Assessing the Efficacy of Pharmacist-Engaged Interventions in Influencing Antibiotic Prescribing Behavior among General Practitioners (meta-analysis)

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DECLARATION

I, Sara Badreldin Rabie, affirm that I am submitting the research titled "Assessing the Effectiveness of Pharmacist-Engaged Interventions in Influencing Antibiotic Prescribing Behavior among General Practitioners (meta-analysis)" as my thesis for the fulfillment of my Master's Degree in the Department of Global Control of Infectious Diseases, Division of Health Policy and Financing at Yonsei University, Seoul. This thesis presents the comprehensive findings of my investigation, and I have duly acknowledged all ideas, references, and content utilized. I further confirm that the outcomes of this study have not been previously submitted for any degree, nor are they presently being considered for any other academic qualification.

_____

Sara Badreldin Rabie December 2023

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ABSTRACT

Background: A meta-analysis study was undertaken to examine antibiotic resistance, specifically by assessing the effectiveness of pharmacist interventions in influencing the rate of antibiotic prescriptions compared to their impact on adherence to antibiotic prescribing guidelines.

Objective: Evaluating the effectiveness of pharmacist interventions in influencing the rate of antibiotic prescriptions, in contrast to their impact on adherence to antibiotic prescribing guidelines.

Method: A comprehensive literature review up to the year 2016 was conducted, examining a total of 215 relevant studies. Among these, 15 specific studies were chosen for inclusion, encompassing a population of 298,339 individuals who initially demonstrated antibiotic resistance. Within this group, 134,004 individuals were exposed to interventions involving pharmacist participation, while 164,335 served as controls. The calculation of odds ratios (OR) and 95% confidence intervals (CIs) was employed to assess antibiotic resistance in pharmacists involved in antibiotic prescribing rates as compared to those involved in antibiotic prescribing adherence rates. This analysis utilized dichotomous approaches and employed both fixed and random models.

Result: When pharmacists participated in interventions targeting antibiotic prescribing rates, a considerable reduction in antibiotic resistance was observed (Odds Ratio, 0.86; 95% Confidence Interval, 0.78-0.95, $p<0.00001$). However, these findings exhibited a significant degree of heterogeneity ($I2 = 90\%$). Conversely, in interventions focusing on improving antibiotic prescribing adherence rates involving pharmacists, a substantial increase in antibiotic resistance was noted (Odds Ratio, 1.96; 95% Confidence Interval, 1.56-2.45, $p<0.00001$), with similarly high heterogeneity in the results ($I2 = 91\%$). These outcomes were specifically evident in individuals grappling with antibiotic resistance issues.

Conclusion: Pharmacist-led interventions targeting antibiotic prescribing rates led to a noteworthy decrease in antibiotic resistance compared to scenarios without pharmacist involvement in such interventions. Nonetheless, it is crucial to approach the interpretation of these results with caution, given the limited sample size in certain studies incorporated into the meta-analysis.

Keywords: antibiotic, pharmacist, physician, pharmacist intervention AMR stewardship

I. INTRODUCTION

1.1 Background

Antibiotic resistance pertains to the capacity of bacteria or other small organisms to endure the impact of antibiotics, rendering the antibiotics ineffective in treating infections caused by these microorganisms.. (Davies & Davies, 2010). This phenomenon can occur when bacteria undergo genetic mutations or acquire genes that confer resistance, enabling them to persist and multiply even when exposed to antibiotics. Antibiotic resistance is an escalating issue in public health, as it can lead to the dissemination of infections that become challenging or even impossible to treat, resulting in elevated levels of sickness, hospitalization, and mortality. Pharmacists hold a crucial responsibility in ensuring the responsible and proper utilization of antibiotics. (Frieri et al., 2017). Pharmacists frequently participate in the distribution of antibiotics and provide guidance to patients on the correct usage of these medications. Furthermore, pharmacists may work alongside healthcare professionals to enhance antibiotic treatment, including ensuring the correct dosage, administration method, and treatment duration. (Khan et al., 2022).

Pharmacists can also actively participate in antimicrobial stewardship initiatives, whose primary objective is to encourage the responsible utilization of antibiotics to mitigate the emergence of antibiotic resistance. This involvement may encompass activities such as assessing antibiotic prescriptions, delivering educational resources to healthcare providers and patients, and tracking the patterns of antibiotic utilization. (Garau & Bassetti, 2018). Through close collaboration with healthcare teams, pharmacists can contribute to enhancing antibiotic prescription practices and ensuring that antibiotics are employed solely when they are both necessary and suitable (Buckel et al., 2018).

Effective collaboration between physicians and pharmacists is essential for the proper utilization of antibiotics. While doctors are responsible for prescribing antibiotics to

address bacterial infections, pharmacists play a critical role in dispensing these medications and ensuring that patients have a clear understanding of the correct way to take them. (Cresswell et al., 2023).

Through a tight-knit collaboration, physicians and pharmacists can jointly advocate for the responsible utilization of antibiotics, thereby decreasing the likelihood of antibiotic resistance. This collaborative effort may encompass the creation and execution of antimicrobial stewardship programs, educating both patients and healthcare providers, and tracking the trends in antibiotic usage to pinpoint areas needing enhancement. By joining forces, doctors and pharmacists can collectively contribute to the appropriate use of antibiotics for infection treatment and the mitigation of antibiotic resistance development. (Klepser et al., 2015).

In recent years, numerous experts have conducted comparative studies examining the impact of pharmacists' involvement in antibiotic prescribing rates versus antibiotic prescribing adherence rates. Furthermore, some meta-analyses have been conducted to assess the advantages and disadvantages of these two strategies. However, a comprehensive assessment of the outcomes of these comparative studies has not yet been carried out, and as a result, definitive conclusions remain elusive. (Rabbani et al., 2023). To compare the impact of pharmacists' involvement in antibiotic prescribing rates with that of antibiotic prescribing adherence rates, a meta-analysis was conducted. The primary objective was to evaluate antibiotic resistance concerning the influence of pharmacists in antibiotic prescribing rates as opposed to their involvement in antibiotic prescribing adherence rates. (Piraux et al., 2022)

1.2 Purpose

The purpose of this study was to assess the efficacy of pharmacist- engaged interventions in influencing antibiotic prescribing behavior among general practitioners.

II. LITERATURE REVIEW

2.1 History of Antibiotics

The utilization of antibiotics for treating bacterial infections traces back to the period between 350 and 550 CE, as evidenced by their detection in the skeletal remains of ancient humans. In ancient Egypt, remedies for infections involved the application of molds and extracts from plants. The understanding of the association between infections and microorganisms, particularly bacteria, did not emerge until the 19th century,(Aminov, 2010). Antibiotics function in the body by either eradicating bacteria or inhibiting their growth. They can be administered through various means, including oral intake (such as pills or liquids), topical application (like creams or sprays), or intravenous delivery. Notably, antibiotics are typically not prescribed for mild conditions like chest infections, ear infections, or sore throats. It's essential to recognize that antibiotics are ineffective against viral infections, such as the common cold and flu. The misuse or overuse of antibiotics poses a significant risk, contributing to the development of antibiotic resistance. This concern is substantial, with over 1.2 million people globally succumbing to infections caused by antibiotic-resistant bacteria in 2019— exceeding the annual death toll from malaria or AIDS. In the same year, nearly 5 million deaths were attributed to drug-resistant bacterial infections,(Dolecek et al., 2022).

Prior to the discovery of antibiotics, infectious diseases posed a significant threat to human health, ranking among the primary causes of illness and mortality. Over 2000 years ago, in regions including Serbia, China, Greece, and Egypt, microbes with antibiotic-producing capabilities were employed as remedies for addressing infectious diseases. An ancient Egyptian medical document, The Eber's Papyrus, dating back to 1550 BC, represents the earliest documented record detailing the utilization of moldy bread and medicinal soils in the treatment of infections. Additionally, human remains from the Dakhleh Oasis in Egypt revealed traces of tetracycline, an antibiotic with

chelating properties, further emphasizing the historical use of such interventions, (Hutchings et al., 2019).

Historical records offer compelling evidence that ancient societies depended on various naturally occurring remedies to address infections, incorporating the utilization of herbs, honey, and even animal waste. Among these remedies, the application of moldy bread topically gained prominence for its notable effectiveness, with multiple references to its healing properties found in ancient civilizations such as Egypt, China, Serbia, Greece, and Rome. The enduring belief in the therapeutic benefits of molds persisted over centuries, as exemplified by mentions from figures like John Parkinson,(1567– 1640) (Gould, 2016) Pyocyanase is considered one of the earliest antibiotics used to treat human infections, and its discovery is attributed to Rudolf Emmerich (1856–1914) and Oscar Löw (1844–1941). They observed that green bacteria present in the bandages of injured patients demonstrated the ability to inhibit the growth of other microorganisms. To harness its potential, they cultivated this bacterium, Pseudomonas aeruginosa, in batches and utilized the liquid portion obtained as a medicinal treatment, although its efficacy varied, (Levy, 2013).

The origin of modern antimicrobial therapy can be credited to Paul Ehrlich (1854–1915), whose investigation into the antibacterial properties of dyes represented a pivotal moment. Initially, Ehrlich's focus was on creating stains for microscopic tissue examination, such as the Ziehl–Neelson stain for tuberculosis and Gram's stain. In the course of his research, he noticed that certain stains displayed toxicity against bacteria, leading him to pursue the concept of the "magic bullet," inspired by German folklore's idea of a weapon to defeat supernatural creatures like werewolves. In 1909, Ehrlich and his team discovered Salvarsan, an arsenic-based compound highly effective in treating syphilis. While not fitting the strict definition of an antibiotic, Salvarsan is considered one of the earliest examples of a genuinely modern antimicrobial agent,(Schwartz, 2004). Paul Ehrlich's influence extended beyond his work in chemical research, as he demonstrated a keen interest in immunology. He collaborated with Robert Koch (1843–

1910) and Emil von Behring (1854–1917) in their endeavors to improve a diphtheria antitoxin, a breakthrough that laid the groundwork for antibacterial therapy. Another notable figure, William Osler (1849–1919), introduced the use of 'anti-streptococcal serum' to treat endocarditis. This method involved injecting bacteria obtained from blood cultures into horses and subsequently administering the serum derived from these horses to patients, (Schwartz, 2004).

The initial antibiotic to be identified was penicillin, credited to Alexander Fleming's discovery in 1928. Fleming, a Scottish physician and microbiologist, observed that a fungus called Penicillium notatum had inadvertently contaminated an uncovered culture plate of Staphylococcus bacteria. The fungus created bacteria-free zones wherever it grew on the plate. Fleming isolated and cultivated the mold in a pure culture, discovering that P. notatum was remarkably effective even at extremely low concentrations. It prevented Staphylococcus growth, even when diluted 800 times, and was less toxic than the disinfectants in use at the time. Following initial trials for treating human wounds, collaborations with British pharmaceutical companies facilitated the mass production of penicillin, the antibiotic chemical produced by P. notatum, (Tan & Tatsumura, 2015)

In 1943, Selman Waksman achieved a groundbreaking milestone by identifying streptomycin, marking the first occurrence of an aminoglycoside compound derived from actinomycetes and serving as the first antibiotic treatment for tuberculosis. Presently, antibiotic resistance persists as a major worldwide public health issue, contributing significantly to global antimicrobial resistance concerns, (Waksman et al., 2010).

In 1945, Giuseppe Brotzu launched the investigation into cephalosporins by isolating the fungus Cephalosporium acremonium from sewage in Sardinia. Noticing a reduced occurrence of typhoid fever in the area, he discovered cephalosporin P and N, antibiotics that demonstrated effectiveness against both Gram-positive and Gram-negative bacteria, (Darville & Yamauchi, 1994).

The timeframe between 1940 and 1960 is commonly known as the "golden age" of antibiotic discovery, as illustrated in Figure 1. Throughout this period, a diverse range of

antibiotics was identified, classified into three primary categories;

Antibiotics derived from actinomycetes encompass a variety of natural compounds, such as aminoglycosides, tetracyclines, amphenicols, macrolides, glycopeptides, ansamycins, lincosamides, streptogramins, and cycloserine.

Antibiotics that have their origins in fungi include notable examples like penicillins and cephalosporins

Man-made antibiotics, including sulfones, nitrofurans, quinolones, azoles, phenazines, ethambutol, and thioamides, belong to the category of synthetic antimicrobial agents.

While the majority of these antibiotics are still employed for therapeutic use, their efficacy has declined over time due to the escalating challenge of antimicrobial resistance, (Hutchings et al., 2019)

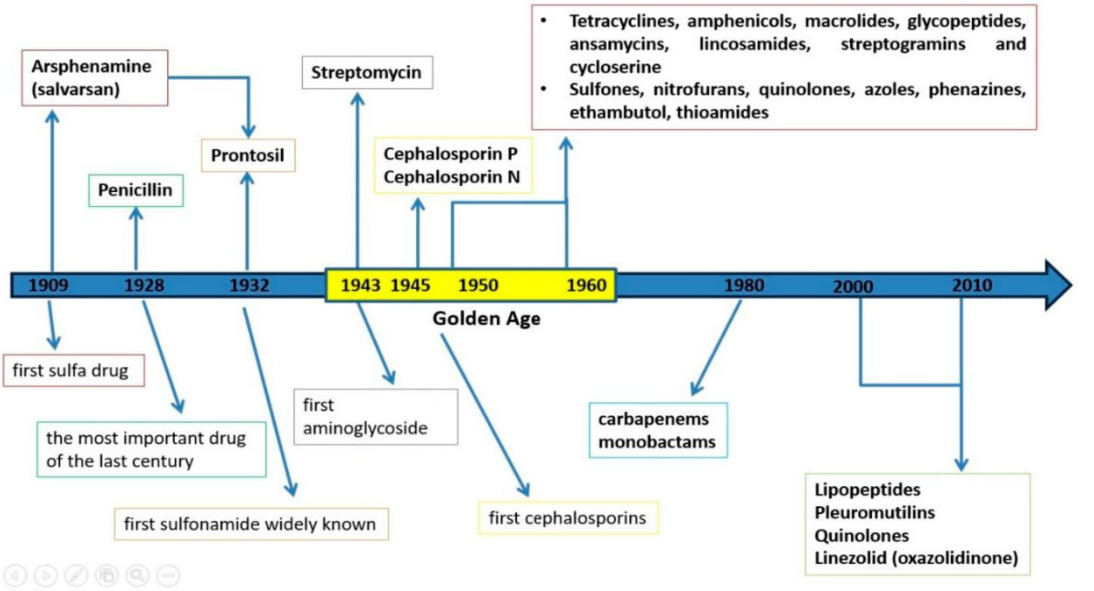

Figure 1. The Evolotion of Antibiotics:

In the 1980s, additional β-lactam antibiotics, such as carbapenems and monobactams, were discovered, expanding the range of anti-infective drugs. Since the year 2000, new antibiotics have been globally introduced, comprising both those derived from natural

sources and those created through synthetic methods. The initial natural product-based antibiotics approved for human use were daptomycin and retapamulin, belonging to the lipopeptide and pleuromutilin categories, respectively. In the realm of synthetic antibiotics, there was limited diversity, with the recently developed antibiotics falling into the quinolone and oxazolidinone classes, with linezolid being the first member of the latter to be synthesized, (Butler & Cooper, 2011).

Over the years, bacteria have adapted in response to changing environmental challenges, leading to a widespread issue of antibiotic-resistant bacteria. A notable example is observed in Staphylococcus aureus, initially susceptible to penicillin. However, over time, the effectiveness of penicillin diminished as bacterial strains developed an enzyme capable of neutralizing its effects. In response to antibiotic resistance, a new form of penicillin resistant to the enzyme was developed. Yet, within a short period, bacteria adapted and became resistant to this new drug as well. Consequently, there has been a growing prevalence of antibiotic-resistant bacteria over the years, (Kim, 2012).

The role of natural products and their derivatives remains crucial in drug development for treating human diseases. However, the current situation is a cause for concern as antibiotic resistance continues to escalate, posing a global threat to human health. Consequently, there is an urgent demand for new classes of antibiotics and modifications to existing antibiotic structures. Over time, it has been observed that microorganisms have produced approximately 40,000 antibiotics, while "higher" organisms, including plants and animals, have contributed roughly 25,000 antibiotics. The estimated total number of natural antibiotics ranges from about 65,000 to 70,000, with around 100,000 semisynthetic and synthetic compounds derived from them. Despite this vast number of compounds, only a limited few hundred are utilized in clinical practice,(Spížek et al., 2016).

2.2 Classification of Antibiotic:

Drawing from information found in the literature, antibacterial agents can be classified

into several notable groups, employing diverse criteria such as their source, chemical structure, mechanism of action, mode of action, and spectrum of effectiveness, (Adzitey, 2015).

2.2.1 Classification of antibiotics based on their source:

Classifying antibiotics based on their source involves grouping them into three categories: (i) natural compounds derived from microorganisms, (ii) semi- synthetic antibiotics, which involve structural modifications to natural products, and (iii) synthetic antibiotics. While natural antibiotics like benzylpenicillin, cephalosporins, and gentamicin exhibit significant drawbacks due to their high toxicity, semi-synthetic antibiotics such as ampicillin and amikacin, along with synthetic antibiotics like moxifloxacin and norfloxacin, provide improved therapeutic advantages and reduced toxicity compared to their natural counterparts. (Oloke, 2000).

2.2.2 Categorization of antibiotics according to their chemical structure:

Within the antibiotic family, there exists a variety of members distinguished by unique chemical structures, each possessing specific therapeutic characteristics linked to its

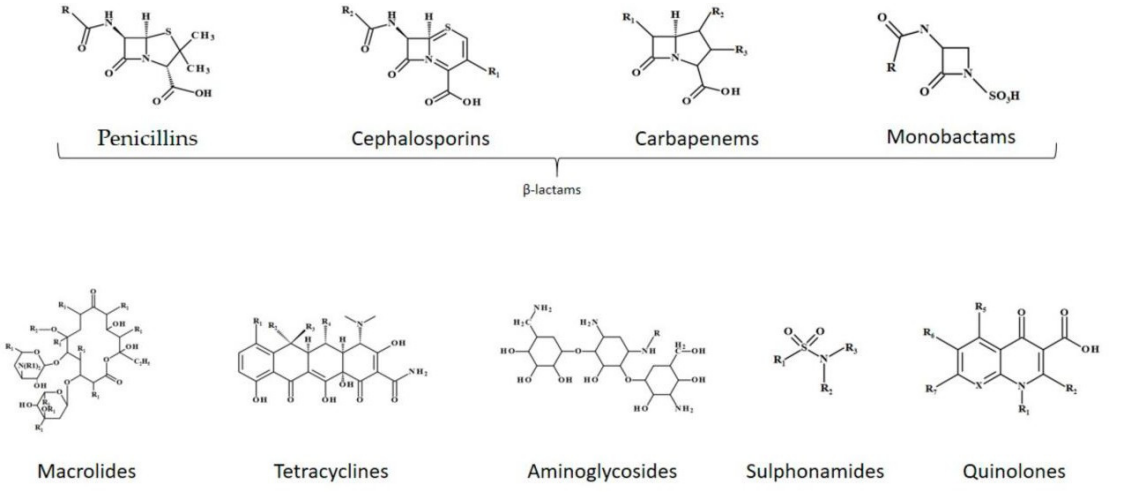

Figure 2. Main classes of antibiotics and their general chemical structure.

structure. Therefore, the chemical structure serves as a reliable criterion for the classification of antibiotics. Applying this criterion, antibiotics are categorized into different classes, such as β-lactams, macrolides, tetracyclines, aminoglycosides, sulfonamides, and quinolones, (Etebu & Arikekpar, 2016)

The β-lactam antibiotics represent a widely used class of antibiotics distinguished by a defining characteristic: the presence of a β-lactam ring. Variations within this class stem from differences in their attached side chains or additional cycles. Included in this category are penicillins, which possess a thiazolidine ring and distinct side chains for each member; cephalosporins, featuring a dihydrothiazine ring and two side chains; carbapenems, with a slightly modified thiazolidine ring compared to penicillins; and monobactams, characterized by the β-lactam ring without an adjacent ring structure, (Hamilton- Miller, 1999).

Sulfonamides represent a noteworthy category of synthetic compounds with substantial medical importance, distinguished by the inclusion of the sulfonamide chemical group (R-SO-NR R) in their structures. In contrast, tetracyclines display a linearly fused tetracyclic core to which various chemical groups are attached. Although the original molecules in this class were sourced from Streptomyces aureofaciens and Streptomyces rimosus, more recently discovered compounds are predominantly of a semisynthetic origin, (Chopra & Roberts, 2001).

Originally derived from Streptomyces species, macrolides are a class of antibiotics defined by the presence of a macrocyclic lactone ring, typically composed of 14, 15, or 16 members, to which various amino sugars are attached,(Retsema & Fu, 2001).

Quinolones, potent synthetic antibacterial agents, are derived from the heterobicyclic aromatic compound called quinoline. The effectiveness of these molecules can be heightened by making substitutions at particular positions of the quinolone nucleus, such as C1 (e.g., difluorophenyl or cyclopropyl), C6 (like fluorine in fluoroquinolones), and C8 (involving halogen, methoxy, or the addition of a fused third ring),(Heeb et al., 2011).

2.2.3 Categorization of antibiotics based on their mode of action:

The diverse structures of antibiotics are intricately linked to specific mechanisms of action. Early investigations revealed that antibiotics primarily target essential bacterial processes, including cell wall synthesis, protein synthesis, cell membrane function, and nucleic acid synthesis, all critical to bacterial growth,(Ullah & Ali, 2017).

As a result, antibiotics can be classified according to their mechanism of action, including inhibition of cell wall synthesis, protein synthesis, cell membrane function, and nucleic acid synthesis. Another established antibiotic mechanism involves the inhibition of crucial metabolic pathways, (Percival, 2017).

Interrupting the synthesis of the bacterial cell wall is a critical measure in impeding bacterial growth by obstructing the formation of the peptidoglycan layer. The distinctive bactericidal activity of the β-lactam antibiotic family arises from its ability to bind to bacterial membrane receptors known as penicillin- binding proteins (PBPs). This binding occurs due to their structural resemblance to the natural PBP substrate, D-alanyl-D-alanine. Within the active site, β-lactams acetylate the serine residues, rendering the enzyme incapable of further interaction with its natural substrate. The penam ring plays a crucial role in establishing essential hydrogen bonds (HBs) within the binding site of PBPs, (Kishida et al., 2006).

Taking ampicillin as an illustration, it demonstrates a robust affinity for the binding site of penicillin-binding proteins (PBPs), forming multiple hydrogen bonds (HBs) with serine and aspartate residues. This interaction involves carboxylic and amide oxygen atoms, as well as heterocyclic nitrogen and sulfur. The binding interactions between ampicillin and PBP are evident in the complex. β-lactam antibiotics, alongside other classes like bacitracin, vancomycin, teicoplanin, novobiocin, etc., are acknowledged for their role in impeding the synthesis of the bacterial cell wall. This inhibition ultimately leads to damage to the cell envelope and subsequent loss of structural integrity,(Kohanski et al., 2010).

Protein synthesis is an essential cellular process crucial for the survival of cells,

whether bacterial or mammalian, making it a reliable target for antibiotics.

In bacterial cells, protein synthesis involves multiple stages, including initiation, elongation (encompassing the introduction of aminoacyl tRNA, proofreading, peptidyl transfer, ribosome translocation), and termination, (Ullah & Ali, 2017).

Antibiotics have the capacity to disrupt any of the steps involved in protein synthesis by binding to either the 30S or 50S ribosomal subunits, contingent upon the specific antibiotic employed. Diverse classes of antibiotics target bacterial protein synthesis, including aminoglycosides, macrolides, tetracyclines, streptogramins, chloramphenicol, clindamycin, and others. Typically, representatives of these classes binding to the larger 50S ribosomal subunit occupy the nascent peptide tunnel site, hindering the formation of new peptides. An intriguing shared characteristic among certain compounds like azithromycin, clindamycin, and quinupristin is their capacity to form hydrogen bonds with the A2099 residue, (mutated as G2099).

Although G2099A mutations do not impact the ability of compounds to form hydrogen bonds, they play a role in diminishing the drug binding potency and are associated with the emergence of drug resistance. The diagram depicts the binding interactions of azithromycin, clindamycin, quinupristin, and linezolid when they form complexes with the 50S large ribosomal subunit, (Tu et al., 2005). Aminoglycosides such as neomycin and paromomycin, along with tetracyclines, share a similar mechanism to hinder protein synthesis by targeting the decoding center of the small 30S ribosomal subunit. Upon binding to this subunit, aminoglycosides induce a structural change in its A-site, leading to errors in codon reading and mRNA translation. Tetracyclines also occupy this A-site, preventing acyl-tRNA from extending into the active site and making it unrecognizable by the mRNA codon. Consequently, this disruption impairs the ribosome's ability to carry out protein synthesis. Intriguingly, crystallographic data reveals that tetracycline not only binds to the decoding site but also interacts with five additional binding pockets within the 30S subunit, (Mehta & Champney, 2002),(Polikanov et al., 2018).

Antibiotics can bring about a cessation in nucleic acid synthesis by impeding the

activity of enzymes responsible for DNA or RNA synthesis in bacterial cells. For instance, antibiotics that obstruct RNA synthesis, such as the rifamycin class and fidaxomicin/ lipiarmycin, disrupt bacterial transcription, resulting in a reduction in cell viability.

Conversely, DNA inhibitors function by suppressing DNA synthesis in bacterial cells through the disruption of type II topoisomerase enzymes, specifically DNA gyrase and DNA topoisomerase IV. Antibiotics such as quinolones and metronidazole are notable for their capacity to inhibit DNA.

In the structure of these antibiotics, they engage with two adenine residues through a conventional hydrogen bond formed between the oxo group of the drug and the amino group of the nucleotide, along with a halogen bond established between the fluorine and the heterocyclic nitrogen atom, (Ma et al., 2016),(Hooper & Jacoby, 2016).

An attractive target for antibiotics in bacteria involves disrupting folate metabolism, particularly by affecting dihydrofolate reductase (DHFR), a crucial enzyme in processes such as thymidylate synthesis, DNA replication, and cell survival. Trimethoprim is a well-known selective inhibitor of bacterial DHFR, and ongoing investigations explore other compounds with similar properties. Trimethoprim exerts its action by binding to the active site of DHFR, forming hydrogen bonds between its amino groups and adjacent amino acid residues. Sulfonamides also function as folate antimetabolites by inhibiting dihydropteroate synthase (DHPS). A significant structural element in sulfa drugs is the sulfonamide group, contributing to binding through hydrogen bonds. Additionally, the phenyl group aids in stabilizing the drug within the active site through π–π stacking interactions with nearby Phe residues. These interactions play a crucial role in the binding of sulfamethoxazole to DHPS,(Wróbel et al., 2019), (Heaslet et al., 2009).

2.2.4 Categorizing Antibiotics Based on Their Pharmacological Effect:

Antibiotics can be classified according to their pharmacological effects, specifically whether they exhibit bactericidal or bacteriostatic properties. Bactericidal antibiotics operate by causing bacterial cell death through the inhibition of processes such as cell

wall synthesis, cell membrane function, or protein synthesis. Examples of bactericidal antibiotics encompass β-lactams, aminoglycosides, glycopeptides, ansamycins, quinolones, streptogramins, lipopeptides, and macrolides.

Conversely, bacteriostatic antibiotics achieve their impact by impeding bacterial cellular activity and growth without directly inducing cell death. This group includes sulfonamides, tetracyclines, chloramphenicol, oxazolidinones, and macrolides,(Loree & Lappin, 2019).

2.2.5 Categorizing Antibiotics According to Their Spectrum of Activity:

Antibiotics can be categorized according to their spectrum of activity into two groups: broad-spectrum and narrow-spectrum antibiotics (refer to figure 3). Broad-spectrum antibiotics are capable of combating a diverse range of pathogenic bacteria, addressing both Gram-positive and Gram-negative types. In contrast, narrow-spectrum antibiotics focus on a specific type of pathogenic bacteria, either Gram-positive or Gram-negative. Supported by existing experimental data, narrow-spectrum antibiotics are considered more favorable as antibacterial agents due to their specificity and the lower probability of bacterial resistance development compared to broad-spectrum antibiotics,(Acar, 1997).

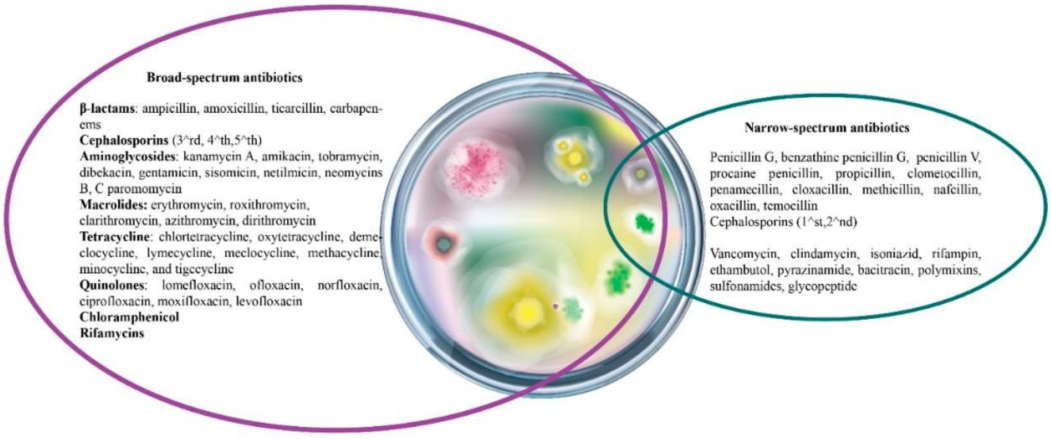

Figure 3. Visual Depiction of Broad-Spectrum and Narrow-Spectrum Antibiotics

2.3 The harmful effects associated with antibiotics.

Antibiotics have been instrumental in enhancing life expectancy by mitigating the impact of infectious diseases. Landmarks such as the identification of penicillin for pneumonia, streptomycin for tuberculosis, and chloramphenicol for typhoid fever were highly pivotal, initially escaping notice of their adverse effects, (Rolain & Baquero, 2016).

Remarkably, antibiotics currently stand as the second most common cause of drug-related side effects and are frequently associated with medical malpractice cases. The adverse effects of antibiotics become more conspicuous in patients with kidney or liver issues and when administered at high doses or for prolonged periods, (Souissi et al., 2017).

Numerous adverse effects of antibiotics are unpredictable owing to individual hypersensitivity, underscoring the importance of understanding the underlying mechanisms and identifying contributing factors in each specific case, (Everts, 2013).

2.3.1 Adverse effects resulting from hypersensitivity:

Drug fever is a common hypersensitivity reaction often associated with antibiotics, especially β-lactams and some sulfonamides. It involves a medication- induced increase in body temperature, accompanied by temporary rises in serum transaminases, a fever of ≥ 38.8 °C, and a slower heart rate. These symptoms typically subside after discontinuing the implicated drug. (Patel & Gallagher, 2010),(Albin & Agarwal, 2014).

Drug-induced rash is an additional hypersensitivity reaction commonly associated with specific antibiotics such as β-lactams or trimethoprim-sulfamethoxazole. This reaction can present as skin abnormalities localized to specific body areas or involve the entire body. The range of skin manifestations spans from maculopapular eruptions to more severe conditions like Stevens– Johnson syndrome, (Nayak & Acharjya, 2008).

Another hypersensitivity reaction linked to antibiotic use is photosensitivity, commonly observed with antibiotics such as tetracycline, sparfloxacin, lomefloxacin, and

clinafloxacin. Occasional reports of this side effect exist for methacycline, minocycline, and other fluoroquinolones as well. Photosensitivity is dosage-dependent and necessitates exposure to direct or indirect ultraviolet light. Consequently, patients are advised to apply sunscreen or avoid direct sunlight for at least one week after completing their antibiotic therapy.

The emergence of photosensitivity is connected to the photodegradation of fluoroquinolones and the antibiotics' capacity to produce free oxygen radicals. These radicals have the potential to harm cellular lipid membranes and initiate inflammatory processes, (Mandell & Tillotson, 2002).

Penicillins are commonly associated with anaphylactoid reactions among antibiotics. Notably, despite the structural similarities between penicillins and alternative antibiotics like monobactams and carbapenems (e.g., aztreonam and meropenem), these substitutes can often be used safely in patients who have experienced anaphylactic reactions to penicillin. Research has suggested a reduced likelihood of cross-reactivity between these compounds and penicillins.

Furthermore, individuals with a history of penicillin allergies might develop tolerance to penicillins later in life, with approximately 80% of patients losing their sensitivity within a decade,(Maker et al., 2019).

Hypersensitivity reactions have been documented as side effects of additional antibiotic classes, including lincosamides and macrolides. Individuals allergic to various drug classes may have an elevated susceptibility to developing allergies to other classes of medications. The occurrence of these allergies can be influenced by factors such as the administered dose and specific disease- and patient-related characteristics, (Legendre et al., 2014)

2.3.2 Adverse effects related to the blood or hematologic system:

Various antibiotics can lead to specific hematologic side effects. Common culprits for isolated leukopenia or thrombocytopenia include β-lactams and trimethoprim-

sulfamethoxazole. β-lactams may also trigger autoimmune hemolytic anemia, while trimethoprim-sulfamethoxazole could be associated with folate deficiency, potentially resulting in megaloblastic anemia. Chloramphenicol, on the other hand, has the potential to induce aplastic anemia, irrespective of its dosage or method of administration (whether oral, rectal, topical, or intramuscular), (Everts, 2013).

Antibiotics can also induce nonimmune hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Anemia resulting from the destruction of erythroid precursors in the bone marrow has been linked to sulfonamides and chloramphenicol. Moreover, there is evidence suggesting that carbenicillin can directly harm bone marrow myeloid precursors, leading to severe neutropenia,(Bang & Kammer, 1983).

Hemorrhagic issues have been linked to antipseudomonal penicillins and cephalosporins, such as cefamandole and cefoperazone. Patients receiving elevated doses of these antibiotics, particularly those with impaired renal function and inadequate nutritional status, are more susceptible to bleeding problems. Identifying risk factors and adjusting the dosage appropriately can assist in addressing the issue of bleeding tendencies, (Lang et al., 1991)

2.3.3 Adverse effects related to the nervous system:

Limited documentation exists regarding the harmful impact of antibiotics on the central nervous system. Various factors related to drug metabolism, including local blood flow, medication absorption rate, and the condition of the blood-brain barrier, can enhance susceptibility to neurotoxicity, (Grill & Maganti, 2011).

Penicillins, including penicillin G, piperacillin, ampicillin, and amoxicillin, are recognized as neurotoxic antibiotics capable of inducing various neurotoxic reactions such as confusion, disorientation, seizures, and encephalopathy

Within the cephalosporin class, cefazolin, ceftazidime, cefoperazone, and cefepime carry the highest risk of neurotoxicity. Clinical manifestations linked to these antibiotics

encompass lethargy, encephalopathy, myoclonus, seizures, nonconvulsive status epilepticus, and coma. The mechanism underlying cephalosporin-induced neurotoxicity mirrors that of penicillins, involving decreased release of GABA, cytokine release, and elevated levels of excitatory amino acids, (Rezaei et al., 2018).

Moreover, antibiotics such as ciprofloxacin, norfloxacin, ofloxacin, gemifloxacin, and levofloxacin are recognized for inducing neurotoxic adverse effects, manifesting as symptoms like headache, confusion, insomnia, seizures, encephalopathy, and myoclonus. The impact of these antibiotics is dose- dependent, involving the inhibition of GABA-A receptors and activation of excitatory NMDA receptors, (Rezaei et al., 2018)

2.3.4 Adverse effects related to the digestive system:

Gastrointestinal side effects are the most commonly reported after antibiotic treatment and encompass symptoms such as anorexia, nausea, vomiting, diarrhea, epigastric pain, and abdominal cramps. The occurrence of these symptoms is typically dosage-related and is frequently observed with oral formulations of antibiotics. Macrolides are generally less well-tolerated when taken orally, and clarithromycin, in particular, is known to cause gastric discomfort and a metallic taste. These manifestations are attributed to a direct irritative or toxic effect of the antibiotics,(Wood, 1991).

To alleviate gastrointestinal adverse effects, strategies such as reducing antibiotic doses, managing symptoms, and taking antibiotics with food can be effective. However, it's important to note that food intake can influence the absorption of erythromycin, oleandomycin, or oral penicillin.

Tetracyclines are generally well-tolerated when taken orally, except for minocycline and doxycycline, which may cause gastrointestinal reactions when taken on an empty stomach. Hence, it is recommended to take minocycline and doxycycline with food. (Everts, 2013).

Another prevalent gastrointestinal side effect induced by antibiotics is diarrhea, and it can stem from various underlying mechanisms. Clostridium difficile diarrhea is deemed

an irritative form, arising from alterations in colonic flora following the administration of β-lactam antibiotics. However, quinolones, doxycycline, and meropenem are seldom associated with Clostridium difficile diarrhea. Non-Clostridium difficile diarrhea associated with antibiotics has been noted in cases involving macrolides, ampicillin, ceftriaxone, or trovafloxacin therapy,(Surawicz, 2005).

2.3.5 Adverse effects pertaining to the kidneys:

Antibiotic-induced nephrotoxicity can be classified into glomerular or tubular toxicity. Prolonged use of aminoglycosides is primarily associated with nephrotoxicity, affecting the tubules of the nephron. When administered intravenously, aminoglycosides can saturate tubular cells. Among these, gentamicin is the most notorious for its nephrotoxic effects, followed by amikacin and tobramycin. Generally, kidney function fully recovers, and tubular regeneration is complete approximately 20 days after discontinuing treatment,(Everts, 2013).

Vancomycin, a glycopeptide antibiotic, is frequently prescribed for patients with multiple health conditions and infections caused by resistant pathogens. Multiple randomized clinical trials have indicated an elevated risk of acute kidney injury linked to vancomycin usage. Kidney damage typically becomes evident after a week of therapy but shows improvement upon discontinuation of the medication. The nephrotoxic effect of vancomycin is believed to be driven by mechanisms such as proinflammatory oxidation, mitochondrial dysfunction, and cellular apoptosis, culminating in proximal tubular injury, (Morales-Alvarez, 2020).

β-Lactam antibiotics are recognized nephrotoxins, with acute interstitial nephritis most commonly linked to nafcillin and methicillin. A prominent indicator of antibiotic-induced acute allergic interstitial nephritis is eosinophiluria, often accompanied by fever and a rash, (Cotner et al., 2017).

2.3.6 Adverse effects related to the heart or cardiovascular system:

A cardiac side effect associated with antibiotics is the prolongation of the QT interval, which can potentially lead to ventricular arrhythmias like torsades de pointes. Antibiotics known to cause QT prolongation include macrolides (intravenous erythromycin, clarithromycin, and azithromycin) and specific quinolones (levofloxacin and moxifloxacin). The mechanism behind the cardiotoxicity of macrolides and fluoroquinolones involves the inhibition of the rapid component (IKr) of the delayed rectifier potassium current in the cell membrane of cardiac myocytes,(Lu et al., 2015).

Researchers have explored the cardiotoxicity of aminoglycosides as well. Studies conducted by Adams et al. revealed that elevated concentrations of gentamicin, kanamycin, amikacin, and sisomicin reduced isometric contractile tension in electrically stimulated left atria of guinea pigs. Additionally, they observed that gentamicin not only exhibited a negative inotropic effect on isolated heart muscle but also attenuated contractile responses to various positive inotropic interventions, (Adams et al., 1978).

2.3.7 Adverse effects associated with the respiratory system:

Pulmonary complications associated with antibiotic treatment are often linked to nitrofurantoin. Nitrofurantoin-induced pulmonary toxicity can present in either an acute or chronic form, each characterized by distinct clinical manifestations. Acute pulmonary reactions typically include fever, varying degrees of pulmonary infiltrates, respiratory issues, pleural effusions, and elevated peripheral eosinophil levels. Conversely, chronic pulmonary reactions represent slowly advancing inflammatory conditions that may eventually result in pulmonary fibrosis, an irreversible lung condition ,(Everts, 2013).

2.3.8 Adverse effects related to the liver or hepatic system:

Penicillins are widely recognized for causing liver injury, with carbenicillin and oxacillin being the antibiotics most frequently associated with drug-induced hepatitis. Isoniazid use has been correlated with elevated serum transaminase levels, as has

trovafloxacin, even after a single oral or intravenous dose. Trovafloxacin can also induce fatal hepatic necrosis through an idiosyncratic hypersensitivity reaction. The administration of nitrofurantoin is known to contribute to antimicrobial-induced cholestasis and, in rare instances, may lead to chronic active hepatitis,(Everts, 2013).

In the macrolide class, erythromycin estolate has been documented to induce subclinical elevations in serum aminotransferases and hepatitis in patients undergoing treatment for more than two weeks. Additionally, some cases of hepatotoxicity have been linked to josamycin and roxithromycin.

Healthcare professionals should possess a comprehensive understanding of the common adverse effects associated with frequently used antibiotics. This knowledge is crucial for minimizing the risk of side effects and avoiding medications linked to chronic or life-threatening toxicities,(Westphal et al., 1994). Types and examples of antibiotics shown in table 1,2 (Bérdy, 1974)

Table 1. Types and examples of antibiotics shown in table

Types	Examples	Targets	Functions	Recommended Dosage	Common Uses
Cell wall synthesis inhibitors	Vancomycin, Beta-lactam drugs, Fosfomycin	Fosfomycin: MurA β-Lactams: Penicillin-binding Proteins (PBPs) Vancomycin: d-Ala-d-Ala terminus	Inhibit cell wall synthesis and promote microbial death	Adult: 1 g every 12 h Children: 40 mg/kg/day	MRSA (Methicillin-Resistant *S. aureus*), Pneumonia, Urinary tract infections, meningitis, Colitis
Membrane function inhibitors	Polymyxins B and E	Lipopolysaccharide (LPS)	Alter the composition of the cell membrane by demonstrating specialty in the outer surface of Gram-negative bacteria against polysaccharide	Intravenous polymyxin B: 1.5 to 2.5 mg/kg/day CMS (Colistimethate sodium): 6.67—13.3 mg/kg/day	Intestinal infections by multidrug-resistant Gram-negative bacteria
Protein synthesis inhibitors	Tetracyclines, macrolides, Aminoglycoside antibiotics	Aminoglycoside: 30S ribosome Macrolides: 50S ribosome Tetracyclines: 30S ribosome	1. Ribosomal structure is altered by aminoglycosides. 2. Macrolides impede peptidyl transfer 3. Protein translation is disturbed by tetracyclines	Adults: 1 g/day Pediatric patients: 25–50 mg/kg In severe infections: 2 g/day	Pelvic inflammatory disease, Lyme disease, Pneumonia, Cholera
Nucleic acid synthesis inhibitors	DNA synthesis inhibitor	Metronidazole, Quinolones, Nitrofurantoin	Quinolones: DNA gyrase, metronidazole: DNA strands	The synthetic quinolone of antimicrobials is used for the alteration of cell division, DNA synthesis, and mRNA transcription	Recommended daily dose is generally 500 mg	Infections in the urinary tract, Respiratory tract, skin, gastrointestinal (GI) tract, and Bone, and Pyelonephritis

Table 2. Types and examples of antibiotics shown in table

Natural Products	Sources of Natural Products	Target Microbiota	Inhibitory Concentrations (V/V)/Amounts	Outcomes
Alkaloids	*Callistemon citrinus*	*S. aureus*, *P. aeruginosa*	0.0025 and 0.21 mg/mL	*C. citrinus*-derived alkaloid extracts at 0.0025 and 0.21 mg/mL showed MIC on *S. aureus* and *P. aeruginosa*, respectively
	Vernonia adoensis	*S. aureus*, *P. aeruginosa*	0.21 and 0.42 mg/mL	*V. adoensis* derived alkaloid extracts at 0.21 and 0.42 mg/mL showed MIC on *S. aureus* and *P. aeruginosa*, respectively
Terpenes	*Helichrysum italicum*	Resistant *Enterobacter aerogenes*	2.5%	Efflux pump inhibition
	Polyalthia longifolia	MRSA	2.5 to 10 µg/mL	Antibiotic potentiation efflux pump modulation
	Callicarpa farinosa	MRSA	2 to 512 µg/mL	Growth inhibition detected
Phenolic compounds	*Guazuma ulmifolia* Lam.	*Trypanosoma cruzi*, *L. brasiliensis*, *L. infantum*	500 µg/mL	Displayed higher leishmanicidal activity due to the presence of quercetin
	n. m.	*S. aureus*	1750 µg/mL	Antimicrobial activity detected against four pathogenic bacteria
		P. aeruginosa	500 mg/mL	
		Listeria monocytogenes	2000 mg/mL	
		E. coli	1500 mg/mL	
Quinones	*Nigella sativa*	*P. aeruginosa*, *S. aureus*, *Bacillus subtilis*, *E. coli*	1.56 to 100 µg/mL	Inhibited biofilm formation
Flavonoids	*Embelia ribes*	*Bacillus cereus*, *Micrococcus luteus*, *S. aureus*, *E. coli*	1.9 ± 0.1 g	Embelin offered a remarkable bacteriostatic and bactericidal activity

2.4 Antibiotic Resistant:

Antibiotics have been celebrated as a remarkable 20th-century discovery, but their widespread use has given rise to the simultaneous emergence of antibiotic resistance in hospitals, communities, and the environment. Microbes, with their remarkable genetic adaptability, have taken advantage of extensive antibiotic use, exploiting various sources of resistance genes and avenues for horizontal gene transfer. As a result, they have developed multiple resistance mechanisms against each newly introduced antibiotic, whether in clinical, agricultural, or other settings. This review highlights key aspects of antibiotic resistance development over the past five decades, emphasizing the urgent call for action. To fully restore the therapeutic potential of antibiotics, a deeper understanding

of the role played by environmental microbiomes in the proliferation of antibiotic resistance is essential. Innovative approaches are particularly needed for the discovery of new antibiotics and their careful, controlled integration into therapy,(Davies & Davies, 2010).

Pinpointing the origins of antibiotic resistance genes has posed challenges for scientists, as antibiotic usage predates our understanding of the biochemical and molecular mechanisms underlying antibiotic resistance. The discovery of antibiotics did not occur until the 1940s, more than a decade after the initial use of penicillin, (Davies & Davies, 2010).

The initial documented cases of antibiotic resistance surfaced in bacterial species such as streptococci and gonococci. The issue of antibiotic resistance became especially prominent in the treatment of tuberculosis (TB).

Natural mutations in DNA constitute an integral aspect of the evolutionary process, where favorable mutations are prone to persist and proliferate over time. In bacteria, advantageous mutations can disseminate rapidly, facilitated by insertion sequences and transposons, enabling transfer across diverse bacterial species. As a result, a mutation that confers survival benefits to a bacterium exposed to antibiotics can swiftly propagate this genetic advantage to other bacteria, even those of different species. It is crucial to prevent circumstances that facilitate such transfer to safeguard human health, (Gillespie, 2002) (Christaki et al., 2020).

Antibiotic self-resistance mechanisms in producer bacteria shown in table 3:

Table 3. Antibiotic self-resistance mechanisms in producer bacteria

Mechanism of antibiotic resistance	Selected examples	Gene location	Reference
Antibiotic modification/degradation	Aminoglycoside modifying enzymes (AME):AAC; APH; ANT Streptomycin-6-phosphotransferase	Chromosome *S. griseus* (*smk*)	Shinkawa et al., 1985; Mak et al., 2014
	β-lactamases Class A,B,C	Chromosome *Streptomyces* species	Ogawara, 2016b
Antibiotic efflux	ABC transporter DrrAB (Dox) OtrC (oxytetracycline)	Chromosome *S. peucetius* (*drr*AB) *S. rimosus* (*otrC*)	Yu et al., 2012; Li et al., 2014
	MFS transporter OtrB (oxytetracycline) Mfs1 (natamycin)	Chromosome *S. rimosus* (*otr*B) *S. chattanoogensis* (*mfs1*)	Ohnuki et al., 1985; Reynes et al., 1988; Wang et al., 2017
Antibiotic sequestration by special proteins	Sequestration TlmA, BlmA, ZbmA (bleomycin)	Chromosome *S. hindustanus* (*tlmA*); *S. verticillus* (*blmA*); *S. flavoviridis* (*zbmA*)	Gatignol et al., 1988; Sugiyama et al., 1994; Rudolf et al., 2015
Antibiotic target modification	Low affinity penicillin-binding proteins (PBP) Class A Class B	Chromosome *Streptomyces* species	Ogawara, 2015, 2016a
	Peptidoglycan remodeling (Glycopeptides) $VanH_{st}$, DdlM, $VanX_{st}$ $VanH_{aov}$, DdlN, $VanX_{aov}$	Chromosome *S. toyocaensis* ($vanH_{st}$, *ddl*M, $vanX_{st}$); *A. orientalis* ($vanH_{aov}$, *ddl*N, $vanX_{aov}$)	Marshall et al., 1998; Binda et al., 2014
	23S rRNA methylation (MLS) Clr, PikR1, PikR2	Chromosome *S. caelestis* (*clr*) *S. venezuelae* (*pik*R1, *pik*R2)	Calcutt and Cundliffe, 1990; Almutairi et al., 2015
	16S rRNA methylation (Aminoglycosides) PCT, Sgm methylase	Chromosome *S. pactum* (*pct*) *M. zionesis* (*sgm*)	Ballesta and Cundliffe, 1991; Kojic et al., 1992
Antibiotic target bypass	DNA gyrase subunit B (novobiocin)	Chromosome *S. sphaeroides* ($gyrB^R$)	Schmutz et al., 2003
Antibiotic target protection	Antibiotic removal DrrC (Dox) OtrA (oxytetracycline)	Chromosome *S. peucetius* (*drr*C) *S. rimosus* (*otr*A)	Doyle et al., 1991; Mak et al., 2014; Prija and Prasad, 2017

2.5 Resistance of bacteria to antibiotics:

During the mid-20th century, antibiotics were celebrated as miraculous drugs with the ability to eliminate disease-causing bacteria without causing harm to the host. The underlying mechanism driving the therapeutic effectiveness of antibiotics is complex, encompassing the inhibition of bacterial cell wall synthesis, protein synthesis, DNA and RNA synthesis, disruption of cell membrane integrity, and various other mechanisms.

Resistance to antibiotics swiftly emerged as a persistent challenge throughout the history of antibiotic development, becoming a universal phenomenon following their

discovery and clinical application. No class of antibiotics has remained unaffected by bacterial resistance, (Aminov, 2010).

The increasing demand for antibiotics and their indiscriminate use has played a significant role in the rise of antibiotic-resistant strains. Initially, the production of antibiotics was directly linked to the emergence of resistant strains. Currently, the predominant strategy to address infections and bacterial resistance involves the modification of existing antibiotics.

Bacterial resistance is evolving swiftly, posing a significant threat to human health. Despite increasing awareness of the adverse consequences associated with resistance to available drugs, actions to address this issue are often limited. In numerous developing countries, antibiotics are easily accessible without prescriptions, serving as a key driver of resistance, (Waglechner & Wright, 2017).

Various organizations, including the World Health Organization (WHO), acknowledge bacterial resistance as a significant concern and have undertaken efforts to mitigate its spread. Nevertheless, global antibiotic resistance remains a persistent challenge with no signs of diminishing. Antibiotics have been instrumental in modern medicine, enabling progress in areas such as organ transplantation, cancer therapy, neonatal care, and major surgeries by managing and preventing bacterial infections. Failing to implement effective global action plans could result in severe social, medical, and economic ramifications, (Aslam et al., 2018).

The basis of bacterial resistance centers on four main mechanisms: (i) impeding drug entry into the cell, (ii) modifying the drug's target, (iii) deactivating the antibiotic, and (iv) activating efflux pumps. Due to structural differences, Gram-negative and Gram-positive bacteria employ distinct resistance mechanisms. Gram-negative bacteria utilize all four mechanisms, while Gram- positive bacteria rely on only two: altering the antibiotic target and deactivating the antibiotic, (Mahon & Lehman, 2022).

With the increasing resistance of bacteria to traditional antibiotics, there is a rising interest in medicinal plants. Extracts obtained from different plants can act as viable

alternatives to conventional antibiotics. Various plant-secreted metabolites possess the ability to combat microorganisms by disrupting host cellular processes, including immune responses, mitosis, apoptosis, and signal transduction. Consequently, bacteria are less likely to develop resistance to herbal products,(Gupta & Birdi, 2017).

2.6 Pharmacist Interventions:

The primary responsibilities of pharmacists encompass various crucial tasks, such as offering drug-related information, managing medications, preparing and dispensing drugs, providing patient counseling, and devising personalized pharmaceutical care plans to enhance patients' well-being. Pharmaceutical care plans represent a tailored service provided by pharmacists with the goal of improving patients' overall health. This practice hinges on a collaborative partnership between pharmacists and physicians, aimed at enhancing patients' health outcomes. A significant shift in pharmacists' roles is foreseen in the future, with a greater emphasis on clinical and administrative functions, routine tasks like counting pills, packaging, and dispensing medications are likely to be delegated to technicians and trainee.

Considerable literature highlights that the implementation of pharmaceutical care has a significant positive influence on healthcare and disease management in developed countries. Nevertheless, the situation contrasts in developing nations, where challenges impede the effective execution of pharmaceutical care. These obstacles encompass time limitations, the absence of standardized reimbursement mechanisms, restricted access to patients' medical records, inadequate communication among healthcare professionals, a shortage of qualified pharmacists, and a lack of supportive policies, (Khan et al., 2020).

Pharmacists occupy a central position within the healthcare system, fulfilling various roles such as academic pharmacists, industrial pharmacists, community pharmacists, clinical pharmacists, hospital pharmacists, veterinary pharmacists, and more. Irrespective of their specific roles, all pharmacists are intricately connected, either directly or indirectly, to the overall health of the population. Ultimately, pharmacists are entrusted

with the responsibility of ensuring that the accurate medication reaches the correct patient, at the designated time, in the proper dosage, through the appropriate route, and administered in the correct manner. This emphasizes the indispensable role that pharmacists play within the healthcare system,(Kokane & Avhad, 2016).

In recent decades, the responsibilities of pharmacists have undergone substantial changes. Beyond merely dispensing medications, pharmacists have become essential participants in healthcare teams. Particularly, community pharmacists, owing to their proximity to patients, can play a pivotal role in addressing the escalating challenge of antibiotic resistance. They have the opportunity to counsel patients against unnecessary antibiotic use for minor, self- limiting infections, contributing to the collective endeavor to mitigate antibiotic resistance.

A key contributor to the rise of antimicrobial resistance is the improper utilization of antibiotics, frequently arising from self-medication and the unnecessary use of antibiotics for viral infections, as indicated in a 2014 report.

The World Health Organization (WHO) has underscored the importance of evaluating and, if needed, strengthening the pharmacist's role as the principal provider and overseer of antibiotics. While numerous initiatives aimed at tackling antibiotic misuse concentrate on improving physicians' prescription practices, other potential avenues of misuse are sometimes neglected. Yet, the manner in which patients employ antibiotics can profoundly influence their efficacy and the likelihood of resistance, (Mansour & Al-Kayali, 2017).

Although antibiotics are generally classified as prescription-only medications, they are available without a prescription in various countries through drug outlets and community pharmacies. While such over-the-counter sales are illegal, they are still prevalent in many places dispensing antibiotics without a prescription, typically involves a consultation with a pharmacist. Consequently, modifying public attitudes and enhancing people's knowledge regarding antibiotic use becomes a responsibility of community pharmacists, who are the primary source of these drugs**.**

In low- and middle-income countries, pharmacies are frequently the first point of

contact for individuals seeking healthcare due to their accessibility and social proximity compared to medical doctors and other healthcare providers. However, staff at these establishments does not consistently recommend appropriate medicines or treatment regimens, raising concerns about public health issues like antibiotic resistance.

The knowledge and attitudes of pharmacists regarding antibiotics play a significant role in shaping how these drugs are used. (Organization, 2014)

III. METHODS

3.1 Eligibility criteria

To generate a summary, we analyze studies investigating the impact of pharmacist interventions on the overall antibiotic prescribing rate, comparing it with the influence on antibiotic prescribing adherence rates, (Hernandez et al., 2020) (Macaskill et al., 2023).

3.2 Information sources

The entirety of the investigation is depicted in Figure 4. The literature was incorporated into the study upon meeting the inclusion criteria.

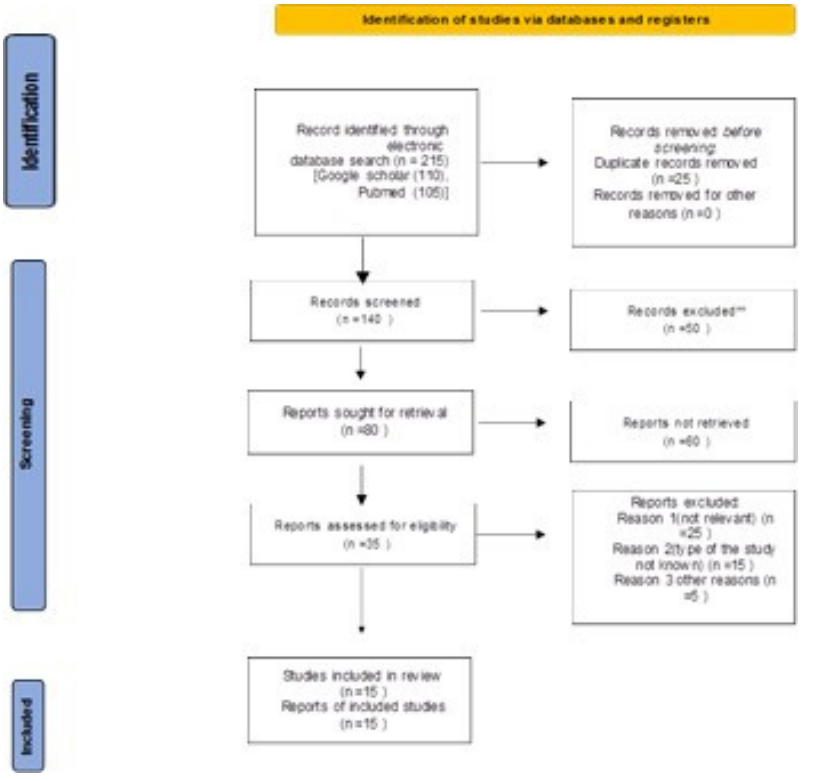

Figure 4. A flow diagram of the investigation process

The research included in the study met specific criteria:

1) The study employed observational, prospective, retrospective, or randomized controlled trial (RCT) designs.
2) Participants selected for the investigation had antibiotic resistance.
3) The intervention assessed the impact of pharmacist involvement on both antibiotic prescribing rates and antibiotic prescribing adherence rates.
4) The study explicitly examined the effect of pharmacist involvement on antibiotic prescribing rates and antibiotic prescribing adherence rates in the management of antibiotic resistance.

Exclusions were made for research that did not highlight the significance of the comparison, studies that did not evaluate the characteristics of antibiotic prescribing rates compared to antibiotic prescribing adherence rates, and those focusing on antibiotic resistance in individuals lacking information on antibiotic prescribing rates and antibiotic prescribing adherence rates.

3.3 Search strategy

The search protocol operations were defined based on the PICOS criteria as follows: "population" included individuals with antibiotic resistance, "intervention" or "exposure" involved pharmacists, the "comparison" focused on the antibiotic prescribing rate versus antibiotic prescribing adherence rate in individuals with antibiotic resistance, "outcome" was considered, and there were no restrictions on the "study design" for the proposed investigation, (Liberati et al., 2009) (Lee & Koo, 2022).

We conducted a comprehensive search on Google Scholar, PubMed, and various databases until 2023, employing a set of keywords and related terms pertaining to antibiotic resistance, antibiotic prescribing rate, antibiotic prescribing adherence rate, pharmacists, and physicians (refer to Table 4). To ensure the exclusion of studies lacking a clear connection between antibiotic resistance consequences and the comparison of

antibiotic prescribing rate versus antibiotic prescribing adherence rate, we excluded replicated papers. The collected studies were organized into an EndNote file, and titles and abstracts were subsequently reviewed.

Table 4. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 antibiotic resistant "[MH]" OR "urinary tract infection"[MH]" OR "pharmacist intervention involved "[MH]". #2 antibiotic prescribing "[TIAB]" "Antimicrobial Stewardship"[TIAB], urinary tract infection "[TIAB]" #3 prescribing behavior"[MH], pharmacist and physician collaboration "[MH].
Google scholar	1- Antibiotic resistant causes "[MH], "urinary tract infection"[MH]" OR "pharmacist intervention involved "[MH]". 2- antibiotic prescribing "[TIAB]" "Antimicrobial Stewardship"[TIAB], urinary tract infection "[TIAB]"
Cochrane library	"pharmacist intervention involved "[MH]", pharmacist and physician collaboration "[MH]", Antimicrobial Stewardship"[TIAB], OR "Antimicrobial Stewardship"[MH]".

Selection process

After the epidemiological declaration, a systematic process was established, subsequently structured and analyzed through a meta-analysis procedure.

Data collection process

The data collection criteria encompassed key details such as the primary author, investigation date, year of the study, geographical location, population type, medical and therapeutic characteristics, categories, quantitative and qualitative assessment methods, data sources, outcome estimates, and statistical analyses.

Data items

In cases where investigations incorporated variable values, we systematically gathered

data, specifically focusing on the evaluation of antibiotic resistance in relation to both antibiotic prescribing rates and antibiotic prescribing adherence rates.

Investigation risk of bias assessment

The two authors evaluated the methodologies employed in the selected publications to assess potential biases in each investigation. Procedural quality was gauged using the "risk of bias instrument" from the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Based on the appraisal criteria, each investigation was assigned one of the following bias risks: low - if all quality criteria were met; medium - if one or more requirements were not met or included; and high - if one or more quality needs were either entirely or partially unmet. Additionally, the Ottawa Quality Assessment Scale for cohort studies was utilized to appraise the risk of bias in observational non-randomized trials.

Effect measures

Sensitivity analyses were exclusively performed on studies that evaluated and reported antibiotic resistance in comparison with both antibiotic prescribing rates and antibiotic prescribing adherence rates. The aim was to contrast the impact of pharmacists involved in antibiotic prescribing rates with the effect of pharmacists involved in antibiotic prescribing adherence rates. Subclass analysis was employed for this examination.

Synthesis methods

A random- or fixed-effect model was utilized to generate the odds ratio (OR) and a 95% confidence interval (CI) utilizing dichotomous or continuous approaches. Between 0 and 100%, the I2 index was determined. The values at 0%, 25%, 50%, and 75%, respectively, presented no, low, moderate, and high heterogeneity. (Sheikhbahaei et al., 2016) Other features that show a strong degree of alikeness amongst the related research were also analyzed to make sure the correct model was being utilized. The random effect was used if I2 was 50% or above; if I2 was <50%, the possibility of utilizing fixed-effect rose. (Sheikhbahaei et al., 2016) A subclass analysis was done by stratifying the initial

estimation by the aforementioned consequence groups. A p-value of <0.05 was utilized in the analysis to specify the statistical significance of differences between subcategories.

Reporting bias assessment

The bias in the studies was assessed both statistically and qualitatively using the Egger regression test and funnel plots, which illustrate the logarithm of the odds ratios (ORs) against their standard errors (the presence of bias was considered if p≥0.05).

Certainty assessment

Two-tailed testing was employed to examine each p-value. The graphs and statistical analyses were generated using Review Manager Version 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark).

IV. Results

15 publications, published between 1994 and 2016, from a total of 215 connected investigations that met the inclusion criteria were chosen for the investigation. (Coenen et al., 2004; Esmaily et al., 2010; Ilett et al., 2000; Martens et al., 2006; Saint et al., 1999; Santis et al., 1994; Smeets et al., 2009; Stålsby Lundborg et al., 1999; Van Driel et al., 2007; Vellinga et al., 2016; Veninga et al., 2000; Vervloet et al., 2016; Weiss et al., 2011; Welschen et al., 2004; Wilf-Miron et al., 2012) (Abdel Reheem et al., 2020; Brooks et al., 2018; Carlsson et al., 2010; Di Pierro et al., 2011; Faddan et al., 2020; Ficarra et al., 2009; Johnson et al., 2018; Lenfant et al., 2021; Menon et al., 2002; Nelson et al., 2007; Osmonov et al., 2018; Pilecki et al., 2014; Qin et al., 2020; Ryu et al., 2013; Sugihara et al., 2014; Tafuri et al., 2020; Tewari et al., 2003; Wallerstedt et al., 2015; Wallerstedt Lantz et al., 2019) The results of these researches are presented in Table 5. 298339 individuals with antibiotic resistant were in the chosen investigations' starting point, 134004 of them were utilizing pharmacists involved intervention, and 164335 were utilizing individual's control. The sample size was between 130 and 154250 Individuals.

pharmacists involved intervention in antibiotic prescribing rate had significantly lower antibiotic resistant (OR, 0.86; 95% CI, 0.78-0.95, $p<0.00001$) with high heterogeneity ($I2 = 90\%$), and individuals control, pharmacists involved intervention in antibiotic prescribing adherence rate had significantly higher antibiotic resistant (OR, 1.96; 95% CI, 1.56-2.45, $p<0.00001$) with higher heterogeneity ($I2 = 91\%$) compared to those with pharmacists involved intervention in antibiotic prescribing rate in individuals with antibiotic resistant as shown in Figures 5 and 6. The sample size was between 130 and 154250 individual.

Table 5. Characteristics of the selected investigations for the meta-analysis

Investigations	Country	Total	Pharmacist intervention	Individual control
Santis, 1994	Australia	802	357	445
Stålsby Lundborg, 1999	Sweden	3737	1857	1880
Saint, 1999	USA	2128	1883	245
Ilett, 2000	Australia	16916	7262	9654
Veninga, 2000	Netherland	5598	2760	2838
Coenen, 2004	Belgium	898	80	818
Welschen, 2004	Netherland	1723	905	818
Martens, 2006	Netherland	1138	652	486
Van Driel, 2007	Belgium	130	70	60
Smeets, 2009	Netherland	2000	1000	1000
Esmaily, 2010	Iran	13480	8052	5428
Weiss, 2011	Canada	2000	1000	1000
Wilf-Miron, 2012	Palestine	91875	47500	44375
Vervloet, 2016	Netherland	154250	59483	94767
Vellinga A, 2016	Canada	1664	1143	521
	Total	298339	134004	164335

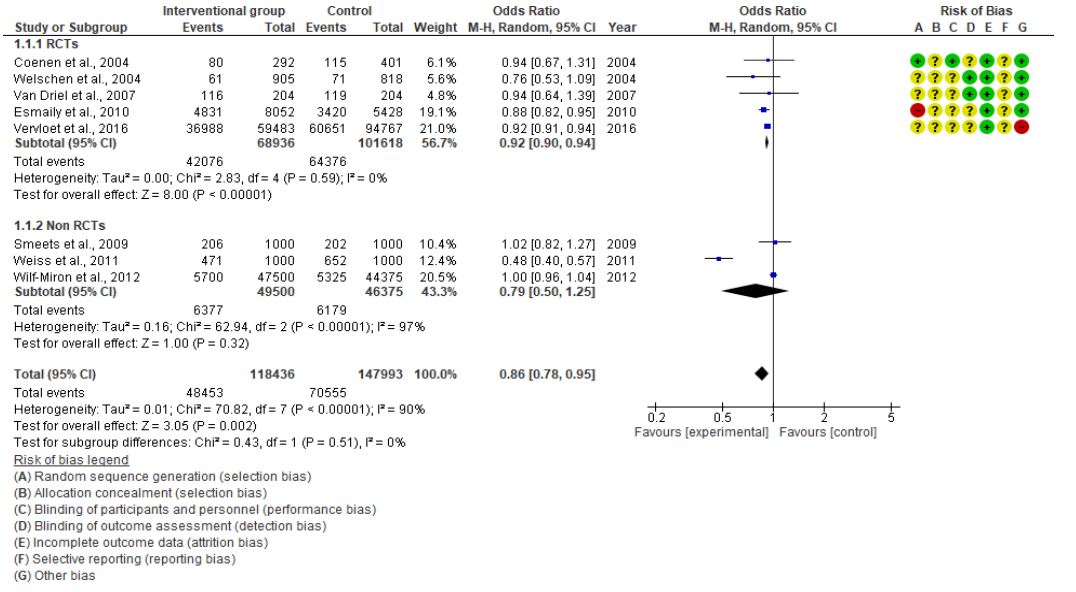

Figure 5. The effect's forest plot of pharmacists involved intervention in antibiotic prescribing rate, and individual control compared pharmacists involved intervention in antibiotic prescribing adherence rate in antibiotic resistant

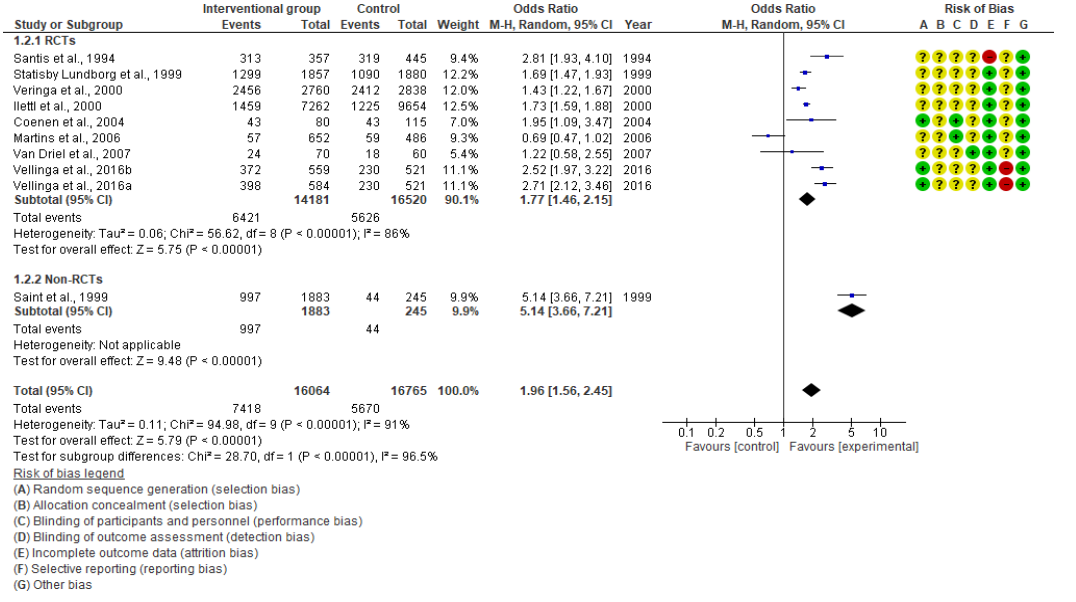

Figure 6. The effect's forest plot of the pharmacists involved intervention in antibiotic prescribing adherence rate and individual control compared with pharmacists involved intervention in antibiotic prescribing rate in antibiotic resistant

The absence of data prevented the use of stratified models to examine the effects of specific factors, such as age and ethnicity, on comparison outcomes. No evidence of investigation bias was found (p = 0.84) using the quantitative Egger regression test and the visual interpretation of the funnel plot as shown in Figures 7 and 8. However, the majority of the implicated RCTs were found to have poor procedural quality and no bias in selective reporting.

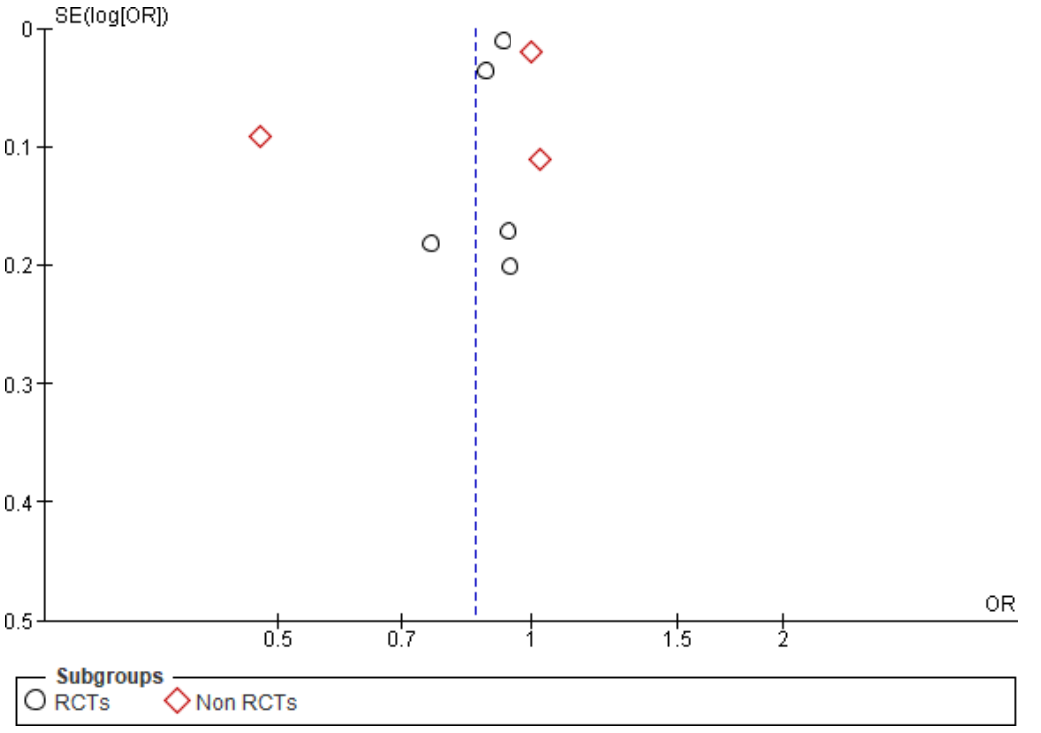

Figure 7. The funnel plot of The effect's forest plot of pharmacists involved intervention in antibiotic prescribing rate, and individual control compared pharmacists involved intervention in antibiotic prescribing adherence rate in antibiotic resistant.

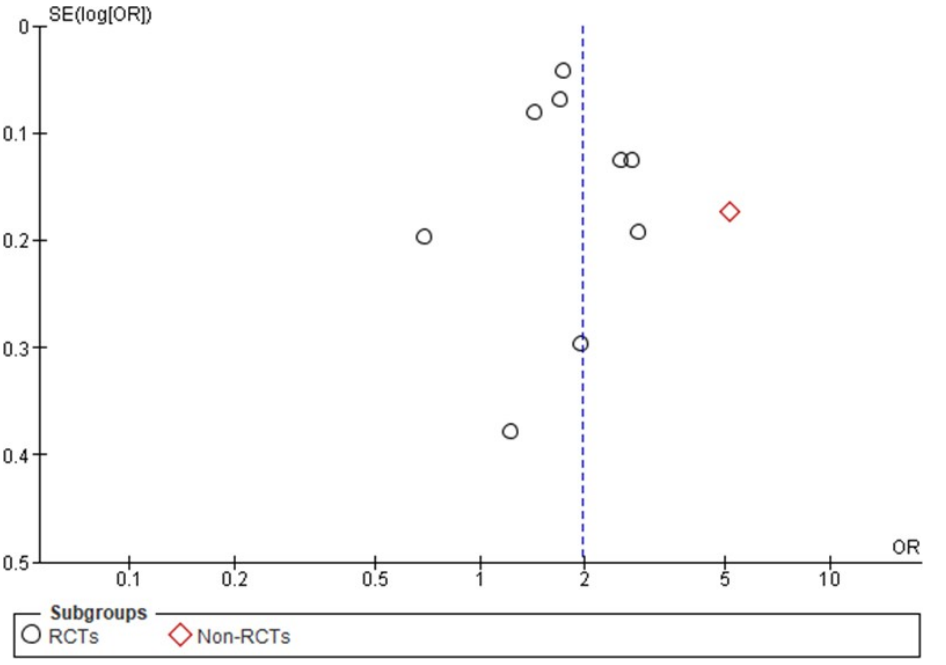

Figure 8. The funnel plot The effect's forest plot of the pharmacists involved intervention in antibiotic prescribing adherence rate and individual control compared with pharmacists involved intervention in antibiotic prescribing rate in antibiotic resistant.

Table 6. Risk of bias assessment for RCTs using the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0

	Random seq. generation	Rand conc.	Blinding participants	Blinding outcome	Incomplete outcome	Selective reporting	Others
Marcia Vervloet1	u	u	u	u	l	u	h
C. Stålsby Lundborg	u	u	u	u	l	u	l
C.C.M. Veningaa	u	u	u	u	l	u	l
Samuel Coenen	l	u	l	u	l	u	l
HAMIDEH M. ESMAILY	H	u	u	u	l	u	l
M L van Driel	u	u	u	l	l	u	l
Jody D Martens	u	u	l	u	l	u	l
Akke Vellinga	l	u	u	u	l	H	l
Ineke Welschen	u	u	u	l	l	u	l
Kenneth F. Ilett	u	u	u	u	l	u	l
Giovanna De Santis	u	u	u	u	ll	u	l

Table 7. Risk of bias for the observational non-randomized trials New - Ottawa Quality Assessment Scale for cohort studies.

Study_ID	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascert. Of exposure	Outcome_not present at start	Comparability	Assess. Of outcome	followup period	Adeq. Followup	Total
Rachel Wif-Miron	*	*	*	*	*	*	*	*	8
HM Smeets	*	*	*	*	*	*	*		7
Sanjay Saint	*	*	*	*	*	*	*	*	8
Karl Weiss	*	*	*	*	*	*	*	*	8

V. Discussion

In investigations that were considered for the meta-analysis, individuals with antibiotic resistant were in the chosen investigations' starting point, 134004 of them were utilizing pharmacist involved in antibiotic prescribing rate and adherence rate, (Coenen et al., 2004; Esmaily et al., 2010; Ilett et al., 2000; Martens et al., 2006; Saint et al., 1999; Santis et al., 1994; Smeets et al., 2009; Stålsby Lundborg et al., 1999; Van Driel et al., 2007; Vellinga et al., 2016; Veninga et al., 2000; Vervloet et al., 2016; Weiss et al., 2011; Welschen et al., 2004; Wilf-Miron et al., 2012) ; (Abdel Reheem et al., 2020; Brooks et al., 2018; Carlsson et al., 2010; Di Pierro et al., 2011; Faddan et al., 2020; Ficarra et al., 2009; Johnson et al., 2018; Lenfant et al., 2021; Menon et al., 2002; Nelson et al., 2007; Osmonov et al., 2018; Pilecki et al., 2014; Qin et al., 2020; Ryu et al., 2013; Sugihara et al., 2014; Tafuri et al., 2020; Tewari et al., 2003; Wallerstedt et al., 2015; Wallerstedt Lantz et al., 2019) and 164335 were utilizing indivisual control, pharmacists involved intervention in antibiotic prescribing rate had significantly lower antibiotic resistant, and indivisual control compared pharmacists involved intervention in antibiotic prescribing adherence rate in individuals with antibiotic resistant.

We identified 35 antibiotic stewardship intervention trials conducted in the USA, UK, Australia, Europe, and Asia, where pharmacists played a key role in optimizing antibiotic prescribing practices by General Practitioners (GPs). Our comprehensive meta-analysis provided compelling evidence, with moderate to high certainty, that Antibiotic Stewardship Programs (ASPs) involving pharmacists led to reduced Antimicrobial Prescription Rates (APR) and increased adherence to Antimicrobial Prescribing Appropriateness Rates (APAR).

Effective strategies included GP education combined with feedback on prescribing and interactive group meetings between GPs and pharmacists. These approaches effectively lowered APR and raised APAR among GPs. Our findings align with a review by Davey

et al., which noted that interactive meetings outperformed didactic lectures and contributed to improvements in laboratory resources.

We also observed that GP education, academic detailing, and workshop training involving pharmacists were effective in enhancing GP APAR. Overall, ASPs involving pharmacists consistently produced gradual improvements in the quality of antibiotic prescribing by GPs. While we couldn't definitively establish the superiority of specific intervention strategies, our results underscore the importance of exploring diverse approaches and implementation methods involving pharmacists in future research.

Our research revealed that Antibiotic Stewardship Programs (ASPs) involving pharmacists were more effective in increasing guideline-compliant antibiotic prescribing by GPs than in reducing overall antibiotic prescribing. Understanding the factors contributing to this difference, including their impact on GPs' prescription behaviors, warrants further investigation.

It's worth noting that there is limited literature available on ASP implementation approaches within community settings. Most of the ASPs analyzed in our meta-analysis followed a team-based implementation approach. Our analysis indicated that interventions were more likely to succeed in reducing the Antimicrobial Prescription Rate (APR) and improving the Antimicrobial Prescribing Appropriateness Rate (APAR) when facilitated jointly by a pharmacist and a GP. Additionally, interventions involving pharmacists and other infectious disease healthcare professionals were effective in enhancing the APAR. While there were limited studies on pharmacist-led ASPs, our findings still suggested their effectiveness in improving the APAR.

Though the precise quantification of pharmacists' impact on intervention success remains challenging, it is clear that pharmacists can significantly contribute to the implementation of community-based Antimicrobial Stewardship Programs (ASPs) in collaboration with General Practitioners (GPs). This assertion is substantiated by a study revealing substantial improvements in stewardship facilitated by pharmacists, even in settings with limited infectious disease resources.

Our review underscores the valuable expertise of pharmacists in delivering effective antibiotic prescribing education and training to GPs. This education can take various forms, including academic detailing, consensus group meetings, and workshop training. When a trained pharmacist provides GPs with education covering topics such as antibiotic pharmacotherapy, pharmacokinetics, pharmacodynamics, problem-based case studies, antibiotic spectra, resistance patterns, and evidence-based local or disease-specific antibiotic guidelines, it can have a positive influence on GPs' antibiotic prescribing behavior.

Furthermore, involving pharmacists in interdisciplinary guideline development and implementing these guidelines using audit and feedback strategies, as is done in the inpatient setting, could prove beneficial in implementing Antibiotic Stewardship Programs (ASPs) in GP settings. However, to effectively implement ASPs involving pharmacists, it is crucial to establish a system-supported network between GPs and pharmacists and to implement a structured mechanism for providing feedback on antibiotic prescribing.

In summary, advocating for the role of pharmacists in the implementation of ASPs among GPs can support the promotion of optimal antibiotic prescribing practices, contribute to the sustainability of available antibiotics, and help mitigate the threat of antimicrobial resistance within the community.

Our review underscores the importance of establishing a policy-driven collaboration between General Practitioners (GPs) and pharmacists to address obstacles to optimal antibiotic prescribing. The WHO European survey, covering 15 European countries, highlights the positive impact of GP-pharmacist network groups in shaping desired antibiotic prescribing behaviors in general practice settings.

While our review has identified models for involving pharmacists in GP Antibiotic Stewardship Programs (ASPs), there remains a need for more substantial evidence regarding the direct influence of pharmacists on GPs' day-to- day antibiotic prescribing practices. Additionally, it is crucial to evaluate the feasibility, long-term sustainability,

and acceptability of such interventions within specific local contexts.

In summary, this review underlines the existing gaps in evidence for interventions aimed at enhancing the quality of antibiotic prescribing by GPs and offers recommendations for future research to address these gaps in the context of pharmacist-involved ASPs.

This review has several limitations that need to be considered. Firstly, although we initially identified 45 eligible studies, our ability to conduct a comprehensive meta-analysis was hampered by the lack of interpretable data in 15 of these studies. This limitation was primarily due to incomplete data reporting, limited author responses, and a high risk of bias. Consequently, our meta-analysis was not as extensive as desired, even though many of the excluded studies did report positive effects for the outcomes under investigation.

Secondly, we were unable to evaluate the effectiveness of individual components within multicomponent Antibiotic Stewardship Programs (ASPs) because many studies reported combined results for interventions. Additionally, we could not determine the potential superiority of one intervention component over others.

Thirdly, our ability to calculate the Antimicrobial Prescribing Appropriateness Rate (APAR) at the level of specific antibiotic doses or regimens was constrained because APAR measurement was typically based on GPs' adherence to guidelines or recommendations in choosing antibiotics.

Fourthly, we couldn't precisely quantify the absolute impact of pharmacist involvement in ASPs due to methodological complexities in intervention design, delivery, and components across different studies. Moreover, there were no studies directly comparing the effectiveness of ASPs with and without pharmacist involvement.

Fifthly, we observed substantial heterogeneity among the included studies, but we couldn't identify the specific factors contributing to this variabilit y. Likely sources of heterogeneity could include the complex settings in which GPs operate, variations in study designs, and the diverse nature of interventions and their implementation strategies.

Sixthly, we conducted numerous subgroup analyses, which can increase the risk of Type I errors. However, these analyses were conducted according to our published

protocol and should be viewed as exploratory, providing a basis for further research in this area.

Lastly, it's important to note that our findings may not be fully generalizable to low- and middle-income countries, as our review primarily focused on higher-income settings.

Our review possessed several notable strengths. It represents the first systematic review, as far as our knowledge extends, that systematically evaluated the impact of Antibiotic Stewardship Programs (ASPs) involving pharmacists on the enhancement of antibiotic prescribing practices by General Practitioners (GPs). To ensure rigor and transparency, we registered this review with PROSPERO and conducted thorough searches across eight prominent medical databases to identify pertinent studies.

Furthermore, we adhered to best practices for systematic reviews, aligning with the PRISMA-P guidelines and employing the TIDieR template to comprehensively describe the interventions under investigation. To assess the quality of evidence, we applied the GRADE framework, ensuring a robust evaluation process.

Our review offers recommendations for future research endeavors in the realm of pharmacist-involved Antibiotic Stewardship Programs (ASPs). It suggests a focus on optimizing implementation strategies through feasibility studies conducted within various contexts. These studies should explore pharmacist-led interventions, those co-led by pharmacists and GPs, and those led by a collaboration between pharmacists and infectious disease health professionals in the context of antibiotic stewardship.

In addition, future research should delve into assessing guideline compliance in antibiotic prescribing at the level of specific doses and dose regimens. The outcomes of interest should encompass changes in the prescription of broad-spectrum antibiotics by GPs and patient safety indicators, including clinical outcomes, allergy occurrences, and side effects.

To enhance the robustness of future research, it is advisable to include comprehensive reporting of antibiotic prescribing data from both pre- and post- intervention periods for both control and intervention groups. Furthermore, the design of future ASPs should

consider incorporating both pharmacy and non- pharmacy intervention arms for a more comprehensive assessment.

Lastly, evaluating the impact of reductions in antibiotic prescribing and adherence to guidelines by GPs on reducing the prevalence of antibiotic resistance within the community is crucial. This assessment can serve as a measure of ASP effectiveness and contribute to building an evidence base for the development of collaborative GP-pharmacist team-based care models for implementing community-based ASPs.

To summarize, our meta-analysis has provided evidence supporting the effectiveness of Antibiotic Stewardship Programs (ASPs) involving pharmacists in reducing antibiotic prescribing and promoting guideline-adherent antibiotic prescribing by General Practitioners (GPs), particularly in the short term. Promising ASP strategies that engage pharmacists include GP education combined with prescribing feedback, group meetings, workshop training, and academic detailing, all of which contribute to enhancing the quality of antibiotic prescribing in community settings.

Implementing team-based ASPs with pharmacists and exploring the barriers to changing GPs' antibiotic prescribing behavior are essential steps for planning and executing future, more complex ASPs in general practices. The dissemination of our findings has the potential to influence policy, promoting greater collaboration between GPs and pharmacists in ASPs.

To further bridge the evidence gap and emphasize the role of pharmacists, there is a need for more high-quality ASP trials involving pharmacists, particularly in the GP and community contexts. These trials should not only focus on generating evidence but also prioritize the utilization of pharmacists in the effective implementation and sustainability of community ASPs.

Lastly, our study underscores the importance of establishing a comprehensive intervention framework within a collaborative GP-pharmacist network to better evaluate appropriate antibiotic prescribing measures. This approach should encompass considerations of feasibility, acceptability, and sustainability within GP ASPs.

This meta-analysis confirmed the efficacy involving the intervention of pharmacists on antibiotic prescribing rate and antibiotic prescribing adherence rate on the management of antibiotic resistant. More inspection is still desirable to clarify these feasible influences. This was also emphasized in former investigations that utilized a related meta-analysis procedure and originate equivalent values of the efficacy. Although the meta-analysis was incapable to discover if differences in these characteristics are related to the outcomes being researched, properly-led RCTs are vital to consider these aspects as well as the mixture of different ages, and ethnicities of individuals. In conclusion, pharmacists involved intervention in antibiotic prescribing rate had significantly lower antibiotic resistant, and individual control compared pharmacists involved intervention in antibiotic prescribing adherence rate.

As we mentioned the 15 studies that were included in our research, those studies had different titles and research topics but were all reaching the same point that our research based on which is including the antibiotic resistant either this were related to the urinary or respiratory tract infection as in some studies included in our research, the education intervention and other topics but all related to the main purpose of our research related to the intervention can lower and end the antibiotic resistant, we managed to collect different kind of studies to analyze the different intervention and targeting the pharmacists as if there intervention will assess with the general physicians to lower and stop the antibiotic resistant , we got the significant outcome of how the pharmacist intervention can make a huge different as part of the health system .

VI. LIMITATIONS

Since some of the investigations involved in the meta-analysis were not included, there might have been selection bias. The omitted publications, however, did not fulfill the necessities for inclusion in the meta-analysis. Also, we lacked the expertise to determine whether factors like age, and ethnicity influenced results. The purpose of the investigation was to measure the effect of pharmacists intervention involved in antibiotic prescribing rate and the efficacy of the pharmacists interventions involved in antibiotic prescribing adherence rate on the management of antibiotic resistant. Bias may have grown because incomplete or incorrect data from earlier research were included. Possible sources of bias involved the individuals' nutritional status in addition to their race, and age. Unwantedly, incomplete data and certain unpublished work may distort the value that is being examined.

VII. SUGGESTIONS AND CONCLUSION

7.1 Suggestions

We are really going to use our research as a start to make a different with the antibiotic misuse and over use and with the cooperation between the physicians and the pharmacists there will be a bigger chances to success and also applying such a program like the antibiotic stewardship in our countries will have a huge impact in a long term .

7.2 Conclusion

Pharmacists involved intervention in antibiotic prescribing rate had an influence significantly, and individual control compared pharmacists involved intervention in antibiotic prescribing adherence rate. However, care must be exercised when dealing with these values due to the low sample size of some of the nominated for the meta-analysis. That would affect the level of significance of the evaluation studied.

REFERENCES

Abdel Reheem, A., Hagras, A., Ghaith, A., Alenzi, M., Elghiaty, A., Gameel, T., Alowidah, I., Ham, W., Choi, Y., El-Bahnasy, A., & Omar, A. (2020). Retzius- sparing robot-assisted radical prostatectomy versus open retropubic radical prostatectomy: a prospective comparative study with 19-month follow-up. *Minerva Urologica e Nefrologica= The Italian Journal of Urology and Nephrology*, *72*(5), 586-594.

Acar, J. (1997). Broad-and narrow-spectrum antibiotics: an unhelpful categorization. *Clinical Microbiology and Infection*, *3*(4), 395-396.

Adams, H. R., Parker, J. L., & Durrett, L. R. (1978). Cardiac toxicities of antibiotics. *Environmental Health Perspectives*, *26*, 217-223.

Adzitey, F. (2015). Antibiotic classes and antibiotic susceptibility of bacterial isolates from selected poultry; a mini review.

Albin, S., & Agarwal, S. (2014). Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. Allergy and asthma proceedings,

Aminov, R. I. (2010). A brief history of the antibiotic era: lessons learned and challenges for the future. *Frontiers in microbiology*, *1*, 134.

Aslam, B., Wang, W., Arshad, M. I., Khurshid, M., Muzammil, S., Rasool, M. H., Nisar, M. A., Alvi, R. F., Aslam, M. A., & Qamar, M. U. (2018). Antibiotic resistance: a rundown of a global crisis. *Infection and drug resistance*, 1645-1658.

Bang, N. U., & Kammer, R. B. (1983). Hematologic complications associated with β- lactam antibiotics. *Reviews of Infectious Diseases*, *5*(Supplement_2), S380-S393.

Bérdy, J. (1974). Recent developments of antibiotic research and classification of antibiotics according to chemical structure. *Adv Appl Microbiol*, *18*(0), 309-406.

Brooks, N. A., Boland, R. S., Strigenz, M. E., Mott, S. L., & Brown, J. A. (2018). Nongenitourinary complications associated with robot-assisted laparoscopic and radical retropubic prostatectomy: A single institution assessment of 1,100 patients over 11 years. Urologic Oncology: Seminars and Original Investigations,

Buckel, W. R., Veillette, J. J., Vento, T. J., & Stenehjem, E. (2018). Antimicrobial Stewardship in Community Hospitals. *Med Clin North Am*, *102*(5), 913-928. https://doi.org/10.1016/j.mcna.2018.05.005

Butler, M. S., & Cooper, M. A. (2011). Antibiotics in the clinical pipeline in 2011. *The Journal of antibiotics*, *64*(6), 413-425.

Carlsson, S., Nilsson, A. E., Schumacher, M. C., Jonsson, M. N., Volz, D. S., Steineck, G., & Wiklund, P. N. (2010). Surgery-related complications in 1253 robot- assisted and 485 open ret-

ropubic radical prostatectomies at the Karolinska University Hospital, Sweden. *Urology*, *75*(5), 1092-1097.

Chopra, I., & Roberts, M. (2001). Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiology and molecular biology reviews*, *65*(2), 232-260.

Christaki, E., Marcou, M., & Tofarides, A. (2020). Antimicrobial Resistance in Bacteria: Mechanisms, Evolution, and Persistence. *J Mol Evol*, *88*(1), 26-40. https://doi.org/10.1007/s00239-019-09914-3

Coenen, S., Van Royen, P., Michiels, B., & Denekens, J. (2004). Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial. *Journal of Antimicrobial Chemotherapy*, *54*(3), 661-672.

Cotner, S. E., Rutter, W. C., Burgess, D. R., Wallace, K. L., Martin, C. A., & Burgess, D. S. (2017). Influence of β-lactam infusion strategy on acute kidney injury.

Antimicrobial agents and chemotherapy, *61*(10), 10.1128/aac. 00871-00817.

Cresswell, K., Hinder, S., Sheikh, A., Pontefract, S., Watson, N. W., Price, D., Heed, A., Coleman, J., Ennis, H., & Beggs, J. (2023). ePrescribing-Based Antimicrobial Stewardship Practices in an English National Health Service Hospital: Qualitative Interview Study Among Medical Prescribers and Pharmacists. *JMIR Formative Research*, *7*(1), e37863.

Darville, T., & Yamauchi, T. (1994). The cephalosporin antibiotics. *Pediatrics in Review*, *15*(2), 54-62.

Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev*, *74*(3), 417-433. https://doi.org/10.1128/mmbr.00016-10

Di Pierro, G. B., Baumeister, P., Stucki, P., Beatrice, J., Danuser, H., & Mattei, A. (2011). A prospective trial comparing consecutive series of open retropubic and robot- assisted laparoscopic radical prostatectomy in a centre with a limited caseload. *European urology*, *59*(1), 1-6.

Dolecek, C., Shakoor, S., Basnyat, B., Okwor, T., & Sartorius, B. (2022). Drug-resistant bacterial infections: We need urgent action and investment that focus on the weakest link. *PLoS biology*, *20*(11), e3001903.

Esmaily, H. M., Silver, I., Shiva, S., Gargani, A., Maleki-Dizaji, N., Al-Maniri, A., & Wahlstrom, R. (2010). Can rational prescribing be improved by an outcome- based educational approach? A randomized trial completed in Iran. *Journal of Continuing Education in the Health Professions*, *30*(1), 11-18.

Etebu, E., & Arikekpar, I. (2016). Antibiotics: Classification and mechanisms of action with emphasis on molecular perspectives. *Int. J. Appl. Microbiol. Biotechnol. Res*, *4*(2016), 90-101.

Everts, S. (2013). Antibiotic side effects explained. *Chem. Eng. News Arch*, *91*(9). Faddan, A. A.,

Shalaby, M. M., Gadelmoula, M., Alshamsi, Y., Osmonov, D. K.,

Mohammed, N., Kurkar, A., Abdel Latif, A. M., Fornara, P., & Jünemann, K. P. (2020). Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a multi-institutional comparative study. *African Journal of Urology*, *26*(1), 1-6.

Ficarra, V., Novara, G., Artibani, W., Cestari, A., Galfano, A., Graefen, M., Guazzoni, G., Guillonneau, B., Menon, M., & Montorsi, F. (2009). Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. *European urology*, *55*(5), 1037-1063.

Frieri, M., Kumar, K., & Boutin, A. (2017). Antibiotic resistance. *Journal of Infection and Public Health*, *10*(4), 369-378.

Garau, J., & Bassetti, M. (2018). Role of pharmacists in antimicrobial stewardship programmes. *International journal of clinical pharmacy*, *40*, 948-952.

Gillespie, S. H. (2002). Evolution of drug resistance in Mycobacterium tuberculosis: clinical and molecular perspective. *Antimicrob Agents Chemother*, *46*(2), 267- 274. https://doi.org/10.1128/aac.46.2.267-274.2002

Gould, K. (2016). Antibiotics: from prehistory to the present day. *J Antimicrob Chemother*, *71*(3), 572-575. https://doi.org/10.1093/jac/dkv484

Grill, M. F., & Maganti, R. K. (2011). Neurotoxic effects associated with antibiotic use: management considerations. *British journal of clinical pharmacology*, *72*(3), 381-393.

Gupta, P. D., & Birdi, T. J. (2017). Development of botanicals to combat antibiotic resistance. *Journal of Ayurveda and integrative medicine*, *8*(4), 266-275.

Hamilton-Miller, J. (1999). β-Lactams: variations on a chemical theme, with some surprising biological results. *Journal of Antimicrobial Chemotherapy*, *44*(6), 729- 734.

Heaslet, H., Harris, M., Fahnoe, K., Sarver, R., Putz, H., Chang, J., Subramanyam, C., Barreiro, G., & Miller, J. R. (2009). Structural comparison of chromosomal and exogenous dihydrofolate reductase from Staphylococcus aureus in complex with the potent inhibitor trimethoprim. *Proteins: Structure, Function, and Bioinformatics*, *76*(3), 706-717.

Heeb, S., Fletcher, M. P., Chhabra, S. R., Diggle, S. P., Williams, P., & Cámara, M. (2011). Quinolones: from antibiotics to autoinducers. *FEMS microbiology reviews*, *35*(2), 247-274.

Hernandez, A. V., Marti, K. M., & Roman, Y. M. (2020). Meta-analysis. *Chest*, *158*(1), S97-S102.

Hooper, D. C., & Jacoby, G. A. (2016). Topoisomerase inhibitors: fluoroquinolone mechanisms of action and resistance. *Cold Spring Harbor perspectives in medicine*, *6*(9).

Hutchings, M. I., Truman, A. W., & Wilkinson, B. (2019). Antibiotics: past, present and future. *Current opinion in microbiology*, *51*, 72-80.

Ilett, K. F., Johnson, S., Greenhill, G., Mullen, L., Brockis, J., Golledge, C. L., & Reid, D. B. (2000). Modification of general practitioner prescribing of antibiotics by use of a therapeutics adviser (academic detailer). *British journal of clinical pharmacology*, *49*(2), 168-173.

Johnson, I., Ottosson, F., Diep, L. M., Berg, R. E., Hoff, J.-R., Wessel, N., Eri, L. M., & Berge, V. (2018). Switching from laparoscopic radical prostatectomy to robot assisted laparoscopic prostatectomy: comparing oncological outcomes and complications. *Scandinavian journal of urology*, *52*(2), 116-121.

Khan, H., Malik, A., Gaur, P. K., Rastogi, S., & Lata, K. (2022). Antibiotic Resistance: A Universal Issue of Concern. *Journal of Pharmacy Practice and Community Medicine*, *8*(1).

Khan, N., McGarry, K., Naqvi, A. A., Iqbal, M. S., & Haider, Z. (2020). Pharmacists' viewpoint towards their professional role in healthcare system: a survey of hospital settings of Pakistan. *BMC Health Serv Res*, *20*(1), 610. https://doi.org/10.1186/s12913-020-05459-0

Kim, B.-N. (2012). Overview of antibiotic use in Korea. *Infection & Chemotherapy*, *44*(4), 250-262.

Kishida, H., Unzai, S., Roper, D. I., Lloyd, A., Park, S.-Y., & Tame, J. R. (2006). Crystal structure of penicillin binding protein 4 (dacB) from Escherichia coli, both in the native form and covalently linked to various antibiotics. *Biochemistry*, *45*(3), 783-792.

Klepser, M. E., Adams, A. J., & Klepser, D. G. (2015). Antimicrobial stewardship in outpatient settings: leveraging innovative physician-pharmacist collaborations to reduce antibiotic resistance. *Health Secur*, *13*(3), 166-173. https://doi.org/10.1089/hs.2014.0083

Kohanski, M. A., Dwyer, D. J., & Collins, J. J. (2010). How antibiotics kill bacteria: from targets to networks. *Nature Reviews Microbiology*, *8*(6), 423-435.

Kokane, J. V., & Avhad, P. S. (2016). Role of pharmacist in health care system. *J Community Health Manag*, *3*(1), 37-40.

Lang, R., Lishner, M., & Ravid, M. (1991). Adverse reactions to prolonged treatment with high doses of carbenicillin and ureidopenicillins. *Reviews of Infectious Diseases*, *13*(1), 68-72.

Lee, S. W., & Koo, M. J. (2022). PRISMA 2020 statement and guidelines for systematic review and meta-analysis articles, and their underlying mathematics: Life Cycle Committee Recommendations. *Life Cycle*, *2*.

Legendre, D. P., Muzny, C. A., Marshall, G. D., & Swiatlo, E. (2014). Antibiotic hypersensitivity reactions and approaches to desensitization. *Clinical Infectious Diseases*, *58*(8), 1140-1148.

Lenfant, L., Sawczyn, G., Aminsharifi, A., Kim, S., Wilson, C. A., Beksac, A. T., Schwen, Z., & Kaouk, J. (2021). Pure single-site robot-assisted radical prostatectomy using single-port versus multiport robotic radical prostatectomy: a single- institution comparative study. *European urol-*

ogy focus, *7*(5), 964-972.

Levy, S. B. (2013). *The antibiotic paradox: how miracle drugs are destroying the miracle*. Springer.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*, *62*(10), e1-e34.

Loree, J., & Lappin, S. L. (2019). Bacteriostatic antibiotics.

Lu, Z. K., Yuan, J., Li, M., Sutton, S. S., Rao, G. A., Jacob, S., & Bennett, C. L. (2015).

Cardiac risks associated with antibiotics: azithromycin and levofloxacin. *Expert opinion on drug safety*, *14*(2), 295-303.

Ma, C., Yang, X., & Lewis, P. J. (2016). Bacterial transcription as a target for antibacterial drug development. *Microbiology and molecular biology reviews*, *80*(1), 139-160.

Macaskill, P., Takwoingi, Y., Deeks, J. J., & Gatsonis, C. (2023). Understanding meta- analysis. *Cochrane handbook for systematic reviews of diagnostic test accuracy*, 203-247.

Mahon, C. R., & Lehman, D. C. (2022). *Textbook of diagnostic microbiology-e-book*. Elsevier Health Sciences.

Maker, J. H., Stroup, C. M., Huang, V., & James, S. F. (2019). Antibiotic hypersensitivity mechanisms. *Pharmacy*, *7*(3), 122.

Mandell, L., & Tillotson, G. (2002). Safety of fluoroquinolones: An update. *Canadian Journal of Infectious Diseases and Medical Microbiology*, *13*, 54-61.

Mansour, O., & Al-Kayali, R. (2017). Community Pharmacists' Role in Controlling Bacterial Antibiotic Resistance in Aleppo, Syria. *Iran J Pharm Res*, *16*(4), 1612- 1620.

Martens, J. D., Winkens, R. A., van der Weijden, T., de Bruyn, D., & Severens, J. L. (2006). Does a joint development and dissemination of multidisciplinary guidelines improve prescribing behaviour: a pre/post study with concurrent control group and a randomised trial. *BMC health services research*, *6*, 1-8.

Mehta, R., & Champney, W. S. (2002). 30S ribosomal subunit assembly is a target for inhibition by aminoglycosides in Escherichia coli. *Antimicrobial agents and chemotherapy*, *46*(5), 1546-1549.

Menon, M., Tewari, A., Baize, B., Guillonneau, B., & Vallancien, G. (2002). Prospective comparison of radical retropubic prostatectomy and robot-assisted anatomic prostatectomy: the Vattikuti Urology Institute experience. *Urology*, *60*(5), 864- 868.

Morales-Alvarez, M. C. (2020). Nephrotoxicity of antimicrobials and antibiotics. *Advances in chronic kidney disease*, *27*(1), 31-37.

Nayak, S., & Acharjya, B. (2008). Adverse cutaneous drug reaction. *Indian Journal of dermatology*, *53*(1), 2.

Nelson, B., Kaufman, M., Broughton, G., Cookson, M. S., Chang, S. S., Herrell, S. D., Baumgartner, R. G., & Smith, J. A. (2007). Comparison of length of hospital stay between radical retropubic prostatectomy and robotic assisted laparoscopic prostatectomy. *The Journal of Urology*, *177*(3), 929-931.

Oloke, J. (2000). Activity pattern of natural and synthetic antibacterial agents among hospital isolates. *Microbios*, *102*(403), 175-181.

Organization, W. H. (2014). The Role of a Pharmacist in Encouraging Prudent Use of Antibiotic Medicines and Averting Antimicrobial Resistance—A Review of Current Policies and Experiences in Europe. *WHO Regional Office for Europe: Copenhagen, Denmark*.

Osmonov, D. K., Faddan, A. A., Aksenov, A. V., Naumann, C. M., Rapoport, L. M., Bezrukov, E. A., Tsarichenko, D. G., & Jünemann, K. P. (2018). Surgical site infections after radical prostatectomy: a comparative study between robot- assisted laparoscopic radical prostatectomy and retropubic radical prostatectomy. *Turkish journal of urology*, *44*(4), 303.

Patel, R. A., & Gallagher, J. C. (2010). Drug fever. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *30*(1), 57-69.

Percival, K. M. (2017). Antibiotic classification and indication review for the infusion nurse. *Journal of Infusion Nursing*, *40*(1), 55-63.

Pilecki, M. A., McGuire, B. B., Jain, U., Kim, J. Y., & Nadler, R. B. (2014). National multi-institutional comparison of 30-day postoperative complication and readmission rates between open retropubic radical prostatectomy and robot- assisted laparoscopic prostatectomy using NSQIP. *Journal of Endourology*, *28*(4), 430-436.

Piraux, A., Hammoud, R., Riou, J., Lebdai, S., & Faure, S. (2022). Assessment of the Compliance of Cystitis Management According to French Recommendations through the Analysis of Prescriptions Collected in Community Pharmacies. *Antibiotics*, *11*(7), 976.

Polikanov, Y. S., Aleksashin, N. A., Beckert, B., & Wilson, D. N. (2018). The mechanisms of action of ribosome-targeting peptide antibiotics. *Frontiers in molecular biosciences*, *5*, 48.

Qin, Y., Han, H., Xue, Y., Wu, C., Wei, X., Liu, Y., Cao, Y., Ruan, Y., & He, J. (2020).

Comparison and trend of perioperative outcomes between robot-assisted radical prostatectomy and open radical prostatectomy: nationwide inpatient sample 2009-2014. *International braz j urol*, *46*, 754-771.

Rabbani, S. A., Sridhar, S. B., Safdar, M., Rao, P. G., Jaber, A. A. S., AlAhmad, M. M., Shaar, K., Emad, I., & Azim, M. A. (2023). Assessment of Prescribing Practices and Factors Related to

Antibiotic Prescribing in Community Pharmacies. *Medicina*, *59*(5), 843.

Retsema, J., & Fu, W. (2001). Macrolides: structures and microbial targets. *International journal of antimicrobial agents*, *18*, 3-10.

Rezaei, N. J., Bazzazi, A. M., & Alavi, S. A. N. (2018). Neurotoxicity of the antibiotics: A comprehensive study. *Neurology India*, *66*(6), 1732.

Rolain, J.-M., & Baquero, F. (2016). The refusal of the Society to accept antibiotic toxicity: missing opportunities for therapy of severe infections. *Clinical Microbiology and Infection*, *22*(5), 423-427.

Ryu, J., Kwon, T., Kyung, Y. S., Hong, S., You, D., Jeong, I. G., & Kim, C.-S. (2013). Retropubic versus robot-assisted laparoscopic prostatectomy for prostate cancer: a comparative study of postoperative complications. *Korean journal of urology*, *54*(11), 756-761.

Saint, S., Scholes, D., Fihn, S. D., Farrell, R. G., & Stamm, W. E. (1999). The effectiveness of a clinical practice guideline for the management of presumed uncomplicated urinary tract infection in women∗. *The American journal of medicine*, *106*(6), 636-641.

Santis, G. D., Harvey, K. J., Howard, D., Mashford, M. L., & Moulds, R. F. (1994). Improving the quality of antibiotic prescription patterns in general practice: the role of educational intervention. *Medical Journal of Australia*, *160*(8), 502-505.

Schwartz, R. S. (2004). Paul Ehrlich's magic bullets. *New England Journal of Medicine*, *350*(11), 1079-1080.

Sheikhbahaei, S., Trahan, T. J., Xiao, J., Taghipour, M., Mena, E., Connolly, R. M., & Subramaniam, R. M. (2016). FDG-PET/CT and MRI for evaluation of pathologic response to neoadjuvant chemotherapy in patients with breast cancer: a meta- analysis of diagnostic accuracy studies. *The oncologist*, *21*(8), 931-939.

Smeets, H., Kuyvenhoven, M., Akkerman, A., Welschen, I., Schouten, G., Van Essen, G., & Verheij, T. (2009). Intervention with educational outreach at large scale to reduce antibiotics for respiratory tract infections: a controlled before and after study. *Family Practice*, *26*(3), 183-187.

Souissi, S. B., Abed, M., Elhiki, L., Fortemps, P., & Pirlot, M. (2017). Reducing the toxicity risk in antibiotic prescriptions by combining ontologies with a multiple criteria decision model. AMIA annual symposium proceedings,

Spížek, J., Sigler, K., Řezanka, T., & Demain, A. (2016). Biogenesis of antibiotics— Viewing its history and glimpses of the future. *Folia microbiologica*, *61*, 347- 358.

Stålsby Lundborg, C., Wahlström, R., Oke, T., Tomson, G., & Diwan, V. (1999). Influencing prescribing for urinary tract infections and asthma in primary care in Sweden–a randomised controlled trial of an interactive educational intervention. *J Clin Epidemiol*, *52*(8), 801-812.

Sugihara, T., Yasunaga, H., Horiguchi, H., Matsui, H., Fujimura, T., Nishimatsu, H., Fukuhara, H., Kume, H., Changhong, Y., & Kattan, M. W. (2014). Robot-assisted versus other types of radical prostatectomy: Population-based safety and cost comparison in Japan, 2012–2013. *Cancer Science*, *105*(11), 1421-1426.

Surawicz, C. M. (2005). Antibiotic-associated diarrhea and pseudomembranous colitis: are they less common with poorly absorbed antimicrobials? *Chemotherapy*, *51*(Suppl. 1), 81-89.

Tafuri, A., Sebben, M., Pirozzi, M., Processali, T., Shakir, A., Rizzetto, R., Amigoni, N., Tiso, L., De Michele, M., Panunzio, A., Cerrato, C., Migliorini, F., Novella, G., De Marco, V., Siracusano, S., Artibani, W., & Porcaro, A. B. (2020). Predictive Factors of the Risk of Long-Term Hospital Readmission after Primary Prostate Surgery at a Single Tertiary Referral Center: Preliminary Report. *Urologia internationalis*, *104*(5-6), 465-475. https://doi.org/10.1159/000505409

Tan, S. Y., & Tatsumura, Y. (2015). Alexander Fleming (1881-1955): Discoverer of penicillin. *Singapore Med J*, *56*(7), 366-367.

https://doi.org/10.11622/smedj.2015105

Tewari, A., Srivasatava, A., Menon, M., & team, V. (2003). A prospective comparison of radical retropubic and robot-assisted prostatectomy: experience in one institution. *BJU international*, *92*(3), 205-210.

Tu, D., Blaha, G., Moore, P. B., & Steitz, T. A. (2005). Structures of MLSBK antibiotics bound to mutated large ribosomal subunits provide a structural explanation for resistance. *Cell*, *121*(2), 257-270.

Ullah, H., & Ali, S. (2017). Classification of anti-bacterial agents and their functions. *Antibacterial agents*, *10*, 1-16.

Van Driel, M., Coenen, S., Dirven, K., Lobbestael, J., Janssens, I., Van Royen, P., Haaijer-Ruskamp, F. M., De Meyere, M., De Maeseneer, J., & Christiaens, T. (2007). What is the role of quality circles in strategies to optimise antibiotic prescribing? A pragmatic cluster-randomised controlled trial in primary care. *BMJ Quality & Safety*, *16*(3), 197-202.

Vellinga, A., Galvin, S., Duane, S., Callan, A., Bennett, K., Cormican, M., Domegan, C., & Murphy, A. W. (2016). Intervention to improve the quality of antimicrobial prescribing for urinary tract infection: a cluster randomized trial. *Cmaj*, *188*(2), 108-115.

Veninga, C., Denig, P., Zwaagstra, R., & Haaijer-Ruskamp, F. (2000). Improving drug treatment in general practice. *Journal of clinical epidemiology*, *53*(7), 762-772.

Vervloet, M., Meulepas, M. A., Cals, J. W., Eimers, M., Van Der Hoek, L. S., & Van Dijk,

L. (2016). Reducing antibiotic prescriptions for respiratory tract infections in family practice: results of a cluster randomized controlled trial evaluating a multifaceted peer-group-based

intervention. *NPJ primary care respiratory medicine*, *26*(1), 1-6.

Waglechner, N., & Wright, G. D. (2017). Antibiotic resistance: it's bad, but why isn't it worse? *BMC biology*, *15*(1), 1-8.

Waksman, S. A., Schatz, A., & Reynolds, D. M. (2010). Production of antibiotic substances by actinomycetes. *Annals of the New York Academy of Sciences*, *1213*(1), 112.

Wallerstedt, A., Tyritzis, S. I., Thorsteinsdottir, T., Carlsson, S., Stranne, J., Gustafsson, O., Hugosson, J., Bjartell, A., Wilderäng, U., & Wiklund, N. P. (2015). Short-term results after robot-assisted laparoscopic radical prostatectomy compared to open radical prostatectomy. *European urology*, *67*(4), 660-670.

Wallerstedt Lantz, A., Stranne, J., Tyritzis, S. I., Bock, D., Wallin, D., Nilsson, H., Carlsson, S., Thorsteinsdottir, T., Gustafsson, O., & Hugosson, J. (2019). 90-Day readmission after radical prostatectomy—a prospective comparison between robot-assisted and open surgery. *Scandinavian journal of urology*, *53*(1), 26-33.

Weiss, K., Blais, R., Fortin, A., Lantin, S., & Gaudet, M. (2011). Impact of a multipronged education strategy on antibiotic prescribing in Quebec, Canada. *Clinical Infectious Diseases*, *53*(5), 433-439.

Welschen, I., Kuyvenhoven, M. M., Hoes, A. W., & Verheij, T. J. (2004). Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. *Bmj*, *329*(7463), 431.

Westphal, J., Vetter, D., & Brogard, J. (1994). Hepatic side-effects of antibiotics. *Journal of Antimicrobial Chemotherapy*, *33*(3), 387-401.

Wilf-Miron, R., Ron, N., Ishai, S., Chory, H., Abboud, L., & Peled, R. (2012). Reducing the volume of antibiotic prescriptions: a peer group intervention among physicians serving a community with special ethnic characteristics. *Journal of Managed Care Pharmacy*, *18*(4), 324-328.

Wood, M. (1991). The tolerance and toxicity of clarithromycin. *Journal of Hospital Infection*, *19*, 39-46.

Wróbel, A., Maliszewski, D., Baradyn, M., & Drozdowska, D. (2019). Trimethoprim: An old antibacterial drug as a template to search for new targets. Synthesis, biological activity and molecular modeling study of novel trimethoprim analogs. *Molecules*, *25*(1), 116.