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Cost-Effectiveness Analysis of Certain Foreign and Local Brands of Antimicrobial Drugs in Yemeni Market

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Abstract:

***Background**: Pharmacoeconomic is an economic evaluation of pharmaceuticals in which the cost-effective analysis is one of the most important types of them that compares the relative costs and outcomes (effects) of different courses of action. **Objective**: The study aimed to Cost-Effectiveness analysis of some local and foreign antibacterial brands in Yemeni market. **Method**: Cost-effective analysis (CEA) was performed for four different antibacterial types (Azithromycin, Ciprofloxacin, Doxycycline and Amoxiclav), and there were four brands from each type that were of different origin, this analysis was carried out by antibacterial test for all brands against two types of sensitive bacteria (Staphylococcus aureus and Escherichia coli) and analysis of the efficacy of antibacterial brands in comparing to the cost or prices of this brands to calculate the cost-effectiveness ratio (CER) and select the best that was the lower value. **Results**: In the present study, from the pharmacoeconomic analysis, the Yemeni brands were the best in three types (Azithromycin, Doxycycline and Amoxicillin/clavulanic acid "Amoxiclav") with the smallest CER that were 10, 4.5, 32.11 in case of Staph. aureus and 13.33, 23.68 ,0 in case of E. coli respectively, while the Indian brand was the best in one type (Ciprofloxacin) with the smallest CER that were 8.13 in case of Staphylococcus aureus and 6.4 in case of Escherichia coli respectively, the four brands of amoxiclav type were showed ineffective against Escherichia coli in comparing to standard that was effective against Escherichia coli. **Conclusion**: This study was concluded the best brands to be selected was Yemeni brand in three antimicrobials (Azithromycin, Doxycycline and Amoxiclav) with 75% and the Indian brand in one type (Ciprofloxacin) with 25%. All the amoxiclav brands of different country were ineffective against E. coli.*

Keywords: Analysis; Antimicrobial activity; Cost effectiveness; Yemeni market.
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Introduction

Pharmacoeconomics is a branch of health economics that usually focuses on balancing the costs and benefits of an intervention towards the use of limited resources, aiming at maximizing value to patients, healthcare payers and society through data driven decision making[1].

Pharmacoeconomics refers to the scientific discipline that compares the value of one pharmaceutical drug or drug therapy to another[2,3].

Pharmacoeconomics centers on the economic evaluation of pharmaceuticals, and can use cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis or cost-utility analysis. Quality-adjusted life years have become the dominant outcome of interest in pharmacoeconomic evaluations, and many studies employ a cost-per-QALY analysis. Economic evaluations are carried out alongside randomized controlled trials and using methods of decision-analytic modelling. Pharmacoeconomics is a useful method of economic evaluation of various treatment options. As more expensive drugs are being developed and licensed it has become imperative especially in context of developing countries where resources are scarce to apply the principles of Pharmacoeconomics for various drugs and treatment options so that maximum improvement in quality of life can be achieved in minimum cost[4].

Cost-effectiveness analysis (CEA) is a form of economic analysis that compares the relative costs and outcomes (effects) of different courses of action. Cost-effectiveness analysis is distinct from cost–benefit analysis, which assigns a monetary value to the measure of effect[5]. Cost-effectiveness analysis is often used in the field of health services, where it may be inappropriate to monetize health effect. Typically, the CEA is expressed in terms of a ratio where the denominator is a gain in health from a measure (years of life, premature births averted, sight-years gained) and the numerator is the cost associated with the health gain[6].

Cost-effectiveness analyses are often visualized on a plane consisting of four quadrants, the cost represented on one axis and the effectiveness on the other axis[7]. Cost-effectiveness analysis focuses on maximising the average level of an outcome, distributional cost-effectiveness analysis extends the core methods of CEA to incorporate concerns for the distribution of outcomes as well as their average level and make trade-offs between equity and efficiency, these more sophisticated methods are of particular interest when analyzing interventions to tackle health inequality[8,9].

Literature review revealed that several previous studies were reported for CEA of different drugs and therapeutic conditions[10-21]. In Yemen, no previous studies were attempted to using the pharmacoeconomic analysis (Cost-effectiveness analysis) for selection of the best therapeutic regiment with lower cost and higher benefits. Therefore, the aim of the study was to assess economically of certain types of foreign & local antimicrobial brands in Yemeni market by using CEA.

Methodology

Standards – drugs and reagents

-Antibiotics reference standard.: Ciprofloxacin 5 µg, Doxycycline 30 µg, Azithromycin 15, Amoxicillin/clavulanic acid “amoxiclav 24/6" (Himedia, India) were gift from the National Center of Public Health Laboratories of Sana’a, Yemen.

-Bacteria: gift from Al-Awlaki Medical Labs, Sana`a, Yemen. *Staphylococcus aureus* ATCC29213, *Escherichia coli* ATCC25922.

-Four different brands of each antibiotic (Ciprofloxacin, Doxycycline, Azithromycin, Amoxiclav") were purchased from the market. Azithromycin 500 mg 4 brands were purchased from the market, these brands were Yemeni (B.N- 57821), Germany (B.N- 26079), India (B.N-ETAZ2101) and Egyptian (B.N-

A089807). Ciprofloxacin 500 mg 4 brands were purchased from the market, these brands were Yemeni (B.N-21357), Germany (B.N-24908), India (B.N-ID20786) and Syrian (B.N- 1620). Doxycycline 100 mg 4 brands were purchased from the market, these brands were Yemeni (B.N-22885), Belgium (B.N-1907E), Jordanian (B.N- X269) and Egyptian (B.N- 2206137). Amoxiclav 1000 mg 4 brands were purchased from the market, these brands were Yemeni (B.N- 22342), Spain (B.N-T003), Turkish (B.N- A22256191) and UAE (B.N- P670). Ethanol 96% (Yamco, Yemen) was purchased from the market. Muller-Hinton agar.

Instrumentations:

UV spectrophotometer (Shimadzu, Japan), Electric balance (Radwag, Poland), Mixture (JJ-1mixer, China), Water bath (HH-4, China), Centrifuge (China), Hot Oven (Labline Stock Centre) India**,** Morter and Pestle, Mixer (Panasonic, Japan), and Filter paper (AU 480, Beckman Coulter, American),

Methods:

Antibacterial susceptibility test

Five tested tablets were milled in a mortar. An equivalent weight of the powder was taken and added to a volume of the specified solvent which were either distilled water (for ciprofloxacin, doxycycline, amoxiclav) or ethanol 96% for azithromycin. The mixtures were filtered and a liquate of the filtrate was diluted with the solvent so as to prepare a dilute solution of 0.05 mg/ml, 0.3 mg/ml, 0.15 mg/ml and 0.24/0.06 mg/ml for ciprofloxacin, doxycycline, azithromycin and amoxiclav, respectively. 100 µl of each solution was equivalent to standard disc of 5 ug, 15 µg, 30 µg and 24 µg/6 µg, of each drug respectively.

The medium used for culturing of bacteria was Muller-Hinton agar prepared as reported in the literature. Bacterial suspension was prepared compared to 0.5 McFarland suspension and then stroked on the agar using Zig-zag method. Agar well diffusion method was used where 4 6-mm holes were bared aseptically (4 for the test samples). The results were compared to standard discs of the tested antibiotics. incubation was made at 37 ^{0}C for 24 hours. Next day, inhibition zones were measured.

Pharmacoeconomic analysis (Cost-effectiveness analysis)

The cost (C) for public of each antibiotic brand per 1 packet of drug was obtained from the market. The average results of inhibition zones of each tested brand were taken as "Effectiveness (E). The method of cost-effectiveness analysis (CEA) was used to compare between the brands using cost-effectiveness ratio (CER) as the comparing parameter.

CER was calculated as follows:[22]

$$CER = \frac{C}{E}$$

Where C is the cost and E is the effectiveness

$$E = \frac{IZ\ of\ Drug}{IZ\ of\ standard} * 100$$

Where E is the effectiveness and IZ is the inhibition zone

The brand with lowest CEA ratio was considered the most cost-effective brand.

Statistical Study:

The Statistical Package for Social Sciences (IBM SPSS) version 30.0 was used to perform statistical analysis. Single-way analysis of variance (ANOVA) was used for comparison of the CER values of the four different brands that was indicated to significant difference in the efficacy of brands against two bacterial species, when the *p*-values less than 0.05, as showed in table 9**.**

Results and Discussion

In present study aimed to work Cost-effectiveness analysis for study of four different antibacterial brands (azithromycin, ciprofloxacin, doxycycline and amoxiclav). These brands were purchased randomly from the Yemeni market. The study of each brand was carried out to compare one local brand to the other three foreign antibacterial brands. This study was reported to previous studies [23-26]. Cost-effectiveness analysis of azithromycin

was as showed in tables 1, 2 and figures 1, 2, the A (Yemeni) brand was the best selection with the smaller CER followed by the D (Egyptian) brand which followed by C (Indian) brand and the final was the B (Germani) brand where CERs were 10, 12, 15, 40 for *Staph. Aureus* and 13.33, 15, 20, 53.33 for *Escherichia coli*, respectively.

Table 1. Pharmacoeconomic analysis of brands of Azithromycin 500 mg tablets against *Staphylococcus aureus* ATCC29213**:**

Tested brands					Inhibition zone (mm) of standard	Inhibition zone (mm) of drug	E	CER
Cost		Code	Origin	Batch No.				
Y. R	Dollar $							
1000	2	A	YEMEN	21357	25	25	100	10
4000	8	B	GERMAN	26079		25	100	40
1500	3	C	INDIA	ETAZ2101		25	100	15
1200	2.4	D	EGYPT	A089807		25	100	12
			SD			0	0	

SD: Standard Deviation, Y.R: Yemeni Rial, E: Effectiveness.

Table 2. Pharmacoeconomic analysis of brands of Azithromycin 500 mg tablets against *Escherichia coli* ATCC25922:

Tested brands					Inhibition zone (mm) of standard	Inhibition zone (mm) of drug	E	CER
Cost		Code	Origin	Batch No.				
Y. R	Dollar $							
1000	2	A	YEMEN	21357	20	15	75	13.33
4000	8	B	GERMAN	26079		15	75	53.33
1500	3	C	INDIA	ETAZ2101		15	75	20.00
1200	2.4	D	EGYPT	A089807		16	80	15.00
			SD			0.5	2.5	

SD: Standard Deviation, Y.R: Yemeni Rial, E: Effectiveness.

Figure 1: Efficacy of 4 brands of Azithromycin 500 mg tablets against *Staphylococcus aurous* and *Escherichia coli.*

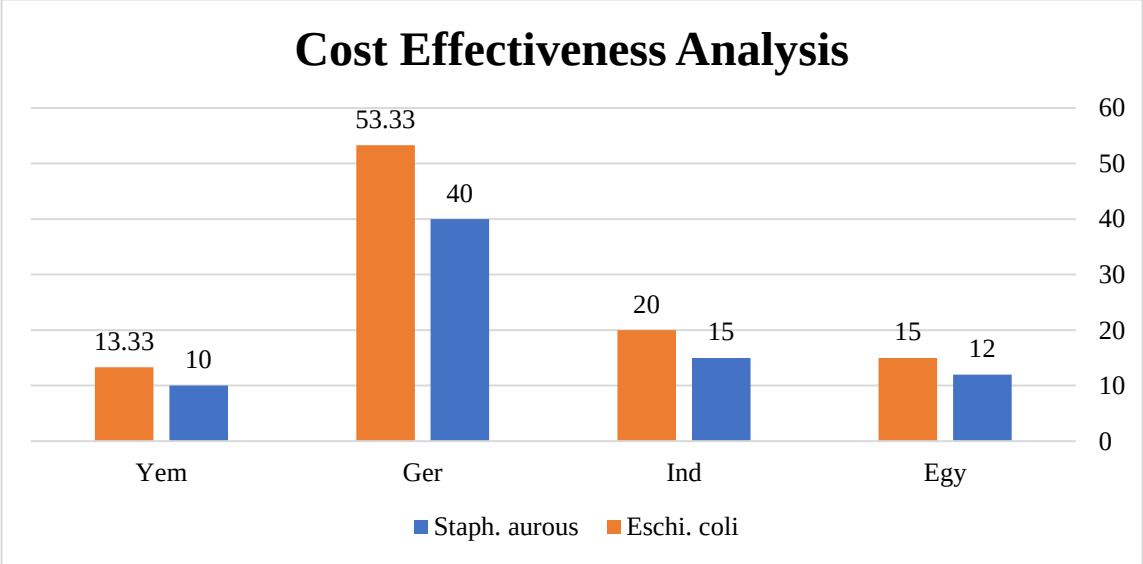

Figure 2: Diagram of pharmacoeconomic analysis of brands of Azithromycin 500 mg tablets against *Staphylococcus aurous* and *Escherichia coli*

Cost-effectiveness analysis of cirofloxacin was as showed in table 3, 4 and figure 3, 4, the C (Indian) brand was the best selection with the smaller CER followed by the A (Yemeni) brand, follow the D (Syrian) brand and the final was the B (Germani) where CERs were 8.13, 8.4, 10.45, 45.29 for *Staphylococcus aureus* and 6.4, 7, 8, 35.67 for *Escherichia coli*, respectively,

Table 3. Pharmacoeconomic analysis of brands of Ciprofloxacin 500 mg tablets against *Staphylococcus aureus* ATCC29213**:**

Tested brands					Inhibition zone (mm) of standard	Inhibition zone (mm) of drug	E	CER
Cost		Code	Origin	Batch No.				
Y. R	Dollar $							
700	1.4	A	YEMEN	57821	36	30	83.33	8.40
3900	7.8	B	GERMAN	24908		31	86.11	45.29
700	1.4	C	INDIA	ID20786		31	86.11	8.13
900	1.8	D	SYRIA	1620		31	86.11	10.45
			SD			0.5	1.389	

SD: Standard Deviation, Y.R: Yemeni Rial, E: Effectiveness.

Table 4. Pharmacoeconomic analysis of brands of Ciprofloxacin 500 mg tablets against *Escherichia coli* ATCC25922

Tested brands					Inhibition zone (mm)	Inhibition zone (mm)	E	CER
Cost		Code	Origin	Batch No.				
Y. R	Dollar $							
700	1.4	A	YEMEN	57821	32	32	100	7.00
3900	7.8	B	GERMAN	24908		35	109.4	35.67
700	1.4	C	INDIA	ID20786		35	109.4	6.40
900	1.8	D	SYRIA	1620		36	112.5	8.00
			SD			1.73	5.412	

SD: Standard Deviation, Y.R: Yemeni Rial, E: Effectiveness.

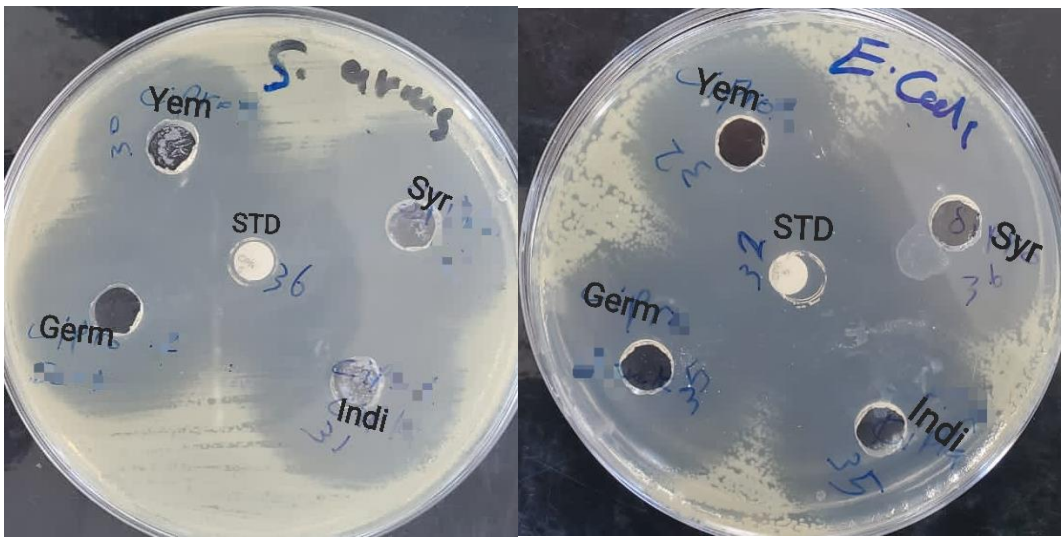

Figure 3: Efficacy of 4 brands of Ciprofloxacin 500 mg tablets against *Staphylococcus aurous* and *Escherichia coli.*

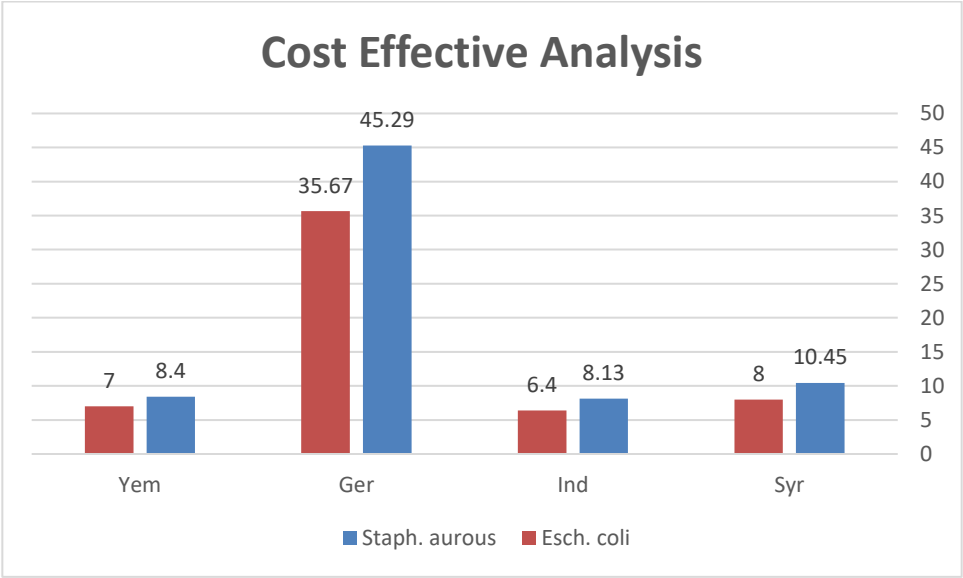

Figure 4: Diagram of pharmacoeconomic analysis of brands of Ciprofloxacin 500 mg tablets against *Staphylococcus aurous* and *Escherichia coli*

CER of doxycycline was as showed in tables 5, 6 and figures 5, 6, the A (Yemeni) brand was the best selection with the smaller CER followed by the C (Jordanian) brand, follow D (Egyptian) brand and the final was the B (Belgium) brand where CERs were 4.5, 8.65, 9, 17.86 for *Staphylococcus aureus* and 23.68, 42.86, 45, 100 for *Escherichia coli*, respectively.

Table 5. Pharmacoeconomic analysis of brands of Doxycycline 100 mg tablets against *Staphylococcus aureus* ATCC29213:

Tested brands					Inhibition zone (mm) of standard	Inhibition zone (mm) of drug	E	CER
Cost		Code	Origin	Batch No.				
Y. R	Dollar $							
450	0.9	A	YEMEN	22885	25	25	100	4.50
2000	4	B	BELGUE	1907E		28	112	17.86
900	1.8	C	JORDAN	X269		26	104	8.65
900	1.8	D	EGYPT	2206137		25	100	9.00
			SD			1.41	5.66	

SD: Standard Deviation, Y.R: Yemeni Rial, E: Effectiveness.

Table 6. Pharmacoeconomic analysis of brands of Doxycycline 100 mg tablets against *Escherichia coli* ATCC25922:

Tested brands					Inhibition zone (mm) of standard	Inhibition zone (mm) of drug	E	CER
Cost		Code	Origin	Batch No.				
Y. R	Dollar $							
450	0.9	A	YEMEN	22885	20	19	95	23.68
2000	4	B	BELGUE	1907E		20	100	100.00
900	1.8	C	JORDAN	X269		21	105	42.86
900	1.8	D	EGYPT	2206137		20	100	45.00
			SD			0.82	4.082	

SD: Standard Deviation, Y.R: Yemeni Rial, E: Effectiveness.

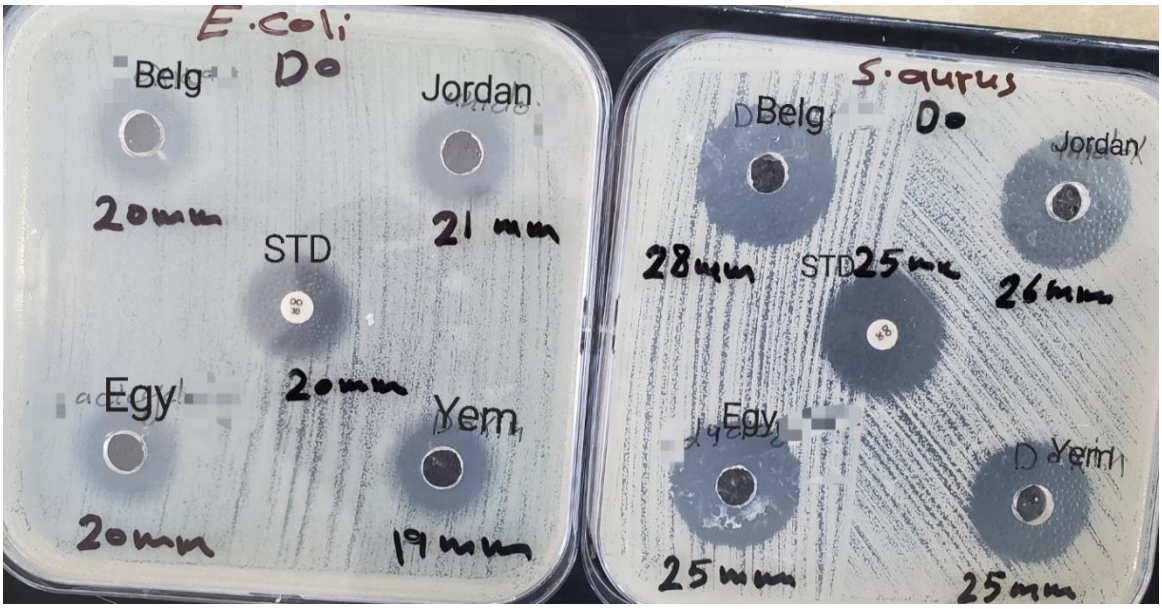

Figure 5: Efficacy of 4 brands of Doxycycline 100 mg tablets against *Staphylococcus aurous* and *Escherichia coli*

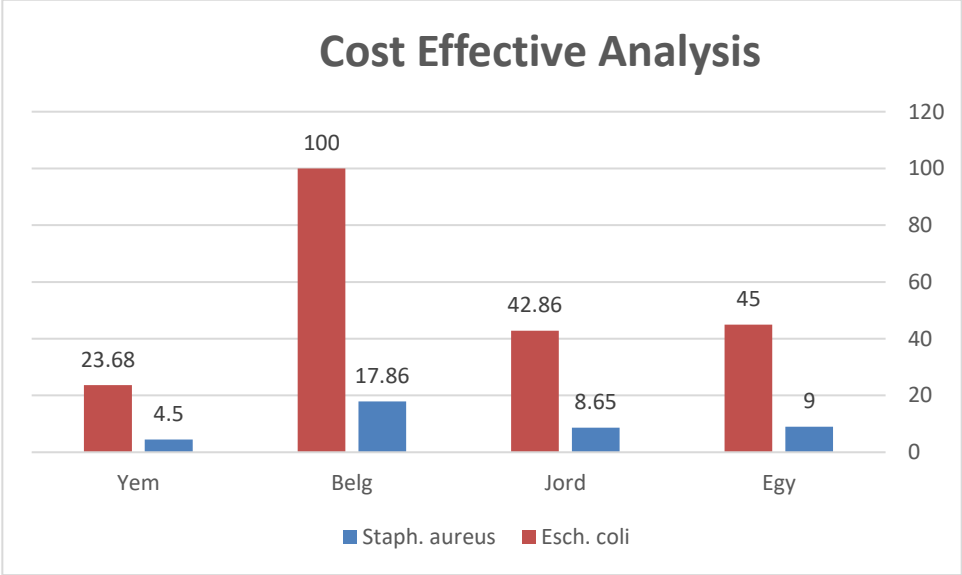

Figure 6: Diagram of pharmacoeconomic analysis of brands of Doxycycline 100 mg tablets against *Staphylococcus aurous* and *Escherichia coli*

Cost-effectiveness analysis of amoxiclav was as showed in tables 7, 8 and figures 7, 8, the A (Yemeni) brand was the best selection with the smaller CER followed by the C (Turkish) brand, follow the D (UAE) brand and the final was the B (Spain) brand, where CERs were 32.11, 34, 44.07, 48.57 for *Staphylococcus aureus* respectively and the four brands have not efficacy on *Escherichia coli*.

Table 7. Pharmacoeconomic analysis of brands of Amoxiclav 1000 mg tablets against *Staphylococcus aureus* ATCC29213:

Tested brands					Inhibition zone (mm) of standard	Inhibition zone (mm) of drug	F	CER
Cost		Code	Origin	Batch No.				
Y. R	Dollar $							
2550	5.1	A	YEMEN	22342	34	27	79.41	32.11
4000	8	B	SPAIN	T003		28	82.35	48.57
2800	5.6	C	TURKY	A22256191		28	82.35	34.00
3500	7	D	UAE	P670		27	79.41	44.07
			SD			0.58	1.98	

SD: Standard Deviation, Y.R: Yemeni Rial, E: Effectiveness.

Table 8. Pharmacoeconomic analysis of brands of Amoxiclav 1000 mg tablets against *Escherichia coli* ATCC25922:

Tested brands					Inhibition zone (mm) of standard	Inhibition zone (mm) of drug	E	CER
Cost		Code	Origin	Batch No.				
Y. R	Dollar $							
2550	5.1	A	YEMEN	22342	20	00	00	00
4000	8	B	SPAIN	T003		00	00	00
2800	5.6	C	TURKY	A22256191		00	00	00
3500	7	D	UAE	P670		00	00	00
			SD			0	0	

SD: Standard Deviation, Y.R: Yemeni Rial, E: Effectiveness.

Figure 7: Efficacy of 4 brands of Amoxiclav 1000 mg tablets against *Staphylococcus aurous* and *Escherichia coli*

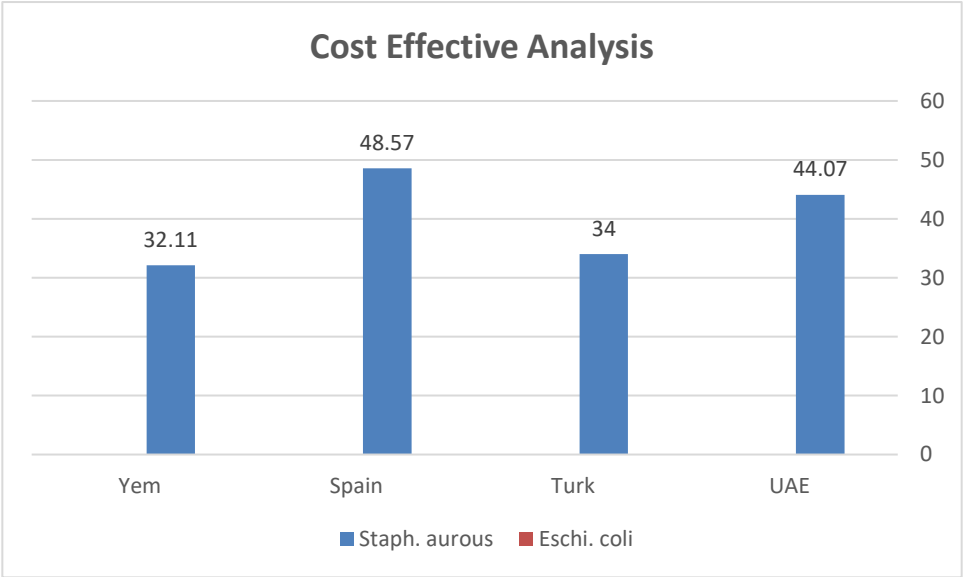

Figure 8: Diagram of pharmacoeconomic analysis of brands of Amoxiclav 1000 mg tablets against *Staphylococcus aurous* and *Escherichia coli*

These results indicate to the best brands to be selected was A (Yemeni) brand in three group (Azithromycin, Doxycycline and Amoxiclav) with 75% then the C (Indian) brand in Ciprofloxacin group with 25%.

Table 9. Results of Statistic analysis of Cost-Effectiveness Analysis of all brands:

Brands	Country	Batch. No	Expire date	Cost in R. Y	Cost in Dollar $	Cost-Effective Ratio	
						Staph. aureus	*E. coli*
Azithromycin 500 mg	Yemen	21357	May-24	1000	2	**10**	**13.333**
	German	26079	Aug-24	4000	8	40	53.333
	India	ETAZ2101	Dec-23	1500	3	15	20
	Egypt	A089807	Oct-23	1200	2.4	12	15
	SD					13.99	55.95
Ciprofloxacin 500 mg	Yemen	57821	Jul-24	700	1.4	8.4	7
	German	24908	Oct-23	3900	7.8	45.29	35.67
	India	ID20786	Feb-25	700	1.4	**8.13**	**6.4**
	Syria	1620	Aug-23	900	1.8	10.45	8
	SD					14.28	18.18
Doxycycline 100 mg	Yemen	22885	Dec-25	450	0.9	**4.5**	**23.68**
	Belgium	1907E	Mar-25	2000	4	17.86	100
	Jordan	X269	Nov-24	900	1.8	8.65	42.86
	Egypt	2206137	Jul-25	900	1.8	9	45
	SD					32.84	5.62
Amoxiclav 1000 mg	Yemen	22342	Aug-24	2550	5.1	**32.11**	**0**
	Spain	T003	Jan-24	4000	8	48.57	0
	Turkey	A22256191	Apr-27	2800	5.6	34	0
	UAE	P670	Nov-23	3500	7	44.07	0
	SD					7.91	0
***p* < 0.05**						**0.03364***	**0.0189#**

SD: Standard Deviation, *ANOVA-single way -test (between cost effective Ratio of four different antimicrobial [Azithromycin, Ciprofloxacin, Doxycycline and Amoxiclav] against *Staphylococcus. aureus* respectively) indicated sig. variation (*p* <0.05), # ANOVA-single way -test (between cost effective Ratio of four different antimicrobial [Azithromycin, Ciprofloxacin, Doxycycline and Amoxiclav] against *Escherichia coli* respectively) indicated sig. variation (*p* <0.05)

Conclusion

Based on results obtained from this study, in the three brands, Azithromycin, Doxycycline and Amoxiclav, the Yemeni brands were having the lowest CER values, so the Yemeni brands were the best economically among other brands (local and foreign). On the other hand, the remaining brand Ciprofloxacin, the Indian brands was having the lowest CER, so the Indian brand of ciprofloxacin was the best economically among other brands (local and foreign). All the amoxiclav brands of different origin were ineffective against *Escherichia coli* in comparing to standard that was effective against *Escherichia coli*, this was one of the drawbacks of this brand.

Authors' Contributions

The reporting author considered the idea, developed the theory, and performed the calculations for the presented work. All authors participated in conducting the experiments, discussing the results, and contributing to the final manuscript.

Declarations

Conflicts of interest: The authors declare that there are no conflicts of interest of publishing this article.

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تحليل فعالية التكلفة لبعض الأصناف التجارية الأجنبية والمحلية للأدوية المضادة للميكروبات في السوق اليمنية

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خلاصة

الخلفية: اقتصاديات الدواء هي تقييم اقتصادي للأدوية حيث يعد التحليل الفعال من حيث التكلفة أحد أهم أنواعها الذي يقارن بين التكاليف والنتائج (الآثار) النسبية لمسارات العمل المختلفة. **الهدف**: هدفت الدراسة إلى تحليل فعالية التكلفة لبعض الأصناف التجارية المحلية والأجنبية المضادة للبكتيريا في السوق اليمنية. **الطريقة**: تم إجراء التحليل الفعال من حيث التكلفة (CEA) لأربعة أنواع مختلفة من مضادات البكتيريا (أزيثروميسين، سيبروفلوكساسين، دوكسيسيكلين وأموكسيكلاف)، وكانت هناك أربع أصناف تجارية من كل نوع كانت من أصل مختلف، تم إجراء هذا التحليل عن طريق اختبار فعاليتها كمضاد للجراثيم لجميع.الأصناف التجارية ضد نوعين من البكتيريا الحساسة (المكورات العنقودية الذهبية والإشريكية القولونية) وتحليل فعالية العلامات التجارية المضادة للبكتيريا مقارنة بتكلفة أو أسعار هذه الأصناف التجارية لحساب نسبة فعالية التكلفة (CER) واختيار الأفضل الذي كان الأقل قيمة. **النتائج**: في الدراسة الحالية، من خلال التحليل الاقتصادي الدوائي، كانت الأصناف التجارية اليمنية هي الأفضل في ثلاثة أنواع (أزيثروميسين، دوكسيسيكلين وأموكسيسيلين/حمض الكلافولانيك "أموكسيكلاف") مع أصغر نسبة لCER والتي كانت 10، 4.5، 32.11 في حالة المكورات العنقودية. aureus و13.33، 0،23.68 في حالة الإشريكية القولونية على التوالي، بينما كان الصنف التجاري الهندي هو الأفضل في نوع واحد (سيبروفلوكساسين) مع أصغر قيمة ل CER حيث بلغت 8.13 في حالة المكورات العنقودية الذهبية و6.4 في حالة الإشريكية القولونية على التوالي. أظهرت أربع أصناف تجارية من نوع الاموكسيكلاف عدم فعاليتها ضد الإشريكية القولونية بالمقارنة مع الدواء القياسي الذي كان فعالا ضد الإشريكية القولونية. **الاستنتاج**: خلصت هذه الدراسة إلى أن أفضل الأصناف التجارية التي تم اختيارها هي الأصناف التجارية اليمنية في ثلاث مضادات للميكروبات (أزيثروميسين، دوكسيسيكلين وأموكسيكلاف) بنسبة 75% والأصناف التجارية الهندية في نوع واحد (سيبروفلوكساسين) بنسبة 25%. جميع ماركات الأموكسيكلاف من مختلف البلدان كانت غير فعالة ضد الإشريكية القولونية.