

# Community Pharmacists' Views of the Enforced Antibiotics Dispensing Law and Its Impact on Oral Antibiotics Sales in Saudi Arabia

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**Objective(s):** The aim of this study was to explore community pharmacists' views toward the antibiotics dispensing law that was enforced in May 2018 and bans the sale of antibiotics without a prescription in community pharmacy settings in Saudi Arabia. Moreover, the potential impact of the law enforcement on the sales of oral antibiotics in Saudi Arabia was also explored.

**Methods:** A questionnaire-based cross-sectional study was conducted between September 2019 and March 2020 in Riyadh, Saudi Arabia. A multistage sampling technique was used to recruit community pharmacists from different districts. Pharmacists who consented to participate and reported practicing prior to the law enforcement were interviewed about their views of the law using a 14-item newly developed questionnaire. The annual sales of oral antibiotics for the years of 2017, 2018, and 2019 were retrieved from the Saudi Food and Drug Authority (SFDA) database.

**Results:** Two hundred and eighty six pharmacists consented to participate and met the inclusion criteria. After the law enforcement, approximately 51% of the participants reported that the percentage of patients seeking antibiotics without a prescription is less than 25%. Moreover, the majority (87.41%) reported a drop in the sales of antibiotics. Additionally, about 90% of the participants believed that the rate of inappropriate use of antibiotics will decrease as a result of the law enforcement. About 41% of the participants reported that the law has negatively impacted their pharmacies' profits. The sales of oral antibiotics have seen a 16.6% drop in the year of 2019 as compared to 2017.

**Conclusion:** The antibiotics dispensing law is favorably perceived among community pharmacists in Saudi Arabia despite some concerns about its impact on their sales. Exploring different business models that delink the profits from the volume of antibiotics sales is necessary for this vital industry to thrive.

**Keywords:** antibiotics, drug resistance, community pharmacy, sales, Saudi Arabia

## Introduction

The advent of antibiotics has revolutionized medicine and made it possible to cure many bacterial infections that were deemed invincible.<sup>1,2</sup> However, the rate of antimicrobial resistance both locally and globally has seen a dramatic increase over the past two decades.<sup>3-8</sup> According to the World Health Organization (WHO) latest estimate, the annual worldwide death toll due to antimicrobial resistance can be as high as 50,000.<sup>9</sup> Unfortunately, many countries and healthcare organizations are not doing enough to stem the spread of antimicrobial resistance as the global consumption of antibiotics increased by over 60% between the years of

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2000 and 2015.<sup>10</sup> The inappropriate use of antibiotics is believed to be the leading cause of antimicrobial resistance.<sup>11</sup> Therefore, dispensing antibiotics without prescription (DAwP) in community pharmacy settings has contributed to the spread of antimicrobial resistance.<sup>12–14</sup> In addition, the public misconceptions of antibiotics led to its misuse and contributed to the increase in the rate of DAwP.<sup>15</sup> This was obvious in multiple studies.<sup>16–20</sup> In a cross-sectional study that was conducted in two large hospitals in Saudi Arabia and aimed to explore the patients' awareness of antimicrobial resistance, only 27% of the patients surveyed were aware of the antimicrobial resistance. Moreover, 40% did not think that the use of antibiotics without a prescription is harmful when obtained from a friend or family member, and 34% were unaware if this is a correct practice or not.<sup>16</sup> Additionally, the prevalence of self-medication using antibiotics without a prescription was as high as 74% according to another study that surveyed the Sudanese population in three cities in Sudan, and community pharmacies were found to be the main source that surveyed participants get antibiotics from.<sup>17</sup> Similarly, another study that explored the rate of DAwP in community pharmacy settings in Egypt using a simulated patient method for two viral infections scenarios (eg, acute bronchitis and common cold) found that antibiotics were dispensed in 98% of 238 visits that were made.<sup>18</sup> Most of the dispensed antibiotics without a prescription were taken for non-bacterial infections, such as sore throat, based on the findings of several studies.<sup>19,20</sup> Thus, improving the public awareness regarding antibiotics is crucial to stem the spread of antimicrobial resistance.

Unfortunately, patients mostly have unlimited access to antibiotics in many countries and particularly in the Middle East.<sup>17–21</sup> In a study that used a simulated-client method to explore the rate of DAwP in community pharmacy settings in the city of Riyadh in Saudi Arabia, antibiotics were dispensed in more than 77% of the visited pharmacies.<sup>21</sup> In contrast, only 7% of the dispensed antibiotics in the European Union were DAwP.<sup>22</sup> Therefore, some countries have started taking actions against such practices that significantly contribute to the rising rate of antimicrobial resistance and put the lives of many at risk.<sup>23,24</sup> In Saudi Arabia, DAwP is illegal but the rate of antibiotics dispensing without a prescription has seen a dramatic increase over the last decade throughout Saudi Arabia.<sup>21,25,26</sup> Therefore, the Saudi Ministry of Health has introduced new amendments to the existing

law and included fines up to \$26,666 against the pharmacy that dispensed any antibiotic without a prescription, license revocation, pharmacy closure, and a six-month jail term. The revised antibiotics dispensing law came into effect as of May 2018.<sup>27</sup> These amendments were introduced and enforced largely due to the failure of the previous measures that were taken by the Ministry of Health to stem the rise of antibiotics dispensing without prescription, and the increasing rate of antimicrobial resistance in the Saudi society.<sup>16,21</sup>

The community pharmacists' views of DAwP are influenced by a multitude of factors, such as their sociodemographic characteristics, professional experience, and their perception of patients who are requesting antibiotics without a prescription.<sup>28</sup> Furthermore, patients are rarely asked to see their doctors if they requested antibiotics without a prescription according to a study that used simulated clients to explore the community pharmacy staff response to an antibiotic request without a prescription in Sri Lanka.<sup>29</sup> Another study that explored community pharmacists' awareness of the illegality of DAwP in Saudi Arabia prior to the enforcement of the law as well as the factors that are associated with it found that more than two-thirds of the surveyed pharmacists were unaware that DAwP is illegal. Moreover, they reported that the main reasons behind the public's requests for antibiotics without a prescription were the lack of willingness to consult a physician for non-serious infections, and the inability to pay for a physician visit.<sup>30</sup> In a qualitative study that explored the reasons behind the rise of antibiotics self-medication among members of the general public who had an experience with antibiotics self-medication prior to the enforcement of the antibiotics dispensing law in Saudi Arabia, the difficulty in accessing healthcare services as well as poor knowledge of antibiotics resistance were found to be the main reasons.<sup>31</sup> In addition, community pharmacists were found to play a significant role in antibiotics acquisition without a prescription by recommending certain antibiotics to pharmacy customers seeking an antibiotic without a prescription as reported in one of the studies that explored the prevalence and reasons for antibiotics self-medication among a sample of surveyed general public in Riyadh, Saudi Arabia.<sup>32</sup> This sentiment was echoed by another cohort from the general public who were qualitatively interviewed in another study that was conducted in the eastern region of Saudi Arabia.<sup>33</sup> However, little is known about the pharmacists' views of the DAwP after the enforcement of the executive

regulations of the health practice law, which is colloquially known as the antibiotics dispensing law. In a recently published study that utilized an online platform to explore the impact of the antibiotics dispensing law on the public's use of antibiotics without a prescription as well as their awareness of antibiotic resistance in Saudi Arabia, only 11% of the participants reported using an antibiotic without a prescription prior to the enforcement of the law; however, this percentage has decreased to 9% after the enforcement of the law. Almost one-third of the participants were unaware of antibiotic resistance, and 84% had either a neutral or a positive attitude toward the enforced antibiotic dispensing law.<sup>34</sup> Alrasheedy et al explored the prevalence of DAWP among community pharmacists in Al-Qassim region in Saudi Arabia using a self-administered questionnaire and a simulated client method (SCM) for two commonly encountered infections (eg, pharyngitis and urinary tract infection) to compare the rate of DAWP before and after the law enforcement. More than two-thirds of the surveyed pharmacists reported that DWaP was common prior to the enforcement of the law; however, only 12.9% of them reported that DAWP is common after the enforcement of the law. With regard to the rate of DAWP that was measured using the SCM, 12.1% and 5.2% of the surveyed pharmacists dispensed antibiotics without prescriptions after the enforcement of the law in comparison to 96.6% and 87.7% prior to the enforcement of the law for pharyngitis and urinary tract infection, respectively.<sup>35</sup> Although these studies have explored the prevalence and attitudes of the general public and community pharmacists about DAWP and antibiotic resistance before and after the antibiotic dispensing law enforcement, none of these studies used a probability sampling technique or explored the prevalence of DAWP in Riyadh, the capital of Saudi Arabia. In addition, the impact of the enforced antibiotics dispensing law on antibiotics sales from the community pharmacists' perspectives has not been explored. Furthermore, the total sales of oral antibiotics in Saudi Arabia has not been compared before and after the enforcement of the antibiotics dispensing law. Therefore, the aims of this study were to explore community pharmacists' views of the DAWP after the enforcement of the antibiotics dispensing law, explore its impact on antibiotics sales from their perspective, and compare the national total sales of oral antibiotics before and after the enforcement of the law. This should help inform the health policy makers in Saudi Arabia and the world about the potential unintended consequences of any law or

regulation aimed at controlling the rate of antibiotic resistance.

## Methods

### Study Design and Setting

This was a questionnaire-based descriptive cross-sectional study that was conducted in the city of Riyadh, Saudi Arabia. Pharmacists with at least one year of work experience who had been practicing in community pharmacy settings prior to the enforcement of the antibiotics dispensing law in May 2018 have been included in the study. A multistage sampling method was used to recruit community pharmacists in the city of Riyadh. Thus, the city was divided into five main areas (North, South, East, West, and Central areas) based on the Ministry of Municipal and Rural Affairs map. These five areas were further divided into 15 main administrative districts, and each district has several neighborhoods. There are about 169 neighborhoods in Riyadh; however, many of these neighborhoods are still sparsely populated. Therefore, we included 105 neighborhoods with a population density of 50 people per square kilometer (km<sup>2</sup>) or more based on the 2018 Saudi census for the city of Riyadh published by the Saudi General Authority of Statistics. A list of all community pharmacies in all of the 105 neighborhoods was created by locating community pharmacies using Google<sup>®</sup> map. Stratified random sampling was then conducted to select three pharmacies from each neighborhood using Microsoft Excel<sup>®</sup>.

### Questionnaire Development

In order to explore community pharmacists' views of the DAWP and the enforced antibiotics dispensing law, a 14-item questionnaire was developed. The first six items collected data about the participants' characteristics, such as age, gender, nationality (eg, Saudi and non-Saudi), years of experience in community pharmacy settings in Saudi Arabia, type of community pharmacy (eg, independent, small-chain with less than 10 pharmacies, large chain with more than 10 pharmacies). Seven statements that inquired about community pharmacists' views of the enforced antibiotics dispensing law were created based on a previously published study,<sup>30</sup> and the potential impact of the law on the sales of antibiotics in community pharmacies that was not investigated before. These statements were created based on identified themes that were uncovered in previously published qualitative studies that utilized the theory of planned behavior to identify the reasons behind DAWP among community pharmacists.<sup>36,37</sup> Moreover, another

item inquired about the most commonly dispensed class of oral antibiotics (eg, penicillins, cephalosporins, fluoroquinolones, macrolides, and tetracyclines) in the community pharmacy settings. The statements were reviewed by a medical consultant in family medicine and an expert in health policy and outcomes to check the content validity. In addition, the statements were pilot-tested among 15 pharmacists to check the face validity prior to the start of data collection. The internal consistency of the questionnaire was examined using the Cronbach's alpha method and was found to be acceptable (ie, Cronbach's  $\alpha=0.67$ ).<sup>38</sup> The questionnaire was developed and administered in English.

## Data Collection

Participants were asked to sign a written consent form that explained the purpose of the study and their right to withdraw from the study at any time. Only those who signed the consent form were included in the study. Five trained medical interns visited the randomly selected pharmacies and interviewed the community pharmacists who consented to participate. The medical interns were provided training through a role play, and they were asked to adhere to a written protocol on how to approach the potential participants, obtain the consent form, and conduct the interview. In case more than one pharmacist was present in a pharmacy, the medical interns were instructed to interview them separately after obtaining their written consent forms. In order to examine any potential impact of the enforced antibiotics dispensing law on the sales of oral antibiotics at the national level, the national sales data of orally administered antibiotics were retrieved from the Saudi Food and Drug Authority (SFDA) database for the years of 2017, 2018, and 2019. This dataset includes the consumption rates and sales of all approved medications by the SFDA. Licensed pharmaceutical importers, local manufacturers, and multinational pharmaceutical companies' representatives in Saudi Arabia are required to provide information on their sales of all registered medications to the SFDA. A query was made to retrieve data on orally administered antibiotics given their high utilization rates in the community.

## Statistical Analysis

The minimum sample size was estimated to be 260 participants for chi-square test based on a  $\beta/\alpha$  ratio of 1, medium effect size (Cohen's  $w=0.2$ ), and power of 0.85 (1- $\beta$  error probability). Descriptive statistics using frequencies and percentages were used to present the findings of the study. Pearson's correlation coefficient ( $r$ ) was used to examine

the association between the views of the community pharmacists and their characteristics (eg, years of experience, age, gender, education, etc.). All statistical analyses were conducted using SAS<sup>®</sup> version 9.4 (SAS institute, Cary, NC, U.S). The study was approved by the institutional review board of the College of Medicine at King Saud University, Riyadh, Saudi Arabia (Research Project No. E-19-4421).

## Results

### Participants' Characteristics

There were 355 pharmacists in over 300 pharmacies who were approached and asked if they would like to participate. However, 33 pharmacists did not consent to participate, and 36 pharmacists did not meet the inclusion criteria (eg, fresh graduates); 286 pharmacists met the inclusion criteria and were included in the analysis. Most of the participants were between 30 to 40 years of age (57.34%), and about one-third (34.97%) were under 30 years of age. The majority of the participants were male (97.90%), and non-Saudi (95.10%). About three-quarters of the participants work in large-chain pharmacies, and only 8.39% of them work in independent pharmacies. Most of the participants have a bachelor of pharmacy degree (97.20%), and only 2.80% of them reported having a post-graduate degree (eg, post-graduate diploma or Master of Science). Almost 54% of the participants had 1 to 5 years of experience in community pharmacy settings in Saudi Arabia, and about 32% had 5 to 10 years of experience (Table 1).

### Pharmacists' Views of the DAWP After the Enforcement of the Antibiotics Dispensing Law

After the enforcement of the law, approximately 51.40% of the participants reported that the percentage of patients who ask for antibiotics without a prescription does not exceed 25% of the total number of patients who visit community pharmacies, while 34.62% reported that the percentage can be as high as 50%. Moreover, the majority (87.41%) reported a decrease in the sales of antibiotics. The inappropriate use of antibiotics is believed to be reduced by 89.51% based on the participants' responses. However, approximately 10% of the participants disagree that the inappropriate use of antibiotics will decrease as a result of the enforcement of the antibiotics dispensing law. Likewise, the majority of participants (90.56%) agreed that the law enforcement will reduce the rate of antimicrobial resistance, but 9.44% disagreed. Most of the participants (64.69%) disagreed that DAWP is still common after the enforcement of

**Table 1** Characteristics of the Participants (N=286)

| Characteristics   | N (%)       |
|---|-------------|
| <b>Age in years (yrs)</b>   |             |
| <30 yrs   | 100 (34.97) |
| 30–40 yrs   | 164 (57.34) |
| >40 yrs   | 22 (7.69)   |
| <b>Gender</b>   |             |
| Male  | 280 (97.90) |
| Female  | 6 (2.10)    |
| <b>Years of experience in community pharmacy settings in Saudi Arabia</b> |             |
| 1–5 yrs   | 154 (53.85) |
| 5–10 yrs  | 91 (31.82)  |
| >10 yrs   | 41 (14.34)  |
| <b>Type of pharmacy</b>   |             |
| Independent   | 24 (8.39)   |
| Small-chain   | 47 (16.43)  |
| Large-chain   | 215 (75.17) |
| <b>Education</b>  |             |
| Bachelor of Pharmacy  | 278 (97.20) |
| Post-graduate degree (eg, Master of Science)                              | 8 (2.80)    |
| <b>Nationality</b>  |             |
| Saudi   | 14 (4.90)   |
| Non-Saudi   | 272 (95.10) |

the law; however, about 35% of them either agreed that DAwp is still common or were not sure. The majority of participants (97.90%) agreed that pharmacists must ask patients to consult their physicians to check if they need antibiotics. Pharmacy profits are believed to be negatively impacted by the law enforcement according to 41.26% of the participants; however, 52.80% of them did not agree that their pharmacies' sales were negatively impacted by the law (Table 2). With the exception of the years of experience in community pharmacy settings in Saudi Arabia, which has shown a negative correlation with the percentage of patients requesting antibiotics without a prescription ( $r=-0.152$ ,  $P=0.009$ ), none of the participants' views were influenced by their sociodemographic characteristics.

## Most Commonly Dispensed Oral Antibiotics and the Law Enforcement Impact on Total Sales of Orally Administered Antibiotics

The majority of the participants (62.6%) reported that penicillins (eg, amoxicillin) and cephalosporins (eg, cephalixin,

cefadroxil, cefaclor, cefuroxime, and cefixime) are the most commonly dispensed oral antibiotics in their pharmacies as shown in Figure 1. According to the SFDA database the total sales of oral antibiotics have seen a decrease from \$480 million in 2017 prior to the enforcement of the antibiotics dispensing law to \$420 million in 2018 where the law was enforced in the month of May of the same year, and to \$400 million in 2019 (Figure 2).

## Discussion

Most of the surveyed community pharmacists in this study viewed the enforced antibiotics dispensing law favorably with regard to reducing the rate of DAwp as well as the antibiotic resistance. However, a significant minority (eg, 41.26%) believed that the law enforcement has negatively affected their pharmacies' profits. These findings are important in informing health policy makers about the impact that such a law could have not only on the incidence rate of antibiotic resistance and misuse but also on the unintended economic consequences of such laws and regulations. This is particularly important in Saudi Arabia which has seen a dramatic increase in the rate of antimicrobial resistance and high rate of DAwp over the last two decades.<sup>3–8</sup> The high rate of DAwp in community pharmacy settings was attributable to weak implementation of regulations, poor understanding of the local regulations and laws that prohibit such practice, and the desire to maximize profits in the absence of any legal deterrence.<sup>25,30,39</sup> However, only 25% of the surveyed community pharmacists in this study reported that DAwp is still a common issue. In addition, about 98% agreed that they should ask the patients to consult their physicians to check if they really need an antibiotic. Moreover, the majority of surveyed community pharmacists (>85%) agreed that the law enforcement will reduce the rates of inappropriate use and resistance to antibiotics. These findings are close to the findings of another study that was conducted in the region of Al-Qassim in Saudi Arabia and found a positive impact of the law enforcement on community pharmacists' knowledge and views of DAwp.<sup>35</sup>

The majority of surveyed community pharmacists have reported a decrease in the sales of antibiotics after the enforcement of the law, which is consistent with the previously published studies.<sup>35,39</sup> Moreover, a significant percentage of participants (41.2%) reported that the law enforcement has negatively impacted their profits, which is close to the percentage reported in the recently published study.<sup>35</sup> This indicates that sales of antibiotics represent a significant

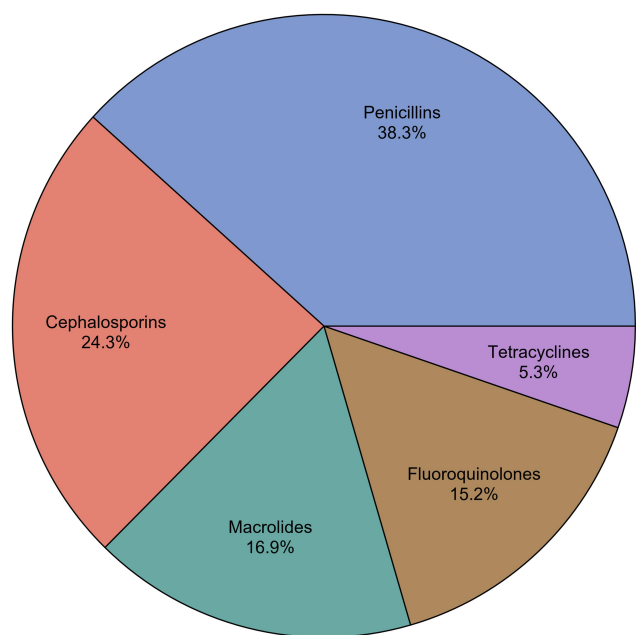
**Table 2** Community Pharmacists' Agreement with Different Statements Regarding the New Antibiotics Dispensing Law and Dispensing Antibiotics without Prescription

| Views of the Enforced Dispensing Law of Antibiotics in Saudi Arabia   | N (%)   |
|---|---|
| <b>1. After the enforcement of the law, the percentage of patients who ask for antibiotics without a prescription in comparison to those who bring a prescription with them is:</b><br><25%<br>25%-50%<br>50%-75%<br>>75% | 147 (51.40)<br>99 (34.62)<br>27 (9.44)<br>13 (4.55) |
| <b>2. The sales of antibiotics after the enforcement of the law has _____:</b><br>Increased<br>Decreased<br>Not changed   | 9 (3.15)<br>250 (87.41)<br>27 (9.44)                |
| <b>3. Pharmacists must ask patients to consult their physicians to check if they need antibiotics.</b><br>Agree<br>Disagree<br>Neutral  | 280 (97.90)<br>4 (1.40)<br>2 (0.70)                 |
| <b>4. The enforced antibiotics dispensing law will reduce the inappropriate use of antibiotics.</b><br>Agree<br>Disagree<br>Not sure  | 256 (89.51)<br>30 (10.49)<br>0 (0.00)               |
| <b>5. The enforced antibiotics dispensing law will reduce the rate of antibiotic resistance.</b><br>Agree<br>Disagree<br>Not sure   | 259 (90.56)<br>27 (9.44)<br>0 (0.00)                |
| <b>6. Antibiotics dispensing without a prescription is common even after the enforcement of the law.</b><br>Agree<br>Disagree<br>Not sure   | 71 (24.83)<br>185 (64.69)<br>30 (10.49)             |
| <b>7. The law enforcement negatively impacted the pharmacy profits.</b><br>Agree<br>Disagree<br>Not sure  | 118 (41.26)<br>151 (52.80)<br>17 (5.94)             |

proportion of community pharmacies' profits in Saudi Arabia. Therefore, community pharmacies need to diversify their revenues by adopting and implementing value-added services, such as anticoagulation services, osteoporosis screenings, travel health, lipid screenings, and smoking cessation counseling.<sup>40</sup> The participants' length of work experience in community pharmacy settings in Saudi Arabia was associated with lower estimates of pharmacy customers who request antibiotics without a prescription. This can be attributable to the better ability of community pharmacists with long work experience to estimate the percentage of patients who requested antibiotics without a prescription in comparison to their counterparts with short work experience. Moreover, customer pressure may play a role as suggested

by one of the studies that explored the factors associated with dispensing sub-therapeutic doses of antibiotics without prescriptions.<sup>41</sup> Pharmacy customers may feel that it is easier to pressure young pharmacists with short experience to dispense antibiotics without a prescription in comparison to older pharmacists who look more experienced.

Beta-lactam antibiotics (eg, penicillins and cephalosporins) were the most commonly dispensed antibiotics in community pharmacies based on the surveyed participants. This is consistent with the previously published research studies that reported high dispensing rates of beta-lactam antibiotics prior to the law enforcement, which contributed to the increasing incidence rates of BLPB.<sup>3,4</sup> The national sales of oral antibiotics have seen a decline after the enforcement of

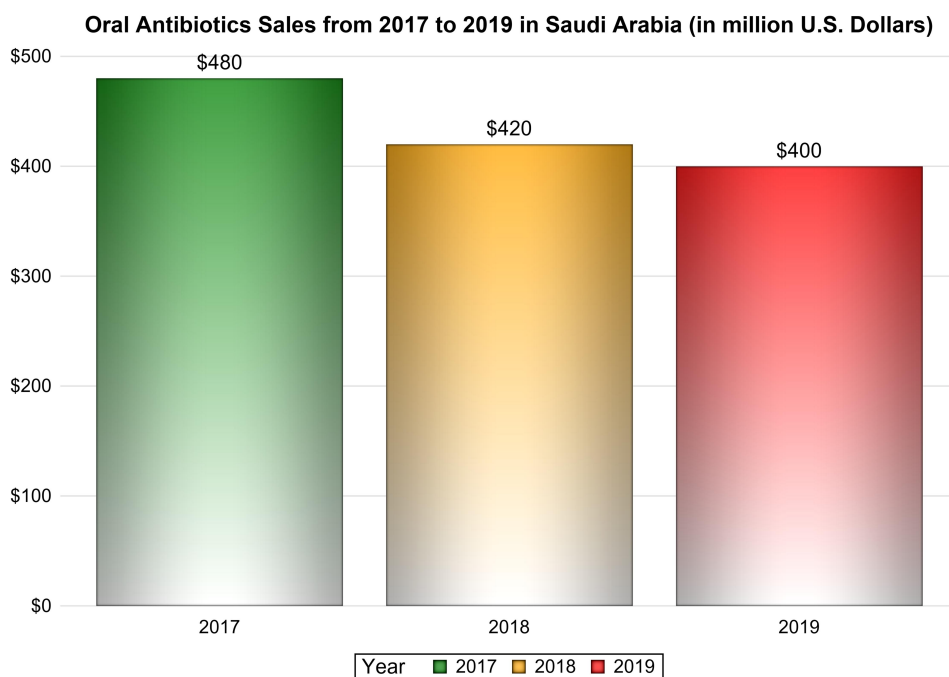


**Figure 1** The most commonly dispensed oral antibiotics in community pharmacy settings based on the participants' responses.

the law in 2019 in comparison to the sales data of 2017 when the law was not enforced. This highlights a potential role of the law enforcement in decreasing the sales of oral antibiotics which were commonly dispensed without a prescription in community pharmacies prior to the enforcement of the law. The high inappropriate use of antibiotics is

one of the main contributors to the increasing rate of antimicrobial resistance.<sup>30,35</sup> However, the antibiotics manufacturers have an incentive to increase their sales of antibiotics in order to generate more profits. Therefore, the sustainability of this business model in light of different antimicrobial stewardship programs and the law enforcement is at stake.<sup>42</sup> The United Kingdom has recently adopted a subscription style model for antibiotics to encourage pharmaceutical companies to invest in developing new antibiotics and secure payment for antibiotics manufacturers upfront based on the value that their antibiotics provide rather than the utilized quantities.<sup>43</sup> This kind of model that delinks the profits from the volume of sales for antibiotics and encourages pharmaceutical manufacturers to invest in the research and development of antibiotics is needed.<sup>43</sup>

Although this study is the first, to the best of our knowledge, to explore community pharmacists' views of the enforced antibiotics dispensing law in Riyadh and the second in the Saudi Arabia, the study is not without limitations. First, this study was only conducted in one city which limits the generalizability of the findings. Moreover, interviewer bias cannot be ruled out since the questionnaire was administered by interviewing participants rather than being self-administered by the participants themselves. In addition, the rate of DAWP from the perspective of community pharmacists was not explored.



**Figure 2** The sales of oral antibiotics in Saudi Arabia between 2017 and 2019 based on the SFDA database.

## Conclusions

The findings of this study suggest that community pharmacists have generally favorable views of the enforced antibiotics dispensing law in Saudi Arabia. Moreover, the enforcement of the law is potentially behind the drop of oral antibiotics sales. Future studies should explore the impact of the law enforcement on the rate of antibiotic resistance in Saudi Arabia. In addition, different payment models for antibiotics based on their therapeutic value rather than the volume of sales should be explored to incentivize local manufacturing of antibiotics and encourage research and development in this vital therapeutic area.

## Abbreviations

DAwP, dispensing antibiotics without prescription; WHO, World Health Organization; SFDA, Saudi Food and Drug Authority; BLPB, beta-lactamase-producing bacteria.

## Data Sharing Statement

Study data are de-identified and can be available upon request from the corresponding author (Yazed AlRuthia).

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## Disclosure

The authors report no conflicts of interest in this work.

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