Original Article

Antibiotic Utilization in Iran 2000–2016: Pattern Analysis and Benchmarking with Organization for Economic Co-operation and Development Countries

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ABSTRACT

Objectives: Antibiotic resistance is the main threat to health all over the world. The consumption of antibiotics is one of the factors causing the emergence of multidrug resistance. The purpose of this study was to recognize the patterns, trends, and changes of consumption in Iran and to compare them with those of Organization for Economic Co-operation and Development (OECD) countries. **Methods:** The data were collected from a national pharmaceutical wholesale data bank. Defined daily dose (DDD) or DDDs per 1000 inhabitants per day (DID) was calculated as a standard indicator for the consumption over 17 years. **Results:** Were benchmarked with the consumption of OECD countries. Drug utilization 90% (DU90%) method was used to assess the drug consumption pattern. **Findings:** The antibiotic consumption jumped up from 33.6 DID to 60 DID from 2000 to 2016. Compared to the average consumption of OECD countries, Iran has consumed antibiotics almost triple times. There were 9–11 chemical substances in the DU90% list during these years. Changes in DU90% list occurred within antibiotics classes during the study period. Although the total consumption growth was equal to 79% during these years, consumption of some pharmacological subgroups such as sulfonamide and aminoglycosides has decreased. **Conclusion:** Albeit the existence of surveillance system for health-related infectious diseases, the consumption of antibiotics has increased drastically, which illustrates the necessity of comprehensive and effective national antibiotic stewardship.

Keywords: *Anatomical Therapeutic Chemical codes, antimicrobial stewardship, de ined daily dose, drug utilization, systemic antibiotics*

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Introduction

Antibiotic medicines have decreased the burden of infectious diseases, and they are assumed as an essential part of many medical procedures such as prophylaxis for surgical procedures or invasive diagnostic interventions.[1,2] According to the Iranian national pharmaceutical sales database in 2015, 605 million US dollars was spent on antibiotics that compromise 11.8% of total expenditure on medicine. Iranian spent 7.58 US dollars per capita on systemic antibiotics in 2015.

Antibiotic resistance is known as an important threat to global health.[3] Bacteria such as carbapenem-resistant *Enterobacteriaceae* and methicillin-resistant *Staphylococcus aureus* are threats to global health security. The inefficiency of antibiotics against common bacteria not only increases the expenditure for high-priced antibiotics but also increases mortality and morbidity in countries where lack of affordability of the last generation of medicines restricts their consumption.[2] The burden of disease caused by multidrug-resistant pathogens is estimated to be >20

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million US dollars annually in the USA and 1.5 billion euros in Europe.[4]

Several decades after the discovery of first antibiotics, we are now threatened by the emergence of multidrug-resistant bacteria.[4] Overconsumption of antibiotics and misuse are two major risk factors for bacterial resistance.[5] Overconsumption and misuse of antibacterial agents can lead to the selective pressure, which is one of the factors that causes emergence and outbreak of resistant pathogens.[6] Studies have proven the correlation between the rate of antibiotic resistance and the amount of antibiotic consumption.[7]

Hence, it is essential to manage the consumption of antibiotics for reducing the associated risk. Thus, surveillance of antibiotics utilization is vital to improve the perception regarding the epidemiology of multidrug-resistance infections and policy-making to control it.[8] Monitoring plans for antibiotics utilization have been initiated in many countries like the USA, EU, and China.[9-11] Unfortunately, no nation-wide monitoring program on antibiotics utilization and bacterial resistance has been established in Iran. However, the nationwide data on antibiotics consumption could be obtained from a national data bank of medicine sales, which is locally called "Amarname" in the Persian language.

Considering the issues mentioned above, this study aimed to find the patterns and reliable nationwide information on antibiotic consumption in Iran from 2000 to 2016 and benchmarking it with the rate of consumption of Organization for Economic Co-operation and Development (OECD) countries. This study demonstrates the necessity of restructuring the antibiotic stewardship at the national level, and it expected to provide data for the assessment and development of related guidelines.

Methods

A retrospective time-series study was conducted to analyze the trend of systemic antibiotics (J01) utilization in Iran (2000–2016).To this end, the systemic antibiotics consumption and consumption rate were benchmarked with data provided from OECD countries.[12] We have used drug utilization 90% (DU90%) that has been developed according to the Anatomical Therapeutic Chemical (ATC)/defined daily dose (DDD) method, and it is a precious tool for assessment of the overall quality in prescribing.[13]

As there were no consumption data at the patient level in Iran, we considered the wholesale data as the best available surrogate for consumption data. The quantities of systemic antibiotics consumption were obtained from wholesale data that are issued annually by the IFDA (Iranian Food and Drug Administration), and this database is called Amarnameh in the Persian language. This database has been established based on the sale's report of distributor companies all over the country. In this database, each medicine (specific dosage and form) is identified by a unique code and generic name. This code is linked to the sales value and volume of each item and share of each manufacturer and distributor.

Systemic antibacterial medicines that have been presented in Iran's market during 2000–2016 were identified based on consulting with specialists and national drug list.

Due to data availability, it was not feasible for us to distinguish between inpatient and outpatient antibiotic consumption. Thus, aggregated consumption data were obtained from the database of the OECD that is available on its website.[12]

Accredited data were analyzed in Microsoft Excel software 2010. Aggregated data that have been used were limited to systemic antibiotics (J01), which did not consist of antibiotics used for tuberculosis and antifungal and topical antibiotics. The data were categorized according to ATC codes and DDD methodology. The latest version of ATC/DDD guideline was taken from the website of the WHO Collaborating Centre for Drug Statistics Methodology.[14]

Population-weighted consumption or DDDs per 1000 inhabitant per day (DID) was calculated by following formula:[10,15,16]

$$\text{DID} = \frac{\text{number DDDs} \times 1000}{\text{number of population} \times 365}$$

Iran population in each year was obtained from the Iran Central Bank.[17]

Compound annual growth rate (CAGR) was used to calculate and compare the growth rate of antibiotics consumption:

$$\text{CAGR} = \left(\frac{C_{End}}{C_{start}}\right)^{\frac{1}{N}} - 1$$

In the above equation, "C" is consumption, and "N" is the number of years between the last and 1st year of study.[2]

We used the DU90% methodology to compare the pattern of J01 consumption during the study period and interpret the change in the rank of subgroups.[13,18]

J01 consumption of 30 OECD countries in 2016 was compared with Iran corresponding data.

Results

Antibiotics consumption has almost doubled over the past 17 years. Antibiotics consumption has raised from about 33.6 DID in 2000 to 60 DID in 2016. According to the linear regression equation, the total systemic antibiotics (J01) consumption increased 1.75 DID per annum (R^2 = 0.91) [Figure 1].

As the high value of the coefficient of determination in the equation indicates, consumption growth is continuous and shows a little fluctuation.

The highest consumption of systemic antibiotics (J01) was equal to 63 DID in 2014, and the lowest consumption was equal to 33.6 DID in 2000. Analysis of antibiotic consumption between pharmacological subgroups shows a high variance. Some pharmacological subgroups of antibiotics have grown, and some have decreased during the study period, for example, Cephalosporins (J01D) have increased from 3.2 DID in 2000 to 13.1 DID in 2016 (311% growth). Similarly, the consumption of Macrolides (J01F) at the beginning of the study was equal to 1.2 DID and has reached to 8.8 DID in 2016 (599% growth). Quinolones (J01M) also have increased from 1.2 DID in 2000 to 4.4 DID in 2016 (267% growth), while the consumption of sulfonamides and aminoglycosides has reduced. Sulfonamides consumption (J01E) has decreased from 3.5 DID in 2000 to 0.8 DID in 2016. Aminoglycoside consumption (J01G) also has decreased from 0.6 DID to 0.2 DID during the study period [Figure 2].

The overall growth rate of systemic antibiotics consumption was equal to 79% during these 17 years. Subgroup analysis revealed a concerning growth of third-generation cephalosporins (J01DD) with 4365% overall growth, other fast-growing subgroups are macrolides (J01FA), beta-lactamase inhibitors-penicillin combinations (J01CR), and fluoroquinolones (J01MA) by 586%, 568%, and 392% overall growth, respectively.

By benchmarking the data in Iran and the OECD countries in 2016, it was found that the consumption of systemic antibiotics in Iran was almost three times more than the average consumption of OECD countries [Figure 3].

Systemic antibiotics experienced a high rate of consumption growth during the studied years in Iran. The CAGR of systemic antibiotics consumption in Iran was equal to 3.7%, while some countries, such as France, Greece, and Belgium had − 0.6%, 1.3%, and 0.5% growth retrospectively, in the same period. Ireland had the highest CAGR by 2%, and the lowest CAGR belonged to Hungary by − 2.7%.[12]

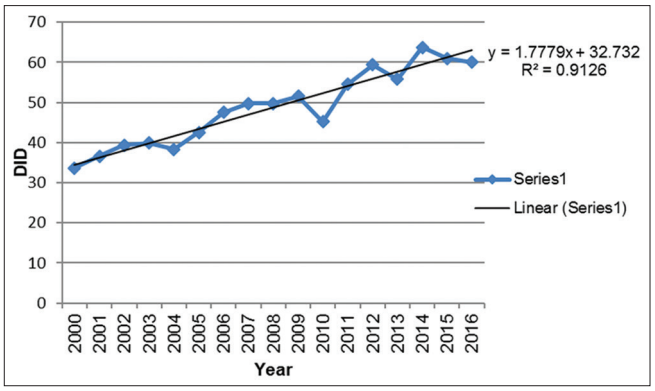

Figure 1: Utilization growth of systematic antibiotics (J01) in Iran (DDD = Defined daily dose)

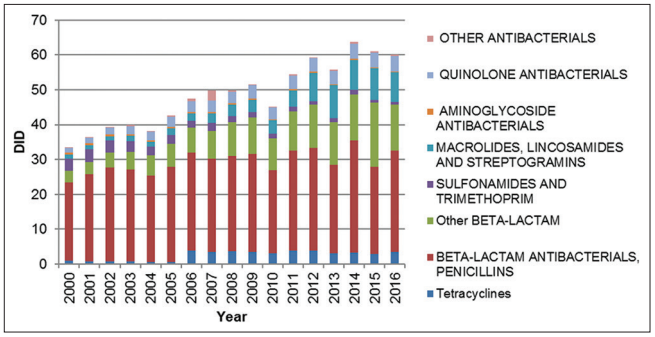

Figure 2: Consumption of antibiotic in Iran 2000–2016

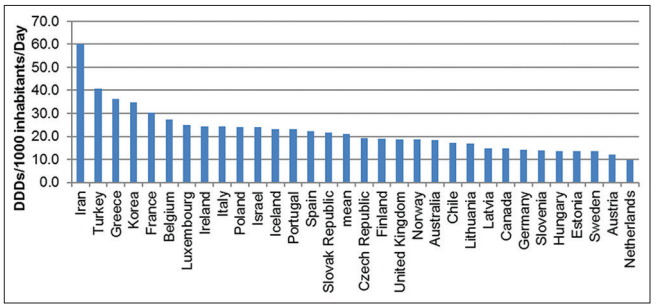

Figure 3: Comparison of systemic antibiotics (J01) utilization in Iran and the Organization for Economic Co-operation and Development countries (2016)

Fifty chemical substances were consumed as systemic antibiotics in 2016 in Iran. Only nine chemical substances constitute the list of DU90%. Four substances in the DU90% list belong to beta-lactam antibacterials (J01C and J01D) [Table 1].

There were 40 systemic antibiotic substances in Iran's national drug list in 2000, which among them ten substances constitute the DU90% list. During the study period, amoxicillin (J01CA04) has always been at the top of the DU90% list, although its percentage of total consumption has decreased from 46.6% to 32.4%.

During 2000–2016, three systemic antibiotic substances from the beta-lactams (ampicillin, penicillin G procaine

800,000 U, and penicillin V potassium) (J01C) were eliminated from the DU90% list and cefixime (J01DD08), as third-generation cephalosporins have appeared in the DU90% list.

Cotrimoxazole and cephalexin have lost their rank in the DU90% list, while ciprofloxacin's rank has risen in this list gradually [Table 2].

Discussion

This research has investigated the quantity of antibiotics consumption at the national level and has compared the rate and trend of antibiotics utilization in Iran with OECD countries.

Our study has calculated the rate of consumption over 17 years, demonstrated the trend of utilization and benchmarked the antibiotic consumption in Iran with OECD countries that can be insightful for policy-makers and health-care professionals.

Table 1: Drug utilization 90% profiles of systemic antibiotics in Iran (2016)

	Antibiotics	Total (%)
1	Amoxicillin	32.4
2	Cefixime	15.6
3	Co-amoxiclav	12.7
4	Azithromycin	12.3
5	Ciprofloxacin	5.3
6	Doxycycline	5.2
7	Cephalexin	4.3
8	Cotrimoxazole	1.3
9	Clarithromycin	1.3
DU90%	1 till 9	90.4
-	9 till 50	9.6
Total	1 till 50	100.0

DU90%=Drug utilization 90%

Table 2: Drug utilization 90% profiles of systemic antibiotics in Iran (2000)

	Antibiotics	Total (%)
1	Amoxicillin	46.6
2	Cotrimoxazole	10.5
3	Cephalexin	8.1
4	Ampicillin	8.1
5	Penicillin G Procaine 800,000 U	4.4
6	Erythromycin	3.6
7	Co-amoxiclav	3.4
8	Tetracycline	2.6
9	Ciprofloxacin	2.2
10	Penicillin V Potassium	1.8
DU90%	1 till 11	91.3
-	11 till 40	8.7
Total	1 till 40	100.0

DU90%=Drug utilization 90%

The consumption of antibiotics is the leading cause for the induction of antimicrobial resistance. Based on the WHO report, Iran and some OECD countries are considered as countries with more than five multidrug-resistance pathogens.[3,19]

As illustrated in Figure 2, the utilization of antibiotics in Iran has risen dramatically during these 17 years, while the OTC sale of antibiotics is illegal. This rise might be explained by three determinants. First, there are >11 pharmaceutical manufacturers that produce antibiotics. The competitive situation forces them on heavy promotion and marketing practice. The promotion activity increases the marginal profit for the retailer and gives them an incentive to sale antibiotics over the counter.[20,21] Second, self-medication, as one of the factors driving the misuse of drugs, is a widespread problem of the health system in Iran.[22] The determinants of these phenomena are multifactorial such as insufficient effective regulation, inappropriate strategy for rational use of drugs, and lack of public awareness about problems associated with irrational use of medications.[23-26] Third, there was not a comprehensive plan and effective stewardship to control misuse and overuse of antibiotics.[27]

We only had access to total consumption data and could not differentiate between the outpatient and inpatient consumption of antibiotics in Iran. OECD data bank provides aggregated data about systemic antibiotics consumption. Hence, we benchmarked the total antibiotics utilization between Iran and OECD countries.

As illustrated in Figure 3, we found that Iran has a higher antibiotic consumption compared to OECD countries. Consumption of OECD members was almost steady, and their change has low slope, but Iran's consumption has increased in this period. The higher consumption and higher growth rate might be explained by factors such as different health-care system, the burden of infectious disease, lack of evidence-based clinical guidelines and adherence to the available ones, promotion practices of the pharmaceutical manufacturer, and pressure resulted from the patients requesting for prescription of antibiotics.

Similar to the EU countries,[28] Republic of Korea,[29] and New Zealand,[30] penicillins (J01C) were the most frequently consumed antibiotics in Iran during 17 years. However, their dominance has been replacing by third-generation cephalosporines in recent years. Broad-spectrum antibiotics were the most consumed group in Iran during 2000–2016. The probable reason for high utilization of broad-spectrum antibiotics in Iran might be Iranian physicians' mindset that the broad-spectrum antibiotics are the best treatments to

cure many infections and they rely upon empirical treatment, instead of waiting for a laboratory test result.

During the study period, DU90% list was prepared for J01 group. We compared the pattern of J01 consumption in 2000 and 2016 by DU90% methodology. By comparing DU90% at the beginning and end of the study, we found that most of the changes occurred within subgroups. For example, erythromycin from the macrolide pharmacological subgroup has been replaced by azithromycin or tetracycline from tetracycline pharmacological subgroup has been replaced by doxycycline during these 17 years.

The limited number of substances of DU90% list and the replacement of drugs within subgroups during these years indicate the adherence of physicians to the first-line treatment guideline.

One of the main problems of public health is multidrug resistance. High utilization of last line and reserve antibiotics is one of the main responsible factors for multidrug resistance. Carbapenem and polymyxins are groups which are mainly used for treating infections caused by multidrug-resistant bacteria.[31] Carbapenems are last-line groups of antibiotics that are used for the treatment of infections caused by multidrug-resistance bacteria. The use of carbapenems increases the risk of infection with some carbapenem-resistant bacteria such as *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.[32] In 2016, the utilization of carbapenems was equal to 0.05 DID in EU countries, but Iran consumed 0.12 DID. The CAGR of carbapenems was equal to 34.5% that makes Iran vulnerable to multi-drug resistance bacteria.

Polymyxins, colistin as the dominant substance in parenteral form, has been utilized for treating carbapenem-resistant bacteria. The consumption of polymyxins in Iran is lower than EU countries (0.006 DID and 0.016 DID, respectively, in 2016). Although the CAGR of consumption in European countries has not changed significantly during 2012–2016, the CAGR of consumption of polymyxins in Iran has increased rapidly in the same time (3.4% vs. 33% CAGR).[31]

Rising concern about antibiotics resistance and falling rate in the discovery of new antibiotics necessitate rational use of antibiotics in order to save their effectiveness.[33] Albeit surveillance system for infectious diseases was implemented since 2007,[19] but our findings illustrate the recent situation of antibiotics utilization in Iran and clarify the necessity of restructuring the stewardship for stopping and controlling this trend. Restricted control on prescription, sale, and consumption of antibiotics that are in the DU90% list can be a useful policy for changing the growing trend.

Authors' Contribution

Hadi Abbasian Research design, literature search, and manuscript preparation. Mohammad Hajimolaali Data acquisition. Alireza Yektadoost: Statistical analysis. Saman Zartab Literature search, manuscript review, supervisor, and guarantor.

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Conflicts of interest

There are no conflicts of interest.

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