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Approvals and Prices of Systemic Antibiotics in Saudi Arabia and the United States

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ABSTRACT

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by Saad Alharthi

Introduction

Antibiotics is one of the therapeutic classes with the highest level of consumption in the world. Despite the global diffusion of antibiotics, their availability and prices vary by country. This study assessed differences in the availability and prices of systemic antibiotics marketed in the United States (US) and Saudi Arabia and evaluated the factors associated with the differences in prices of systemic antibiotics marketed in both countries.

Material and Methods

We collected regulatory data from the US Food and Drug Administration (FDA) and the Saudi Food and Drug Authority (SFDA), the National Average Drug Acquisition Cost (NADAC) and the average sales price (ASP) data from the Center for Medicare and Medicaid Services (CMS), and Saudi prices from the SFDA website. We concerted Saudi rials to dollars and current dollars to purchasing power parity dollars (PPS$). We conducted descriptive statistics and linear mixed-effects regression analysis using Rstudio.

Results

As of January 2022, 125 active systemic antibiotics were marketed in the United States and 68 in Saudi Arabia. The median $PPP Saudi/US price was higher for oral capsules and tablets (56.4%, n=71) than for oral suspension and syrup forms (33.2%, n=24). However, the

median $PPP Saudi/US price of injectable forms was similar in Saudi Arabia and the US (94.9%, n=28).

Strength (χ^2 =29.19, $p<0.05$), pharmaceutical form (χ^2=36.76,$p<0.05$), and country of incorporation of the marketing company (χ^2=36.58,$p<0.01$) were significantly associated with higher median $PPP Saudi/US prices.

Conclusions

Half of the systemic antibiotics marketed in the US were also available in Saudi Arabia. The PPP prices of antibiotics were lower in Saudi Arabia than in the US, except for injectable drugs. PPP price differences between Saudi Arabia and the US varied according to the drug form and strength and the country of incorporation of the marketing company.

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LIST OF ABBREVIATIONS

AMR	Antimicrobial Resistance
ASP	Average Sales Price
ATC	Anatomical Therapeutic Chemical
AWP	Average Wholesale Price
EMA	European Medicines Agency
EML	Essential Medicines List
FDA	Food and Drug Administration
HCPCS	Health Common Procedure Coding System
MMA	Medicare Prescription Drug, Improvement, and Modernization Act
NADAC	National Average Drug Acquisition Cost
PMB	Pharmacy Benefit Manager
SFDA	Saudi Food and Drug Authority
USD	United States Dollars
WAC	Wholesale Acquisition Cost
WHO	World Health Organization

1 Introduction

Antibiotics are essential drugs used to treat and prevent infectious diseases and are one of the therapeutic classes with the highest consumption globally (WHO 2019). The use of antibiotics is increasing, especially in low and middle-income countries (WHO 2019).

The increase in antibiotic utilization has resulted in the inappropriate use of antibiotics and the development of antibiotic-resistant bacteria, a phenomenon that exposes humans to untreatable strains of bacterial infections (Gould 2009) (Marquet 2015). As drug-resistant bacteria spreads, declining effectiveness shapes new antibiotics' development, demand, and pricing (Gould 2009). A recent systematic review revealed that high utilization of antibiotics is associated with a significant increase in antibiotic resistance, with long-term consequences for patients and health care systems (Rambliere 2021). As antimicrobial resistance affects the performance of first-line antibiotics, the cost of second and third-line products has increased, often leading to cost barriers for these essential drugs (Cars 2011) (Moore 2019). Consequentially, the cost of healthcare due to resistance to antibiotics is growing as the duration and severity of infectious diseases are increasing (WHO, World Health Assembly addresses antimicrobial resistance, immunization gaps and malnutrition 2015). The availability and affordability of systemic antibiotics are critical to ensuring patients' access to essential antimicrobial treatments.

The pharmaceutical industry is a globalized and complex market with a variety of national and international policies regarding drug approval, production, sales, and marketing (Miller 2006). Differences in drug pricing policies in the US, Canada, and Mexico systematically affect drug availability and costs in North America and its trade partners (Danzon 2004).

Country-specific regulations and policies also affect drug availability and affordability (Olson 2018). Differences in regulations and policies also directly affect the legal, illegal, and grey-market distribution of drugs (Hemphill 2019).

The US Food and Drug Administration's (FDA) primary responsibility is to protect and promote public health by supervising food safety, tobacco products, dietary supplements, prescription, and over-the-counter medications, vaccines, and biopharmaceuticals. The Center for Drug Evaluation and Research regulates new drugs and therapeutic biologics (FDA 2022). The Centers for Medicare and Medicaid Services (CMS) administer Medicare, Medicaid, and the Children's Health Insurance Program. Medicare covers drugs through Parts A (hospitals), B (physician offices), and D (outpatient pharmacy). Medicare Part D was established by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.

Drug prices paid by the private sector are not regulated by the US federal government. Price benchmarks such as the average wholesale price or the wholesale acquisition cost are used as the basis for determining drug reimbursement. Benchmark prices represent prices paid by different parties at various stages of the drug manufacturing, acquisition, and dispensing processes. Since price benchmarks are closely related, the prices paid throughout the drug distribution process affect the final price paid by public and private programs (Rachel 2020).

The Saudi Food & Drug Authority (SFDA) was established with the primary purpose of regulating, overseeing, and monitoring food, drugs, and medical devices and setting mandatory standards and specifications for those products (Alrasheedy 2020).

The SFDA determines the price of drugs according to their therapeutic value; the prices of similar drugs already registered in Saudi Arabia; a pharmacoeconomic evaluation of the

drug; the ex-factory, wholesale, and retail prices in the country of origin; drug cost; insurance; prices for all countries in which the product is marketed; the official reference price; and the price suggested by the company for Saudi Arabia.

In addition, the price of a brand medicine is reduced by 20% upon registration of the first generic product. The first generic drug must be priced at least 35% lower than the original brand drug, the second generic must be 10% lower than the first generic, and the third generic must be 10% lower than the second. After the fourth generic drug, the price is fixed without further reductions (Alrasheedy 2020).

2 Objectives and Hypothesis

2.1 Objectives

This study assessed the availability and prices of systemic antibiotics marketed in Saudi Arabia and the United States and evaluated the factors associated with the differences in prices of systemic antibiotics marketed in both countries.

2.2 Hypothesis

We hypothesize that the antibiotic prices are similar in Saudi Arabia and the US.

3 Material and Methods

3.1 Data Sources

We collected the National Average Drug Acquisition Cost (NADAC) and the average sales price (ASP) from the Centers for Medicare and Medicaid Services (CMS). The NADAC is the average price paid by community pharmacies for drugs reimbursed by the Medicaid program. NADAC data includes the National drug code (NDC), the NDC description, effective date, and pharmacy acquisition cost per unit. The NADAC does not account for the pharmacy dispensing fee or rebates and discounts provided by the pharmaceutical companies to pharmacies, PMBs and other managed care organizations, insurers, and payers. The ASP represents the average manufacturer transaction cost calculated by weighing all non-federal sales to wholesalers and pharmacies, net of chargebacks, discounts, rebates, and other credits linked to drug purchases (Mullins 2010). We collected the ASP for systemic antibiotics used in outpatient clinics and physician offices reimbursed by Medicare Part B from the CMS. The ASP includes the HCPCS Code and dosage unit, a short description, and the payment limit. The ASP prices are increased by 6% for reimbursement of physician-administered drugs (Law 2003).

We collected Saudi drug prices from the Saudi Food and Drug Authority (SFDA). Saudi healthcare services and drugs are offered free of charge via public hospitals and clinics (Al-Aqeel 2012) (Bawazir 2019). The drug prices published by the SFDA are the final prices for drugs sold in community pharmacies and include the distribution cost and the pharmacy dispensing fee. The SFDA price list contains the active ingredient, dosage form, strength unit, and drug cost.

We classified the systemic antibiotics according to World Health Organization Anatomical Therapeutic (ATC) Classification System (WHO 2022). We compared systemic antibiotics with the same active ingredients, route of administration, dosage form, and strength in Saudi Arabia and the US.

We converted Saudi prices to US dollars using the rate of 3.75 Saudi Riyals to $1.00 as reported by the Saudi Central Bank on January 5, 2022. We also converted the Saudi drug prices to purchasing power parity dollars (PPP$) (World Bank 2022). The PPP is the currency conversion rate that equalizes the purchasing power of different currencies by eliminating the differences in price levels between countries.

Typically, outpatient pharmacies sell the drugs by the unit in the US and by the package in Saudi Arabia. As the package sold in Saudi Arabia represents the typical course of therapy, we converted units to packages to compare both countries' prices. As Saudi prices include the dispensing fee, we added to the NADAC the national estimated dispensing fee ($12.40) paid to community pharmacies in the US (Cost of Dispensing Study 2020). We used the median price when CMS or the SFDA reported several prices for the same active ingredient, route, form, and strength. When several strengths were available for a drug, we indexed the strengths by dividing each by the lowest available strength.

3.2 Data Analysis

We measure the median purchasing power parity of SFDA prices as a percentage of NADAC or ASP and use a linear mixed-effect regression model to evaluate the factors associated with differences in antibiotic prices in Saudi Arabia and the US. The independent variables evaluated in the regression model included the pharmaceutical form (injection, oral

capsule and tablet, or oral suspension and syrup), strength, company country of incorporation for Saudi Arabia antibiotics (local, Middle East, European Union, or other countries), marketed date, therapeutic class (tetracyclines, macrolides, fluoroquinolones, penicillins with extended-spectrum, cephalosporins, and other antibiotics), and combination or single active ingredient.

The linear mixed-effects model derives its estimates from the expectation (mean) rather than the medians. The linear mixed effect was used as a random effect to account for multiple measurements per active ingredient.

Multicollinearity diagnostics were carried out by analyzing variance inflation factors, which reflected the degree of linear dependency between each regressor and all other regressors. We used post hoc analysis of the difference between the significant levels of the categorical variables using the estimated margin means with p-value computed using the Kenward-Roger method for calculating the degree of freedom and Tukey adjustment for multiple comparisons. We used R studio for the analysis.

4 Results

4.1. Descriptive Analysis

The WHO ATC system listed 231 systemic antibiotics, of which 125 were marketed in the US and 68 in Saudi Arabia as of January 5, 2022. The NADAC and ASP databases included 1,299 and the SFDA 788 single active ingredient or fixed-dose combinations antibiotics. There were 276 antibiotics listed by the SFDA without a comparable salt, fixed-dose combination, dosage form, or strength listed in the NADAC or the ASP databases. There were 71 oral capsules and tablets, 28 injection forms, and 24 suspension and syrup forms marketed in both countries.

The antibiotics available in Saudi Arabia were marketed by Saudi and Middle Eastern companies (n=514, 65%), European companies (n=232, 29%), US companies (n=22, 2.7%), and companies from other countries (n=19, 2.4%).

Table 1. Prices of Systemic Antibiotics in Saudi Arabia and the US.
SFDA Prices as a percentage of NADAC or ASP Prices as of January 5, 2022 ($PPP)

Variable		Mean	Standard Deviation	95% Confidence Interval		Median	Inter-quartile Range
				Lower	Upper		
Form	Injection	108.1%	56.1%	86.3%	129.8%	94.9%	70.7%
	Capsule, Tablet	80.3%	111.2%	54.0%	106.6%	56.4%	60.6%
	Suspension, Syrup	40.8%	25.2%	30.2%	51.5%	33.2%	39.8%
Company Country of Incorporation	Middle East	56.9%	40.3%	44.9%	68.9%	43.8%	63.8%
	Saudi Arabia	88.8%	49.5%	73.2%	104.4%	83.7%	69.1%
	European Union	73.9%	51.9%	54.5%	93.4%	68.7%	44.3%
	Other Countries	204.9%	361.2%	-174.2%	584.0%	74.8%	283.5%
Therapeutic Class	Tetracyclines	56.9%	27.0%	23.4%	90.5%	67.7%	44.8%
	Penicillins with extended spectrum	56.2%	39.6%	41.6%	70.7%	45.9%	38.1%
	Cephalosporins	74.0%	36.4%	61.3%	86.7%	72.5%	61.7%
	Macrolides	42.8%	30.0%	23.8%	61.9%	45.0%	47.9%
	Fluoroquinolones	94.9%	49.9%	74.3%	115.5%	97.1%	82.2%
	Other	142.4%	224.3%	22.8%	261.9%	77.2%	136.4%
Strength		1.74	1.41	1.49	2.00	1.00	1.00
Combination	Yes	63.0%	46.8%	38.1%	88.0%	52.6%	45.2%
	No	81.3%	96.5%	62.8%	99.8%	68.8%	70.7%

The median $PPP Saudi/US price was higher for oral capsules and tablets (56.4%, n=71) than for oral suspension and syrup forms (33.2%, n=24). However, the median $PPP Saudi/US price of injections was similar in Saudi Arabia and the US (94.9%, n=28) (Table 1).

The median $PPP Saudi/US price was higher for antibiotics marketed by Saudi Arabia companies (83.7%, n=48) than by companies from the US and other countries (74.8%, n=6), the Middle Eastern (43.8%, n=46), and the European Union (68.7%, n=30).

The median $PPP Saudi/US price was the lowest for the ATC pharmacological group macrolides (median 45.0%, n=12), followed by penicillins with extended spectrum (45.9%, n=31), tetracyclines (67.7%, n=5), and cephalosporins (72.5%, n=34). The median $PPP Saudi/US price different for fluoroquinolones (97.1%, n=33) and other antibiotic (77.2%, n=16) was lower in the Saudi Arabia than in US.

The median $PPP Saudi/US price was higher for single active ingredients (68.8%, n=107) than fixed-dose combination drugs (52.6%, n=16).

4.2. Linear Mixed-Effect Regression

The results of the linear mixed-effects regression model showed that strength, company country of incorporation for Saudi Arabian antibiotics, and pharmaceutical form were significantly associated with the price difference between Saudi Arabia and the US. The summary of scaled residuals shows that the data are within a reasonable range (Table 2), and the residual maximum likelihood criterion at convergence was 98.7, confirming the model's accuracy. And the variance of the active ingredient effect was 0.10919. The model results indicate that the random effects accounted for 60% of the effects not considered in the fixed effects. We calculated the variance of the random effect by dividing it by the sum of the random effects and the variance of the residual component: 0.109/(0.065+0.109)=0.626. These results confirm that each effect of the active ingredients should be included in the model (Table 3).

Table 2. Linear Mixed Model Regression Summary of Scaled Residuals

Min	1Q	Median	3Q	Max
-3.2603	-0.4851	-0.0083	0.4985	2.7089

Table 3. Linear Mixed Model Regression Summary of Random Effects

Groups Name	Variance	Standard Deviation
Active Ingredient (Intercept)	0.10919	0.3304
Residual	0.06537	0.2557
Observations= 122. Active Ingredient Groups= 32		

The generalized variance inflation factors (both corrected and uncorrected for the number of degrees of freedom) were <2 and did not exceed the commonly used thresholds of <5 or <10 (Table 3). Accordingly, standard errors were not seriously affected by the linear dependence among regressors. Multicollinearity diagnostics indicated the lack of association of the independent variables (Table 4)

Table 4. Multicollinearity Diagnostics

Factors	GVIF	Degree of freedom	GVIF^(1/(2*Df))
Strength	1.749	1	1.323
Combination	1.403	1	1.184
CountryCompany	1.291	3	1.043
Market Year	1.346	1	1.160
Therapeutic Class	1.283	5	1.025
PharmaceuticalForm	1.641	2	1.132

The results of the linear mixed-effects regression model indicate that strength, company country of incorporation for Saudi Arabian antibiotics, and pharmaceutical form were significant predictors of the $PPP Saudi/US price ($p < 0.01$) (Table 5).

Table 5. Analysis of Deviance Table (Type II Wald Chi-Square Tests).
$PPP SFDA Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Response: Proportion	Chi Square	Degree of freedom	Pr (>Chi Square)
Strength	29.1970	1	>0.0001
Combination	0.2566	1	0.6125
Company's Country	36.7614	3	>0.0001
Market Year	2.8005	1	0.0942
Therapeutic Class	6.6724	5	0.2462
Pharmaceutical Form	36.5819	2	>0.0001

The fixed effects shows that the $PPP Saudi/US price was significantly and positively associated with the strength (0.1504615) (Table 6). The $PPP Saudi/US price proportion was significantly higher for injection than tablet and capsule forms. The $PPP Saudi/US price proportion was higher for Saudi Arabian than European Union companies.

Table 6. Linear Mixed Model Regression Summary of Fixed Effects

Fixed effects:	Estimate	Std. Error	t.value	p-value
(Intercept)	-13.7532	8.3431128	-1.648	0.102
Strength	0.15046	0.0278456	5.403	<0.0001
Combination	-0.05561	0.1097943	-0.507	0.61
Company's Country: Middle East	-0.00014	0.0707282	-0.002	0.987
Company's Country: Others	-0.25034	0.1448452	-1.728	0.087
Company's Country: Saudi Arabia	0.29920	0.0737581	4.057	<0.0001
Market Year	0.00695	0.0041571	1.673	0.097
Therapeutic Class: Fluoroquinolones	0.27844	0.2298355	1.212	0.245
Therapeutic Class: Macrolides	-0.08797	0.2197932	-0.400	0.695
Therapeutic Class: Other antibacterial	0.16722	0.1799252	0.929	0.367
Therapeutic Class: Penicillins with ER.	-0.33202	0.2197796	-1.511	0.145
Therapeutic Class: Tetracyclines	0.15351	0.2973453	0.516	0.61
Pharmaceutical Form: Injection	0.62694	0.1054440	5.946	<0.0001
Pharmaceutical Form: Syrup, Suspension	0.00238	0.0893790	0.027	0.975

The company's country marginal mean of $PPP Saudi/US price proportion was higher for Saudi Arabian companies (average 0.97) than companies from the EU and the Middle East (0.67) or other countries (0.42) (Table 6).

Table 7. Means (Company's Country)
SFDA PPP Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Company's Country	Mean	SE	df	Lower.CL	Upper.CL
EU	0.679	0.0985	54.8	0.482	0.877
Middle East	0.679	0.0960	48.6	0.486	0.872
Others	0.429	0.1577	104.0	0.116	0.741
Saudi Arabia	0.978	0.1018	57.3	0.775	1.182

Saudi Arabian companies had a significantly higher $PPP Saudi/US price proportion in pairwise comparisons of marginal means than companies from the European Union and the Middle East (-0.30) and with other countries at (-0.55) ($p < 0.01$) (Table 7).

Table 8. Contrast (Company's Country)
SFDA PPP Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Contrast	Estimate	SE	df	t.ratio	p.value
EU - Middle East	0.00014	0.0710	90.1	0.002	1.0000
EU – Others	0.25035	0.1457	94.8	1.718	0.3201
EU - Saudi Arabia	-0.29921	0.0741	92.2	-4.035	0.0006
Middle East – Others	0.25021	0.1409	95.2	1.776	0.2913
Middle East - Saudi Arabia	-0.29935	0.0593	87.8	-5.048	<.0001
Others - Saudi Arabia	-0.54956	0.1412	95.7	-3.893	0.0010

Injections (1.12) had a higher marginal mean of $PPP Saudi/US price proportion than capsules and tablets (0.48) and syrup and suspensions (0.48) (Table 9).

Table 9. Means (Pharmaceutical Form)
SFDA PPP Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Pharmaceutical Form	Mean	SE	df	Lower.CL	Upper.CL
Capsule, Tablet	0.482	0.0961	46.7	0.288	0.675
Injection	1.109	0.1209	59.0	0.867	1.350
Syrup, Suspension	0.484	0.1212	77.8	0.243	0.725

Injections have a significant $PPP Saudi/US price proportion contrast (-0.63) than capsules and tablet (-0.002) and syrup and suspension (0.63) ($p<0.001$) (Table 9).

Table 10. Contrast (Pharmaceutical Form)
SFDA PPP Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Contrast	Estimate	SE	df	t-ratio	p-value
Capsule, Tablet – Injection	-0.62695	0.1079	96.2	-5.811	<.0001
Capsule, Tablet – Syrup, Suspension	-0.00238	0.0902	98.1	-0.026	0.9996
Injection – Syrup, Suspension	0.62456	0.1275	102.4	4.900	<.0001

The visualization summary for the estimated marginal means and confidence interval of the company's country of incorporation showed a significant difference between Saudi Arabian and companies from other countries (Figure 1) and among pharmaceutical forms (Figure 2).

Figure 1. Estimated Marginal Means by Company Country of Incorporation

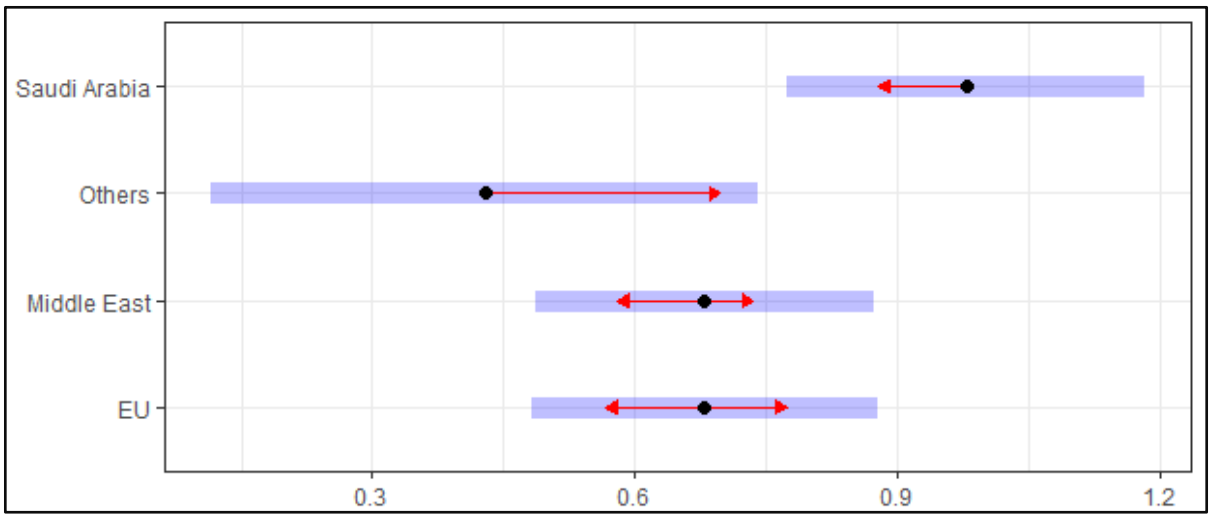
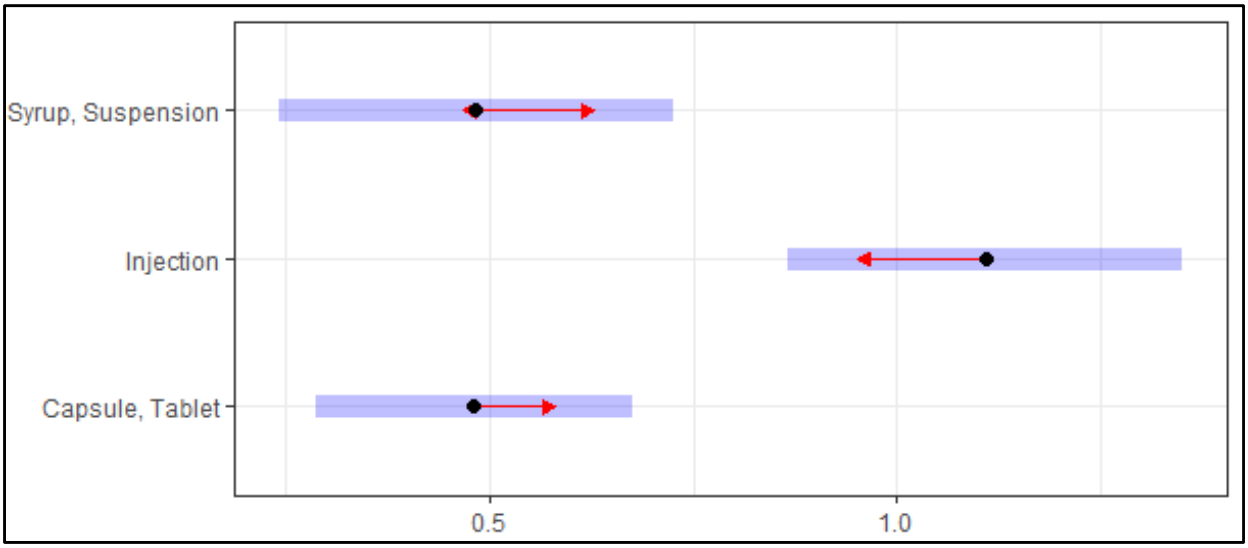


Figure 2. Estimated Marginal Means by Pharmaceutical Form



5 Discussion

This study found that antibiotics prices were higher in the US than in Saudi Arabia. However, we can reject our hypothesis that prices were similar except for injectable drugs. The price differences between the two countries varied depending on the route of administration, strength, and country of incorporation of the sponsor company.

Our study found that the prices of injectable systemic antibiotics were similar in both countries. Injectables are more challenging to manufacture and have lower competition than oral formulations. Thus, the relatively high price of injectable drugs in Saudi Arabia may be related to less competition than in the United States. Additionally, the smaller size of the Saudi pharmaceutical market may limit the potential for companies to achieve significant economies of scale associated with drug production. Similar arguments could explain why the prices in Saudi Arabia increase with the antibiotic strengths.

There are significant differences in socio-economic characteristics between Saudi Arabia and the US. The healthcare systems of both countries also have substantial differences. The US has the world's largest economy, health care system, and pharmaceutical sector.

Additionally, there are differences in price regulation. Saudi Arabia regulates the prices of the drugs marketed in the country. The United States does not regulate prices in the private sector. The relatively small market size may result in less competition and higher manufacturing costs in Saudi Arabia than in the United States. Additionally, Saudi Arabia has less stringent drug import regulation than the US, which could result in more competition and lower prices for some drugs, especially, solid oral formulations

We use the analysis's purchasing power parity (PPP) to account for the differences in price levels from one country to another. The differences in prices between Saudi Arabia and the US are lower using the PPP than current dollars.

In general, international differences in drug prices are amplified by the participation in the pharmaceutical market of multiple distributors (Starc 2021). Without legal requirements to disclose the drug prices and profits, payers pay high prices based on each country's market characteristics and regulation (Starc 2021). In healthcare systems where the market power is concentrated in a single-payer, a combination of regulations and negotiations results in lower prices than in countries with many payers (Himmelstein 2020) (Hay 2010). This distinction is important when comparing nations with multi-payer, private healthcare systems like the US and single-payer healthcare systems like Saudi Arabia.

Pharmaceutical companies use discriminatory pricing to adapt their pricing structure of each country to the socio-economic characteristics of the population and their access to healthcare insurance, subsidies, and discounts (Lichtenberg 2010). Additionally, drug prices are regulated in Saudi Arabia, while pharmaceutical companies may extend discounts to large private health care systems in the US while increasing the prices charged to patients paying out-of-pocket or with limited insurance coverage (Lichtenberg 2010). Additionally, policymakers consider the price of drugs should vary by country, with the lowest prices being offered to countries with the lowest income (Judith 2004).

International price differences can also be related to differences in the drug distribution systems of different countries. Approximately 25% of prescription drug payments in the United

States go to wholesalers and retail pharmacies and 75% manufacturers (CBO 2022). Similar information is not available in Saudi Arabia.

6 Limitations

This is a cross-sectional study and did not evaluate price trends. Some antibiotics marketed in Saudi Arabia and the US had different dosages, drug names, and pharmaceutical salts. We only compared the price of pharmaceutical equivalent antibiotics in Saudi Arabia and the US. We excluded non-systemic antibiotics, so the analysis cannot be generalized to all antibiotics or other therapeutic classes.

The list prices also do not reflect discounts for volume purchases. In the US, pharmacy benefit managers (PBMs) assist health plans by processing payments for prescription drugs on behalf of their clients. In exchange for leading their health plans' patients and physicians to specific drugs, PBMs receive rebates. However, PBMs do not disclose the effective price paid by final purchasers, where they negotiate discounts with pharmacies and rebates with manufacturers (Frank 2001).

The NADAC is a publicly available price commonly used for price reimbursement in the US (Law 2003). The NADAC does not represent the final price for payers because it excludes certain rebates and discounts that pharmaceutical companies provide to pharmacies, PBMs and other managed care organizations, insurers, and payers.

7 Conclusions

Half of the antibiotics marketed in the US were available in Saudi Arabia. The PPP prices of antibiotics were lower in Saudi Arabia than in the US. PPP differences between Saudi Arabia and the US varied according to the drug form and strength and the country of incorporation of the marketing company. Saudi PPP prices were lower for oral solid and liquid forms and similar for injectable forms compared to the United States. PPP Prices were also higher for antibiotics marketed by Saudi companies than companies from other countries.

8 References

Al-Aqeel, S. (2012). State of Health Economic Evaluation Research in Saudi Arabia: A Review. *ClinicoEconomic Outcomes Research, 4*, 177-184.

Alrasheedy, A. A. (2020). Pharmaceutical Pricing Policy in Saudi Arabia: Findings and Implications. *Generics and Biosimilars Initiative Journal, 9*(1), 14-21.

Audrey, L. E. (2014). Solid Oral Forms Availability in Children: a Cost Saving Investigation. *British Journal of Clinical Pharmacology, 78*(5), 1080-1089.

Bawazir, A. A.-S.-S. (2019). Prevention and Control of Non-Communicable Diseases in Saudi Arabia. *Saudi Medical Journal, 40*(6), 614-618.

Cars, O. H. (2011). The Global Need for Effective Antibiotics—Moving Towards Concerted Action. *Drug Resistance Updates, 4*(12), 68-69.

CBO. (2022). *Prescription Drugs: Spending, Use, and Prices.* US Congress: Congressional Budget Office. Retrieved from http://www.nacds.org/wmspage.cfm?parm1=507

CMS. (2022, February 25). *Services, Center of Medicaid and Medicare*. Retrieved from https://www.cms.gov

Danzon, P. F. (2004). Price and Availability of Pharmaceuticals: Evidence from Nine Countries. *Health Affairs*, 521-536.

FDA. (2022, March 14). *United States Food and Drug Administration*. Retrieved from https://www.fda.gov/

Frank, R. G. (2001). Prescription Drug Prices: Why Do Some Pay More Than Others Do. *Health Affairs, 20*(2), 115–28.

Gould, I. (2009). Antibiotic Resistance: The Perfect Storm. *International Journal of Antimicrobial Agents*, 2-5.

Hay, J. S. (2010). Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analyses: Issue and Recommendations. *The ISPOR Drug Cost Task Force Report—Part I, 13*(1), 3-7.

Hemphill, T. (2019). Generic Drug Competition: The Pharmaceutical Industry "Gaming" Controversy. *Business and Society Review, 124*, 467-477.

Himmelstein, D. W. (2020). Single-Payer Reform: Heed the Evidence Not the Soothsayers. *AJPH, 110*(4), 447-448.

Judith L. Wagner, E. M. (2004). International Difference in Drug Prices. *Institute of Medicine, Washington, 25*, 475–95.

Law, P. (2003). Medicare Prescription Drug, Improvement, and Modernization Act. Social Security.

Lichtenberg, F. (2010). Pharmaceutical Price Discrimination and Social Welfare. *Capitalism and Society, 5*(1), 1-32.

Marquet, K. L. (2015). Incidence and Outcome of Inappropriate in-Hospital Empiric Antibiotics for Severe Infection: A Systematic Review and Meta-Analysis. *Critical Care, 19*(1), 63-65.

Miller, W. R. (2006). Evaluing Health for Regulatory Cost-Effectiveness Analysis. *National Academies Press*, 15-40.

Moore, C. (2019). Changes in Antibiotic Resistance in Animals Science. *Science*, 1251 - 1252.

Mullins, C. S.-V. (2010). Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analyses: Medicare, Medicaid and Other US Government Payers Perspectives. *ISPOR Drug Cost Task Force Report—Part IV., 13*(1), 18-24.

Olson, L. W. (2018). Estimating the Causal Effect of Entry on Generic Drug Prices Using Hatch–Waxman Exclusivity. *The Industrial Organization Society, 53*(1), 139-172.

Rachel, D. M. (2020). *Issue Brief Pricing and Payment for Medicaid Prescription Drugs.* San Francisco: Kaiser Family Foundation.

Rambliere, L. G.-A. (2021). Impact of mass and Systematic Antibiotic Administration on Antibiotic Resistance in Low and Middle-Income Countries: A Systematic Review. *International Journal of Antimicrobial*, 106364.

Starc, A. S. (2021). Preferred Pharmacy Networks and Drug Costs. *American Economic Journal: Economic Policy, 13*(3), 406-446.

WHO. (2015, May 25). *World Health Assembly addresses antimicrobial resistance, immunization gaps and malnutrition*. Retrieved from https://apps.who.int/mediacentre/news/releases/2015/wha-25-may-2015/en/index.html

WHO. (2019, July 22). *WHO Report on Surveillance of Antibiotic Consumption: 2016-2018, Early Implementation*. Retrieved 2022, from WHO: https://www.who.int/publications/i/item/who-report-on-surveillance-of-antibiotic-consumption

WHO. (2022, February 1). *WHO Anatomical Therapeutic Code*. Retrieved from https://www.who.int/tools/atc-ddd-toolkit/atc-classification

World Bank. PPP conversion factor, G. (2022, February 1). *World Bank*. Retrieved 2022, from https://data.worldbank.org/indicator/PA.NUS.PPP

Appendix. Results of the Regression Analysis Using Current Prices

Table 1a. Linear Mixed Model Regression Summary of Scaled Residuals for Current Saudi Prices

Min	1Q	Median	3Q	Max
-2.5136	-0.5597	-0.0066	0.4464	2.1697

Table 2a. Linear Mixed Model Regression Summary of Random Effects for Current Saudi Prices

Groups Name	Variance	Standard Deviation
ActiveIngredient (Intercept)	0.04110	0.2027
Residual	0.03254	0.1804
Number of observations: 122, groups: Active Ingredient, 32		

Table 3a. Multicollinearity diagnostics for Current Saudi Prices

Factors	GVIF	Df	GVIF^(1/(2*Df))
Strength	1.727066	1	1.314179
Combination	1.401329	1	1.183778
CountryCompany	1.298450	3	1.044490
MarketYear	1.347734	1	1.160920
TherapeuticClass	1.339442	5	1.029657
PharmaceuticalForm	1.645351	2	1.132569

Table 4a. Analysis of Deviance Table (Type II Wald Chi Square Tests).
Current SFDA Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Response: Proportion	Chi Square	Degree of freedom	Pr (>Chi Square)
Strength	16.1167	1	0.000059556
Combination	0.2114	1	0.6457
Company's Country	28.5065	3	0.000002843
Market Year	3.5345	1	0.0601
Therapeutic Class	6.8162	5	0.2347
Pharmaceutical Form	23.6668	2	0.000007258

Table 5a. Linear Mixed Model Regression Summary of Fixed Effects

Fixed effects:	Estimate	Std. Error	t.value
(Intercept)	-10.708463	5.778014878	-1.853
Strength	0.078041	0.019439556	4.015
Combination	-0.035067	0.076263818	-0.460
Company's Country: Middle East	-0.007122	0.049635426	-0.143
Company's Country: Others	-0.053020	0.101310296	-0.523
Company's Country: Saudi Arabia	0.194909	0.051680513	3.771
Market Year	0.005412	0.002878899	1.880
Therapeutic Class: Fluoroquinolones	0.174072	0.143642432	1.212
Therapeutic Class: Macrolides	-0.057642	0.139200952	-0.414
Therapeutic Class: Other antibacterial	0.072762	0.114824268	0.634
Therapeutic Class: Penicillins with ER.	-0.241711	0.139335858	-1.735
Therapeutic Class: Tetracyclines	0.066791	0.189367381	0.353
Pharmaceutical Form: Injection	0.339662	0.071254130	4.767
Pharmaceutical Form: Syrup, Suspension	0.000006	0.062316085	0.000

Table 6a. Means (Company's Country)

SFDA Current Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Company's Country	Mean	SE	df	Lower.CL	Upper.CL
EU	0.385	0.0650	60.0	0.255	0.515
Middle East	0.378	0.0630	52.1	0.251	0.504
Others	0.332	0.1078	105.7	0.118	0.545
Saudi Arabia	0.580	0.0673	61.8	0.445	0.714

Table 7a. Contrast (Company's Country)

SFDA Current Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Contrast	Estimate	SE	df	t.ratio	p.value
EU - Middle East	0.00712	0.0499	91.6	0.143	0.9990
EU – Others	0.05302	0.1020	96.3	0.520	0.9541
EU - Saudi Arabia	-0.19491	0.0520	94.0	-3.749	0.0017
Middle East – Others	0.04590	0.0986	96.7	0.466	0.9664
Middle East - Saudi Arabia	-0.20203	0.0417	89.0	-4.844	<.0001
Others - Saudi Arabia	-0.24793	0.0987	97.1	-2.512	0.0643

Table 8a. Means (Pharmaceutical Form)

SFDA Current Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Pharmaceutical Form	Mean	SE	df	Lower.CL	Upper.CL
Capsule, Tablet	0.305	0.0630	49.2	0.179	0.432
Injection	0.645	0.0799	58.8	0.485	0.805
Syrup, Suspension	0.305	0.0813	81.2	0.143	0.467

Table 9a. Contrast (Pharmaceutical Form)

SFDA Current Prices as a percentage of NADAC or ASP Prices as of January 5, 2022

Contrast	estimate	SE	df	t.ratio	p.value
Capsule, Tablet – Injection	-0.3396627	0.0729	89.3	-4.656	<.0001
Capsule, Tablet - Syrup, Suspension	-0.0000061	0.0630	101.0	0.000	1.0000
Injection - Syrup, Suspension	0.3396566	0.0867	97.2	3.918	0.0005