UiT The Arctic University of Norway

Faculty of Medicinal Sciences / Department of community medicine

Self-Medication and Over-The-Counter Dispensing of Antibiotics in Egypt_ Prevalence, Reasons and Outcomes

A systematic review

Khaled Srour

HEL-3950 Master's thesis in Public Health

Dec-2020

Supervisor: Nils Maarten Daulaire

Abstract

Background: The excessive and unwarranted consumption of antibiotics is the leading factor in promoting the spread of antimicrobial resistant (AMR), which is considered to be a potential major threat to global public health and economic growth. Several systematic reviews have been published exploring the pattern of antibiotic use in the Middle East and low-and middle-income countries without including studies from Egypt. Because of the strategic importance of Egypt as the most populated country in the Middle East and the largest producer of health workers in the area, a systematic review focusing on the situation in Egypt is timely and useful.

Objective: Investigating the problem of self-medication and non-prescription dispensing of antibiotics in Egypt and suggesting interventions that could fit in the Egyptian context.

Methods: A thorough search was done across databases (Medline, ProQuest and Scopus) using MeSH terms and regular keywords generated from the research question. The Inclusion and Exclusion criteria were applied, and the included studies were critically appraised using NOS.

Results: The review included 10 studies after screening processes. The aggregate rate was 46% for self-medication with antibiotics and 76% for dispensing of antibiotics without prescription. Financial issues, time-consuming doctor visits and the lack of strict regulations were the leading reasons for such high rates. β-lactam antibiotics were the most used antibiotic class.

Discussion: The prevalence of over-the-counter use and dispensing of antibiotics is quite high in Egypt, with serious consequences nationally and globally, which call for taking corrective actions. Awareness campaigns for public and health personnel and the enforcement of strict regulations are straightforward and effective interventions.

Conclusion: Intense international efforts are essential to control the inappropriate antibiotic-use in order to limit the spread of AMR and keep our disease-fighting tools effective.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

- AMR …… Antimicrobial Resistance.
- CAPMAS … Central Agency for Public Mobilization and Statistics in Egypt.
- CDC …… Centers for Disease Control and Prevention
- CSF …… Cerebrospinal Fluids
- ESPA …… Egypt Service Provision Assessment
- GDP …… Gross domestic product
- HCV …… Hepatitis C Virus
- MDR …… Multi-Drug Resistant
- MeSH …… Medical Subjected Headings
- MOH …… Ministry of Health
- MRSA …… Methicillin-Resistant Staphylococcus Aureus
- NOS …… Newcastle-Ottawa Quality Assessment Scale
- PICO …… Population, Intervention/Exposure, Comparison & Outcome
- PRISMA … Preferred Reporting Items for Systematic reviews and Meta-Analyses
- UNWO … United Nations World Tourism Organization
- URTIs …… Upper Respiratory Tract Infections
- USA …… United States of America
- USD …… United States Dollar
- UTIs …… Urinary Tract Infections
- WHO …… World Health Organization

1.0. Introduction and Background

For more than 90 years, since Sir Alexander Fleming discovered penicillin (Fleming, 1980), antibiotics have been side by side with humans supporting their immune systems in their vital fight against pathogenic microbes. However, this defense arrangement has become weaker and weaker as a result of the growing spread of antibiotic-resistant bacteria. Generally speaking, bacteria are living microorganisms that exists in nature with a huge variety of strains with different characteristics, and a wide range of them could be pathogenic for humans and animals. A very important characteristic of bacteria is that they are organisms that evolve quickly to respond to challenges, as over the years, they were able to develop different mechanisms and enzymes that made them able to protect themselves against the effect of antibiotics as well as other threats in nature and pass these genes across new generations. It is noteworthy that this is exactly what Sir Fleming warned about in his acceptance speech for Nobel Prize in Medicine 1945, as he stressed on the fact that microbes could easily become resistant to penicillin as a result of using it wrong (Fleming, 1945).

The discovery of penicillin and the further development of the wide range of effective antimicrobials has brought about a medical revolution in treating and controlling the spread of several communicable diseases. A unique success story is the crucial role that the successively developed antibiotics and antibiotic-combinations have been playing in the treatment of tuberculosis since the discovery of the cause of tuberculosis by Robert Koch in 1882 and until present time (Murray, Schraufnagel, & Hopewell, 2015).

As a result of the increasing spread of antibiotic-resistant bacteria, humans seem to be losing their critical advantage over bacteria in this "micro-war", and here is exactly where the problem lies. There is a growing threat that we humans could be on our way to enter a dark tunnel where an initially mild infection could become a dangerous and even fatal disease in the absence of an effective antibiotic, just like our old days before discovering antibiotics.

The reason that makes antimicrobial resistance (AMR) a global public health threat is that antibiotic-resistant bacteria are widely spreadable and not limited to specific regions or countries. The open world that we live in nowadays, where it is easy to travel around the world (except for this year 2020), makes all the edges of the world brought together, from developing to developed countries. A perfect and very live example of the world being interconnected is the super rapid spread of SARS-COV-2 which causes COVID-19 around the world, where there is no longer a single country without positive cases of such disease.

There is a growing attention from the scientific world of studying the role of tourism and international travel in the dissemination of AMR worldwide. It has been shown that several factors can lead to the development of a drug-resistant bacteria in a certain region such as low-quality healthcare, lack of clean water source, insufficient sanitation, and most significantly the excess and inappropriate use of antibiotics (Frost, Van Boeckel, Pires, Craig, & Laxminarayan, 2019). These factors are some of the classic characteristics of most low- and middle-income countries. But with global traveling being easier and more affordable, it would not be challenging for such bacteria to spread across borders. According to the 2018 report from World Tourism Organization (UNWTO), there were more than 1.3 billion tourist arrivals in 2017 (Figure 1), and much higher projections of this number are expected in the future (World Tourism Organization, 2018), unless the SARS-CoV-2 pandemic has a lasting impact.

The consequences of AMR could range from an economic burden to the complete treatment failure of an entire class of infectious diseases. A study published in 2016 found that the treatment of a single case of carbapenem-resistant Enterobacteriaceae infection in the United States could cost more than USD $60,000, and that is a very high load on the healthcare system compared with a non-resistant bacterial infection (Bartsch, et al., 2017).

One of the most infamous examples of AMR is the multidrug-resistant Staphylococcus Aureus (MRSA) which is a common cause of severe infections in health facilities and communities. People with MRSA are more likely to die than people with a non-resistant form of the infection. Furthermore, according to the World Health Organization (WHO), the failure of third-generation cephalosporin antibiotics in treating gonorrhea has been confirmed in at least 10 countries (WHO, 2020). Most of these countries are developed countries, where they have very good antimicrobial stewardship and with low level of antibiotic-misuse. Therefore, AMR is already a universal problem and should be of a global concern, with close surveillance across all countries in order to limit the excess and unnecessary use of antibiotics.

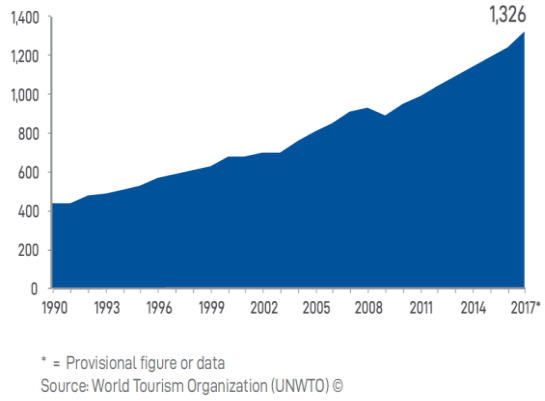


Figure 1: International tourist arrivals (million)

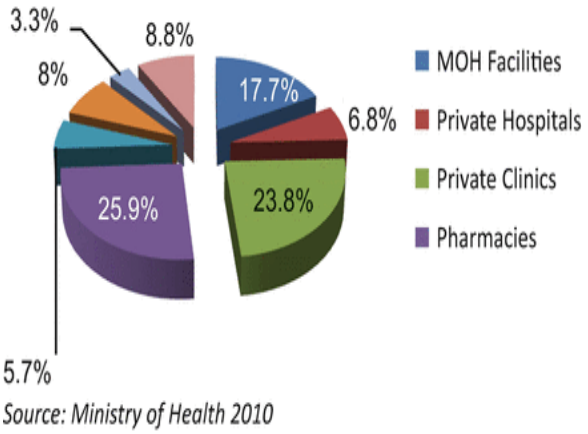


Figure 2: Health expenditure by type of health service provider in Egypt

As mentioned before, several factors can lead to the emergence of bacterial resistance against a certain antibiotic. However, the inappropriate use of antibiotics is considered to be the leading reason, where inappropriate use could mean excessive, insufficient, or unnecessary use. Its importance comes from its huge impact on the evolution and spread of AMR worldwide, and also because it is inexpensive and not so hard to take actions that could limit that issue. This thesis is investigating the problem of excess and unnecessary use of antibiotics in Egypt to determine the size of the problem, its main causes, and possible interventions that could help in promoting a better antibiotic-use practices.

Egypt is the most populous country in the Middle East, and is by many considered to be the region's capital (Sheth, 2017). It is also the largest producer of health personnel in the area so that a great percentage of the non-national work force within health sector, especially pharmacists, in the Gulf countries are Egyptians. A study published in 2018 that investigated the status of licensed pharmacists in Saudi Arabia found that more than 80% of pharmacists are non-Saudis, and 57% of them are Egyptians (AlRuthia, Alsenaidy, Alrabiah, AlMuhaisen, & Alshehri, 2018). Moreover, a systematic review published in 2008 studying pharmacy education and practice in 13 Middle Eastern countries, showed that more than 14,000 students get admission into pharmacy schools every year, and over 75% of them are in Egypt (Kheir, et al., 2008). These facts give the country a strategic importance in regard to suggesting interventions to decrease antibiotics overconsumption and raise the awareness of health professionals about the serious effects of the development and spread of AMR. Another way to look at it is that the situation in Egypt regarding antibiotic dispensing resembles the situation in many low-and middle-income countries, so the results and recommendations could be generalized on a large scale of countries, hence we can plan actions to limit such a problem.

A basic and brief overview of the structure of the healthcare system in Egypt follows; a more detailed explanation is published in the Egypt Service Provision Assessment (ESPA) Survey of 2004 (Ministry of Health and Population, 2005). Egypt spends only 4.75% of GDP on health which is a very low percentage when compared with other low- and middle-income countries (Gericke, Britain, Elmahdawy, & Elsisi, 2018). Briefly describing the assembly of healthcare system and healthcare providers in Egypt, the Ministry of Health (MOH) is responsible for managing the public sector and monitoring the private sector. Health service providers in Egypt could be public hospitals, private hospitals, private clinics, pharmacies, and other minor organizations. When someone feels sick, the first-choice destination would be the pharmacy due to the easy access and the low costs of a medical advice or even treatment

recommendations. If there is a need for reference, the pharmacist would recommend visiting a doctor to get a more comprehensive evaluation of the case. In that instance, the majority would choose to visit a private health facility whether a hospital or a clinic, and that is because of the low service quality and high out-of-pocket payments within the public sector. Figure 2 shows that more than half of health expenditure is received by pharmacies and private clinics and hospitals.

Pharmacies in Egypt represents the low-threshold point of access to health services due to their availability almost all day long, even on weekends, and also because customers do not have to pay extra fees to get medical advice. Most first contact for mild illnesses and minor infections - for which antibiotics are often inappropriately given - is with the local pharmacy. We have data to show that pharmacies tend to give out antibiotics indiscriminately. Hence, these are a very appropriate first target in trying to make a change in antibiotic usage patterns. A pharmacist or a pharmacy technician/assistant can dispense almost any medication without the need of a prescription. However, they refrain from recommending medicines for chronic diseases without a professional medical advice from a doctor. This thesis focuses on the over-the-counter dispensing of antibiotics as it might cause antibiotic misuse, which is a leading reason for the development of AMR. Several studies investigated the dispensing patterns of antibiotics in Egypt, and one of them was a simulated patient study in Upper Egypt. The study found that almost all pharmacies (99%) included in the study dispensed amoxicillin for a simulated patient with a common cold or viral infection, and the majority did it even without collecting enough information that could support that recommendation (Abdelaziz, et al., 2019).

This unattended and irresponsible dispensing of antibiotics from community pharmacies can be explained by the lack of knowledge of the pharmacy worker about the unwanted magnitudes of such practice. A large proportion of the pharmacy staff in Egypt are not trained pharmacists

or even have any pharmaceutical study background; as we see in the previously cited study (Abdelaziz, et al., 2019), in nearly half (44%) of the cases, a non-pharmacist provided the service.

Knowing that antibiotics usually lie in the middle- or high-priced medicines category, seeking financial profit could be a motive that drives a pharmacist to recommend an antibiotic as a treatment choice. First and foremost, a pharmacy is a business that pursues profit, and with the lack of strict rules and regulations that control antibiotics' dispensing, making profit could rule over professionalism. In a study investigating the pharmacists' motives for selling non-prescription antibiotics, that was the statement of a community pharmacist "So, the owner is thinking for the business and getting more money and the pharmacist is under pressure to sell and to get more profit" (Black, Cartwright, Bakharaiba, Al-Mekaty, & Alsahan, 2014).

The WHO commissioned a multi-country public awareness survey to investigate public awareness about antibiotic use, carried out in 2015 among the public of 12 countries, among them Egypt. The survey reported that 32% of all respondents thought that they should stop taking antibiotics when they felt better, and particularly respondents in Egypt and Sudan were likely to think so. Furthermore, 34% of the respondents from Egypt agreed that it is okay to take antibiotics from a friend or a family member so long it was apparently used for the same illness (WHO, 2015). This indicates that there are several ways for people to get antibiotics with, other than a hospital or a pharmacy, and with the absence of a well-established prescription registry, it is almost impossible to track down the actual use of antibiotics in Egypt in order to monitor and control the consumption of such valuable substances.

The Egyptian law of Pharmacy has classified pharmaceutical products into categories according to their toxicity and conditions of purchasing, preservation and dispensing in the pharmacy. The law states that all antibiotics are in Category-2 with other products like

anaesthetics and opioids where dispensing or re-dispensing of such products should only happen according to a prescription from a specialised physician (Ministry of Health, 1971). So, it turns out that there are in fact regulations that prevent selling antibiotics without a prescription, but no one is following them, and no one is monitoring or inspecting the dispensing activities. Pharmacist Asem Seada, who works as a pharmaceutical inspector in the Egyptian pharmacy administration, was asked if they check the regime of antibiotic dispensing during a pharmacy inspection and he answered "For now, we do not have any assignments to check antibiotic dispensing in our inspection procedures" (Seada, 2019). Moreover, despite the availability of the practice guidelines and the complete awareness of physicians over these guidelines, a large share of them tend to prescribe antibiotics even if it is not necessary for the case due to the financial and scientific incentives and other privileges they might get from the pharmaceutical companies selling these antibiotics. However, that is another issue, which is not covered in this thesis.

All of this reinforces the presumption that the inappropriate and unnecessary use of antibiotics in Egypt is a potential problem that calls for urgent and effective interventions. Therefore, the main goal of this thesis is investigating the size of the problem of self-medication and over-the-counter dispensing of antibiotics in Egypt, as well as suggesting some policy prototypes that could fit in the Egyptian context and other countries that have similar conditions as Egypt that may help in controlling and limiting the problem. The thesis is a systematic literature review of the published literature studying the prevalence of antibiotic dispensing without prescription and self-medication with antibiotics. A similar systematic review published in 2017 reviewed the situation of self-medication with antibiotics in the Middle East, but it did not include any studies from Egypt (Alhomoud, et al., 2017). Therefore, it appeared to be useful to conduct such a review about the situation in Egypt in order to point out the problem and suggest possible interventions to limit its consequences.

1.1 Objectives

1.1.1 Primary Objective

The main aim of this thesis is investigating the problem of self-medication and over-the-counter dispensing of antibiotics in Egypt to determine the size of the problem and its main causes.

1.1.2 Secondary Objective

Designing prototypes of policies that are applicable in the Egyptian context to limit the unwarranted overuse of antibiotics.

1.1.3 Research Question

What is the prevalence of self-medication and over-the-counter dispensing of antibiotics in Egypt?

2.0. Methodology

2.1. PICO (Population, Intervention/Exposure, Comparison & Outcome)

The population studied in this review is the Egyptian population generally, with primary focus on Egyptian antibiotic consumers and pharmacy workers. The exposure of interest here is the purchase of antibiotics without a prescription. The comparison would be against people who do not use non-prescription antibiotics or pharmacists who refrain from dispensing antibiotics without a prescription. The primary outcome here is actually getting an antibiotic without a professional medical advice, which in turn might lead to antibiotic misuse, which can plausibly promote the development of antimicrobial resistance as a secondary outcome.

2.2. Definitions, search terms, and search strategy

Self-medication and self-administration are terms that prescribe the action of taking medicine on one's own initiative, or on the advice of another person, without a prescription or consulting a doctor (Hernandez-Juyol & Job-Quesada, 2002). Over-the-counter drug dispensing is the action of selling drugs in pharmacies or elsewhere without a prescription from a registered medical practitioner (Nagaraj, Chakraborty, & Srinivas, 2015). An antibiotic or antibacterial is a natural or synthetic material that can kill or suppress the growth of bacteria with different mechanisms (Felman, 2019).

I have conducted a systematic search of all the available published literature through different databases: Medline, Scopus and ProQuest using different keywords derived from the main keywords (self-medication, over-the-counter, antibiotic and Egypt). The search strategy from the systematic review of Alhomoud et al. was adopted with some reforms to comply with my research question (Alhomoud, et al., 2017). Some keywords were searched as Medical Subjected Headings (MeSH) terms and others as normal phrases. Table 1 shows the search strategy where terms in the same box were combined with OR and the boxes themselves were

combined with AND. Reference lists were also followed up to identify more eligible unidentified studies.

Table 1: A list of search terms used in databases (Medline, ProQuest and Scopus).

Search terms for "Antibiotics"		Search terms for "Self-medication"		Search terms for "Egypt"
"Antibiotic(s)" OR "Antibacterial(s)"	**AND**	"Self-medication" OR "Self-treatment" OR "Self-prescription" OR "Rational use" OR "Appropriate use" OR "Non-prescription"	**AND**	"Egypt" OR "Egyptian" OR "Arab Republic of Egypt"

2.3. Inclusion and exclusion criteria

The literature search included all the published literature until September 2020, and all the identified records were title-screened to exclude duplicated records and studies that were not relevant to the research question. Further screening of the studies' abstracts led to the exclusion of studies; (1) conducted in countries other than Egypt, (2) addressed self-medication generally without exclusive results for antibiotics, (3) based on qualitative analysis, (4) investigated the pattern of antibiotic prescription in hospitals, (5) were systematic reviews not focusing on Egypt, and (6) with unavailable full text. During full-text screening an additional study was excluded due to the unavailability of the results' tables and figures in the study (El Maraghy, Younis, & Abbas, 2016). Studies would be eligible for inclusion, if they were quantitative studies with full texts, investigating the pattern of self-medication with antibiotics, and/or the purchase of antibiotics without a physician's prescription in Egypt. Figure 3 describes the whole process of literature search from records identification and screening to inclusion and exclusion, in the form of a PRISMA diagram (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.4. Quality assessment of included studies

Since all studies included in the review are cross-sectional studies, I have used a Newcastle-Ottawa Quality Assessment Scale (NOS) modified by Modesti et al. in order to assess the methodological quality of the included studies (Modesti, et al., 2016). NOS is a quality assessment tool developed by a collaboration between the Universities of Newcastle, Australia and Ottawa, Canada to assess the quality of non-randomized studies included in systematic reviews and meta-analyses (Wells, et al., 2020). The model used here was modified to fit cross-sectional studies where each study can gain a maximum of 10 stars on a star-based grading system, in which a study is judged on three different aspects: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest (Appendix 1). I also followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines during the development of the study protocol and the analysis plan (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.5. Data extraction and management

I have developed a data abstraction tool and used it to extract data from the included papers (Appendix 2). The characteristics of each study such as the author, study population, study design, and others were noted and arranged in Table 2. The form of result presentation was not consistent in all studies due to the diversity of study subjects. While pharmacy workforce was the study population in some of the studies, other studies took standard citizens or students as their study subjects. Some of the studies presented the results in percentages, others presented them in numbers. Whenever it was possible, results presented in the same way were gathered to obtain a larger study sample and more representative estimates. It is worth mentioning that I attempted to obtain primary data about the overall sales of antibiotics in Egypt across public and private sectors, but the data was only commercially available and at a price that made it unfeasible for this analysis.

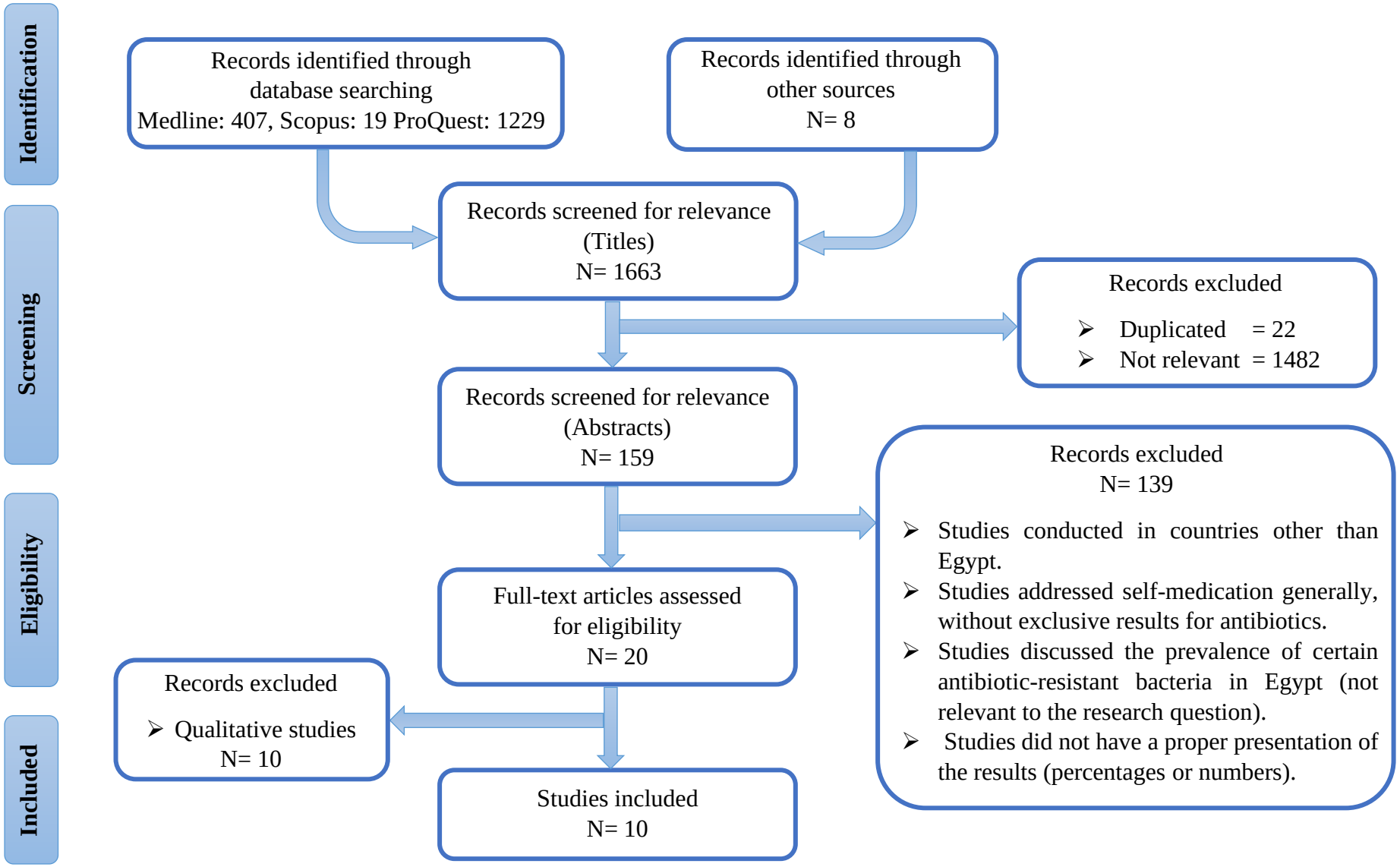


Figure 3. PRISMA diagram of the study identification and selection process.

Table 2: Characteristics of the included studies.

Author	Year	Study subjects	City	Settings	Number of respondents	Age range	Gender	Educational level
Sabry et al.	2014	General public	Cairo	Pharmacies	884	2 – 55	Males 57% Females 43%	Middle school or above 83.5%
Scicluna et al.	2009	General public	----	Out-patient clinics	300	18 – 66	Males 48% Females 50%	Primary education and lower 29% Secondary education and higher 71%
Ghazawy et al.	2017	General public	Minia	Participants' houses	422	18 – 27	Males 46% Females 54%	Primary education and lower 14% Secondary education and higher 86%
El Nimr et al.	2015	General public	Alexandria	Participants' houses	1100	18 – 85	Males 46% Females 54%	Primary education and lower 34% Secondary education and higher 66%
Elmasry et al.	2013	General public	Cairo	Out-patient clinics and University campus	1006	16 – 70	Males 39% Females 61%	Primary education and lower 6% Secondary education and higher 94%
El Hawy et al.	2017	General public	Alexandria	University campus, pharmacies and cafes	359	----	Males 38% Females 62%	Primary education and lower 18% Secondary education and higher 82%
El Ezz et al.	2011	Medical students	Cairo	University campus	300	17 – 24	Males 33% Females 67%	University education 100%
Dooling et al.	2014	Pharmacy workforce	Minia	Public and private pharmacies	483	18 – 68	Males 56% Females 44%	BSc in Pharmacy 63% University level (not pharmacy) 18% Less than university level 18%
Amin et al.	2017	Pharmacy workforce	Alexandria	Private community pharmacies	104	----	-----	------
Abdelaziz et al.	2019	Pharmacy workforce	Minia	Private community pharmacies	238	25 – 51	Males 71% Females 29%	BSc in pharmaceutical sciences 61% Non-pharmaceutical education 29%

Table 3: Summary of methods of data collection and results from the included studies.

Author	Method of data collection	Recall / Study period	Results (Percentage of respondents used non-prescription antibiotics)	Source of antibiotic/ information	Most used class of antibiotics	Quality score (NOS)
Sabry et al.	Questionnaire + Survey	3 months	Out of 884 patients, 404 patients (45.7%) were given an antibiotic without a prescription.	Pharmacy 100%	β-lactams (Penicillins & Cephalosporins)	**6**
Scicluna et al.	Questionnaire	12 months	(30%) of the respondents admitted acquiring antibiotics without a prescription during the last 12 months.	Pharmacy 58.7% Friend or relative 26.3% Leftovers 15%	Amoxicillin/ Ampicillin	**7**
Ghazawy et al.	Questionnaire	1 month	Self-medication with antibiotics was reported by 260 of 422 respondents (61.6%) during the month prior to the study.	Pharmacy 86.7% Family/friends 22.7% Leftovers 79.9%	------	**7**
El Nimr et al.	Questionnaire	12 months	More than half of participants reported self-medication with antibiotics (53.9%).	Old prescription 73.9% Pharmacist 42.7%	------	**8**
Elmasry et al.	Questionnaire	3 months	The total usage rate of unprescribed antibiotics during the 3 months of the study was (29.8%).	------	β-lactams (Penicillins & Cephalosporins)	**7**
El Hawy et al.	Questionnaire	12 months	The use of antibiotics without prescription in the past 12 months was reported by 231 participants (64.3%).	Pharmacies 57% leftovers 12%	Amoxicillin/clavulanic acid combination	**9**
El Ezz et al.	Questionnaire	1 month	Overall consumption of non-prescribed antibiotic was (41.5%).	------	------	**5**
Dooling et al.	Questionnaire	2 months	Overall, 326 (81%) pharmacists reported dispensing antibiotics for treating colds without a prescription.	Pharmacy 100%	β-lactams (Penicillins & Cephalosporins)	**8**
Amin et al.	Simulated Client Approach	1 month	The Simulated Client visited 104 pharmacies and was sold an antibiotic without a prescription at 68 pharmacies in total (65%).	Pharmacy 100%	β-lactams (Penicillins & Cephalosporins)	**7**
Abdelaziz et al.	Simulated Client Approach	3 months	Out of 238 visits of the Simulated Client, Amoxicillin was dispensed without a prescription in (98.3%) of the cases.	Pharmacy 100%	Amoxicillin	**6**

3.0. Results

3.1. Characteristics of the included studies

After the exclusion of duplicated records (n=22) and non-relevant studies based on both title and abstract screening (n=1621), twenty full-text studies were read to check their eligibility. Furthermore, 10 more studies were excluded as they did not meet the inclusion criteria and finally, the remaining 10 studies were included in the review (Figure 3). All the included studies are cross-sectional studies where authors either used Simulated Client approach, questionnaires and/or surveys to collect data on self-medication with antibiotics and its dispensing without prescription. Table 2 shows the detailed characteristics of the included studies.

The included studies were conducted in three major cities across Egypt, namely Cairo, Alexandria and Minia, and were published in the years from 2009 and 2019. Study subjects varied between general public, students or pharmacy workforce, with various study settings such as pharmacies, out-patient clinics, university campuses, houses, cafes and streets. In most of the cases, sample sizes were justified and satisfactory with the peak at 1100 respondents and a minimum of 104 cases. Study subjects had a wide age variation which ranged from (2 – 85 years), as children were represented by their parents or caregivers. Participants in all studies had different educational levels, except for one study (Abou El-Ezz & Ez-Elarab, 2011) where all study subjects were university students.

3.2. Prevalence rate of non-prescription use/dispensing of antibiotics

3.2.1. Self-medication with antibiotics

Out of the 10 studies included in the review, 7 studies investigated the pattern and the rate of self-medication with antibiotics among general public and/or university students. The prevalence rate of non-prescription consumption of antibiotics recorded by the studies ranged from 29.8% (Elmasry, et al., 2013) to 64.3% (El-Hawy, et al., 2017). Gathering results from

the 7 studies yielded a sample size of 4371 participants, out of which 2001 respondents (46%) reported the use of antibiotics during the recall period established by each study, which ranged from 1 to 12 months. Table 4 describes the rate of using antibiotics without prescription from each study separately as well as the overall prevalence rate after combining the results together.

3.2.2. Dispensing antibiotics without prescription

While most of the included studies used questionnaires interviewing general public, three studies focused on pharmacy workforce as study subjects to inspect their pattern of dispensing antibiotics without prescriptions. One study used interview questionnaire also as a method of data collection (Dooling, et al., 2014) and the other two studies used Simulated Client approach (Abdelaziz, et al., 2019) (Amin, Amine, & Newegy, 2017). As it appears in table 5, the rate of dispensing non-prescription antimicrobials ranged from 65% to 98%. I considered the results from the three studies as similar and combined them to get a sample size of 825 pharmacists and assistants with 76% as an overall rate of non-prescription dispensing of antibiotics.

Table 4: The total rate of self-medication with antibiotics among general public in Egypt.

Author	Number of respondents	Prevalence of non-prescription antibiotic use
Sabry et al.	884	404 (45.7%)
Scicluna et al.	300	90 (30%)
Ghazawy et al.	422	258 (61.6%)
El Nimr et al.	1100	593 (53.9%)
Elmasry et al.	1006	300 (29.8%)
El Hawy et al.	359	231 (64.3%)
El Ezz et al.	300	125 (41.5%)
Total	**4371**	**2001 (45.8%)**

Table 5: The total rate of dispensing antibiotics without prescription among pharmacy workforce in Egypt.

Author	Number of respondents	Prevalence of dispensing antibiotics without prescription
Dooling et al.	483	326 (81%)
Amin et al.	104	68 (65%)
Abdelaziz et al.	238	234 (98.3%)
Total	**825**	**628 (76.1%)**

3.3. Indications and motives for non-prescription use/dispensing of antibiotics

Except for (El-Nimr, Wahdan, Wahdan, & Kotb, 2015) and (Abou El-Ezz & Ez-Elarab, 2011), all the other included studies reported the most frequent symptoms that required using/dispensing a non-prescription antibiotic. Common cold, flu, fever, tonsilitis and sore throat came as the most reported symptoms, and all of them are respiratory tract symptoms. Urinary tract infections (UTIs) was reported by (Sabry, Farid, & Dawoud, 2014) as the leading cause to urge dispensing or recommending an antibiotic by a pharmacy staff. Acute bronchitis, common cold and fever were used as case scenarios in pharmacy visits by the simulated-client studies (Amin, Amine, & Newegy, 2017) (Abdelaziz, et al., 2019).

Seven of the included studies focused on general public as study subjects and their pattern of self-medication with antibiotics. Almost all these studies mentioned the most recurrent reasons and motives of self-medication. Both physician's consultation being time consuming and financial issues were reported as the leading causes for self-medication, followed by having a previous experience with the same symptoms being "cured" by antibiotics (by their own subjective assessment). While (Elmasry, et al., 2013) and (Ghazawy, Hassan, Mohamed, & Emam, 2017) reported that perceiving common illnesses as minor and not worthy of physician's consultation was a common motive for self-medication, (Scicluna, et al., 2009) stated that a large proportion of participants believed that they did not need a prescription to purchase an antibiotic from the pharmacy.

On the other side, only one study discussed the motives that drive pharmacy staff to dispense antibiotics without prescriptions (Dooling, et al., 2014). Client demand and seeking financial profit came in the front of possible motives, followed by the pursuit of gaining client's loyalty. While some pharmacists argued that they are capable of properly evaluating whether an antibiotic treatment was necessary or not, most of them thought that antibiotics are available

and easily accessible without a prescription, and if they refrained from dispensing an antibiotic upon a customer's request, he will definitely get it from another pharmacy.

3.4. Source of antibiotic, information and recommendations, and the antibiotic classes most frequently used/dispensed without a prescription.

The commonest source of self-medication antibiotics as well as the recommendations and information regarding self-medication was the pharmacy, namely pharmacists and assistants. (El-Nimr, Wahdan, Wahdan, & Kotb, 2015) stated that pharmacies were common sources of non-prescribed antibiotics because of the fact that pharmacists do not request a prescription to dispense an antibiotic or charge for their medical advice. Leftovers and old prescriptions were the second most common source of self-medicated antibiotics followed by friends and family as the least common source.

The most frequently used antibiotic class was β-lactam antibiotics in all the papers. While Amoxicillin name was mentioned by (Scicluna, et al., 2009) and (Abdelaziz, et al., 2019), (Elmasry, et al., 2013) ranked them by class as Penicillins being the most common followed by cephalosporins, macrolides and least used were quinolones. The combination of Amoxicillin/Clavulanic acid was reported by (El-Hawy, et al., 2017) as the popular choice for self-medication.

3.5. Factors associated with non-prescription use/dispensing of antibiotics

Half of the included studies tried to investigate the correlation between self-medication and a number of factors. Elmasry reported a significant correlation between self-medication and age, socio-economic level, and occupation, along with Ghazawy who found that number of family members had also a strong relation with self-medication (Elmasry, et al., 2013) (Ghazawy, Hassan, Mohamed, & Emam, 2017). Moreover, El Nimr declared a significant association between self-treatment and almost all the factors, while gender was the only

considerably correlated factor in El Hawy's study (El-Nimr, Wahdan, Wahdan, & Kotb, 2015) (El-Hawy, et al., 2017). On the other hand, only one study tested the association between non-prescription antibiotic dispensing and the characteristics of the pharmacy staff, and they found that having less than a university education was the only factor strongly correlated with inappropriately recommending antibiotics for colds by a pharmacy staff (Dooling, et al., 2014).

4.0. Discussion

Antimicrobial resistance is a serious public health threat that affects the whole world medically and economically. The inappropriate and unnecessary use of antibiotics that results from either self-medication, non-prescription dispensing or over prescription, is documented as an important contributing factor in exacerbating the spread of AMR (Michael, Dominey-Howes, & Labbate, 2014). It is true that antimicrobial self-medication and non-prescription dispensing of antibiotics are issues not just limited to low- and middle-income countries, since a high prevalence was reported by a study from Spain, where more than half of the visited pharmacies dispensed antibiotics without a prescription (Guinovart, Figueras, & Llor, 2018). However, the magnitudes of AMR would negatively affect low- and middle-income countries the hardest, due to the weak infrastructure of health systems and the generally low healthcare standards in these countries.

According to a comprehensive study by Klein and colleagues, Egypt was ranked third among the highest low- and lower-middle-income countries regarding antibiotic consumption during the year 2015 (Klein, et al., 2018). Several systematic reviews have been conducted to address the issue of excessive and unnecessary use of antibiotics in developing countries, and countries of the Middle East, without reporting the situation in Egypt (Alhomoud, et al., 2017) (Sakeena, Bennett, & McLachlan, 2018). Therefore, this review aimed to gather the results available from the published literature to provide solid evidence on the improper use of antibiotics in Egypt and highlight the strategic importance of applying corrective interventions in Egypt in tackling the spread of AMR.

The initial idea of the thesis was getting primary data of antibiotic sales in Egypt during the period from 2000 to 2020 and comparing them with the numbers of Norway after adjusting for several confounding factors. I requested the data from IQVIA, which is an international

company that possesses reliable statistical sales data of medications across the world and sells this data for marketing and scientific purposes (IQVIA, 2020). However, it turned out that obtaining this primary data was far too expensive for the purposes of a master thesis. Thus, I modified the thesis methodology to be a systematic review depending on the data collected by published literature.

4.1. Statement of the principal findings and its consistency

This review aimed at summarizing the situation in Egypt regarding the pattern of non-prescription use and dispensing of antibiotics. The overall prevalence rate of self-medication with antimicrobials among general public was relatively high (46%), as well as the rate of dispensing antibiotics without prescription (76%), which are quite alarming. Also, the review tried to identify some of the reasons and factors related to this high prevalence. Financial issues, time consuming doctor visits and the ease of accessing antibiotics were the most commonly cited reasons for self-medication. Occupation was a leading factor that had a significant effect in most of the studies, and that is understandable since it is a fundamental aspect of socio-economic status. As per pharmacy staff, pursuing financial profit and the absence of strict regulations were the driving motives for dispensing non-prescription antibiotics, while the staff's level of education was the factor with the strongest effect. Identifying these factors and reasons is very important when it comes to designing policies and interventions to tackle such a problem.

Antimicrobial use, whether it is prescription or non-prescription, exerts antimicrobial selection pressure, which is a core mechanism in developing bacterial resistance against antibiotics (Spellberg, et al., 2008). However, non-prescription dispensing of antibiotics is usually accompanied with the lack of proper counselling and complete instructions on how to use medications, as mentioned by most of the studies included in the review. Hence, a high

tendency was reported among the public to stop taking medications once the symptoms disappeared and keep antibiotic leftovers to use it further if they became sick again. Moreover, Scicluna et al. found a significant association between the act of hoarding antibiotics and self-medication, and therefore, leftovers were an important source of acquiring non-prescription antibacterial agents (Scicluna, et al., 2009). Furthermore, it is so common in Egyptian pharmacies to dispense sub-therapeutic doses of antibiotics either upon client request or as a part of a cold treatment course called as "Cold Group", and this gives the same result as discontinuing medications upon symptomatic improvement (Amin, Amine, & Newegy, 2017). All these factors make non-prescription more problematic than prescription use of antibiotics.

Numerous similar systematic reviews were published exploring the rate of self-medication with antibiotics and their non-prescription dispensing on either global, regional or country levels. The rate of self-medication in this current review was similar to that of a global review, where the rate of using non-prescription antibiotics within African population was 48% (Morgan, Okeke, Laxminarayan, Perencevich, & Weisenberg, 2011). An even higher global rate (59%) was calculated by another worldwide review, with studies conducted in developing countries reporting the highest prevalence (Limaye, Limaye, Krause, & Fortwengel, 2017). The most commonly used antibiotic class in both these reviews was Penicillins, while amoxicillin was mentioned by name as the most popular antibiotic in another systematic review (Aceijas & Henry Selvaraj, 2019), which are all in line with the results of this review. Just like it is in this review, the most recurrent source of antibiotic and information in all the three other systematic reviews was the pharmacy (Aceijas & Henry Selvaraj, 2019) (Morgan, Okeke, Laxminarayan, Perencevich, & Weisenberg, 2011) (Limaye, Limaye, Krause, & Fortwengel, 2017). Furthermore, two other worldwide systematic reviews were published investigating the practice of dispensing antibiotics without prescription. The pooled rate in this review was 76%, whereas Auta et. al. found that the overall proportion of non-prescription supply of antibiotics

was 62% (Auta, et al., 2019). However, the prevalence rate in the other review was extremely variable, as it ranged from 8% to 100% without calculating a pooled estimation (Sakeena, Bennett, & McLachlan, 2018).

4.2. Consequences and magnitudes of the excessive unnecessary use of antibiotics

4.2.1. Multi-drug resistant bacterial infections

The improper and careless use of such exceptionally valuable substances as antimicrobial agents would definitely result in worldwide negative effects on the scale of public health and economic development. The inappropriate use of antibiotics in Egypt is not limited to non-prescription use, as physicians' prescribing practice is not optimal in either private or public sectors. A point prevalence survey of antibiotics use conducted in 18 public Egyptian hospitals reported a very high rate, as 59% of the patients admitted to these hospitals received at least one antibiotic (Hassan, Ibrahim, & Guinaidy, 2011). Another study was performed in Orthopedic Department, Tanta University hospital stated a remarkably high rate of antibiotic prescription (98%) and a very low appropriateness level (11%) (Talaat, et al., 2014). Moreover, Aboelhassan and colleagues found that 46% of the patients admitted to Cairo University Hospital were improperly prescribed antibiotics for treating acute viral respiratory tract infections, which are not susceptible to antibacterial agents (Aboelhassan, Rezk, Saber, & Al-Harrass, 2019).

This excessive and unwarranted use of antibiotics could lead to dire consequences for the public health status of Egyptians; this has already begun to manifest in the form of the spread of multi-drug resistant (MDR) bacteria in the Egyptian community. In a semi-international study reporting the incidence of β-lactam resistant Enterobacteriaceae in 17 different countries, the rate was very high in Egypt (38.5%) compared to countries with better profile of antibiotic stewardship, like The Netherlands (2%) and Germany (2.6%) (Bouchillon, et al., 2004).

Numerous studies have estimated the prevalence of MDR bacteria in Egypt and found that proportions were either high or very high. In a study performed in 3 large university hospitals in Egypt on bloodstream infections, they found that 60% of the isolated *Staphylococcus Aureus* cultures were methicillin resistant, whereas 79% and 39% of *Klebsiella Pneumonia* and *Escherichia Coli* isolated cultures respectively exerted β-lactamase enzymes (Saied, et al., 2011). Another study, focused on meningitis-causing bacteria through testing antibiotic susceptibility on cultures isolated from cerebrospinal fluids (CSF), revealed that 37% of the isolates were MDR and 100% of them were resistant against *Penicillin* and *Ampicillin* (Abdelkader, Aboshanab, El-Ashry, & Aboulwafa, 2017). Unlike the previous two studies, Khalifa and colleagues gathered bacterial cultures from diverse body tissues like blood, urine, respiratory sputum, and skin, and they reported that the proportion of MDR bacterial phenotypes were as high as 93%, where 75% of the bacterial cultures released β-lactamase enzymes and 59% of them were resistant against quinolones (Khalifa, et al., 2019).

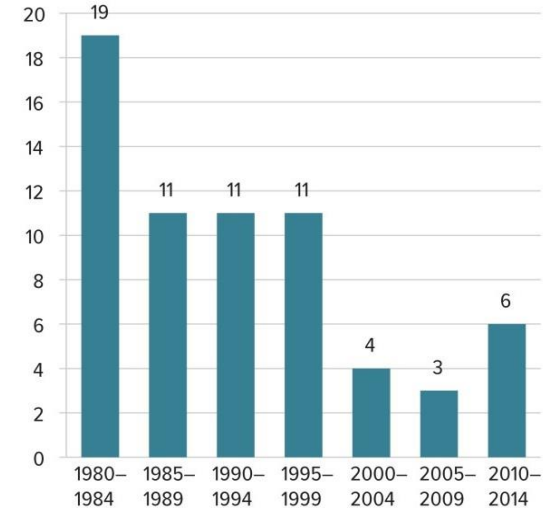
As mentioned before, AMR could create a huge financial load on health systems due to the complexity of treating multi-drug resisting bacterial infections. This financial burden would be worse in low- and middle-income countries given the magnitude of the problem and the limited healthcare budgets of these countries. In Egypt, the public healthcare system is poorly constructed with a very low proportion of the GDP spent on health (4.75%) (Gericke, Britain, Elmahdawy, & Elsisi, 2018). With the increasing spread of bacterial infections resistant to conventional antibiotics, it would be necessary to use new and expensive treatment choices. These extra costs could be beyond the limited means of the healthcare system as well as the patients themselves, leading to the system's collapse with higher rates of mortality from communicable diseases.

4.2.2. Imbalance in the supply and demand curves of antimicrobial agents

The excessive and unnecessary use of antibiotics poses a heavy weight on the demand side of the scale causing an imbalance between demand and supply, along with the critical decline of investment in researching new antibiotics. The number of new antibacterials approved for use in the USA has fallen over time, which is a potential indicator on the drop of research activities developing new agents (Figure 4) (Ventola, 2015). The lack of interest in this research field is understandable and can be attributed to multiple factors. Firstly, the improper use of antimicrobial agents leading to the accelerating spread of bacterial resistance makes the pharmaceutical companies reluctant to spend huge funds for developing a new drug that could lose its efficacy in short time. According a report by the Centers for Disease Control and Prevention (CDC), several bacterial strains has developed resistance against newly approved antibiotics in a very brief period after their approval such as *Daptomycin* and *Ceftazidime-Avibactam* (Figure 5) (CDC, 2019). This actually corresponds with the reality that Egyptian pharmacists would tend to promote and dispense newer antibiotics preferentially as a mark of cleverness to gain the loyalty of new customers as stated by the pharmacists themselves (Dooling, et al., 2014). In addition, high profit margins at the point of sale for these costly new drugs are a further incentive for pharmacists to dispense them.

Secondly, antibiotics are primarily intended to be short term curative drugs, where the treatment course is short and less expensive when compared with drugs treating chronic and complicated diseases. Along the same lines, when a pharmaceutical company invests in a new drug and brings it to market, they put a high price on it to compensate its development costs that could reach nearly 1 billion USD (Wouters, McKee, & Luyten, 2020). This would limit the new product's market to high-income countries that are capable of buying and applying it in their treatment regimens, while low- and middle-income countries, where infectious diseases

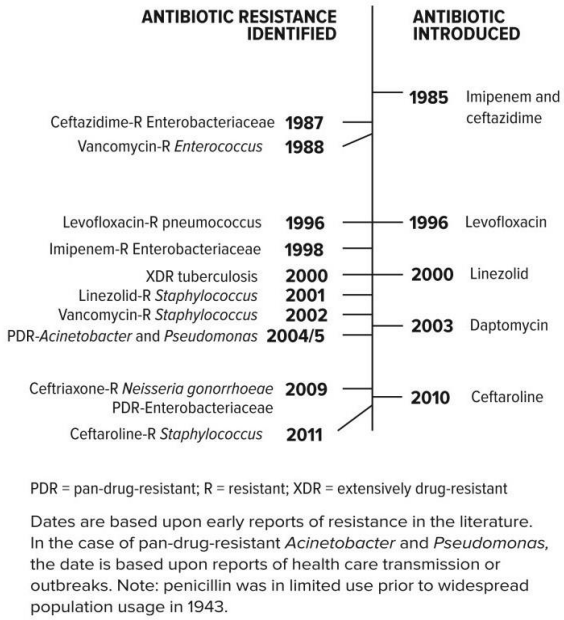
are most common, would not be able to afford it. These factors and more make researching new antibiotics less appealing to investors and pharmaceutical companies.



The number of new antibiotics developed and approved has decreased steadily over the past three decades (although four new drugs were approved in 2014), leaving fewer options to treat resistant bacteria.

Figure 4: Number of new antibiotics approved in USA versus year intervals

Source: (Ventola, 2015)



PDR = pan-drug-resistant; R = resistant; XDR = extensively drug-resistant

Dates are based upon early reports of resistance in the literature. In the case of pan-drug-resistant *Acinetobacter* and *Pseudomonas*, the date is based upon reports of health care transmission or outbreaks. Note: penicillin was in limited use prior to widespread population usage in 1943.

Figure 5: The development of antibiotic resistance: A timeline of key events.

Source: (Ventola, 2015)

4.3. Interventions applied globally to limit the unwarranted use of antibiotics

Interventions intended to halt the inappropriate use, dispensing and prescribing of antibiotics should originate from the factors and reasons causing such behavior. For instance, to overcome physicians' over-prescription of antimicrobials, we need educational and legislative measures addressed to this category of community, and so on. A group of effective government policies and interventions applied in various regions around the world to reduce human antimicrobial use were reviewed in a comprehensive systematic review published in 2019 (Rogers Van Katwyk, et al., Government policy interventions to reduce human antimicrobial use: A systematic review and evidence map, 2019). The interventions listed in the review were directed to health care workers, pharmacists and general public, and they ranged from educational and awareness campaigns to the making of new laws and regulations or the enforcement of already existing ones. Solutions could also come from decreasing the need and

demand for antibiotics at the first place. This could be achieved by improving the level of sanitation and the access to a clean water supply, especially in the poor districts of low- and middle-income countries. Promoting vaccination against MDR bacteria is also a good approach to lessen the complexity of treating infectious diseases. Another promising intervention could be establishing publicly funded laboratories with high capacities to identify infectious agents through bacterial cultures and determine the antibiotic of choice for each infection and avoid wasting valuable last resource antibiotics on simple cases. Facilitating the access to proper and reasonable health services is very important too, and therefore, strengthening the infrastructure of healthcare systems is decisive in combating the viciously growing antimicrobial resistance.

4.4. Possible effective interventions that could fit in the Egyptian context

4.4.1. Public awareness campaigns

The highly digitalized world we live in, makes it appear easy and inexpensive to deliver any sort of message to a wide range of audiences through different communication channels such as TV, radio and all kinds of social media platforms. This represents a golden opportunity to educate the public about the dire consequences of AMR and engage them more as vital contributors in promoting healthy use of antibiotics, through producing creative shows, TV-spots and commercials. Since the 1990s, television and radio have played a critical role in discussing and improving the social and health behaviors of Egyptians with series and podcasts specifically developed to address such issues (Elkamel, The use of television series in health education, 1995). While family planning and anti-female genital mutilation (FGM) TV-promotions were the most famous campaigns with many catchy phrases, TV-spots and commercials have targeted other health issues such as vaccination, breastfeeding, hepatitis C (HCV) and nutrition (Elkamel, 2020). These campaigns appeared to have a notable effect in modifying social and health behaviors, as described by Farag Elkamel in his paper “Knowledge and Social Change” (Elkamel, 2019).

Social media platforms are also a great arena for sharing educational awareness messages by using the advertising tools connected to these websites, which is usually cheaper and often more targeted than using television advertisements. A comprehensive report on the internet-penetration in Egypt found that 41% of the population are active social media users, with Facebook, YouTube, WhatsApp, FB Messenger and Instagram as the top 5 most commonly used platforms in Egypt (Kemp, 2020). The same report stated that more than 75% of the advertising audience are from 18 to 44 years old. This age range is an important target for such campaigns to raise their awareness of proper antibiotic use and the possible harmful effects of AMR, as they are either independent university students, educated working youths, or fathers and mothers.

4.4.2. Educational and training-based interventions directed to healthcare personnel

Health care workers, either physicians or pharmacists, are the corner stone in the cycle of antibiotic use by prescribing or dispensing. Therefore, they are crucial targets in the action-plan for limiting the inappropriate medicine-use. The educational curriculum of medical and pharmacy schools should give AMR a higher attention and stress on the importance of adhering to the international guidelines for treating infectious diseases. Even for practicing physicians and pharmacists, it has been proven that educational interventions always have positive effect in decreasing the rate of antibiotic prescription and dispensing as well as the appropriateness of the prescribed antibiotic class (Roque, et al., 2014).

Numerous studies were conducted to explore the effect of educational approaches in raising the level of adherence to guidelines and shrinking the frequency of antibiotic prescription. Two studies have found a significant change in the antibiotic-prescription practice between before and after applying educational courses to the physicians treating upper respiratory tract infections (URTIs), with 8% reduction in the rate of antibiotic prescription (Ahmed & Soltan,

2018) and an adherence rate improved from 54.7% to 78.2%, and these improvements were statistically significant (Amer, Bedwani, Shehata, & Abouelfetouh, 2018). Another study focused on the use of antimicrobials for surgical prophylaxis in five Egyptian surgical hospitals and found that all the parameters of prescribing practice have significantly improved after holding a two-day training program for the physicians involved in surgical procedures in these hospitals (Saied, et al., 2015). However, Kandeel and his group chose to direct their educational campaign to a wider range of audience including the physicians, pharmacists and general public in Minya district, Egypt, and reported positive outcomes of their campaign at all levels of study subjects (Kandeel, et al., 2019). All that indicates the crucial corrective role that educational interventions could play in improving antibiotic use patterns in Egypt.

4.4.3. Designing new policies and regulations along with enforcing the existing ones

As a pharmacist, I was privileged to practice pharmacy in Egypt, Saudi Arabia and Norway and experience the very distinct patterns of dealing with antibiotics in three countries that have widely different levels of personal income. In Egypt, despite the existence of laws and regulations that designate antibiotics as a prescription-only drugs, pharmacy workforce kept dispensing antibiotics without prescriptions and ignoring these regulations, and that is due to the lack of control from governmental bodies (Ministry of Health, 1971). This situation was the same in Saudi Arabia until May 2018 when the Saudi government decided to put the law in action and revealed that lawbreakers will be subjected to legal penalties such as withdrawal of pharmacy practicing license, a massive fine that could reach to $ 25,000 or even spending 6 months in prison in case of violations (Saudi Ministry of Health, 2018). Nevertheless, the situation is very different in Norway with quite low level of antibiotic consumption, as they have always been prescription-only medicines, along with a strong commitment to the guidelines in both primary care and hospitals and the presence of a surveillance system for outpatient antibiotic use (Gravningen, Field, Blix, Asfeldt, & Småbrekke, 2020).

The effect of the law enforcement in Saudi Arabia was phenomenal as the non-prescription antibiotic sales declined sharply. In fact, I have experienced that influence myself, but it was also scientifically proved by a before-and-after study that used the Simulated Client approach and found that dispensing antibiotics without prescription dropped from 96% and 87% to 12% and 5% for pharyngitis and urinary tract infection simulated client scenarios, respectively (Alrasheedy, et al., 2020). Applying legal interventions has been evidenced effective in many countries around the world, especially low- and middle-income countries like in Latin America as reported in several studies from this area (Rogers Van Katwyk, et al., 2019). In Egypt, the regulations and inspection teams are already there, but what is needed is to put these rules in action and assign those inspectors with tasks related to antibiotic dispensing control.

Another promising policy prototype that could be directed to improper prescription practices, is excluding antibiotics from the marketing activities of pharmaceutical companies by designing regulations that force physicians to prescribe antibiotics by their generic names. Despite the availability of the guidelines and the full awareness of physicians with it, a large proportion of them incline to prescribe antibiotics unnecessarily, tempted by the scientific and financial privileges they might get from the pharmaceutical companies when they prescribe their medicines frequently. I could not find a paper to support this claim, but it is well-known in the Egyptian drug-marketing community that pharmaceutical companies tend to make deals with physicians in order to increase the sales of their products on prescriptions. The application of this policy would neglect any bias factors that could affect the physician's recommendation other than the case itself.

4.4.4. Strengthening the healthcare system's infrastructure

While all the previous interventions would not need so much funding and should be relatively simple to carry out, the upcoming ones could be more complicated and would certainly need a higher proportion of GDP to be assigned for health sector.

One of the important factors that drive people towards the community pharmacy when they are sick is the weakness of the public healthcare system and its inferior service quality. Since 32.5% of Egyptians live under the poverty line (CAPMAS, 2019, p. 77), it would be unaffordable for most of them to access a proper health service when needed. In Egypt, only students and regular employees have health insurance (Gericke C. B., 2018). Expanding the coverage of health insurance would secure the access to appropriate health services and decrease the financial burden of healthcare on poor families. Therefore, improving the public health sector to have better service quality and less out-of-pocket payments would be crucial for enhancing the public health of Egyptians and reduce the unwarranted use of antibiotics. The health care system reform should also involve the establishment of laboratories with high capacities to perform bacterial cultures and determine the antibiotic of choice for each infection case.

Despite the accelerated penetration of technology in nearly all life activities around the world, a very minor share of pharmacies in Egypt use computers and internet in their work, while the rest are operating 100% manually. That makes it almost impossible to monitor and accurately track the change in antibiotic dispensing patterns, and as a well-known proverb says, "If you cannot measure it, you cannot improve it". Therefore, it is important to push for the digitalization of pharmaceutical services in Egypt, which can be achieved on several steps as a long-term action-plan. This action-plan could start with introducing a new prerequisite about having a computer and internet connection as one of the requirements for opening a new

pharmacy and allow a specific deadline for the already existing pharmacies to apply this term. Having a well-established network between pharmacies and other health care providers would pave the way for establishing a national prescription registry, that would facilitate keeping prescribing and dispensing activities under surveillance, just the way it is in developed countries like Norway (Gravningen, Field, Blix, Asfeldt, & Småbrekke, 2020).

4.5. Strengths and limitations of the review

To the best of my knowledge, this is the first systematic review to assess the prevalence, possible causes, and clinical outcomes of antibiotic self-medication and non-prescription dispensing as well as to identify recommendations to reduce the irrational use of antibiotics in Egypt. The manual follow-up of and texts within articles allowed the inclusion of additional relevant articles that did not appear in search results. The strategic importance of Egypt as a target for applying corrective interventions has made the review meaningful and necessary.

Despite the thorough search that has been done on various databases, this review is still affected by a degree of publication bias. The absence of a national prescription registry or any other authentic record for dispensing activities, makes it challenging and demanding to conduct studies exploring antibiotic-use patterns in Egypt. Therefore, the scarcity in the published literature studying the situation of self-administration and non-prescription purchasing of antibiotics necessarily limited the number of included studies. More relevant studies could have given more precise and representative results. Also, only studies published in English language were included, which might have caused missing a number of relevant studies. Being the only reviewer could be another limitation which could lead to a bias in selecting relevant studies and applying the inclusion and exclusion criteria. All the included studies were performed in 3 major cities in Egypt raising the possibility of population selection bias, although these three cities do account for about 30% of Egypt's total population (CAPMAS, 2020). Also, the

methodology of the included studies was not consistent. However, as most of the studies used questionnaires, the impact of methodological variation on the validity of the results is likely to be minimal.

Some limitations originated from the methodological nature of he included studies. Since the majority of the studies used self-reported measuring tools, there was a high potential for social desirability bias, which is the tendency of participants to choose socially acceptable responses rather than choosing responses that reflect their true feelings or practices. Also, studies based on questionnaires are usually prone to recall bias, but some of the included studies tried to overcome this bias by limiting the recall period to 1 – 3 months (Elmasry, et al., 2013). Although only three studies had a grade 8 or higher on the NOS assessment scale, just one of them got a grade lower than 6.

4.6. Recommendations

There is an urgent need for more studies exploring the pattern of antibiotic use in Egypt and not just in the big cities, as it was challenging to find plenty of relevant studies. Also, the lack of a validated method for collecting the data on antimicrobial use would suggest establishing a standardized, validated survey instrument that can efficiently assess antibiotic-use behaviour on a large scale. In my opinion, studies based on simulated client approach were more reliable and resistant to bias. Therefore, I would recommend conducting more studies by the same methodology in various regions within Egypt.

This systematic review is meant to be utilized by decision-makers in Egypt to take actions against the inappropriate use of antibiotics and halt the growing threat of AMR. Since the issue of AMR is a global problem, it is not expected that a single country would be able to control its growth. Therefore, it is important that WHO and other international health organizations apply some pressure on the governments of countries that have high rates of non-prescription

antibiotic-use to put all the needed laws and regulations into action. As not every intervention would be effective in every country, it was essential to identify just some of the solutions that could make a difference in the Egyptian context and similar communities. There are a lot of missed chances to raise the public health of Egyptians, and it is to be hoped that decision makers will be able to take the necessary actions in order to seize some of these opportunities.

5.0. Conclusion

According to the WHO, at least 700,000 people die of an antimicrobial resistant infection every year (WHO, 2019). However, by 2050, it is estimated that 10 million lives would be in danger, and a possible cumulative economic loss of nearly 100 trillion USD due to the growing spread of AMR (WHO, 2019). Being a global threat, AMR calls for urgent international efforts to limit the unnecessary consumption of antibiotics and launch antibiotic-stewardship programs around the world especially in low- and middle-income countries.

The results of this systematic review indicate high rates of non-prescription dispensing and use of antibiotics. These activities are usually linked with the improper use of antibiotics, which can be avoided through the application of various strategies and policies that have been proven effective in other countries with similar conditions as Egypt. Public awareness campaigns, educational and training programs for physicians and pharmacists, improving the infrastructure of the health delivery system and the enforcement of laws and regulations are very promising strategies to decrease the unwarranted use of antimicrobials in Egypt. Most of these corrective measures are not too complicated to be applied and not financially demanding either.

The WHO and other international health organizations should apply some pressure on the government to enforce the already existing laws and regulations and establish more stringent inspecting procedures. Despite the announcement of finalizing a national action-plan to combat AMR in Egypt, it was neither published nor applied (WHO, 2018). The WHO should enact its parental role to monitor the release of such action-plan and ensure its application.

The most challenging phase of producing this review was finding relevant studies, due to the scarcity of published literature from Egypt. Therefore, more studies are needed and best to be conducted using the simulated client approach as it could be more representative with less sources of bias.

References

Abdelaziz, A. I., Tawfik, A. G., Rabie, K. A., Omran, M., Hussein, M., Abou-Ali, A., & Ahmed, A.-S. F. (2019). Quality of Community Pharmacy Practice in Antibiotic Self-Medication Encounters: A Simulated Patient Study in Upper Egypt. *Antibiotics*, 8-35.

Abdelkader, M. M., Aboshanab, K. M., El-Ashry, M. A., & Aboulwafa, M. M. (2017). Prevalence of MDR pathogens of bacterial meningitis in Egypt and new synergistic antibiotic combinations. *PLoS One*, 12(2), e0171349.

Aboelhassan, U. E., Rezk, M. S., Saber, T., & Al-Harrass, M. (2019). Inappropriate Antibiotic Prescription for Acute Viral Respiratory Tract Infections in Egypt, Single Center Experience. *EC Pulmonology and Respiratory Medicine*, 8.7: 579-585.

Abou El-Ezz, N. F., & Ez-Elarab, H. S. (2011). Knowledge, attitude and practice of medical students towards self medication at Ain Shams University, Egypt. *Journal of preventive medicine and hygiene*, 52, 196-200.

Aceijas, C., & Henry Selvaraj, D. (2019). Global Availability and Use of Over the Counter Antibiotics (OTCA): A Systematic Literature Review. *Acta Scientific Dental Scienecs*, 3:9, 92-104.

Ahmed, S. F., & Soltan, E. M. (2018). Optimizing Clinical Diagnosis and Antibiotic Prescribing for Common Respiratory Tract Infections, Fanara Family Health Center-Rural Egypt. *The Egyptian Journal of Community Medicine*, 36(1), 105-115.

Alhomoud, F., Aljamea, Z., Almahasnah, R., Alkhalifah, K., Basalelah, L., & Alhomoud, F. K. (2017). Self-medication and self-prescription with antibiotics in the Middle East—do they really happen? A systematic review of the prevalence, possible reasons, and outcomes. *International Journal of Infectious Diseases*, (57) 3-12.

Alrasheedy, A. A., Alsalloum, M. A., Almuqbil, F. A., Almuzaini, M. A., Aba Alkhayl, B. S., Albishri, A. S., . . . Anaam, M. S. (2020). The impact of law enforcement on dispensing antibiotics without prescription: a multi-methods study from Saudi Arabia. *Expert Review of Anti-infective Therapy*, 18(1), 87-97.

AlRuthia, Y., Alsenaidy, M. A., Alrabiah, H. K., AlMuhaisen, A., & Alshehri, M. (2018). The status of licensed pharmacy workforce in Saudi Arabia: a 2030 economic vision perspective. *Human resources for health,*, 16-28.

Amer, S. K., Bedwani, R. N., Shehata, G. M., & Abouelfetouh, A. (2018). Improving Physicians' Adherence to Guidelines Regarding Antibiotics Use in Acute Upper Respiratory Tract Infections in Adult Patients Attending Ministry of Health Hospitals in Alexandria, Egypt: An Interventional Study. *Journal of Microbial & Biochemical Technology*, 10(1), 16-19.

Amin, M., Amine, A., & Newegy, M. (2017). Injudicious Provision of Subtherapeutic Doses of Antibiotics in Community Pharmacies. *INNOVATIONS in pharmacy*, 8(1): Article 18.

Auta, A., Abdul-Hadi, M., Oga, E., Adewuyi, E. O., Abdu-Aguye, S. N., Adeloye, D., . . . Morgan, D. J. (2019). Global access to antibiotics without prescription in community pharmacies: A systematic review and meta-analysis. *Journal of Infection,* 78, 8-18.

Bartsch, S. M., McKinnell, J. A., Mueller, L. E., Miller, L. G., Gohil, S. K., Huang, S. S., & Lee, B. Y. (2017). Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. *Clinical microbiology and infection*, 23(1): 48.e9–48.e16.

Black, E., Cartwright, A., Bakharaiba, S., Al-Mekaty, E., & Alsahan, D. (2014). A qualitative study of pharmacists' perceptions of, and recommendations for improvement of antibiotic use in Qatar. *Int J Clin Pharm*, 36, 787–794.

Bouchillon, S. K., Johnson, B. M., Hoban, D. J., Johnson, J. L., Dowzicky, M. J., Wu, D. H., . . . Bradford, P. A. (2004). Determining incidence of extended spectrum beta-lactamase producing Enterobacteriaceae, vancomycin-resistant Enterococcus faecium and methicillin-resistant Staphylococcus aureus in 38 centres from 17 countries: the PEARLS study 2001-2002. *International journal of antimicrobial agents,*, 24(2), 119–124.

CAPMAS. (2019). *Income, expenditure and consumption survey.* Cairo: Central Agency for Public Mobilization and Statistics (CAPMAS). Retrieved from http://www.capmas.gov.eg/Pages/StaticPages.aspx?page_id=7183

CAPMAS. (2020, November 23). *The population of Egypt now*. Retrieved from Central Agency for Public Mobilization And Statistics: https://www.capmas.gov.eg/Pages/populationClock.aspx

CDC. (2019). *Antibiotic Resistance Threats in the United States.* Atlanta, GA: U.S. Department of Health and Human Services, CDC.

Dooling, K. L., Kandeel, A., Hicks, L. A., El-Shoubary, W., Fawzi, K., Kandeel, Y., . . . Talaat, M. (2014). Understanding Antibiotic Use in Minya District, Egypt: Physician and Pharmacist Prescribing and the Factors Influencing Their Practices. *Antibiotics (Basel, Switzerland)*, 3(2), 233–243.

El Maraghy, D., Younis, A., & Abbas, N. (2016). Survey on the irrational use of antibiotics among adults in Egyptian community. *International Journal of Pharmacology and Pharmaceutical Sciences*, Vol 3(6) 6-9.

El-Hawy, R. M., Ashmawy, M. I., Kamal, M. M., Khamis, H. A., Abo El-Hamed, N. M., Eladely, G. I., . . . Hamdy, D. A. (2017). Studying the knowledge, attitude and practice of antibiotic misuse among Alexandria population. *European Journal of Hospital Pharmacy*, 24, 349-354.

Elkamel, F. (1995). The use of television series in health education. *Health Education Research*, 10(2), 225-232.

Elkamel, F. (2019). Knowledge and Social Change: Impact of 40 Years of Health and Population Communication in Egypt. *Arab Media & Society*. Retrieved from https://www.arabmediasociety.com/knowledge-and-social-change-impact-of-40-years-of-health-and-population-communication-in-egypt/

Elkamel, F. (2020, July 08). *Saving a Million Lives*. Retrieved from Youtube: https://www.youtube.com/watch?v=UHkESsQxQgs

Elmasry, A. A., Bakr, A. S., Kolkailah, D. A., Khaskia, M. A., Mohammed, M. E., Riad, , O. H., & Abdelrahman, S. A. (2013). Pattern of antibiotic abuse – a population based study. *Egyptian Journal of Chest Diseases and Tuberculosis*, 62, 189-195.

El-Nimr, N. A., Wahdan, I. M., Wahdan, A. M., & Kotb, R. (2015). Self-medication with drugs and complementary and alternative medicines in Alexandria, Egypt: prevalence, patterns and determinants. *Eastern Mediterranean Health Journal*, 21(4), 256-265.

Felman, A. (2019, January 18). *What to know about antibiotics*. Retrieved from Medical News Today: https://www.medicalnewstoday.com/articles/10278

Fleming, A. (1945, December 11). Penicillin. *Noble Prize.* Stockholm, Sweden: Elsevier Publishing Company.

Fleming, A. (1980). Classics in infectious diseases: on the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae by Alexander Fleming, Reprinted from the British Journal of Experimental Pathology 1929. *Reviews of Infectious Diseases*, 2(1), 129-139.

Frost, I., Van Boeckel, T. P., Pires, J., Craig, J., & Laxminarayan, R. (2019). Global geographic trends in antimicrobial resistance: the role of international travel. *Journal of Travel Medicine*, 26(8).

Gericke, C. A., Britain, K., Elmahdawy, M., & Elsisi, G. (2018). Health System in Egypt. Health Services Research. In E. B. van Ginneken, *Health Care Systems and Policies* (pp. 1-18). New York: Springer.

Gericke, C. B. (2018). Health System in Egypt. Health Services Research. In E. B. van Ginneken, *Health Care Systems and Policies* (pp. 1-18). New York: Springer.

Ghazawy, E. R., Hassan, E. E., Mohamed, E. S., & Emam, S. A. (2017). Self-Medication among Adults in Minia, Egypt: A Cross Sectional Community Based Study. *Health*, 9, 883-895.

Gravningen, K., Field, N., Blix, H. S., Asfeldt, A. M., & Småbrekke, L. (2020). Non-prescription purchase of antibiotics during travel abroad among a general adult population in Norway: Findings from the seventh Tromsø Study. *PLOS ONE*, 15(2), e0228792.

Guinovart, M. C., Figueras, A., & Llor, C. (2018). Selling antimicrobials without prescription - Far beyond an administrative problem. *Enfermedades infecciosas y microbiologia clinica*, 36(5), 290–292.

Hassan, A., Ibrahim, O., & Guinaidy, M. (2011). Surveillance of antibiotic use and resistance in Orthopaedic Department in an Egyptian University Hospital. *International Journal of Infection Control*, 7: 1-10.

Hernandez-Juyol, M., & Job-Quesada, J. R. (2002). Dentistry and self-medication: a current challenge. *Medicina oral : organo oficial de la Sociedad Espanola de Medicina Oral y de la Academia Iberoamericana de Patologia y Medicina Bucal*, (7) 344-347.

IQVIA. (2020, October 04). Retrieved from IQVIA: https://www.iqvia.com/

Kandeel, A., Palms, D. L., Afifi, S., Kandeel, Y., Etman, A., Hicks, L. A., & Talaat, M. (2019). An educational intervention to promote appropriate antibiotic use for acute respiratory infections in a district in Egypt- pilot study. *BMC Public Health*, 19(3), 498-507.

Kemp, S. (2020, February 17). *DIGITAL 2020: EGYPT*. Retrieved from DATAREPORTAL: https://datareportal.com/reports/digital-2020-egypt

Khalifa, H. O., Soliman, A. M., Ahmed, A. M., Shimamoto, T., Nariya, H., Matsumoto, T., & Shimamoto, T. (2019). High Prevalence of Antimicrobial Resistance in Gram-Negative Bacteria Isolated from Clinical Settings in Egypt: Recalling for Judicious Use of Conventional Antimicrobials in Developing Nations. *Microbial drug resistance (Larchmont, N.Y.)*, 25(3), 371–385.

Kheir, N., Zaidan, M., Younes, H., El Hajj, M., Wilbur, K., & Jewesson, P. J. (2008). Pharmacy education and practice in 13 Middle Eastern countries. *American journal of pharmaceutical education*, 72(6), 133.

Klein, E. Y., Van Boeckel, T. P., Martinez, E. M., Pant, S., Gandra, S., Levin, S. A., . . . Laxminarayan, R. (2018). Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences of the United States of America*, 115(15), E3463–E3470.

Limaye, D., Limaye, V., Krause, G., & Fortwengel, G. (2017). A Systematic Review of the Literature to Assess Self-medication Practices. *Annals of Medical and Health Sciences Research*, 7: 1-15.

Michael, C. A., Dominey-Howes, D., & Labbate, M. (2014). The antimicrobial resistance crisis: causes, consequences, and management. *Frontiers in public health*, 2, 145.

Ministry of Health. (1971, September 27). Decision no. 430 for the year 1971. *The Egyptian Low of Pharmacy*. Cairo, Egypt: The Egyptian Journal of Facts (Only Arabic version).

Ministry of Health and Population. (2005). *Egypt Service Provision Assessment Survey 2004.* Calverton, Maryland: USA: Ministry of Health and Population and ORC Macro.

Modesti, P. A., Reboldi, G., Cappuccio, F. P., Agyemang, C., Remuzzi, G., Rapi, S., . . . Parati, G. (2016). Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. *PLOS ONE*, 11(1): e0147601.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine*, 6(7): e1000097.

Morgan, D. J., Okeke, I. N., Laxminarayan, R., Perencevich, E. N., & Weisenberg, S. (2011). Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet. Infectious diseases*, 11(9), 692–701.

Murray, J. F., Schraufnagel, D. E., & Hopewell, P. C. (2015). Treatment of Tuberculosis. A Historical Perspective. *Annals of the American Thoracic Society*, 12(12) 1749-1759.

Nagaraj, M., Chakraborty, A., & Srinivas, B. N. (2015). A Study on the Dispensing Pattern of Over the Counter Drugs in Retail Pharmacies in Sarjapur Area, East Bangalore. *Journal of clinical and diagnostic research : JCDR*, 9(6), FC11–FC13.

Rogers Van Katwyk, S., Grimshaw, J. M., Nkangu, M., Nagi, R., Mendelson, M., Taljaard, M., & Hoffman, S. J. (2019). Government policy interventions to reduce human antimicrobial use: A systematic review and evidence map. *PLoS medicine*, 16(6), e1002819.

Rogers Van Katwyk, S., Grimshaw, J. M., Nkangu, M., Nagi, R., Mendelson, M., Taljaard, M., & Hoffman, S. J. (2019). Government policy interventions to reduce human antimicrobial use: A systematic review and evidence map. *PLoS medicine*, 16(6), e1002819.

Roque, F., Herdeiro, M. T., Soares, S., Rodrigues, A. T., Breitenfeld, L., & Figueiras, A. (2014). Educational interventions to improve prescription and dispensing of antibiotics: a systematic review. *BMC Public Health*, 14(1), 1276.

Sabry, N. A., Farid, S. F., & Dawoud, D. M. (2014). Antibiotic dispensing in Egyptian community pharmacies: an observational study. Research in social & administrative pharmacy. *Research in social & administrative pharmacy*, 10((1), 168-184.

Saied, T., Elkholy, A., Hafez, S. F., Basim, H., Wasfy, M. O., El-Shoubary, W., . . . Talaat, M. (2011). Antimicrobial resistance in pathogens causing nosocomial bloodstream infections in university hospitals in Egypt. *American journal of infection control*, 39(9), e61–e65.

Saied, T., Hafez, S., Kandeel, A., El Kholy, A., Ismail, G., AbuShady, M., . . . Talaat, M. (2015). Antimicrobial stewardship to optimize the use of antimicrobials for surgical prophylaxis in Egypt: A multicenter pilot intervention study. *American journal of infection control*, 43(11), e67-e71.

Sakeena, M. H., Bennett, A. A., & McLachlan, A. J. (2018). Non-prescription sales of antimicrobial agents at community pharmacies in developing countries: a systematic review. *International journal of antimicrobial agents*, 52(6), 771–782.

Saudi Ministry of Health. (2018, May 06). *MOH starts implementation of law enforcement to prohibit dispensing antibiotics without valid medical prescription (in Arabic)*. Retrieved from Ministry of Health: https://www.moh.gov.sa/Ministry/MediaCenter/News/Pages/news-2018-05-06-001.aspx

Scicluna, E. A., Borg, M. A., Gur, D., Rasslan, O., Taher, I., Ben Redjeb, S., . . . Daoud, Z. (2009). Self-medication with antibiotics in the ambulatory care setting within the

Euro-Mediterranean region; results from the ARMed project. *Journal of infection and public health*, 2(4), 189-197.

Seada, A. (2019, March 14). Pharmaceutical inspection procedures in Egypt. (K. Srour, Interviewer)

Sheth, K. (2017, April 25). *Ten Most Populous Countries In The Middle East*. Retrieved from World Atlas: https://www.worldatlas.com/articles/ten-most-populous-countries-in-the-middle-east.html

Spellberg, B., Guidos, R., Gilbert, D., Bradley, J., Boucher, H. W., Scheld, W. M., . . . Edwards, J. J. (2008). The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 46(2), 155–164.

Talaat, M., Saied, T., Kandeel, A., Abul-Ata, G. A., El-Kholy, A., Hafez, S., . . . Calfee, D. P. (2014). A Point Prevalence Survey of Antibiotic Use in 18 Hospitals in Egypt. *Antibiotics (Basel, Switzerland)*, 3(3), 450–460.

Ventola, C. L. (2015). The antibiotic resistance crisis: part 1: causes and threats. *Pharmacy & Therapeutics (P&T)*, 40(4), 277–283.

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2020, September 05). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Retrieved from Ottawa Hospital Research Institute: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

WHO. (2015). *Antibiotic resistance: Multi-country public awareness survey.* Geneva: WHO Press.

WHO. (2018, March 20). *Finalizing the national action plan on antimicrobial resistance in Egypt*. Retrieved from World Health Organization: http://www.emro.who.int/egy/egypt-infocus/finalizing-the-national-action-plan-on-antimicrobial-resistance-in-egypt.html

WHO. (2019, April 29). *New report calls for urgent action to avert antimicrobial resistance crisis*. Retrieved from World Health Organization: https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis

WHO. (2020, August 08). *Antimicrobial rsistance: Global trends – bacteria*. Retrieved from World Health Organization: https://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/about-amr/global-trends-bacteria

World Tourism Organization. (2018). *UNWTO International Tourism Trends, 2018 edition.* Madrid: UNWTO.

Wouters, O. J., McKee, M., & Luyten, J. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*, 323(9), 844-853.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (Sabry, Farid, & Dawoud, 2014) **Grade: 6**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
    a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
    b) Somewhat representative of the average in the target population. ★ (non-random sampling).
    c) Selected group of users.
    d) No description of the sampling strategy.
2) Sample size:
    a) Justified and satisfactory. ★
    b) Not justified.
3) Non-respondents:
    a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
    b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
    c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
    a) Validated measurement tool. ★★
    b) Non-validated measurement tool, but the tool is available or described. ★
    c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
    a) The study controls for the most important factor (select one). ★
    b) The study control for any additional factor (Class of the dispensed antibiotic). ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
    a) Independent blind assessment. ★★
    b) Record linkage. ★★
    c) Self-report. ★
    d) No description.
2) Statistical test:
    a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
    b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (Scicluna, et al., 2009) **Grade: 7**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
    a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
    b) Somewhat representative of the average in the target population. ★ (non-random sampling).
    c) Selected group of users.
    d) No description of the sampling strategy.
2) Sample size:
    a) Justified and satisfactory. ★
    b) Not justified.
3) Non-respondents:
    a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
    b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
    c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
    a) Validated measurement tool. ★★
    b) Non-validated measurement tool, but the tool is available or described. ★
    c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
    a) The study controls for the most important factor (Education level). ★
    b) The study control for any additional factor (Gender). ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
    a) Independent blind assessment. ★★
    b) Record linkage. ★★
    c) Self-report. ★
    d) No description.
2) Statistical test:
    a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
    b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❄ (adapted for cross sectional studies)

Reference: (Ghazawy, Hassan, Mohamed, & Emam, 2017) **Grade: 7**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
   a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
   b) Somewhat representative of the average in the target population. ★ (non-random sampling).
   c) Selected group of users.
   d) No description of the sampling strategy.
2) Sample size:
   a) Justified and satisfactory. ★
   b) Not justified.
3) Non-respondents:
   a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
   a) Validated measurement tool. ★★
   b) Non-validated measurement tool, but the tool is available or described. ★
   c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (Educational level). ★
   b) The study control for any additional factor (Gender). ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
   a) Independent blind assessment. ★★
   b) Record linkage. ★★
   c) Self-report. ★
   d) No description.
2) Statistical test:
   a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
   b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (El-Nimr, Wahdan, Wahdan, & Kotb, 2015) **Grade: 8**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
   a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
   b) Somewhat representative of the average in the target population. ★ (non-random sampling).
   c) Selected group of users.
   d) No description of the sampling strategy.
2) Sample size:
   a) Justified and satisfactory. ★
   b) Not justified.
3) Non-respondents:
   a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
   a) Validated measurement tool. ★★
   b) Non-validated measurement tool, but the tool is available or described. ★
   c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (Socio-demographic status). ★
   b) The study control for any additional factor (Gender). ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
   a) Independent blind assessment. ★★
   b) Record linkage. ★★
   c) Self-report. ★
   d) No description.
2) Statistical test:
   a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
   b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (Elmasry, et al., 2013) **Score: 7**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
   a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
   b) Somewhat representative of the average in the target population. ★ (non-random sampling).
   c) Selected group of users.
   d) No description of the sampling strategy.
2) Sample size:
   a) Justified and satisfactory. ★
   b) Not justified.
3) Non-respondents:
   a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
   a) Validated measurement tool. ★★
   b) Non-validated measurement tool, but the tool is available or described. ★
   c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (Socio-economic status). ★
   b) The study control for any additional factor (. ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
   a) Independent blind assessment. ★★
   b) Record linkage. ★★
   c) Self-report. ★
   d) No description.
2) Statistical test:
   a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
   b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (El-Hawy, et al., 2017) **Grade: 9**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
    a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
    b) Somewhat representative of the average in the target population. ★ (non-random sampling).
    c) Selected group of users.
    d) No description of the sampling strategy.
2) Sample size:
    a) Justified and satisfactory. ★
    b) Not justified.
3) Non-respondents:
    a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
    b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
    c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
    a) Validated measurement tool. ★★
    b) Non-validated measurement tool, but the tool is available or described. ★
    c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
    a) The study controls for the most important factor (Socio-economic status). ★
    b) The study control for any additional factor (Gender). ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
    a) Independent blind assessment. ★★
    b) Record linkage. ★★
    c) Self-report. ★
    d) No description.
2) Statistical test:
    a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
    b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (Abou El-Ezz & Ez-Elarab, 2011) **Grade: 5**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
    a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
    b) Somewhat representative of the average in the target population. ★ (non-random sampling).
    c) Selected group of users.
    d) No description of the sampling strategy.
2) Sample size:
    a) Justified and satisfactory. ★
    b) Not justified.
3) Non-respondents:
    a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
    b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
    c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
    a) Validated measurement tool. ★★
    b) Non-validated measurement tool, but the tool is available or described. ★
    c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
    a) The study controls for the most important factor (select one). ★
    b) The study control for any additional factor (Gender). ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
    a) Independent blind assessment. ★★
    b) Record linkage. ★★
    c) Self-report. ★
    d) No description.
2) Statistical test:
    a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
    b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (Dooling, et al., 2014) **Grade: 8**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
    a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
    b) Somewhat representative of the average in the target population. ★ (non-random sampling).
    c) Selected group of users.
    d) No description of the sampling strategy.
2) Sample size:
    a) Justified and satisfactory. ★
    b) Not justified.
3) Non-respondents:
    a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
    b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
    c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
    a) Validated measurement tool. ★★
    b) Non-validated measurement tool, but the tool is available or described. ★
    c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
    a) The study controls for the most important factor (Educational level). ★
    b) The study control for any additional factor (Gender). ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
    a) Independent blind assessment. ★★
    b) Record linkage. ★★
    c) Self-report. ★
    d) No description.
2) Statistical test:
    a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
    b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (Amin, Amine, & Newegy, 2017) **Grade: 7**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
    a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
    b) Somewhat representative of the average in the target population. ★ (non-random sampling).
    c) Selected group of users.
    d) No description of the sampling strategy.
2) Sample size:
    a) Justified and satisfactory. ★
    b) Not justified.
3) Non-respondents:
    a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
    b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
    c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
    a) Validated measurement tool. ★★
    b) Non-validated measurement tool, but the tool is available or described. ★
    c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
    a) The study controls for the most important factor (socio-economic status). ★
    b) The study control for any additional factor. ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
    a) Independent blind assessment. ★★
    b) Record linkage. ★★
    c) Self-report. ★
    d) No description.
2) Statistical test:
    a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
    b) The statistical test is not appropriate, not described or incomplete.

Appendix 1.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

❋ (adapted for cross sectional studies)

Reference: (Abdelaziz, et al., 2019) **Grade: 6**

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
    a) Truly representative of the average in the target population. ★ (all subjects or random sampling).
    b) Somewhat representative of the average in the target population. ★ (non-random sampling).
    c) Selected group of users.
    d) No description of the sampling strategy.
2) Sample size:
    a) Justified and satisfactory. ★
    b) Not justified.
3) Non-respondents:
    a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. ★
    b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
    c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (self-medication):
    a) Validated measurement tool. ★★
    b) Non-validated measurement tool, but the tool is available or described. ★
    c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
    a) The study controls for the most important factor (Education level). ★
    b) The study control for any additional factor (Gender). ★

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
    a) Independent blind assessment. ★★
    b) Record linkage. ★★
    c) Self-report. ★
    d) No description.
2) Statistical test:
    a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). ★
    b) The statistical test is not appropriate, not described or incomplete.

Appendix 2.

Example of the used data extraction form

Reference	(Ghazawy, Hassan, Mohamed, & Emam, 2017)
Author	Ghazawy et al.
Study design	Cross-sectional study
Year of the study	2017
Study subjects	General population
Settings	Participants' houses
City	Minia
Sample size	422 Adult respondents (Response rate 91.7%)
Age range	from 18 to 72 years with a mean (34.5 ± 13.4)
Gender	Males 45.7 %, Females 54.3 %
Level of education	Lower than High school 14.2 % High school or higher 85.8 %
Method of data collection	Interview questionnaire
Recall period	1 month
Source of antibiotic	Private pharmacy 86.7 % Leftover prescription medication 79.9 % Family/friends 22.7 %
Most used antibiotic	
Results	Self-medication with antibiotics was reported by 260 of 422 respondents (61.6%), 47.3% of which used antibiotics more than once during the past month prior to the study. About 64% reported that they discontinued medication on improvement.
Reasons for self-medication	Illness was perceived as minor 59.7 % Previous experience with the treatment 40.9 % Saving time 29.8 % Saving money 25 %
Quality Score (NOS)	**7/10**