]. Since antibiotic poor access and insufficient affordability are still a problem in low- and middle-income countries in the world, this is expected to worsen the AMR problem by not being able to afford full treatment for infections [2,3]. This can be considered as recognition of the inverse relationship between cost of treatment and consumption of drugs.

Ideally, 'Access' antibiotics should have an affordable cost to enhance its use as first or second line of treatment [5,16]. Discovering that 'Access' antibiotics were more affordable than other classes, or that 'Reserve' antibiotics had higher prices, may aid in achieving the target of reaching higher relative consumption of 'Access' antibiotics while reserving the 'Reserve' antibiotics for limited serious cases of infection.

Broad-spectrum antibiotics are more commonly available as injection rather than as oral dosage forms. Injectable antibiotics were most commonly administered in hospital settings in west and central Asia, Latin America, and eastern and southern Europe. Jordan is a country located in west Asia, where broad-spectrum parenteral antibiotics such as third-generation cephalosporins are frequently prescribed for both treatment and prophylaxis in the hospitals. Versporten et al. stated that in 2015, more than 80% of inpatients in these areas, including Jordan, had administered broad-spectrum antibiotics [17].

This study was aimed to explore registered antibiotics for adults in Jordan according to their AWaRe classification, and determine the relationship between cost, availability and affordability, and how the antibiotic was classified.

2. Results

Until the end of August 2023, the total number of antibiotics for adults that had been registered in Jordan by the JFDA was 43 injectable and 43 oral antibiotics. Injectable and oral antibiotics for adults in Jordan with their WHO AWaRe groups, listing status on EML in 2023, DDD, mean cost of the DDD, and number of MAH, are listed in Tables 1 and 2. Injectable and oral antibiotics for adults in Jordan belonged to various pharmacological classes. About 40% of types of injectable antibiotics were third-generation cephalosporins (12%), fluoroquinolones (9%), glycopeptides (9%), and penicillins (9%). At the same time, fluoroquinolone antibiotics represented the majority of oral types of antibiotics (18%), followed by macrolides and penicillins with 12% share for each of them (Figure 1).

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Table 1. Injectable antibiotics and their classification and cost.

WHO AWaRe category	Antibiotic	ATC code	Listed on EML	DDD (g)	Mean cost (JOD/DDD)	Number of MAH
Access	Amikacin	J01GB06	Yes	1	7.66	4
	Amoxicillin/clavulanic-acid	J01CR02	Yes	3	4.45	3
	Ampicillin	J01CA01	Yes	6	3.9	2
	Benzathine-benzylpenicillin	J01CE08	Yes	3.6	4.67	1
	Cefazolin	J01DB04	Yes	3	5.76	2
	Clindamycin	J01FF01	Yes	1.8	14.89	3
	Cloxacillin	J01CF02	Yes	2	4.65	1
	Gentamicin	J01GB03	Yes	0.24	2.2	3
	Metronidazole	J01XD01	Yes	1.5	4.75	8
	Procaine-benzylpenicillin	J01CE09	Yes	0.6	2.54	1
	Spectinomycin	J01XX04	Yes	3	5.93	1
	Sulfamethoxazole/trimethoprim	J01EE01	Yes	2	7.24	1
Watch	Azithromycin	J01FA10	Yes	0.5	8.03	3
	Cefepime	J01DE01	No	4	20.74	3
	Cefotaxime	J01DD01	Yes	4	21.15	3
	Cefoxitin	J01DC01	No	6	35.76	1
	Ceftazidime	J01DD02	Yes	4	11.59	6
	Ceftizoxime	J01DD07	No	4	33.58	2
	Ceftriaxone	J01DD04	Yes	2	11.31	11
	Cefuroxime	J01DC02	Yes	3	5.92	7
	Ciprofloxacin	J01MA02	Yes	0.8	30.61	7
	Clarithromycin	J01FA09	Yes	1	27.1	1
	Delafloxacin	J01MA23	No	0.6	111.28	1
	Ertapenem	J01DH03	No	1	24.18	2
	Imipenem/cilastatin	J01DH51	No	2	31.91	5
	Levofloxacin	J01MA12	No	0.5	13.94	6
	Lincomycin	J01FF02	No	1.8	5.34	5
	Meropenem	J01DH02	Yes	3	31.33	5
	Moxifloxacin	J01MA14	No	0.4	16.15	3
	Piperacillin/tazobactam	J01CR05	Yes	14	30.75	4
	Teicoplanin	J01XA02	No	0.4	7.73	5
	Tobramycin	J01GB01	No	0.24	12.69	1
	Vancomycin	J01XA01	Yes	2	18.74	9
Reserve	Ceftaroline-fosamil	J01DI02	No	1.2	72.47	1
	Ceftazidime/avibactam	J01DD52	Yes	6	268.38	1
	Ceftobiprole-medocaril	J01DI01	No	1.5	133.9	1
	Ceftolozane/tazobactam	J01DI54	No	3	221.96	1
	Colistin	J01XB01	Yes	9	63.03	1
	Daptomycin	J01XX09	No	0.28	49.06	1
	Linezolid	J01XX08	Yes	1.2	64.45	1
	Oritavancin	J01XA05	No	1.2	609.93	1
	Telavancin	J01XA03	No	0.75	93.6	1
	Tigecycline	J01AA12	No	0.1	60.58	2

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Table 2. Oral antibiotics and their classification and cost

WHO AWaRe category	Antibiotic	ATC code	Listed on EML 2023	DDD (g)	Mean cost (JOD/DDD)	Number of MAH
Access	Amoxicillin	J01CA04	Yes	1.5	0.46	12
	Amoxicillin/clavulanic-acid	J01CR02	Yes	1.5	0.83	10
	Ampicillin	J01CA01	Yes	2	0.46	4
	Cefadroxil	J01DB05	No	2	1.37	6
	Cefalexin	J01DB01	Yes	2	0.78	9
	Clindamycin	J01FF01	Yes	1.2	1.66	5
	Cloxacillin	J01CF02	Yes	2	0.78	2
	Doxycycline	J01AA02	Yes	0.1	0.24	8
	Flucloxacillin	J01CF05	No	2	0.83	1
	Metronidazole	P01AB01	Yes	2	0.34	7
	Ornidazole_oral	P01AB03	No	1.5	1.76	2
	Phenoxymethylpenicillin	J01CE02	Yes	2	0.39	1
	Secnidazole	P01AB07	No	2	3.38	1
	Sulfamethoxazole/trimethoprim	J01EE01	Yes	2	0.37	3
	Tetracycline	J01AA07	No	1	0.24	1
	Tinidazole	P01AB02	No	2	2.28	3
Watch	Azithromycin	J01FA10	Yes	0.3	0.72	16
	Cefaclor	J01DC04	No	1	1.19	8
	Cefdinir	J01DD15	No	0.6	3.72	4
	Cefditoren-pivoxil	J01DD16	No	0.4	1.97	1
	Cefixime	J01DD08	Yes	0.4	2.41	10
	Cefpodoxime-proxetil	J01DD13	No	0.4	2.9	5
	Cefprozil	J01DC10	No	1	3.25	2
	Cefuroxime	J01DC02	Yes	0.5	0.59	10
	Ciprofloxacin	J01MA02	Yes	1	1.15	17
	Clarithromycin	J01FA09	Yes	0.5	0.87	11
	Delafloxacin	J01MA23	No	0.9	66.66	1
	Erythromycin	J01FA01	No	2	0.58	2
	Levofloxacin	J01MA12	No	0.5	1.46	14
	Lincomycin	J01FF02	No	1.8	0.85	1
	Lomefloxacin	J01MA07	No	0.4	1.29	1
	Moxifloxacin	J01MA14	No	0.4	1.77	8
	Norfloxacin	J01MA06	No	0.8	0.58	4
	Ofloxacin	J01MA01	No	0.4	1.54	1
	Pefloxacin	J01MA03	No	0.8	1.09	2
	Rifabutin	J04AB04	No	0.15	2.91	1
	Rifampicin	J04AB02	No	0.6	0.43	2
	Rifaximin	A07AA11	No	0.6	1.57	1
	Roxithromycin	J01FA06	No	0.3	0.76	5
	Spiramycin	J01FA02	No	3	0.66	3
	Fosfomycin	J01XX01	No	3	4.48	2
	Minocycline	J01AA08	No	0.2	0.85	1
Reserve	Linezolid	J01XX08	Yes	1.2	45.98	4

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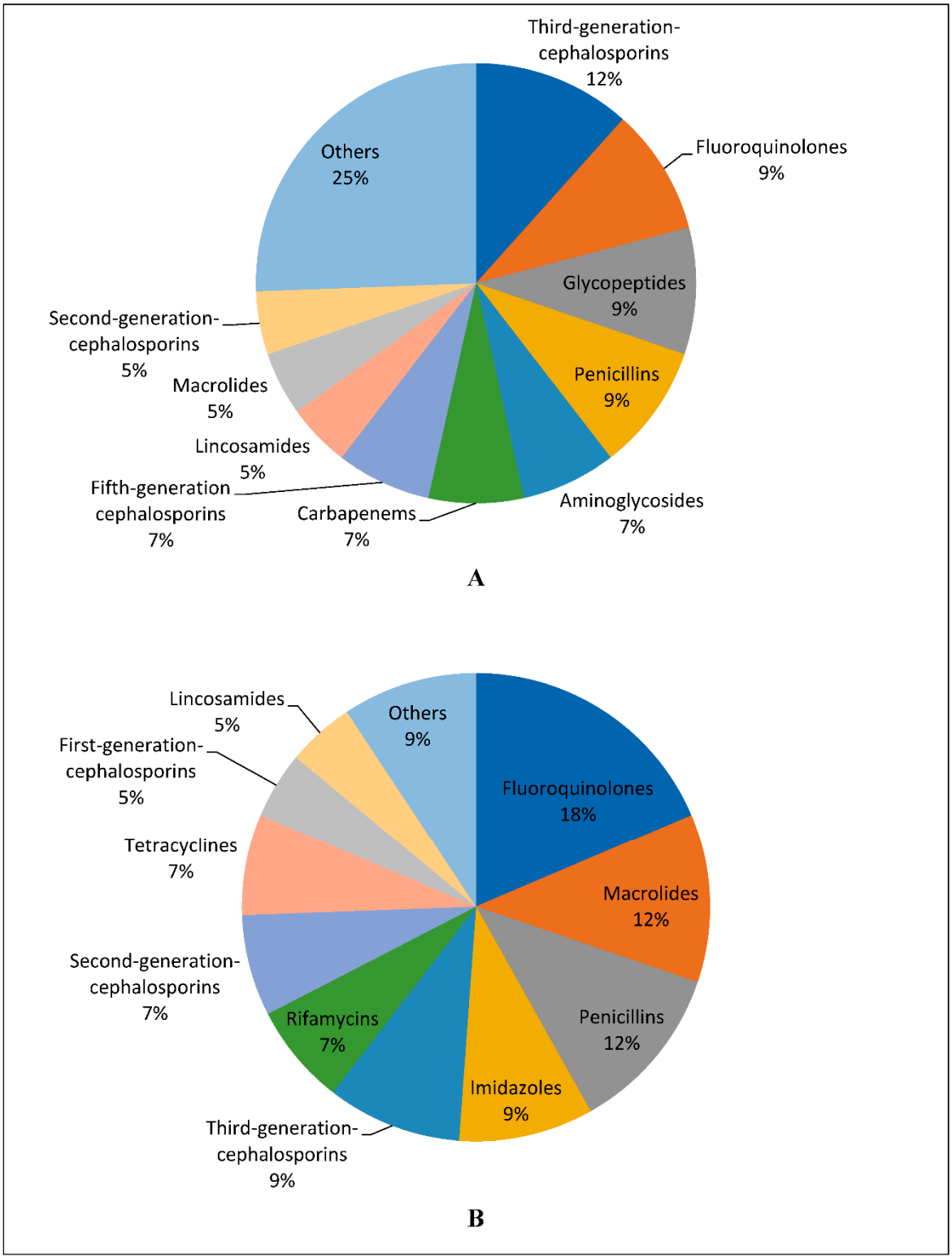

Figure 1. Percentage of types of antibiotics according to pharmacological class (**A**): injection, (**B**): oral.

About half of the injectable antibiotics for adults in Jordan (48.8%) belonged to 'Watch' group. 'Access' and 'Reserve' groups represented 27.9% and 23.3%, respectively. All of the 'Access' injectable antibiotics were listed on the EML. The majority of 'Reserve' injectable antibiotics (9 out of 10) had only one MAH in the Jordanian market.

Gentamycin, an 'Access' injectable aminoglycoside, had a mean public cost per DDD equals to 2.20 JOD/DDD. It was found to be the lowest cost of DDD out of the injectable antibiotics. It had three alternative brands in the market, and was listed on the EML. The antibiotic with the highest mean

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public cost per DDD was oritavancin (609.93 JOD/DDD). Oritavancin is a 'Reserve' glycopeptide with only the originator drug available in Jordan that was not listed on the EML.

Similar to injectable antibiotics, the majority of the oral antibiotics for adults belonged to 'Watch' group, which represented more than 60% of the total oral antibiotics, followed by 'Access' antibiotics (37.3%). Linezolid was the only oral antibiotic for adults in Jordan belonged to 'Reserve' group. It was listed on the EML and had a total of four originator and generic alternatives. Most of the 'Access' oral antibiotics were listed on the EML. At the same time, only about 30% of oral 'Watch' antibiotics could be found in EML.

Doxycycline, an 'Access' oral tetracycline, had a mean public cost per DDD equals to 0.24 JOD/DDD. It was found to be the lowest cost of DDD out of the oral antibiotics. It had eight alternative brands in Jordan, and was listed on the EML. The antibiotic with the highest mean public cost per DDD was delafloxacin (66.66 JOD/DDD). Delafloxacin is a 'Watch' fluoroquinolone with only the originator was available in Jordan and was not listed on the EML.

The injectable antibiotic with the highest number of alternatives (originator and generics) was ceftriaxone. Ceftriaxone, a 'Watch' group third-generation cephalosporin had 11 MAH in Jordan. It also had the highest cost ratio and % of cost variation, i.e. 6.78 and 577.9%, respectively (Table 3). On the other hand, ciprofloxacin was the oral antibiotic with the highest number of alternatives. This 'Watch'-classified fluoroquinolone had 17 MAHs in Jordan. However, the oral amoxicillin had higher cost ratio (5.92) and % cost variation (492.3%) (Table 4).

Table 3. Cost ratio and cost variation of injectable antibiotics in Jordan.

WHO AWaRe category	Antibiotic	Cost range (JOD/DDD)	Cost ratio	% Cost variation	Affordable
Access	Amikacin	6.15 - 8.83	1.44	43.6	Yes
	Amoxicillin/clavulanic-acid	3.27 - 5.58	1.71	70.6	Yes
	Ampicillin	2.99 - 4.91	1.64	64.2	Yes
	Benzathine-benzylpenicillin	4.67	1.00	0.0	Yes
	Cefazolin	4.70 - 6.48	1.38	37.9	Yes
	Clindamycin	6.09 - 19.20	3.15	215.3	Yes
	Cloxacillin	4.03 - 5.27	1.31	30.8	Yes
	Gentamicin	1.11 - 3.78	3.41	240.5	Yes
	Metronidazole	3.26 - 9.14	2.80	180.4	Yes
	Procaine-benzylpenicillin	2.54	1.00	0.0	Yes
	Spectinomycin	5.93	1.00	0.0	Yes
	Sulfamethoxazole/trimethoprim	7.24	1.00	0.0	Yes
Watch	Azithromycin	5.24 - 10.62	2.03	102.7	Yes
	Cefepime	14.64 - 25.40	1.73	73.5	No
	Cefotaxime	11.92 - 24.24	2.03	103.4	No
	Cefoxitin	35.76	1.00	0.0	No
	Ceftazidime	6.88 - 18.56	2.70	169.8	Yes
	Ceftizoxime	22.90 - 37.44	1.63	63.5	No
	Ceftriaxone	2.98 - 20.20	6.78	577.9	Yes
	Cefuroxime	3.39 - 10.12	2.99	198.5	Yes
	Ciprofloxacin	11.96 - 56.34	4.71	371.1	Yes
	Clarithromycin	27.10	1.00	0.0	Yes
	Delafloxacin	111.28	1.00	0.0	No
	Ertapenem	18.69 - 29.66	1.59	58.7	No
	Imipenem/cilastatin	25.00 - 39.68	1.59	58.7	No
	Levofloxacin	7.30 - 22.94	3.14	214.2	Yes
	Lincomycin	4.68 - 6.66	1.42	42.3	Yes
	Meropenem	16.69 - 57.11	3.42	242.2	No
	Moxifloxacin	7.20 - 22.19	3.08	208.2	Yes

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	Piperacillin/tazobactam	25.13 - 36.69	1.46	46.0	No
	Teicoplanin	3.69 - 12.40	3.36	236.0	Yes
	Tobramycin	12.69	1.00	0.0	No
	Vancomycin	8.01 - 29.28	3.66	265.5	Yes
Reserve	Ceftaroline-fosamil	72.47	1.00	0.0	No
	Ceftazidime/avibactam	268.38	1.00	0.0	No
	Ceftobiprole-medocaril	133.90	1.00	0.0	No
	Ceftolozane/tazobactam	221.96	1.00	0.0	No
	Colistin	59.72 - 66.33	1.11	11.1	No
	Daptomycin	49.06	1.00	0.0	No
	Linezolid	61.06 - 67.84	1.11	11.1	No
	Oritavancin	609.93	1.00	0.0	No
	Telavancin	93.60	1.00	0.0	No
	Tigecycline	51.66 - 69.50	1.35	34.5	No

Table 4. Cost ratio and cost variation of oral antibiotics in Jordan.

WHO AWaRe category	Antibiotic	Cost range (JOD/DDD)	Cost ratio	% Cost variation	Affordable
Access	Amoxicillin	0.13 - 0.77	5.92	492.3	Yes
	Amoxicillin/clavulanic-acid	0.61 - 1.29	2.11	111.5	Yes
	Ampicillin	0.30 - 0.79	2.63	163.3	Yes
	Cefadroxil	0.85 - 2.48	2.92	191.8	Yes
	Cefalexin	0.29 - 1.22	4.21	320.7	Yes
	Clindamycin	1.38 - 2.00	1.45	44.9	Yes
	Cloxacillin	0.67 - 0.83	1.24	23.9	Yes
	Doxycycline	0.17 - 0.35	2.06	105.9	Yes
	Flucloxacillin	0.83	1.00	0.0	Yes
	Metronidazole	0.19 - 0.69	3.63	263.2	Yes
	Ornidazole_oral	1.56 - 1.95	1.25	25.0	Yes
	Phenoxymethylpenicillin	0.39	1.00	0.0	Yes
	Secnidazole	3.01 - 3.75	1.25	24.6	Yes
	Sulfamethoxazole/trimethoprim	0.21 - 0.63	3.00	200.0	Yes
	Tetracycline	0.21 - 0.26	1.24	23.8	Yes
	Tinidazole	2.09 - 2.78	1.33	33.0	Yes
Watch	Azithromycin	0.47 - 0.90	1.91	91.5	Yes
	Cefaclor	0.78 - 1.43	1.83	83.3	Yes
	Cefdinir	3.40 - 4.47	1.31	31.5	Yes
	Cefditoren-pivoxil	1.97	1.00	0.0	Yes
	Cefixime	1.19 - 3.12	2.62	162.2	Yes
	Cefpodoxime-proxetil	2.30 - 3.83	1.67	66.5	Yes
	Cefprozil	3.00 - 3.66	1.22	22.0	Yes
	Cefuroxime	0.38 - 0.78	2.05	105.3	Yes
	Ciprofloxacin	0.45 - 2.38	5.29	428.9	Yes
	Clarithromycin	0.55 - 1.32	2.40	140.0	Yes
	Delafloxacin	66.66	1.00	0.0	No
	Erythromycin	0.31 - 0.80	2.58	158.1	Yes
	Levofloxacin	0.62 - 1.81	2.92	191.9	Yes
	Lincomycin	0.75 - 0.94	1.25	25.3	Yes
	Lomefloxacin	1.14	1.26	26.3	Yes
	Moxifloxacin	1.01 - 2.17	2.15	114.9	Yes
	Norfloxacin	0.50 - 0.73	1.46	46.0	Yes

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	Ofloxacin	1.41 - 1.66	1.18	17.7	Yes
	Pefloxacin	1.03 - 1.13	1.10	9.7	Yes
	Rifabutin	2.91	1.00	0.0	Yes
	Rifampicin	0.41 - 0.47	1.15	14.6	Yes
	Rifaximin	1.57	1.00	0.0	Yes
	Roxithromycin	0.67 - 0.83	1.24	23.9	Yes
	Spiramycin	0.380.96	2.53	152.6	Yes
	Fosfomycin	3.78 - 5.17	1.37	36.8	Yes
	Minocycline	0.73 - 0.96	1.32	31.5	Yes
Reserve	Linezolid	29.70 - 82.50	2.78	177.8	No

Means of costs of DDDs for all registered injectable and oral adult antibiotics in Jordan according to their mean prices for public were notably different according to their AWaRe classification. The difference in costs of DDDs was statistically significant between AWaRe groups (Kruskal-Wallis test) (Table 5). More specifically, the difference in mean cost was statistically significant between 'Access' and 'Watch' antibiotics in one side and 'Reserve' antibiotics in the other side (ϱ <0.001) according to post hoc Tukey HSD. While the mean cost/DDD for 'Reserve' antibiotics exceeded 150 JOD, mean cost/DDD for 'Watch' and 'Access' antibiotics was around 13 JOD and 3 JOD, respectively.

Table 5. Costs of antibiotics (JOD/DDD) and number of MAHs according to AWaRe classification.

	Access	**Watch**	**Reserve**	**Sig. (ϱ)**
N	28	47	11	
Mean JOD/DDD (S.E.)	3.03 (0.61)	13.11 (2.94)	153.03 (50.81)	<0.001*
Mean MAHs (S.E.)	3.75 (0.60)	4.74 (0.60)	1.36 (0.28)	0.003*
Affordable (%)	28 (100.0%)	36 (75.6%)	0 (0.0%)	<0.001**

* Statistically significant according Kruskal-Wallis test. ** Statistically significant according Pearson Chi-Square test.

AWaRe groups of antibiotics were also variable regarding number of MAHs. 'Watch' injectable and oral antibiotics had the highest mean number of MAHs (4.74), while mean MAHs for 'Reserve' antibiotics was 1.36. The difference was statistically significant (ϱ= 0.003).

The costs of DDDs of adult injectable antibiotics in Jordan were found inversely correlating with number of MAHs (i.e. available number of alternatives registered by the JFDA). Spearman's rho correlation coefficient was -0.354, and it was statistically significant (ϱ= 0.020). Similar correlation could not be found upon comparing costs of DDDs of oral antibiotics with number of available brands. Although had an inverse relationship like the injectable antibiotics, Spearman's rho correlation was not statistically significant for the oral cost of DDDs with number of MAHs.

2.1. Affordability of the Antibiotics

A total of 26 injectable antibiotic (60.5%) and 18 oral antibiotic (41.9%) were listed on the EML. However, the difference in percentage of listing in the EML between injectable and oral antibiotics was not found statistically significant. At the same time, oral antibiotics were significantly more affordable (ϱ <0.001) than injectable antibiotics (Figure 2).

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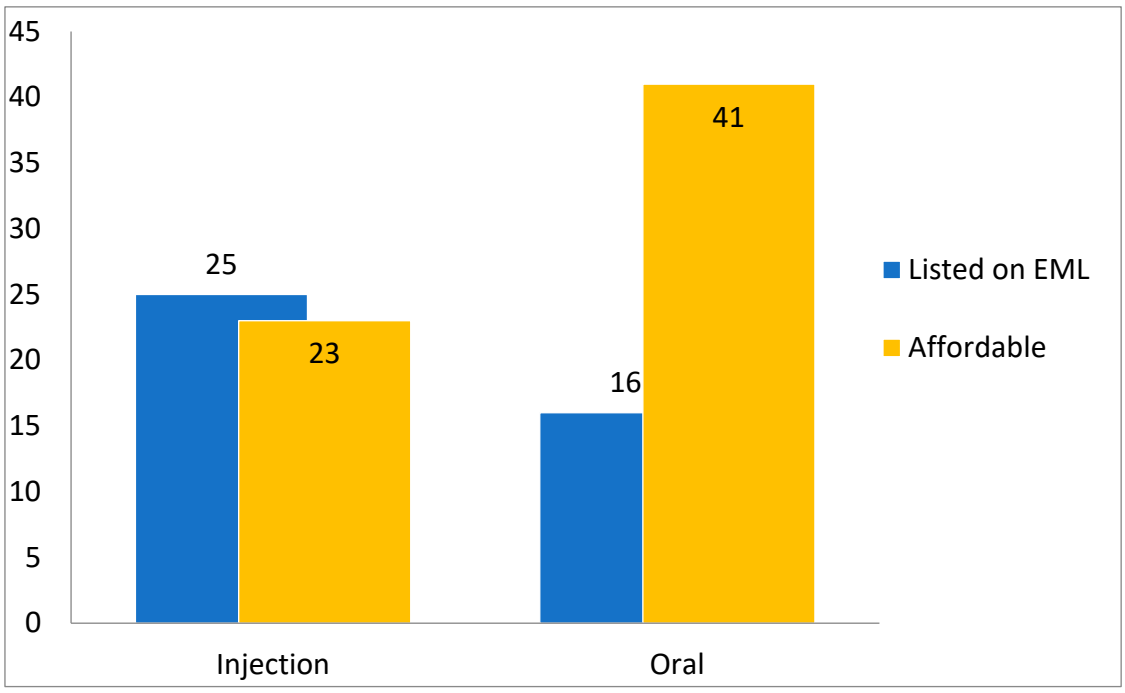

Figure 2. Number of injectable and oral antibiotics according to listing on the EML and affordability.

Of those listed on the EML, the 'Reserve' antibiotic linezolid was the only oral antibiotic considered as non-affordable. The non-affordable injectable antibiotics that were listed on the EML were 3 'Watch' antibiotics (cefotaxime, meropenem, and piperacillin with tazobactam) and 3 'Reserve' antibiotics (ceftazidime with avibactam, colistin, and linezolid).

All injectable and oral antibiotics that belong to the 'Access' group were found affordable. On the other hand, all ''Reserve' group antibiotics for both routes of administration were found not affordable. Delafloxacin was the only oral 'Watch' antibiotic to be considered not affordable. In contrary, approximately half of the 'Watch' injectable antibiotics (11 antibiotics) were considered affordable. The difference in affordability between all adults' antibiotics in Jordan according to the AWaRe classification was statistically significant. Affordability was ranging from 100% for 'Access' antibiotics and 0% for 'Reserve' antibiotics, with a ~75% affordability among 'Watch' antibiotics (Table 5).

By comparing number of MAHs for all the antibiotics according to their affordability classification, 64 antibiotics were found affordable with 4.69 mean number of MAHs (alternatives). The other 22 non-affordable antibiotics had a mean number of MAHs equals to 1.95. The difference in MAHs was statistically significant (ϱ= 0.001) (Table 6).

Table 6. Number of MAHs according to affordability of the antibiotics.

	Affordable	Non-affordable	Sig. (ϱ)
N	64	22	
Mean MAH (S.E.)	4.69 (0.50)	1.95 (0.30)	0.001*

* Statistically significant according Mann-Whitney U test.

The injectable and oral antibiotics had mean cost ratio of approximately 1.9. The mean % cost variation was 92.4 for the injectable and 97.3 for the oral antibiotics. Neither of the cost ratio nor the % cost variation was significantly different.

3. Discussion

This research aimed to draw a picture of availability of antibiotics for adults in Jordan, with brief cost and regulatory comparisons. All the included data were extracted from the WHO sources or the JFDA; the sole governmental drug regulatory body in Jordan.

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In addition to the AWaRe classification, the route of administration of the antibiotic was considered a primary classification for the antibiotics. The antibiotics for adults can be given to or administered by patients in different dosage forms via different routes according to the settings, indication, and severity of the condition. Sometimes, injectable and oral antibiotics can be notably different in DDDs and cost.

An extensive literature searching was conducted trying to find published studies or statistics about prescribing or consumption of antibiotics by AWaRe groups in Jordan. There was a shortage of published statistics about consumption of antibiotics according to AWaRe classification in Jordan at a national or large scale. An interventional study that was published in 2023 had used a single hospital's antibiotic prescribing data grouped according to AWaRe classification. It calculated antibiotics DDDs for adults and pediatrics that were dispensed by the hospital [24]. Al-Azzam et al. used the JFDA-derived annual national antimicrobial consumption for 2019 and 2020 to assess the impact of COVID-19 on national antimicrobial consumption in Jordan. 'Watch' antibiotics faced an increase in consumption in 2020. Azithromycin showed a great leap in prescribing rates during the pandemic [25]. In confirmation, this study shows that azithromycin as a 'Watch' antibiotic for adults had 16 MAHs for oral azithromycin and 3 MAHs for the injection, which makes it one of the highly available antibiotics in Jordan.

A considerable number of antibiotics for adults, whether formulated to be taken orally or parenterally, were not found registered in Jordan. Many of the 'missing' antibiotics from the Jordanian market can be described as old antibiotics that belong to 'Access' group. Regardless of the benefits from their use, old antibiotics will lack active marketing and will have relatively low prices and high registration and re-registration fees to a limit that the MAHs might decide not to keep them available [13].

A great proportion of the registered antibiotics in Jordan belonged to third-generation cephalosporins, fluoroquinolones, and penicillins. Third-generation cephalosporins and fluoroquinolones, in addition to penicillins with β-lactamase inhibitors as pharmacological classes were among the highest prescribed antibiotics in hospitals in Jordan and worldwide [7,17,26,27]. Route of administration, e.g. parenteral or oral, can be considered an important variable in studies that are concerned about exploring availability and affordability of antibiotics. In fact, in 2015, more than 80% of hospital inpatients in Jordan and other countries had administered broad-spectrum antibiotics such as third-generation cephalosporins – which are mainly injectable 'Watch' antibiotics - for treatment or surgery prophylaxis purposes [17]. Ceftriaxone, being a third-generation cephalosporin, seems to be the most available injectable antibiotic in Jordan. It had the highest number of alternatives, that had led to a wide cost ratio and cost % cost variation.

The reported consumption of 'Access' antibiotics in 28 European countries in 2021 was approximately 60% of the total consumed antibiotics in both the community and hospital sectors [6]. Our study shows that the majority of registered antibiotics for adults in Jordan belonged to 'Watch' group. At the same time, number of MAHs, representing available originators and generics, was the highest among 'Watch' group. Published results of surveillance on antibiotic consumption in 2015 showed that about 60% of consumed DDDs of antibiotics per 1,000 inhabitants per day in Jordan belonged to 'Watch' group [2], which is found consistent with global analysis of pharmaceutical sales data between 2000 and 2015 [16]. It seems that more actions, such as reviewing and implementing the policies related to antibiotic prescribing practices and regulatory and drug pricing guidelines, should be taken to enhance prescribing 'Access' group of antibiotics over other antibiotics.

It was found that the registered 'Reserve' group of antibiotics in Jordan had the highest mean cost/DDD and the lowest mean number of MAHs (originators and generics). The least expensive oral and injectable DDDs of antibiotics were (i.e. doxycycline and gentamycin, respectively) belong to 'Access' group. Generally, the low price of a drug can make it more affordable [11]. Cost-effectiveness of the drugs, including antibiotics, can partially be attained by enhancing competition between available treatments. This competition can sustain by enabling more generics of antibiotics available for prescribers, which can eventually decrease prices and cost [12]. It must be noted that generics are priced by the JFDA and their price never exceed 70% of the new drug or originator's price.

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None of the 'Reserve' antibiotics considered affordable in Jordan, in contrary to 'Access' antibiotics. Such finding supports the target of keeping 'Access' antibiotics more affordable while leaving 'Reserve' antibiotics as a last resort choice [5,16].

A limitation that can be mentioned regarding this study is that it lacks correlation with antibiotic consumption real-time data. However, the conducted research can still be conclusive. Restricting the number of available alternatives of 'Reserve' antibiotics could ensure higher prices and less affordability; and hopefully limited consumption and lower resistance rates in the future.

4. Methods

4.1. Sources of Data

The data that were collected to conduct this study were extracted from four electronic resources that were available online. The resources were:

1- The WHO AWaRe classification of antibiotics for evaluation and monitoring of use, 2023, which was downloaded from the 2023 AWaRe classification webpage of the WHO [4]. Information such as 2023 AWaRe classification of antibiotics, pharmacological class, and the Anatomical Therapeutic Chemical (ATC) code of the antibiotics were extracted from this source.
2- The 23rd List of Essential Medicines (EML) that was issued in 2023 [18] was utilized to determine the status of listing of each antibiotic (according to its dosage form and route of administration).
3- An index that uses ATC codes to find each antibiotic's Defined Daily Dose (DDD). The ATC/DDD index is a searchable version of the complete ATC index with DDDs provided online by the WHO Collaborating Centre for Drug Statistics Methodology and the Norwegian Institute of Public Health [19].
4- Drug information, prices, and leaflets webpage by Jordan Food and Drug Administration (JFDA) [20]. Prices of registered antibiotic items in all available packs for all marketing authorization holders in Jordan could be found by this official webpage.

Each antibiotic mentioned and classified in the WHO AWaRe classification list was searched for its registration in Jordan via the JFDA website. Antibiotics that were included in the study were the antibiotics registered and priced in Jordan in a dosage form for adults (i.e. vial or ampule for injection, or oral tablet or capsule) to be given parenterally or orally.

4.2. Cost of DDD

The WHO defined a DDD as "the assumed average maintenance dose per day for a drug used for its main indication in adults" [21]. The route of administration of the antibiotic for adult was considered for determination of the DDD. The DDDs for each antibiotic being either given parenterally or orally was directly matched with the ATC code of that specific antibiotic. To calculate cost of DDD as Jordanian Dinar (JOD) per DDD (JOD/DDD), the equation required having the public price of the antibiotic as a drug item, its pack size (i.e. number of units in the pack), strength of the antibiotic, and its DDD. The mean cost per DDD was then calculated for each antibiotic. Highest and lowest cost per DDD were also collected.

4.3. Affordability

The highest and lowest cost/DDD for each antibiotic were used to calculate cost ratio and percentage (%) of cost variation. The cost ratio was calculated by dividing the highest cost/DDD on the lowest cost/DDD. The % cost variation was calculated as the percentage difference of the highest and lowest cost/DDD to the lowest cost/DDD [22]. Antibiotic affordability was calculated referring to the WHO and HAI definition [15,22]. The Jordanian Ministry of Labor had set the minimum monthly wage for the years 2023 and 2024 on 260 JOD [23]. Threshold of antibiotic affordability was set to be the daily wage that was had been set by the government. If the lowest cost/DDD of each antibiotic was less than the minimum daily wage (~8.67 JOD), it would have been considered 'affordable'.

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In this study, the Marketing Authorization Holder (MAH) in Jordan was considered to be the pharmaceutical company or drug store that holds the registration rights and responsible for the regulatory affairs related to the antibiotic drug. The MAH can register an originator with more than one generic of the same antibiotic, and each type of antibiotic can be available in different dosage forms (e.g. oral tablets and capsules), different strengths, and different pack size. Number of MAHs aimed to represent scale of alternatives to the same registered antibiotic, and indirectly, its availability.

4.4. Statistical analysis

All data were transferred to IBM SPSS® Statistics 24 and underwent descriptive analysis. Pearson's Chi square test was used for categorical comparison, specifically listing on EML and affordability. Nonparametric tests were conducted because of nature of the data. Kruskal-Wallis test was used to determine difference in mean cost of DDDs and mean number of MAHs according to AWaRe classification. Further determination of the statistically significance of the difference between the categories was via conducting ANOVA post hoc Tukey HSD. Mann-Whitney U test was used to determine difference in mean cost ration and % cost variation according to route of administration, and the difference in mean number of MAH according to affordability. For the correlation between costs of the DDDs and number of MAHs, the test was Spearman's correlation.

5. Conclusions

In conclusion, a relationship was confirmed between the AWaRe classification of the antibiotic and its cost, availability, and affordability parameters. Availability and affordability of the antibiotic can be enhanced by having lower price and higher number of generics. Jordan has more available and affordable 'Access' antibiotics for adults than 'Reserve' antibiotics. However, more effort should be put to enhance prescribing 'Access' over 'Watch' antibiotics by encouraging the registration of the missing antibiotics, granting privileges to registration of more generics, and increasing prices of the 'Watch' and 'Reserve' antibiotics.

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