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Self-medication: COVID-19: Pandemic; Knowledge; Causes; Practice, Pakistan

#### **Editorial Note:**

You are viewing the latest version of this article having minor corrections related to the use of English language.



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# Abstract

ackground: Self-medication (SM) is a public health issue upsurge day by day and its side effects accelerate the burden on healthcare, pharmacists, and the economy. The demand for self-prescribed medicines during the COVID-19 pandemic was found to be on the rise globally.

Methods: The survey was conducted during June-August 2021 to analyze knowledge, causes, and practices of self-medication in Pakistan. The Chi-square test was used to examine the relationships between the categorical variables: The Pearson Correlation coefficient determined the relationship between quantitative variables. Age, gender, marital status, education, profession, field, knowledge, causes and practice of SM were variables included in survey.

Results: 203 responses were received in the online survey and results from demographic factors were 104 (51.7%) male, 114(56.7%) single, 20-30 years (42.3%) age group, 44.8% were MS/M. Phil, 31.3% were teacher and 74.1% respondents belong to the bioscience field. 20.4% considered it good practice while 42.3% responded to it as acceptable practice. Quarantine was the most significant factor for SM during COVID-19 (68.7%). Discrimination after infection (37.8%) was also of higher priority and SM practiced under the influence of friends and social media, emergency illness, distance to hospitals (19.9%), and prescribed by medical personnel in a health facility (31.3%) followed by own self (22.9%), 19.9% by a friend, and 15.4% by pharmacist. 52.7% used self-prescribed antibiotics with the appearance of symptoms of fever, chills, and tiredness (37.30%).

**Conclusion:** This population-based survey suggested that legislation, awareness campaigns, media, community, and government should play their part to fight misinformation about alleged COVID-19 preventive medicines on different platforms.



# Introduction

Self-medication (SM) is defined by the World Health Organization (WHO) as the choice and use of medications for treating self-recognized signs or diseases without visiting a professional medical specialist [1]. It also covers excessive consumption of over-the-counter (OTC) medications, including the use of or re-use of previously prescribed or abandoned medicines, outright buying of prescription medications prior evaluation, and improper use of prescription medications. SM is a worldwide prevalent common practice, according to several studies, with a frequency of 32.5–81.5 percent globally [2]. Many variables impact SM patterns, including a lack of awareness about drug side effects, socioeconomic level, access to health care, pandemic illnesses, and patients' attitudes and conventions [1].

Self-medication, or taking medications without seeing a medical specialist, is a serious health concern, particularly during COVID-19. Coronavirus 2 (SARS-CoV-2) has posed a significant public health danger to the worldwide society as a pandemic. Influenza, cough, sore throat, dyspnea, tiredness, and malaise are common COVID-19 symptoms. The illness is usually moderate; nevertheless, it can develop into pneumonia, respiratory failure, and multi-organ malfunction in the aged and individuals with comorbidities. SARS-CoV-2 (also known as 2019-nCoV) exposure affects numerous systems, including the cardiac, hormonal, and gastrointestinal systems, but it is most dangerous to the respiratory system. The WHO (World Health Organization) proclaimed a pandemic on March 11, 2020, as a result of the infection's rapid spread across several states in just a few months [1, 3].

Factors such as medication availability, simple access to pharmaceuticals without time limitations, increased supply of numerous kinds of medicines at cheap rates, and convenience in accessing drugs comparison to receiving treatment in medical centers all contribute to non-prescription drug use. The demand for selfmedication during the COVID-19 epidemic was found to be on the rise in a current online search analysis. That's because the pandemic was proclaimed, there has been a rise in the number of queries for self-medication throughout the world, which might indicate a global surge in demand for self-medication [4].

According to studies, although SM encourages people and communities to take charge of their health, it has also been linked to health problems by using wrong dose or using medications for extended periods than the manufacturing companies suggest which might have a negative influence on individual life. People began taking medications without being detected or tested for COVID-19 due to various typical symptoms such as soreness or discomfort in the throat, dry cough, temperature, muscle aches, and dyspnea. Acetaminophen was frequently used to control the COVID associated fever [5]. Apart from the risk of misusing or overusing these drugs, which can lead to immediate or interrupted health problems such as medication errors, drug interactions, and disruption or devastation of vital organs such as the kidneys and liver, self-medication can also give a false sense of security by disguising the proper treatment. Furthermore, inappropriate drug storing, improper drug treatment, and a high frequency of pathogenic susceptibility to medications, can also lead to a few of the negative consequences [6, 7].

Self-medication with antibiotics is linked to the danger of improper drug usage, which puts patients at risk for drug interactions, masks symptoms of underlying diseases, and leads to the development of microbe resistance [8, 9]. Though, the COVID associated Pneumonia and Acute Respiratory Distress Syndrome (ARDS) require a precise use of wide variety of antibiotics and steroidal medicines as supportive treatment but an improper use of them without a prescription has been linked to development of multidrug resistant bacteria and steroids linked obesity. Selfmedication practices that include improper drug usage include short treatment durations, insufficient doses, sharing of medications, and delaying therapy until symptoms improve [10]. Globally, the emergence of antibiotic-resistant bacterial species that are resistant to many antibiotic classes has generated serious concerns about antibiotic resistance. Resistant bacteria and viruses can cause more serious health problems such as longer hospitalizations, higher medical costs, and even death [11].

Self-medication is common throughout the world, with rates as high as 68 percent in European countries and considerably higher in underdeveloped nations. In Palestine, it is as high as 98 percent. Only a few studies in Pakistan, all of which were representative of a specific group of individuals, have verified high rates of self-medication prevalence of approximately 51 percent. Because of the absence of healthcare facilities in rural regions, this percentage is significantly greater. Seventy percent of Pakistan's population does not have easy access to medications or physicians. It's particularly concerning because, despite attempts to curb the problem, prevalence rates are rising. In Sub-Saharan Africa, the total percentage of self-medication ranges from 11.9 percent to 75.7 percent. Self-medication was previously believed to be common in Uganda's northern and southwestern regions [12].

# Methods

## **Study Design and Participants**

During June 2021-August 2021, an internet crosssectional survey was done, with willing individuals accessing the survey via digital platforms such as Facebook and WhatsApp. Considering the current COVID-19 preventative laws at the time of information collection, we chose a social media survey over a conventionally structured questionnaire. The NCOC and WHO advocated for and implemented the COVID-19 physical distancing current practices in Pakistan. Depending on a prior study's reported SM frequency of 52.1 percent, the number of respondents of 384 was computed by using the Cochran formula for crosssectional surveys at the confidence level of 95 percent and a 5% error margin [13].

#### **Questionnaire Design**

The survey was divided into two parts: a demographics part and a portion with questions about SM knowledge, causes, and practice (KCP). Gender, age, level of education, profession, and field were among the demographic factors. There were 5 respondents in the knowledge questions (K1-K5), and 7 (C1-C7), and 15 (P1-P15) questions in the causes and practice of SM questions, respectively.

#### **Data Collection**

Between June 6, 2021, to August 8, 2021, data was collected utilizing computerized questionnaires. Based on a prior study, the authors created and evaluated the questionnaire. The study uses a convenient sampling strategy due to COVID-19 safety criteria, and the researchers deployed their connections and social platforms to approach the participants. Through these networks, a survey was circulated to those who own smart phones and live in cities or villages with internet access.

#### **Statistical Analysis**

The information was obtained from Google Forms by using the comma-separated values (CSV) option and then imported into SPSS Version 23 for data analysis. The descriptive and frequencies are calculated to understand the overall respondents perceptions. The Bar and Pie charts are used to show the graphical representation of results. The Chi-square test was used to examine the relationships between the categorical variable: Age, gender, marital status, education, profession, field, knowledge, causes and practice of SM. Among these variables age, gender, marital status, education, profession, field were demographic variables. The Pearson Correlation coefficient is used to measure the relationship between quantitative variables. Statistical significance was defined as a P-

value of less than 0.05 and a 95 percent confidence interval.

# Results

A total of 203 participants were included in this online goggle form questionnaire. Variables were gender, marital status, age groups, education level, professions, and field of participants either bioscience or not. Among 203 participants highest frequency and percentage was 104(51.7%) male,114(56.7%) were single,20-30 years (42.3%) age group, 44.8% were MS/M.Phil,31.3% were the teacher and 74.1% respondents belong to the bioscience field. Other percentages are shown in the table.

Variables	Frequency	Percentage					
Gender							
Male	104	51.7					
Female	97	48.3					
Marital Status							
Single	114	56.7					
Married	87	43.3					
Age in Years							
20-30 Years	85	42.3					
30-40 Years	68	33.8					
40-50 Years	27	13.4					
Above 50 Years	21	10.4					
Education Level							
BS	37	18.4					
MS/M.Phil.	90	44.8					
PhD	37	18.4					
Others	37	18.4					
Profession							
Teacher	63	31.3					
Student	33	16.4					
Medical Specialist	41	20.4					
Community	43	21.4					
Pharmacist	19	9.5					
Bioscience field							
Yes	149	74.1					
No	50	24.9					

Table 1: Percentage and frequency of variable

# Knowledge of SM

The 1<sup>st</sup>section of the questionnaire was related to the awareness of self-medication and 92.5% of respondents have awareness and 75.1% also know about its harmful effects. Despite the harmful effects of SM 55.2% of respondents were sure to treat several diseases by themselves and 26.4% (highest percentage) agreed that SM for COVID-19 is better than seeking medical consultation, 20.4% considered it good practice and 42.3% responded to it as acceptable practice on account of various factors.

#### Causes of SM

Self-medication during COVID-19 was owing to many reasons as people were distressed with infection or contact with a suspected or known case of COVID-19. Due to the fear of getting infected, there was a surge in the prophylactic use of some medicines too. Evidence revealed that quarantine during COVID-19 infection develops nervousness that is why68.7% shows the response in yes that they had fear for isolation and this percentage is surely higher which urged the people to medications without prescription take and procrastination to visit health care centers. 37.8% percent of respondents were scared for stigma or discrimination of infection as the demeanor of society.52.2% told that there was uncertainty about the shortage of drugs in the market and health care facilities and 50.7% have the opinion that delay in treatment urged for SM. 40.8% percentage of responses reveals that SM was done by the influence of friends to restrict COVID-19 infection. In addition to the influence of friends, 18.9% were strongly agreed that the prevalence of SM was also influenced by television, radio, newspaper, and social media.41.3% get selfprescribed medicines from the pharmacy, 20.4% from hospitals, and 14.25% from an herbalist. The response rate is described in a bar chart.



Figure 1: Response for SM as better than medical consultation.



disease

Fear of stigma or discrimination if I contact the

Figure 2: Response for fear of stigma if individuals infected with COVID-19

#### **Practices of Self-Medication**

Use of self-prescribed medicines frequency was highest 121(60.2%) during COVID-19 and the majority of them used it for 3 days to 2 weeks with a valid percentage of 32.3% and 30.3% respectively. Factors for SM were diverse, but the emergency illness was most significant for SM followed by distance to health care centers (19.9%) which is shown in the graph. Medicines were

prescribed by medical personnel in a health facility (31.3%) followed by own self (22.9%), 19.9% by a friend, 15.4% by the pharmacist, and 10.4% did not respond to this question.

Among all participants, 105(52.2%) confirmed infection by test and 57(28.4%) felt severe nervousness and uneasiness, 41(20.4%) felt mild distress, 25(12.4%) did not affect at all however 16(8%) respondents become stronger during the period of infection.

Self-medication practice is common practice, and this practice level goes higher during a pandemic. When it was analyzed by this survey 50.2% did SM during a pandemic to avoid infection and make the immune system stronger. Cough and sneezing were symptoms urged for SM during pandemic others also urged but with a lower percentage. Percentage with symptoms depicted in the graph.



Figure 3: Factors for Self-medication during COVID-19 pandemic in Pakistan.

Antibiotics are important antimicrobial agents which provide protection from various infections, but selfprescription or inappropriate prescription was done during the era of COVID-19 irrespective of its harmful impacts on health even that a higher percentage of the population was enlightened. During the pandemic, of the population used self-prescribed 52.7% antibiotics regardless of side effects. Dosage of antibiotics was determined in various ways including instruction on the package insert consultation from a family member, doctors, and pharmacist. 15.9% consulted from various easily available doctors while strikingly 15.4% consulted from family members based on their experience 11.2% checked it from the package insert. In essence, adverse reaction of self-prescribed antibiotics or medicine majority of population consulted doctors (25.4%) that indicates lack of enough knowledge of population for self-prescription. After adverse reactions, the highest percentage of the combined response of participants consulted both pharmacy staff and doctors (8.0%), 9% stopped taking self-prescribed antibiotics while 3.5% switched to another antibiotic. Results have been described in the form of a bar chart. This pie chart shows the percentage

of symptoms that urged the population for selfmedication and the highest percentage was observed with fever and chills and tiredness (37.30%). The symptoms of fever create uneasiness or fear of COVID-19 infection and urged for SM.



**Figure 4:** Pie chart shows the percentage of symptoms that urged the population for self-medication and the highest percentage was observed with fever and chills and tiredness.

# Symptoms for COVID-19 urged for SM in Pakistan during June-August 2021

Pearson Correlation coefficient was used to measure how strong a relationship is between two quantitative variables. Responses state that variables "Can selfmedication practices result in harmful effects? and "Do vou belong to bioscience field?" have r=0.264 and this response to the statements were correlated and correlation was significant as the significant values are <0.05. Similarly, correlation of variables "Can selfmedication practices result into harmful effect(r=0.304)" "Is self-medication for COVID-19 better than seeking medical consultation(r=0.168)?" "Do you think you can treat common infectious diseases successfully by yourself (r=.217)" "Fear of infection or contact with suspected or known case of COVID-19 (r=0.293)" is correlated with statement "Have you ever heard about self-medication" and these correlations were significant as sig values are <0.05.In addition to these responses , response do you belong to bioscience field, have you ever heard about selfmedication and what do you think about selfmedication are correlated with statement "can selfmedication result into harmful effect ?" values r=0.264, 0.304 and 0.218 respectively and all these results were also significant as sig values were <0.05.

Further responses for statements "Can selfmedication practices result into harmful effect?", "What do you think about self-medication?" were correlated with "Is self-medication for COVID-19 better than seeking medical consultation?" with response values r=0.294, 0.888 respectively and this correlation was also significant as significant values are 0.000 and0.008 which are <0.05. Two indispensable variables "Fear of infection or contact with suspected or known case of COVID-19 "and "Fear of being quarantine or self-isolation if I contact the disease" are correlated and significant as significant value is <0.05. Additionally, statements" Do you think you can treat common infectious diseases successfully by yourself? "What do you think about self-medication?" Fear of infection or contact with suspected or known case of COVID-19" are correlated with variable "No drugs and treatment for COVID-19 in the health facilities" and revealed significant results with sig value <0.05.

Parameter		Age	Gender	Marital Status	Educational Level
Did you confirm it by COVID-19 test?	Chi-square	7.985	.040	.359	7.233
	Df	6	2	2	6
	Sig.	.239 <sup>a,b</sup>	.980ª	.836ª	.300ª
Did you feel anxiety or psychological distress during infection?	Chi-square	28.976	4.636	7.212	17.695
	Df	15	5	5	15
	Sig.	.016 <sup>a,b,*</sup>	.462	.205	.279 <sup>a,b</sup>
After infection, which symptoms do you feel or get through?	Chi-square	133.882	34.036	41.612	113.925
	Df	117	39	39	117
	Sig.	.136 <sup>a,b</sup>	.695 <sup>a,b</sup>	.358 <sup>a,b</sup>	.563 <sup>a,b</sup>
What did you use for self-medication? (can be more than one)	Chi-square	160.032	48.976	45.302	116.248
	Df	123	41	41	123
	Sig.	.014 <sup>a,b,*</sup>	.184 <sup>a,b</sup>	.297 <sup>a,b</sup>	.654 <sup>a,b</sup>
Which of the following	Chi-square	18.833	3.604	9.572	12.712
symptom urged for	Df	15	5	5	15
self-medication during a pandemic?	Sig.	.221 <sup>a,b</sup>	.608 <sup>b</sup>	.088 <sup>b</sup>	.625 <sup>a,b</sup>
Who prescribed the medication (s) for you?	Chi-square	25.211	7.298	7.916	9.852
	Df	12	4	4	12
	Sig.	.014 <sup>a,*</sup>	.121	.095	.629
Where did you buy the medicines?	Chi-square	38.072	7.763	8.636	34.753
	Df	18	6	6	18
	Sig.	.004 <sup>a,b,*</sup>	.256ª	.195ª	.010 <sup>a,*</sup>
Did you use antibiotics as self-medication?	Chi-square	30.102	1.855	1.503	10.878
	Df	9	3	3	9
	Sig.	.000ª,*	.603	.682	.284
Did you ever check the	Chi-square	25.741	6.502	6.130	18.813
instructions that come	Df	9	3	3	9
with the package insert of antibiotics for self- treatment?	Sig.	.002 <sup>a,*</sup>	.090	.105	.027 <sup>a,*</sup>
How did you know the	Chi-square	81.488	21.289	24.270	68.290
dosage of antibiotics? (check more than one if applicable)	Df	63	21	21	63
	Sig.	.059ª,b	.441 <sup>a,b</sup>	.280 <sup>a,b</sup>	.302 <sup>a,b</sup>
What did you do for the	Chi-square	89.849	14.631	15.898	61.792
adverse reactions?	Df	57	19	19	57
(check more than one if applicable)	Sig.	.004 <sup>a,b,*</sup>	.746 <sup>a,b</sup>	.664 <sup>a,b</sup>	.309 <sup>a,b</sup>

 Table 2: Pearson Chi-Square Tests

The chi-square test was performed to observe relationships among various categorical variables. Confirmation of COVID-19 infection by test and their response rate with age group was  $.239^{a,b}$ , gender  $.980^{a}$ , marital status  $.836^{a}$  and education level  $.300^{a}$ . A non-Significant relationship was observed in all variables. Next to this psychological distress during infection was calculated and age group results were .016(significant), gender .462, marital status .205, educational level  $.279^{a,b}$ 

The sig. values in red color in above table are < 0.05 so the responses for the categories of variables are not

independent for those variables and they have significant results while other results are nonsignificant.



**Figure 5:** Symptoms contributed to Self-medication during pandemic in Pakistan during June-Aug 2021.

# Discussion

Self-medication is a common self-care practice and this practice has become significantly higher in the pandemic era to keep themselves protective from illness [2]. Results of our survey revealed that majority of the population has awareness (92.5%) for SM and itsside effects (75.1%). They considered that SM during the period of a pandemic is better than visiting health care centers due to prevalent uncertain conditions. Several studies have been conducted to estimate the prevalent attitude of self-medication and it has been reported that in developing countries its ranges between 12.7% and 95% [14].

Self-medication was prevalent globally and in our country due to the fear of COVID-19 infection (75.1%), self-isolation (68.7%), and unusual behavior of society on getting an infection (37.8%). A significantly higher percentage (52.2%) reveals that there was also uncertainty for a shortage of medicines at pharmacies, markets, and health centers. They used self-prescribed medicines by the influence of television, radio, newspaper, and social media. In a study conducted by Wegbom, A.I., et al., the population was involved in SM because of stigmatization of COVID-19 (79.5%), fear of quarantine (77.3%), consternation for infection from a contact of various surfaces (76.3%). In addition to these, there were many other reasons which urged for SM as distress pandemic condition there was a delay in receiving treatment at health care centers (55.6%), and people were greatly influenced by information of death and reported cases provided by electronic media that's why the influence of friends urged for the use selfmedication to overcome COVID-19 (55.2%). However, other factors including television, radio, newspaper, and social media can influence self-medication for COVID-19 (54.3%) and non-availability of drugs for COVID-19 treatment in the health facilities (53%) this

study also shows the various factors for self-medication and emergency illness is most prevailing (49.1%) for SM. Others including delay in provision of health care treatment (28.1%), remote health facility (23%), nearby the pharmacy (21%), and non-availability of medicines in hospitals (19.3%) with charges (15.3%) [6]. One other study reveals factors for self-medication and one of them is fear of forgetting of infection from various sources and the non-availability of medicines and other facilities at hospitals. People used self-prescribed medicines by consulting a friend, relative, and pharmacist. This study was conducted in India and unfortunately, there was also the availability of various medicines in pandemic times. In addition to this other factors such as poverty as people were unwilling to spend money for treatment of diseases and unavailability of doctors in underdeveloped areas [15]. The frequency for self-medication was highest 121 (60.2%) during COVID-19 and the majority of the Pakistani population used it for 3 days to 2 weeks with the valid percentage of 32.3% and 30.3% respectively. People involved in the practice of SM due to emergency illness and distance to hospitals (19.9%). Medicines were prescribed by medical personnel in health facilities (31.3%) followed by self-prescription (22.9%), 19.9% by a friend, 15.4% by a pharmacist, and 10.4% did not respond to this question. Among all participants 105 (52.2%) of our survey who get an infection and

confirmed it by test. The majority of COVID-19 positive 57 (28.4%) feel severe nervousness and uneasiness, 41 (20.4%) feel mild distress, 25 (12.4%) did not affect at all however 16(8%) respondents become stronger during a period of quarantine. In another study, it was revealed that people did self-medication to keep themselves safe and prevent getting of deadliest infection. People seek it better to self-manage health issues due to distant health facilities. Moreover, they have easy access to medicines and used them without any hesitation [16]. A study conducted by Aziz et al. also revealed factors for self-medication including easy availability of medicines, excessive marketing, no implementation of legislation, and inappropriate facilities at healthcare centers [17].

Self-medication practice is common practice and this practice level becomes higher during a pandemic. From our survey, it was calculated that 50.2% population did SM during a pandemic to avoid infection and makethe immune system stronger. Cough and sneeze were found as the main symptoms urged for SM during pandemic others such as fever and body pain also urged but with lower percentage. Percentage of symptoms which urged population during COVID-19 pandemic for self-medication and highest percentage was observed with fever and chills and tiredness (37.30%). Feverduring pandemic developed uneasiness or fear of COVID-19 infection and urged for SM. People get various symptoms at one time and the combined percentage was in the range of 0.5-1% while the individual percentage for each symptom is significantly higher. In a comparison of our study, a study was conducted in Dhaka and people used non-prescribed medicines for fever (37.61%), cough (14.20%), loss of smell (9.21%) body pain (4.99%), and sore throat (28.79%) [18].

Self-medication practice with various antibiotics is recognized as a major contributing factor for antibiotics resistance [19]. Antibiotics are important antimicrobial agents which provide protection from various infections but self-prescription or inappropriate prescription was done during the era of COVID-19 without knowing their harmful effects. During the COVID-19 pandemic, 52.7 % used Selfprescribed medicines/antibiotics and they decide dosage from package insert instructions (11.2%), friends or family members (15.4%) doctors (15.9%), and pharmacists (13.4%). Many of the respondents also face adverse reactions and then they consulted with doctors (25.4%). After adverse reactions highest percentage of the combined response of participants consulted both pharmacy staff and doctors (8.0%), 9% stopped taking self-prescribed antibiotics while 3.5% switched to another antibiotic. In a study conducted at Maputo City, Mozambique three factors convinced people for self-medication of antibiotics including health-related systems, health-seeking behavior, and socioeconomic factors. As the health care system provides treatment of diseases but several limitations contribute to selfmedication including easy access to the pharmacy, long time for access to proper facilities and doctors because of poor management and people mostly seek public health facilities at hospitals when there is a severe medical emergency. Health-seeking behavior also urged for self-medication as people use previously prescribed or leftover medicines for minor illnesses. In concern of socioeconomic factors less time, financial issues, and minor illness also contribute to selfmedication [20]. Prevalence of high rates of antibiotic resistance in Syria was reported before pandemic but in a recent study 45% of the respondents were taking selfprescribed medicines when they suspect with COVID-19 infection and strikingly 1/5<sup>th</sup> were taking with this belief that antibiotic could protect from the severity of the infection and 34% population did same in another study [21]. In another study, there were significantly higher rates of SM for antibiotics were found including Pakistan (81.25%), Spain(54.1%), Bangladesh (26.69%), and India (39.3%) creating public health issues [22].

This study concluded that self-medication is acceptable practice in several cases but not always recommended due to side effects that can be life-

threatening. The prevalence of SM during the COVID-19 pandemic was also significantly higher which may provide facilitation within a short time but lead to public health issues and resistance against antibiotics developed or may develop which is a major public health issue. Self-medication results in public health threats and the most disastrous peril of SM are AMR which can be resulted in another public health issue. Pakistan ranked in developing countries and has a great burden on health care centers. Therefore, there is needful to overcome the practice of SM by various campaigns at the institutional and public level or by social media, strict legislation in the provision and supply of medicines,Legislations should he implemented to restrict the self-medication for antibiotics, OTC drugs, and other medicines to avoid public health issues globally. Healthcare sectors should take care in this regard by educating staff and professionals through campaigns and workshops.

# Competing Interest

The authors declare that there is no conflict of interest.

# Author Contributions

All authors contributed equally in this study.

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