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EXPLORING THE IMPACT OF ANTIBIOTIC RESISTANCE: SPREAD AND IMPLICATIONS

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ABSTRACT

Antibiotics are drugs that have been used to treat bacterial infections since their discovery in the early 20th century. However, antibiotics are becoming less effective or even ineffective for treating bacterial infections due to bacterial mutation and adaptation. Nowadays, antibiotic resistance is becoming a global threat as it increases continuously, while antibiotic development remains stagnant due to high research costs and slow approval processes. Antibiotic resistance correlates with antibiotic overdoses, which can be caused by many factors, for instance, self-medication, overuse, etc. Therefore, we should consider this condition a serious issue that we should be aware of. To control or reduce the rate of antibiotic-resistant bacteria, we need improved infection prevention measures and more accurate diagnostic tools. These can help cope with the currently available antibiotic agents. The main purpose of this article is to summarize current knowledge about antibiotics and provide up-to-date data on the antibiotic resistance crisis, which has caused millions of deaths worldwide, including over three hundred thousand in South Asia. This review article mentions the causes, the environmental factors, the consequences, the mechanisms, the transmissions, the strategies, and lastly, case studies focusing on Southeast Asia. Moreover, future directions are also discussed for further discussion and alternative purposes.

Keywords: Antibiotics, Antibiotic resistance, Antibiotic agents

INTRODUCTION

1. Antibiotics

For millennia, humanity has grappled with mysterious and formidable infections, often escalating to epidemic scales with severe death tolls globally. The advent of antibiotics marked a revolutionary chapter in the annals of medical treatment, emerging as a potent form of chemotherapy. The countless lives saved and the significant stride they represent in combating infectious diseases—historically the primary culprits of illness and death—is a fact that speaks for itself and requires little emphasis **(Bassett *et al*., 1980; Nelson *et al*., 2010)**.

1.2 A brief history of Antibiotics

For over two millennia, traditional remedies involving mouldy bread poultices have been applied to open wounds, leveraging the antibiotic-producing properties of microbes. This ancient treatment has roots in various cultures, including those of Serbia, China, Greece, and Egypt, and has been in use for over 2,000 years **(Haas *et al*.,1999)**. A recipe from the Anglo-Saxon era, dating back a millennium, has been demonstrated to effectively combat MRSA (methicillin-resistant Staphylococcus aureus) **(Harrison *et al*., 2015)**. Paul Ehrlich pioneered the development of synthetic arsenic-based prodrugs, notably Salvarsan. This marked one of the first systematic approaches to drug discovery, involving extensive experimentation with numerous compounds. Ehrlich's innovative work was inspired by his earlier research on dyes that selectively stained bacterial cells **(Gelpi *et al*., 2015)**. On the other hand, Salvarsan was supplanted by the sulfonamide prodrug Prontosil, which was discovered by Gerhard Domagk **(Otten H, 1986)**. Sulfonamides, marking a milestone in medical history, were the first effective antibiotics used clinically and remain in use. However, their prominence was eclipsed by the groundbreaking discovery of penicillin. In 1928, Dr. Alexander Fleming made a significant observation: a petri dish containing Staphylococcus bacteria was contaminated with mould, leading to the revolutionary development of penicillin **(Fleming *et al*., 1929)**. Dorothy Hodgkin's resolution of the beta-lactam structure of penicillin in 1945, as reported in her 1949 publication, was a pivotal breakthrough. This discovery facilitated the development of semi-synthetic derivatives that could overcome penicillin resistance.

The pioneering work of Selman Waksman in the field of microbiology, inspired by the groundbreaking findings of penicillin and tyrocidine, initiated a comprehensive investigation into microorganisms. Waksman's focus was on the Streptomyces family, leading to an in-depth study of Streptomyces griseus. This research path culminated in the discovery by Albert Schatz, a graduate student under Waksman, that Streptomycin derived from this organism was an effective treatment against tuberculosis **(Waksman *et al*., 2010)**. Waksman's research in the 1940s marked the start of a prolific era in antibiotic discovery that lasted until the 1960s. Many antibiotics from this period are still used today. However, antibiotic resistance has significantly diminished their effectiveness. The rapid and somewhat effortless discovery of various antibiotic classes during this era led to their widespread overuse. Post-1970, there was a notable decline in new antibiotic discoveries, contributing to the present scenario where there are few novel antibiotics in clinical trial stages. Currently, most antibiotics undergoing trials are modifications of existing synthetic types rather than completely new categories. This has resulted in a decrease in the discovery of new natural product (NP) families. As a result, numerous major pharmaceutical and agrochemical companies with NP discovery departments have been impacted **(Katz *et al*., 2016)**.

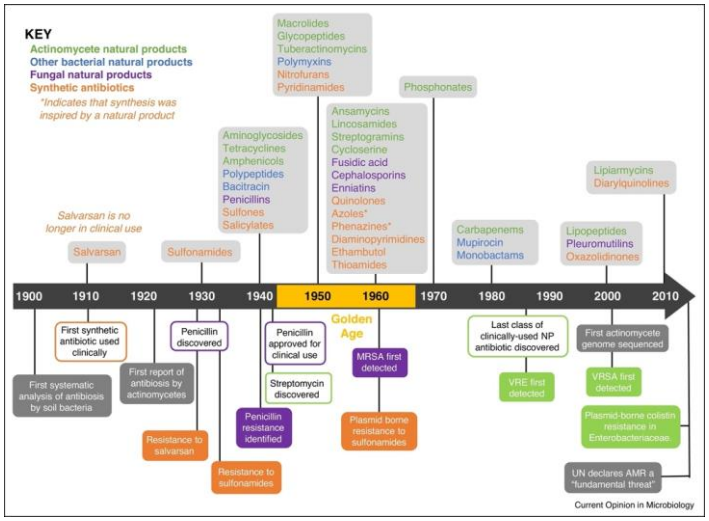

Figure 1 Timeline showing the decade new classes of antibiotic reached the clinic. The antibiotics are coloured per their source: green = actinomycetes, blue = other bacteria, purple = fungi and orange = synthetic. At the bottom of the timeline are key dates relating to antibiotic discovery and antimicrobial resistance (Frieri *et al*., 2017)

1.3 Types of Antibiotics

Antibiotics are primarily designed to impede bacterial growth, either by killing bacteria or halting their proliferation. They are broadly categorized into two types: bactericidal and bacteriostatic antibiotics. Both types are used to treat infections, but they function differently. Bactericidal antibiotics directly kill bacteria, often through hydroxyl radical-mediated DNA damage, with effectiveness varying based on the drug's potency and the specific type of bacteria targeted. Bacteriostatic antibiotics, on the other hand, prevent bacteria from growing further, allowing the body's immune system to combat the infection **(Feikin *et al*., 2000)**. Bacteriostatic agents halt bacterial growth by quenching intrinsic hydroxyphenyl fluorescein, with each drug targeting a specific type of bacteria. While these agents help inhibit bacterial growth, there are risks associated with overdose, which can be fatal **(Giberlin *et al*., 1997)**. Utilizing these drugs once daily can be as effective as traditional multiple dosing. An example of a bacteriostatic antibiotic is tetracyclines, while beta-lactam antibiotics, such as penicillin derivatives (penams), serve as examples of bactericidal antibiotics.

1.4 Mechanism of action

Antibiotic classes are designed to combat bacteria by targeting specific aspects of their structure. Antibiotics work in five main mechanisms, each related to the structure and function of bacteria. These include blocking the construction of cell walls, impairing the structure or functionality of cell membranes, hindering the formation and function of nucleic acids, obstructing the synthesis of proteins, and stopping critical metabolic pathways from functioning **(Talaro Kent *et al*., 2008)**.

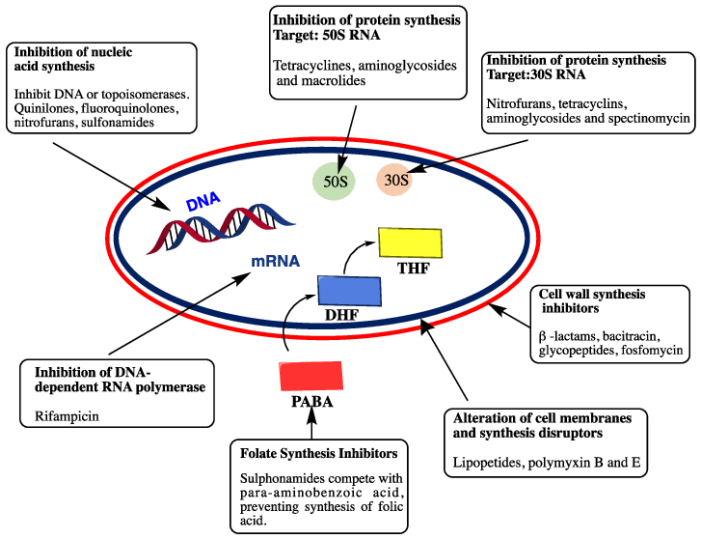

Figure 2 Mechanisms of action of some antibiotics. Adapted and modified image **(Grenni P *et al*., 2018; Sanserverino I *et al*., 2018; Kapoor G *et al*. 2017)**

1.4.1 Inhibition of the synthesis of cell walls

Bacterial cells are surrounded by a peptidoglycan (PG) layer, which protects them against the intense osmotic pressure found in their often-challenging environments **(Etebu *et al*., 2016)**. For their survival, bacteria synthesize peptidoglycan using penicillin-binding proteins (PBPs), which function as transglycosylases and transpeptidases. These enzymes are crucial in cross-linking strands of peptidoglycan during formation and in extending the glycan strands of existing peptidoglycan by adding disaccharide pentapeptides (Park J *et al*., 2008). Penicillin and similar beta-lactam antibiotics, among the earliest and most widely used, are known to disrupt the construction of bacterial cell walls, a key aspect of their antibacterial action **(Park J *et al*., 1957)**.

1.4.2 Disruption of the structure or function of cell membranes

The bacterial cell membrane serves as a protective barrier against external environments and provides structural support for metabolic and regulatory proteins, as described by **Nguyen *et al*. (2022)**. Different groups of microorganisms, each with unique lipid compositions in their cell membranes, are targeted by specific classes of antibiotics that damage these membranes, a concept outlined by **Etebu *et al*. (2016)**. Polymyxins, for example, function by interacting with lipopolysaccharide lipids in the bacterial outer membrane, leading to permeabilization, as explained by **Nikaido *et al*. (2003)**. Polymyxins inhibit bacterial growth by creating pores in the outer membrane, causing leakage of internal components, a process detailed by **Khondker *et al*. (2020)**. They induce curvature in the membrane and overcome the membrane's resistance to insertion. The hydrophobic tail of polymyxins can penetrate the bacterial membrane, disrupting lipid interactions and creating defects. Once fully integrated, polymyxins become highly mobile within the membrane core, forming aggregates that facilitate water intake and cause structural instabilities, as further detailed by **Khondker *et al*. (2020)**. Another antibiotic, daptomycin, is effective against Gram-positive bacteria by targeting the cell membrane, as described by **Gray *et al*. (2020)**. It exhibits rapid bactericidal activity by interacting with the bacterial cytoplasmic membrane, leading to potassium efflux and subsequent bacterial death, as explained by **Silverman *et al*. (2003)**.

1.4.3 Inhibition of nucleic acid structure and function

The synthesis of nucleic acids, a vital metabolic process, is a key target of certain antibiotics. Antibiotics like the quinolone family disrupt nucleic acid creation either by hindering replication or by inhibiting transcription **(Etebu *et al*., 2016)**. Quinolones, specifically, can impair DNA unwinding by interfering with helicase enzyme activity **(Chen *et al*., 1996)**. These antibiotics also target bacterial topoisomerase II and IV, essential for nucleic acid production. Disruption of these enzymes in bacteria affects RNA polymerase, leading to halted RNA synthesis **(Etebu *et al*., 2016)**. Low concentrations of quinolones can suppress gyrase and topoisomerase IV, key enzymes in replication and transcription, thereby blocking these processes **(Bush *et al*., 2020)**. However, halting replication has a minimal effect on the lethal action of quinolones **(Bush *et al*., 2020)**. The primary impact of stopping transcription bubbles and replication forks is a decrease in DNA and RNA production, as quinolones significantly reduce DNA and RNA synthesis rates **(Chen *et al*., 1996)**. Nevertheless, the slow killing effect of quinolones may result from secondary events triggered by replication inhibition **(Drlica *et al*., 2009)**.

1.4.4 Inhibition of protein synthesis

Proteins play a crucial role in the body, being responsible for structural integrity, metabolic activities, physiological responses, and stress reactions. DNA, containing specific information, dictates the type of protein produced by a bacterial cell. Messenger RNA (mRNA), a form of Ribonucleic acid (RNA), transports this genetic information as codons. Another related biomolecule, transfer RNA (tRNA), produced under DNA's guidance, travels with mRNA to ribosomes, the sites of protein synthesis in cells. The translation of mRNA into proteins involves ribosomes and various cytoplasmic components in three phases: initiation, elongation, and termination. Ribosomes, composed of ribosomal RNA (rRNA) and proteins, have two subunits: small (SSU) and large (LSU).
Protein synthesis is vital for metabolic functions and survival in all organisms. Disrupting this process in bacterial cells can inhibit their effectiveness, stunt growth, or lead to death. Antibiotics targeting protein synthesis fall into two categories: 50S inhibitors and 30S inhibitors. The 50S inhibitors, including erythromycin, clindamycin, and others, block protein synthesis initiation or amino acid addition to peptide chains. 30S inhibitors, like tetracycline and streptomycin, prevent aminoacyl-tRNAs from accessing the ribosome. Notably, tetracycline also affects some proteins at 50S ribosomes.

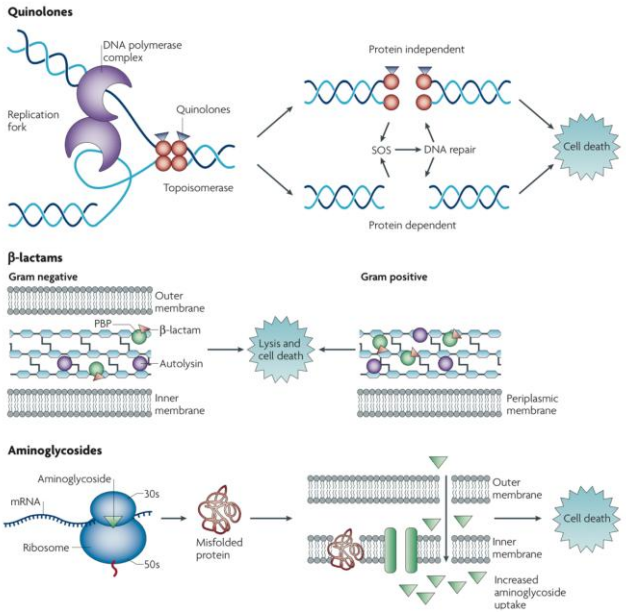

Figure 3 Drug-target interactions and associated cell death mechanisms **(Kohanski *et al*., 2010)**

Clindamycin, a bacteriostatic antibiotic, inhibits microbial protein synthesis by binding to the 50S ribosomal subunit. Unique among antibiotics, it reduces bacterial adhesion to epithelial cells on mucosal surfaces by suppressing virulence factor expression. Clindamycin also curbs the release of proinflammatory cytokines, which can damage periodontal tissues. Additionally, it enhances polymorphonuclear neutrophils' (PMNs) bacterial eradication abilities. PMNs are

essential in combating bacterial infections, and their functionality is crucial in preventing periodontal diseases.

1.4.5 Blockage of significant metabolic pathways

It has been demonstrated that several antibiotics, including sulphonamides and trimethoprim, mimic a substrate required for bacterial cellular metabolism. Due to this trick, bacterial enzymes connect to the antibiotic rather than the expected substrate. Sulphonamides specifically mimic the effects of tetrahydrofolate, which is necessary for the synthesis of folic acid in bacterial cells. Sulphonamides ultimately disturb the formation of nucleic acids and amino acids because they resemble the substrates needed for folic acid metabolism. Folic acid is essential for the metabolism of nucleic acids and amino acids **(Talaro, 2008)**.
Sulfamethoxazole/trimethoprim (SMX-TMP) is the most widely used for the treatment of several infectious diseases. It has a blocking effect on the metabolism of both bacteria and protozoa. Sulfamethoxazole interferes with the formation of folic acid by preventing para aminobenzoic acid from entering bacterial metabolism. Trimethoprim inhibits the enzyme difolate reductase, which prevents the formation of folic acid **(Shtroblya *et al*., 2021)**. Thus, SMX-TMP, inhibit two stages of folic acid synthesis cells and thus exhibits synergistic antibacterial activity **(Baskaran *et al*., 2014)**.

Table 1 Antibiotic target sites **(Etebu *et al*., 2016; Westblade *et al*., 2020; Coates *et al*., 2011; Andrade *et al*., 2020; Shinabarger *et al*., 1999; Beyer *et al*., 1998; Beckert *et al*., 2021; Mankin *et al*., 2018).**

Inhibition the synthesis of cell walls	Disruption of the structure or function of cell membranes	Inhibition of nucleic acid structure and function	Inhibition of protein synthesis	Blockage of significant metabolic pathways
Penicillin Penicillin G, Penicillin V, Methicillin, Oxacillin, Cloxacillin, Dicloxacillin, Nafcillin, Ampicillin, Amoxicillin, Carbenicillin, Ticarcillin, Mezlocillin, Piperacillin, Azlocillin, Temocillin Cephalosporins First generation : Cephalothin, Cephapirin, Cephradine, Cephaloridine, Cefazolin Second generation : Cefamandole, Cefuroxime, Cephalexin, Cefprozil, Cefaclor, Loracarbef, Cefoxitin, Cefmetazole Third generation: Cefotaxime, Ceftizoxime, Ceftriaxone, Cefoperazone, Ceftazidime, Cefixime, Cefpodoxime, Ceftibuten, Cefdinir Fourth generation : Cefpirome, Cefepime Fifth generation : Ceftaroline, Ceftobiprole Carbapenems Imipenem, Meropenem, Doripenem Monobactam Aztreonam Glycopeptides Vancomycin, Teicoplanin, Telavancin Others Cycloserine, Bacitracin	Lipopeptides Daptomycin Others Polymixin B	*DNA directed RNA polymerase* Rifamycins Rifampicin (rifampin), Rifapentine, Rifabutin, Bezoxazinorifamycin, Rifaximin Others Streptovaricins	*30s inhibitors* Aminoglycosides Streptomycin, Neomycin, Kanamycin, Paromomycin, Gentamicin, Tobramycin, Amikacin, Netilmicin, Spectinomycin, Sisomicin, Dibekacin, Isepamicin Tetracyclines Tetracycline, Chlortetrecycline, demeclocycline, minocycline, oxytetracycline, methacycline, doxycycline, tigecycline	Sulphonamides Sulphanilamide, Para-aminobenzoic acid, Sulfadiazine, Sulfisoxazole, Sulfamethoxazole, Sulfathalidine, Others Trimethoprim
		DNA Gyrase Quinolones Nalidixic acid, Oxolinic acid, Norfloxacin, Pefloxacin, Enoxacin, Ofloxacin/Levofloxacin, Ciprofloxacin, Temafloxacin, Lomefloxacin, Fleroxacin, Grepafloxacin, Sparfloxacin, Trovafloxacin, Clinafloxacin, Gatifloxacin, Moxifloxacin, Sitafloxacin Others Novobiocin	*50s inhibitors* Macrolides Erythromycin, Azithromycin, Clarithromycin Ketolides Telithromycin Lincosamides Lincomycin, Clindamycin Streptogramins Quinupristin, Dalfopristin, Pristinamycin Oxazolidinones Linezolid Others Chloramphenicol	
		RNA elongation Actinomycin	*tRNA* Mupirocin, Puromycin	

1.5 The dark side of Antibiotics

Antibiotics are crucial in treating bacterial infections, but they can also lead to a dangerous condition known as antibiotic resistance. This resistance makes it difficult for the body to fight off infections, often resulting in severe consequences or even death. A study by **Iqbal *et al*. (2023)** focused on urinary tract infections (UTIs), a prevalent bacterial illness, in children to investigate this resistance. In 2021, urine samples were collected for analysis from children aged 0 to 6 years with UTIs at two hospitals in Lahore, Pakistan. These samples were used to identify the presence of resistance genes. The bacteria isolated from these hospitals underwent testing with various antibiotics. Remarkably, all bacterial strains tested exhibited complete resistance to antibiotics like amoxicillin, ampicillin, and cefuroxime, highlighting the severity of antibiotic resistance in these cases.

2. Antibiotic Resistance

2.1 Introduction

Following the golden age of antibiotic discovery, the issue of antibiotic resistance has escalated, largely due to antibiotics being overused and misused, combined with a slowdown in the development of new antibiotics **(Gould *et al*., 2013)**. Antibiotic resistance arises when bacteria evolve to withstand the effects of antibiotics. This resistance is a consequence of genetic mutations in microbes, which give mutated bacterial strains a survival advantage. As a result, resistant bacteria can thrive and multiply, exacerbating the problem and leading to a global crisis **(Habboush *et al*., 2023)**. The Centers for Disease Control and Prevention (CDC) has identified numerous bacteria that present urgent, serious, and concerning threats, significantly impacting clinical outcomes and imposing economic burdens on patients, families, and the American healthcare system **(Centers for Disease Control and Prevention, 2013)**.
Antibiotic resistance accounts for over 1.27 million deaths annually **(Antibiotic Resistance Collaborators, 2022)**. Without intervention, the death toll attributable to antibiotic resistance could rise to 10 million worldwide, with an associated cumulative economic loss of 100 trillion US Dollars **(O'Neill *et al*., 2023)**. Antibiotic resistance's effects extend beyond health, also impacting economic stability. A World Bank report suggests that antibiotic resistance could lead to a decrease of up to 3.8% in global exports and a yearly reduction of up to 7.5% in livestock production. This could result in an additional 1 trillion US Dollars in healthcare costs by 2050 **(The World Bank, 2016)**.
A key factor contributing to the overprescription of antibiotics, particularly antibiotics, in the US and other affluent nations, is inadequate indications for prescribing. Factors such as uncertainty in treatment decisions, lack of patient follow-up, ignorance about optimal treatments, and patient demands lead to inappropriate prescriptions. In many developing countries, antibiotics are easily available without a prescription, exacerbating the problem (Lemon *et al*., 2003). Notable examples of resistant pathogens include Penicillin-Resistant Streptococcus pneumoniae (PRSP), Methicillin-Resistant Staphylococcus aureus (MRSA), Vancomycin-Resistant Enterococci (VRE), and Multiple-Drug-Resistant Gram-Negative Bacilli (MDR GNB) **(Adedeji *et al*., 2016)**.

2.2 Causes

The causes of antibiotic resistance are multifaceted, stemming from both natural bacterial evolution and human activities. The main driver behind the rise in antibiotic resistance is the widespread and often inappropriate use of antibacterial drugs. In human healthcare, antibiotics are used in about 80% of cases, with at least half of these being for incorrect indications, mostly viral infections. Several factors contribute to antibiotic resistance, including misuse of antibiotics, patient factors, prescriber habits, monotherapy, hospital and veterinary prescriptions, commercial promotions, over-the-counter antibiotic sales, misuse of microbiological tests, and globalization. Understanding these causes is crucial for developing effective strategies to combat antibiotic resistance and ensure the continued effectiveness of antibiotics in treating bacterial infections.
Incorrect use of antibiotics always heightens the risk of bacterial resistance. This includes using antibiotics for the wrong reasons, for too short a period, at too low a dose, or with inadequate potency. Misuse is largely driven by patient factors, where many believe newer, more expensive drugs are more effective than older ones. This misconception promotes resistance to both new and older drugs, leading to unnecessary healthcare costs. Major contributors to resistance include patient misconceptions about antibiotic efficacy for viral infections, poor compliance with treatment, and self-medication. Increased demand for antibiotics is partly due to patient ignorance and past experiences. Hospital doctors often prescribe antibiotics unnecessarily due to patient expectations.
Antibiotics have also been increasingly used in animals and plants since proving effective in humans. They are often administered routinely for growth or as a preventative measure, exposing many animals to subtherapeutic levels of antibiotics, thereby increasing the likelihood of resistance.

2.3 Environmental factors influencing Antibiotic resistance

Beyond the misuse and overuse of antibiotics, various environmental aspects play a significant role in shaping the landscape of antibiotic resistance. Pollution from pharmaceutical manufacturing **(Rees V. *et al*., 2020)**, agricultural runoff **(Fang *et al*., 2023)**, and inadequate wastewater treatment all contribute to the dissemination of resistant bacteria and genes in the environment **(Hanna *et al*., 2023)**. According to recent studies, the environment plays a significant role in both the creation of resistance diseases and the spread of resistant microorganisms. The importance of the environment as a source and a means of resistance propagation has been recognized more and more in recent years **(Martinez, 2008; Wright *et al*., 2010; Ashbolt *et al*., 2013; Finley *et al*., 2013; Pruden *et al*., 2013; Bengtsson-Palme *et al*., 2014; Bondarczuk *et al*., 2015)** including both the ecological and evolutionary environmental factors.

2.3.1 Evolutionary

Two opposing evolutionary mechanisms are at work for the long-term preservation of antibiotic resistance genes in bacterial communities: selection favoring resistance phenotypes and selection resulting in a decrease in the fitness costs connected to carrying resistance genes **(Andersson *et al*., 2010; Baquero *et al*., 2011; Hernando-Amado *et al*., 2017)**. However, mobile resistance genes may be favored by co-selection by other compounds, such as metals and biocides, even in the absence of a direct selection pressure from an antibiotic **(Baker-Austin *et al*., 2006; Wales *et al*., 2015)**. The expression of genes encoding efflux pumps may also be selected for by exposure to stimuli other than antibiotics, which may make

bacteria less susceptible to antibiotics overall. While this might not have an immediate effect on the spread of resistance factors, it might aid in the evolution of more effective resistance genes by allowing bacteria to endure extended exposure to low concentrations of antibiotics. This would allow a newly acquired resistance gene to evolve into one that is less expensive and more effective in the new host.

Furthermore, resistance genes may be preserved because they offer advantages to the cell even in the absence of a selection pressure, effectively allowing bacteria to fulfill intrinsic functions more efficiently when they carry the resistance gene **(Enne *et al*., 2004)**. Carrying and maintaining resistance genes, on the other hand, typically comes with a cost in terms of decreased fitness by reducing the prevalence of resistance genes in bacterial populations **(Andersson *et al*., 2010)**. Random losses of resistance genes from bacterial cells happen all the time but rarely result in complete elimination of the gene from the community, which means that once a selection pressure for resistance re-emerges, resistance development of previously subjected bacterial populations can be quick **(Levin *et al*., 1997)**. Selection pressure acting especially against the carrying of resistance genes is thus critical for completely eradicating resistance factors from a population.

2.3.2 Ecological

There are four main steps that leads to antibiotic resistance including emergence of novel resistance factors, mobilization, transfer to human pathogens, and dissemination **(Walsh *et al*., 2003; Arzanlou *et al*., 2017)**. These steps do not have to happen in this specific order. The arsenal of resistance factors currently seen in pathogens and opportunistic diseases represents a group of genes in the later stages of this pathway. A resistance gene's ability to reach human pathogens is dependent on its persistence throughout all of these stages. Resistance genes with high fitness costs are more likely to be lost in the absence of selection pressure, especially if they are located on a mobile genetic element. Moreover, a scenario with a constant selection pressure by antibiotics is doubtful, although one could argue that this may be achievable in some regions around the world. Taken together, it is likely that successfully maintained resistance genes have either evolved to low fitness cost in a mobile context or were linked with low fitness costs from the beginning **(Gonzalez *et al*., 2013)**.

Since resistance genes are likely to be lost as long as they impose a major fitness cost on their carriers, newly mobilized genes that do not provide a clear fitness advantage are probably filtered out early from mobile genetic components such as plasmids **(Baquero *et al*., 2013)**. This emphasizes the significance of situations in which resistance genes provide a strong selection advantage, such as milieus subjected to industrial pollution with antibiotics **(Larsson *et al*., 2014)**. This is because these environments would also present bacteria with conditions that favor increased mutation frequency, one consequence could be that resistance genes are present in several slightly different variants, all selected for detoxification efficiency, of which only those with a low fitness cost are maintained when the selection pressure is removed.

2.4 Consequences

To understand the entire extent of antibiotic resistance requires an understanding of its causes and the environmental elements that impact it. The significant effects that antibiotic resistance has on the global economy, healthcare systems, and public health must also be taken into consideration. The consequences of bacterial resistance to antibiotics are severe. Risk variables linked to poor outcomes frequently complicated the evaluation of hospital-acquired infections with resistant pathogens. However, the mortality, probability of hospitalization, and duration of hospital stay for patients infected with drug-resistant strains of the same bacteria were typically at least twice as high as those infected with drug-susceptible strains for both nosocomial and community-acquired infections **(Holmberg *et al*., 1987)**. Effective therapy is often delayed by resistance, and the most important element contributing to this delay is a discrepancy between empirical therapy and subsequent antibiotic susceptibility test result **(George *et al*., 2003)**. If infection control measures are not put in place, patients who do not receive the proper treatment on time run the danger of developing a more serious illness or dying. They also remain infectious for extended periods of time, which increases the possibility of the resistant germs spreading **(Jacques *et al*., 1997).**

2.5 Mechanism

After examining the origins, environmental factors, and extensive effects of antibiotic resistance, it is crucial to investigate the mechanisms underlying this phenomenon. Understanding how bacteria develop and propagate resistance at the molecular level provides valuable insights into combating this growing threat. Antibiotic resistance occurs when bacteria evolve mechanisms to evade the effects of antibiotics, raising significant environmental and public health concerns **(Hayder *et al*., 2019)**. This resistance can render antibiotics ineffective, as some bacteria alter their component properties or surface structures, preventing antibiotic attachment **(Kreamer *et al*., 2019)**. Other bacteria may actively expel antibiotics. Such adaptations allow these bacteria to resist specific antibiotics and potentially share their resistance with others through growth. There are four primary categories of antibiotic resistance: intrinsic resistance, acquired resistance, cross-resistance, and multi-drug and other types of resistance.

Intrinsic resistance involves inherent characteristics of bacteria that naturally resist certain antibiotics, like bacteria without cell walls being immune to penicillin **(Kadhum *et al*., 2019)**. Acquired resistance happens when bacteria previously sensitive to an antibiotic develop defenses against it, either through new mutations or by acquiring resistant DNA from another bacterium **(Aljananby *et al*., 2018)**, as seen in Mycobacterium tuberculosis's resistance to Rifamycin **(Krause *et al*., 2016)**. Cross-resistance refers to the resistance that certain microorganisms have to a particular antibiotic when they use similar or related mechanisms and are also resistant to other antibiotics **(Etebu *et al*., 2016)**. This can be seen in antibiotics with common structures such as resistance to erythromycin, neomycinkanamycin, or resistance to cephalosporins and penicillins **(Jahne *et al*., 2015)**. Last category is multi-drug and other types of resistance, which multidrug-resistant species are pathogens that were resistant to their antibiotics; the bacteria will no longer be eliminated by a single drug **(Alanis *et al*., 2005)**. Inappropriate utilization of antibiotics for treatment culminated in the introduction of multidrugresistant pathogenic bacteria **(Dheda *et al*., 2017)**. These two mechanisms can lead to multidrug resistance in bacteria **(Rello *et al*., 2016)**.

Antibacterial resistance mechanisms are broadly categorized as reducing intracellular drug accumulation by acquiring mutations in porins and enhancing efflux, modification of binding sites, enzymatic inhibition or inactivation of antibiotic drugs, and biofilm formation.

2.5.1 The modifications

The effects of antibiotics on drug-related receptors and target regions vary, including complex enzymes and ribosomes **(Prashanth *et al*., 2012)**. Resistance to macrolide antibiotics is mostly caused by changes in the ribosomal target **(Shaikh *et al*., 2007)**. Penicillin resistance in Staphylococcus aureus, Streptococcus pneumoniae, Neisseria meningitides, and Enterococcus faecium strains is mostly caused by changes in penicillin-binding proteins beta-lactamase enzymes **(Southon *et al*., 2016)** (Figure 4).

2.5.2 Enzymatic inactivation of Antibiotics

Bacteria primarily antibiotic-degrading enzymes, making enzymatic inactivation a key route for antibiotic resistance **(Pérez-Llarena *et al*., 2016)**. Beta-lactamases, aminoglycosidase, chloramphenicol, and erythromycin modifying enzymes are the most common examples **(Sharkey *et al*., 2019)** (Figure 4).

2.5.3 Reduction of the inner and outer membrane permeability

This mechanism results from changes in the permeability of the internal and exterior membranes, causing diminished medication absorption or fast ejection from pump systems **(Santajit *et al*., 2016)**. Because of the decrease in membrane permeability which is a result of porin mutations in resistant strains such as OprD, can lead to carbapenem resistance in *Pseudomonas aeruginosa* **(Nikaido *et al*., 2012)**. Reduced outer membrane permeability can contribute to quinolone and aminoglycoside resistance **(Li *et al*., 2012)** (Figure 4).

2.5.4 Pumps System

The active pump systems in the tetracycline class of antibiotics are the most typical route via which resistance arises **(Breidenstein *et al*., 2011)**. Tetracyclines are expelled and unable to concentrate inside the cell due to an energy-dependent active pumping system **(Li *et al*., 2020)**.This method of resistance is mediated by plasmid-mediated endosomal control. For instance, active pumping systems are efficient at fending off quinolones, beta-lactams, 14-membered macrolides, and chloramphenicol **(Guo *et al*., 2020)** (Figure 4).

2.5.5 Biofilm formation

One strategy employed by microorganisms to evade the effects of antibiotics is biofilm development **(Hall *et al*., 2017; Sial *et al*., 2020; Ejaz *et al*., 2021)**. Bacterial cells in a biofilm are 10-10,000 less susceptible to antibiotic treatments than bacteria in the wild. Antibiotic resistance is higher in bacteria that create biofilms than in those that do not **(Gilbert *et al*., 2002; Neopane *et al*., 2018)**. Communities of bacteria known as biofilms are made up of either a single species of microorganisms or a combination of different species of microbes that coexist in a polymer matrix that the microbial mass is embedded in **(Muhammad *et al*., 2020)**. Three phases make up the creation of biofilms: attachment, growth and maturation, and separation **(Laverty *et al*., 2014)**. This polymer matrix makes up over 90% of the biofilm, with less than 10% being made up of microbial matter **(Flemming *et al*., 2001)**. The organisms that form biofilms possess a greater number of virulence genes than bacteria that do not produce biofilms. Furthermore, bacteria that form biofilms usually exhibit higher resistance than planktonic cells because of the presence of a rigid polymeric matrix that hinders the penetration of antibiotics **(Masadeh *et al*., 2013)** (Figure 5).

2.5.6 Using an alternative metabolic pathway

In contrast to some of the changes in the targets of bacteria, the most recent drug-susceptible pathway does not require objective development **(Fatahi-Bafgh *et al*., 2019)**. Rather than generating folic acid to make it resistant to sulfonamide and trimethoprim, bacteria can prepare folic acid from the environment **(Tan *et al*., 2020)**.

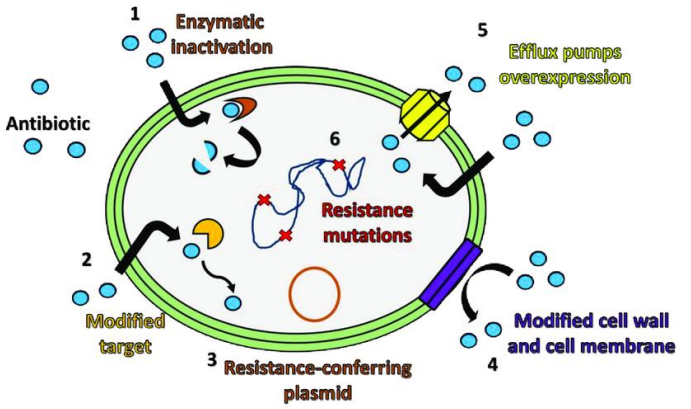

Figure 4 Mechanisms of antibiotic resistance. A simplified bacterium is depicted in which various mechanisms for resistance to antimicrobial substances are highlighted. A generic antibiotic is represented as a blue ball and its fate, after having contact with the bacterium, is analyzed in six potential occasions: (1) drug inactivation by enzymes; (2) drug target modification; (3) plasmid-carrying genes conferring antibiotic resistance; (4) changes in drug permeability following cell wall and cell membrane modifications; (5) expression of efflux pumps that expel drugs outside the bacterial cell; (6) selective DNA mutations altering the bacterial genome expression **(Giuseppe *et al*., 2023).**

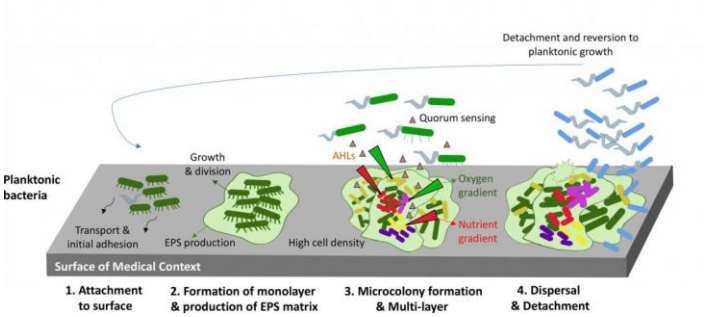

Figure 5. Schematic representation of biofilm formation on a medical context surface **(Yuanzhe *et al*., 2020)**.

2.6 Transmission

The transmission of antibiotic-resistant bacteria can occur through various pathways, including direct contact, contaminated food and water, and healthcare-associated infections. To address the transmission of antibiotic resistance requires an understanding of the transmission routes of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARG). However, recognizing that there is little overlap between antibiotic-resistant bacteria (ARB) and antibiotic-resistance genes (ARG) in the human microbiome and potential environmental sources should not be interpreted as a risk-free condition. Therefore, screening ARG pools is not a reliable indicator of the risk of human transmission.

It is necessary to evaluate the hazards of antibiotic resistance spreading from the environment to humans based on ARB, not just ARG, that can colonize and multiply in the human body. Their fitness in the human body as well as the existence of resistance and virulence genes determine the danger. Even at incredibly low concentrations in environmental sources, ARB might pose a serious threat to public health. It's possible that the quantification limits of techniques frequently used to check for ARG in environmental samples are too high to provide accurate risk evaluations.

2.6.1 Risk Associated with the Environmental Antibiotic Resistome

Three separate views have been used to discuss the hazards connected with the environmental antibiotic resistome: the transmission of resistance, the microbial community level, and the genome level. The first concerns the potential for environmental pollutants or physicochemical conditions to exacerbate the development of clinically significant antibiotic resistance **(Varela *et al*., 2014; Christgen *et al*., 2015; Bengtsson-Palme *et al*., 2016; Jutkina *et al*., 2016)**.

First perspective mainly approached at the bacterial community level, using either culture-based or culture-independent methods, which requires an understanding of how processes like wastewater treatment, water disinfection, applying manure to soils, or environmental pollution may contribute to the environment becoming more enriched in antibiotic-resistant bacteria (ARB). Second perspective focuses on the genome level, concentrating on the threat posed by genes that might confer antibiotic resistance, but differ in terms of the range of medications against which they may be active as well as their potential for horizontal gene transfer. Their clinical significance is impacted by these characteristics, which raises the related human risk **(Andersson *et al*., 2015; Martinez *et al*., 2015)**. Lastly, the third perspective which concerned the transfer of antibiotic-resistance genes (ARG) from the environment to humans **(Ashbolt *et al*., 2013; Hujibers *et al*., 2015; Woolhouse *et al*., 2015)**. This kind of risk is most likely the least studied due to several significant gaps that make risk evaluations unreliable, including the lack of databases that include environmental and human resistance data **(Berendonk *et al*., 2015)**.

2.6.2 Transmission Chain of Reservoirs, Carriers, and Vectors

Even though the transfer of antibiotic-resistance genes (ARG) from the environment to humans are poorly understood, there are multiple evidence of the wide and rapid spread of both ARB clones and ARG variants. According to the current data, a complex combination of variables referring to different environmental compartments, ubiquitous bacteria, and human–bacteria interaction may rule the risks of transmission to humans **(Woolhouse *et al*., 2015; Holmes *et al*., 2016)**.

The environmental resistome comprises both the natural antibiotic-resistance pool and contaminant antibiotic resistome. The natural resistome, marking the start of the entire antibiotic-resistance cycle, where genes that significantly resemble those of clinically relevant multidrug-resistant (MDR) microorganisms have been discovered **(D'Costa *et al*., 2011)**. Therefore, these ARB can be thought of as reservoirs, the most of which are likely merely environmental **(D'Costa *et al*., 2006; Riesenfeld *et al*., 2004)**. Reservoirs are made up of phylogenetically varied bacteria that are members of phyla like Actinobacteria, Proteobacteria, or Bacteroidetes. These bacteria are frequently makers of antibiotics or have the ability to metabolize or change **antibiotics (D'Costa *et al*., 2011; D'Costa *et al*., 2006; Riesenfeld *et al*., 2004; Dantas *et al*., 2008; Forsberg *et al*., 2012)**. However, it is improbable that every ARG that has emerged in clinical infections and is still spreading is the result of a direct transfer from reservoirs alone. Therefore, it is conceivable that in order to finish this process, certain intermediary agents are needed. Bacteria with significant genomic plasticity, abundance in the contaminant resistome, and the ability to disperse ARG across many environmental compartments and bacterial populations are thought to play this role. Contaminant ARB and ARG may be able to spread quickly and extensively, however the transfer of ARG from reservoirs (natural) to other bacteria may be an uncommon and random event **(Nicolas-Chanoine *et al*., 2016; Walsh *et al*., 2011; Rao *et al*., 2015)**. As a result, the contaminant likely poses a greater risk of ARB transmission to people than the natural resistome does.

Two main categories of players make up the contaminant antibiotic resistome: (i) ARB carriers that aid in the spread of ARG in the environment but are unable to colonize or infect humans, and (ii) ARB vectors that have the ability to colonize and occasionally invade humans. Vectors and carriers may differ at the physiological or ecological level, and they are not always affiliated with different taxonomic groupings. In other words, vectors have the potential to come into contact with humans but not carriers, or they have the capacity to colonize the human body but not carriers. According to the available literature, among the most active potential carriers and vectors seem to be members of the classes Gammaproteobacteria and Betaproteobacteria and of the phyla Actinobacteria and Firmicutes **(Vaz-Moreira *et al*., 2014; Li *et al*., 2015)**. Members of the family *Enterobacteriaceae*, and of genera such as *Aeromonas*, *Acinetobacter*, *Pseudomonas*, *Enterococcus*, or *Staphylococcus*, have been frequently described as carriers, and some of them are also recognized vectors **(Vaz-Moreira *et al*., 2014; WHO, 2014)**.

It is necessary to evaluate the risks of antibiotic resistance spreading from the environment to humans based on bacteria rather than resistance genes. Specifically, this includes bacteria that can colonize the human body (vectors) and simultaneously harbor acquired antibiotic resistance genes (ARGs). Vector bacteria need to occasionally or often coexist in the same environment as humans in order to have the opportunity to come into touch with human tissue and begin the colonization process. In fact, based on the data at hand, several lineages comprise bacteria that are present in both the human microbiome and ambient sources, indicating that vectors may be members of a broad range of bacterial taxa **(Vaz-Moreira *et al*., 2014)**. The ability of vectors to spread ARGs to the host microbiome through free-DNA, plasmids, or phages by horizontal gene transfer (through transformation, conjugation, or transduction processes) and to encourage genetic recombination, for example through transposons or integrons, will increase the threat that they pose. Antibiotic resistance surveillance programs across the globe concur that certain genera or species, such as MRSA, vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL), carbapenemase-producing *Enterobacteriaceae*, multidrug-resistant *Pseudomonas aeruginosa*, and

Clostridium difficile, fit the description of widely disseminated antibiotic resistance vectors **(WHO, 2014)**.

2.7 Examples of Antibiotic resistance bacterias

Methicillin-resistant Staphylococcus aureus (MRSA) is a type of bacteria that has evolved to resist common antibiotics. It spreads through contact, primarily affecting the skin, but can also infect blood and lungs, as noted by Leigh Ann Anderson in 2023. According to **Dancer *et al*. (2008)**, certain medications can trigger the rapid multiplication of MRSA on the skin, leading to clinical infection, treatment difficulties, and the potential to infect others. Inappropriate antibiotic use may exacerbate MRSA's pathogenicity, contributing to severe infections through mechanisms like quorum sensing, adhesion, phage mobilization, exotoxin production, intracellular persistence, and biofilm formation.

Carbapenem-resistant *Enterobacteriaceae* (CRE) can cause serious infections, including pneumonia and bloodstream infections. These bacteria have developed resistance to carbapenems, traditionally the most effective antibiotics for treating *Acinetobacter baumannii*, as described by **Li *et al*. (2023)**. The rise of carbapenem-resistant *Acinetobacter baumannii* (CRAB) has led to increased bloodstream and respiratory infections globally. A nanosystem delivering imipenem, enhanced by CRISPR-Cas9 gene editing, has shown potential in reversing drug resistance and promoting healing in infected tissues through nitric oxide production.

Drug-resistant Streptococcus pneumoniae, which causes pneumococcal disease, can originate from the inhalation of germs from the stomach or mouth. This bacterium can lead to various diseases, including lung, heart, liver, and kidney diseases, as highlighted by Leigh Ann Anderson in 2023. The conjugate vaccine has been beneficial in reducing the overall incidence of invasive pneumococcal disease and antibiotic resistance, particularly in children, as found by **Kyaw *et al*. (2006)**. The vaccine's impact varies with age and geography.

Vancomycin-resistant Enterococcus (VRE) is a common bacterium in the human body that can spread through contact with contaminated feces, urine, or wounds. Its spread and a weakened immune system can activate an infection **(Drugs.com, 2023)**. Research by **Chang *et al*. (2023)** focuses on the effects of reducing VRE isolation protocols in hospitals with shared rooms, aiming to understand the prevalence of VRE bacteremia in healthcare settings and the necessity for patient isolation.

Acinetobacter, commonly found in soil and water, can cause infections in wounds, the blood, urinary tract, and lungs. It can persist on surfaces, facilitating transmission through contact or from person to person, as stated by the CDC in 2023. **Zhang, Hong, *et al*. in 2023**, explored the efficiency of Acinetobacter sp. LW-1 in degrading LDPE, revealing insights into the molecular and structural changes during the process and its potential role in addressing LDPE pollution.

3. Strategies to control Antibiotic Resistance

Beginning with antibiotic resistance surveillance in 2013, India has progressively increased its efforts under two networks: the National Center for Disease Control (NCDC) and the Indian Council of Medical Research (ICMR). In order to track changes in the antibiotic susceptibility profile of clinically significant bacteria and fungi that are restricted to human health, the ICMR established the antibiotic Resistance Surveillance and Research Network (AMRSN) in 2013. According to the WHO Priority List of Pathogens (2017), the pathogens that are being monitored include sepsis-causing *Enterobacteriaceae*, non-fermenting Gram-negative bacteria, enteric fever pathogens, diarrheagenic bacterial species, Gram positive bacteria (staphylococci and enterococci), and fungal pathogens. The AMRSN consists of 16 regional centers situated at tertiary care hospitals as well as six nodal centers, one for each pathogenic group. (Fusire T., 2022)

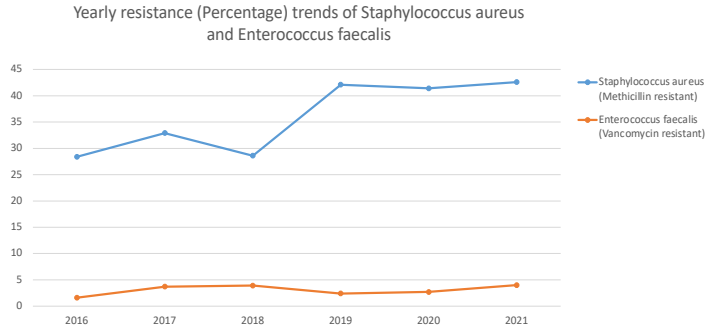

Table 2. Yearly resistance (Percentage) trends of Staphylococcus aureus and Enterococcus faecalis

However, there are strategies to combat this issue. **Pickens *et al*. (2019)** found that antibiotic stewardship programs could effectively reduce antibiotic use and resistance rates without impacting patient mortality in ICUs. **Ye *et al*. (2022)** highlighted the ongoing efforts to develop new methods to control or prevent antibiotics from becoming clinically ineffective. One approach involves modifying the basic chemical structure of antibiotics, as seen in omadacycline, which was modified at the C-7 and C-9 positions to enhance its resistance. Approved in the United States, omadacycline is used for skin infections and bacterial pneumonia acquired in community settings. Nanomedicine, as described by **Ferreira *et al*. (2021)**, offers another promising avenue. Using nanoparticle carriers, these medicines can deliver antibiotics to otherwise inaccessible areas and minimize side effects associated with high doses. **Zazo *et al*. (2016)** and **Greenhalgh *et al*. (2009)** note that these nanoparticles are low in toxicity and exhibit anti-MRSA activity.

Alternative treatments to antibiotics are also being explored. **Nikolich *et al*. (2020)** discusses the advancements in bacteriophage therapies, which can destroy bacterial biofilms, a particularly challenging issue for medical treatment. **Adnan M *et al*. (2020)** explain that bacteriophages can indirectly break down biofilms by attacking bacteria before or after they adhere to surfaces. However, the long-term impacts of using viruses for treatment are still uncertain. Finally, the role of probiotics is being considered. **Ye *et al*. (2022)** mention that probiotics, like Bacillus subtilis, which is a common strain in human gut microbiota, can produce bacitracin to inhibit cell wall synthesis in MRSA and other GPBPs. Probiotics are seen as a beneficial health strategy, though more scientific evidence is needed to fully understand their impact.

4. Case studies

Insights into the changing difficulties experienced by medical professionals and researchers in treating drug-resistant illnesses can be gained greatly from case studies of antibiotic resistance. An estimated 88,000 diseased individuals in Thailand are susceptible to antibiotic resistance, and an estimated 38,000 of them pass away annually **(Sumpradit *et al*., 2017)**. Indirect expenses for morbidity and premature death came to a total of $1100 million in 2010, whereas direct costs related to antibiotic resistance were estimated to be between 70 and 170 million dollars **(Sumpradit *et al*., 2017)**. In a 2014 health study including 19,468 Thai citizens, it was found that half of those with mild wounds, diarrhea, and colds took antibiotics to treat their ailments **(Pumtong *et al*., 2020)**. The International Health Policy Program and the National Statistical Office of Thailand report that 8% of Thais have taken antibiotics for a fever or sore throat **(Pumtong *et al*., 2020)**. The majority of antibiotics are really freely available to locals at retail pharmacies without a prescription. According to the data, in 2013, Thai citizens spent 0.9% of their income on antibiotic purchases; in 2014, that amount rose to 1.6% **(Siltrakool *et al*., 2021)**. Because antibiotics are used so widely, low- and middle-income countries (LMICs) are particularly affected by the issue of antibiotic resistance **(Do *et al*.,2021; O'Neill *et al*., 2016)**. Across the globe, over 50% of antibiotics are bought without a prescription, and using antibiotics for self-medication is become more widespread **(Cars *et al*., 2005; Morgan *et al*., 2011)**.In contrast to the target of reducing antibiotic consumption by 20% and improving antibiotic knowledge and resistance by 20%, over the three years from 2017 to 2019, knowledge of antibiotic resistance and antibiotic use increased by 0.6% from 23.7% to 24.3%, while human antibiotic consumption increased by 20.9% from 68.4% to 83.0% of the defined daily dose per 1000 inhabitants per day **(Torumkuney *et al*., 2022; Sumpradit *et al*., 2021)**. According to data from 2022, the proportion of hospital-origin bloodstream infections (BSIs) per 100,000 patients tested for BSIs was 4472 (range 1460-11968) due to carbapenem-resistant *Acinetobacter baumannii* (CRAB), 1306 (range 0–5432) due to carbapenem-resistant *Klebsiella pneumoniae* (CRKP), and 129 (range 0–1204) due to carbapenem-resistant *Escherichia coli* (CREC). With hospital-origin AMR BSI, the median number of all-cause in-hospital fatalities was 1 (range 0–18), 10 (range 0–77) from CRKP, and 56 (range 7–148) from CRAB **(Voranadda *et al*., 2023)**. Thailand encompassed 513 120 km2 and has 77 provinces with 66.1 million people living there in 2022 **(Voranadda *et al*., 2023)**. Using the decentralization model, health regions in Thailand were split into 13 regions, including 12 groupings of provinces plus Bangkok.The Ministry of Public Health (MoPH) under Thailand's Health Administration Division oversaw 127 public TCHs and SCHs in health regions 1 through 12 across the nation **(Voranadda *et al*., 2023)**.

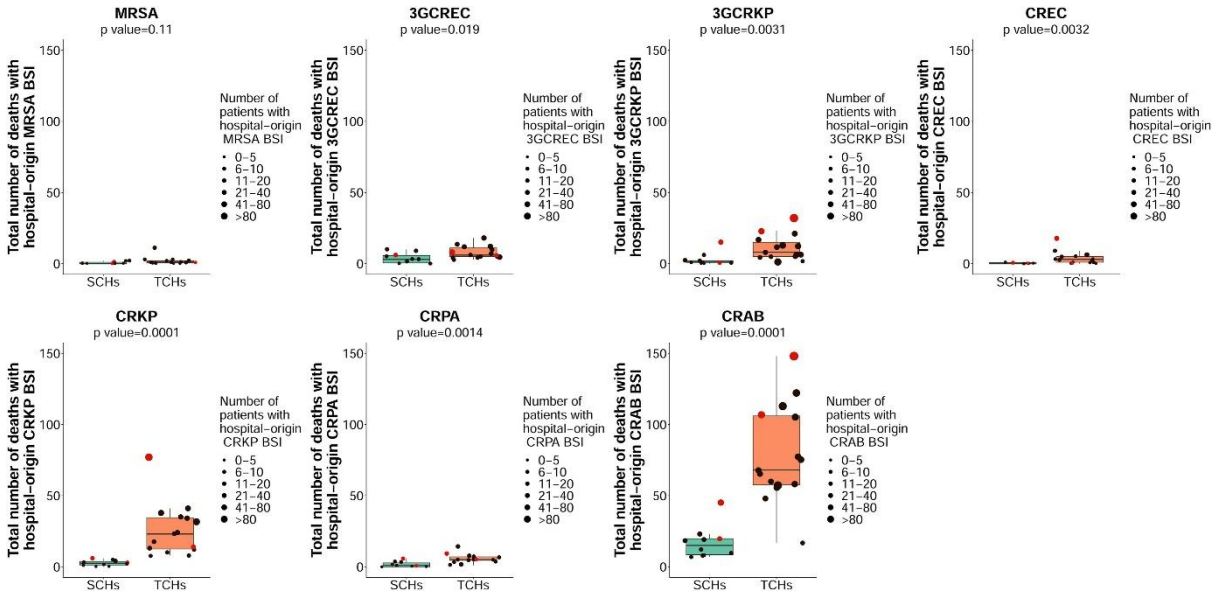

Figure 6 Total number of deaths with hospital-origin AMR BSI in 15 TCHs and 10 SCHs in Thailand in 2022. All-cause in-hospital mortality was used. Each dot represents a hospital. Red dots represent anonymous hospitals no. 22 and 24 (among TCHs) and anonymous hospitals no. 16 and 25 (among SCHs) **(Voranadda *et al*., 2023).**

5. Discussion and future direction

Antibiotic resistance is an urgent worldwide issue that necessitates all-encompassing approaches to lessen its growing danger and guarantee future bacterial diseases can be effectively treated. From the aforementioned study examples, we may infer that antibiotic resistance is progressing more quickly and if we are unable to stop it, more lives may be lost. We can pass legislation to restrict the sale of antibiotics, pharmaceutical companies will be more stringent about this medication. Future intitiatives should be focus on encouranging safe use of antibiotics, creating substitude treatments, and strengthening international surveillance. Promoting global cooperation and educating people about the appropriate use of antibiotics. Another factor contributing to the usage of antibiotics is lack of regulations governing their use. Consequently, restrictions governing the handing out of antibiotics ought to be put in place so that patients cannot purchase the medication without a doctor's prescription.

6. Conclusion

Antibiotics are antibacterial agents that work against bacteria, but due to the overusing of these drugs, leading to the mutation of bacteria known as "Antibiotic resistance". Bacteria develop antibiotic resistance due to the pressure caused by the presence of antibiotics and antifungals, making the antibiotic-resistant grems survive. This results in higher mortality; longer duration of hospital stay for patients and higher probability of transmission since the resistant bacteria are not eliminated and still available for further transmission. Additionally, since the environment and living things are interdependent, this medical condition may have an impact on the environment. Currently, farmers are feeding animals by mixing food and medicine, which raises the risk of antibiotic resistance in the animal. The primary cause of this issue is the ease with which antibiotics can be obtained from pharmacies, since the animals we fed will either be used to prepare our food or their waste may find its way into water supplies, the effects of this minor problem could become a major one. However, there are strategies to deal with this issue such as modification of the basic chemical structure of an antibiotic to reduce the rate of bacteria becoming resistant and using alternative ways of treatment have also been taken into consideration because to use the alternative way of treatment helps to trigger the bacteria to carry out mutation. Furthermore, the sale of antibiotics should raise concerns as well because it would be preferable if legislation restricting their sale could be passed in order to lower the rate of antibiotic resistance and other illnesses that could result from taking excessive amounts of antibiotics.

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