International Journal of Ecophysiology
Journal homepage: https://talenta.usu.id/ijoep

Literature Study: Genetic Mutations in Antibacterial Resistance

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ARTICLE INFO

Article history:
Received 20 April 2025
Revised 7 June 2025
Accepted 21 August 2025

E-ISSN: 2656-0674

How to cite:

Riska Wahyuni, Maria Cintiana Tambunan, Walida Fitri, Melva Silitonga. (2025). Literature "Study: Genetic Mutations in Antibacterial Resistance". *International Journal of Ecophysiology*, (7) 2, 85-93.

http://doi.org/10.32734/ijoep.v7i2.20544

ABSTRACT

This study aims to understand how molecular and genetic mechanisms contribute to the development of antibacterial resistance and its impact on public health. The method used is a literature review by analyzing various books and scientific journals. Antibacterial resistance occurs when microorganisms become resistant to drugs that should effectively eliminate them, making treatment less effective. The misuse and overuse of antibiotics are the main causes of this issue. In Indonesia, easy access to antibiotics without a prescription worsens the situation. As a result, infections become more difficult to treat, prolonging illness and increasing the risk of death. Several bacteria, such as *Pseudomonas aeruginosa*, *Escherichia coli,* and *Klebsiella pneumoniae*, have shown high levels of resistance, particularly in hospitals. This resistance can develop through genetic mutations and the transfer of genetic material between bacteria. Therefore, antibacterial resistance is a serious threat that requires special attention in its control efforts.

Keyword: Antibacterial resistance, antibiotics, genetic mechanisms,

ABSTRAK

Penelitian ini bertujuan untuk memahami bagaimana mekanisme molekuler dan genetik berkontribusi terhadap perkembangan resistensi antibakteri serta dampaknya terhadap kesehatan masyarakat. Metode yang digunakan adalah tinjauan pustaka dengan menganalisis berbagai buku dan jurnal ilmiah. Resistensi antimikroba terjadi ketika mikroorganisme menjadi kebal terhadap obat yang seharusnya efektif untuk membunuhnya, sehingga pengobatan menjadi kurang efektif. Penyalahgunaan dan penggunaan antibiotik yang berlebihan merupakan penyebab utama masalah ini. Di Indonesia, akses mudah terhadap antibiotik tanpa resep memperburuk situasi. Akibatnya, infeksi menjadi lebih sulit diobati, memperpanjang masa sakit, dan meningkatkan risiko kematian. Beberapa bakteri, seperti Pseudomonas aeruginosa, Escherichia coli, dan Klebsiella pneumoniae, telah menunjukkan tingkat resistensi yang tinggi, terutama di rumah sakit. Resistensi ini dapat berkembang melalui mutasi genetik dan transfer materi genetik antar bakteri. Oleh karena itu, resistensi antimikroba merupakan ancaman serius yang memerlukan perhatian khusus dalam upaya pengendaliannya..

Kata kunci: *Resistensi antibakteri, antibiotik, mekanisme genetik*

1. Introduction

Antibacterials are a type of treatment used to combat infections. There are various types of antibacterials categorized based on the type of microorganisms they target, including antibiotics or antibacterials, antivirals, antifungals, and antiprotozoals. In Indonesia, the use of antibacterials for medical purposes is already widely recognized by the public. Many individuals obtain antibacterials independently for self-medication. The ease of access to antibacterials without a prescription at health centers, as well as their affordable prices, are among the main factors contributing to inappropriate antibacterial use [6].

Antibacterial resistance (AMR) is the ability of microorganisms to withstand the effects of antibacterial treatment, rendering it no longer effective in clinical practice. This situation creates an urgent need for comprehensive control strategies to stop or reduce the incidence of resistant microbes. Inappropriate

and uncontrolled use of antibiotics is a major driver of the development and spread of antibacterial resistance globally, including the emergence of microorganisms that are resistant to multiple types of antibiotics—particularly in hospital environments [2].

The decline in sensitivity to antibacterials can interfere with the immune response and prolong the duration of illness. Drug-resistant microbes also have the potential to evolve more rapidly and spread more widely. The World Health Organization (WHO) has identified antibacterial resistance as one of the top ten global health threats. Resistance is a dynamic phenomenon, influenced by human behavior and continuously evolving [6].

One example of failure in AMR control was the case of Gram-negative bacteremia that occurred in Germany in 1983. Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter cloacae*, and *Klebsiella pneumoniae* were frequently isolated from pediatric intensive care units. Urinary tract infections and pneumonia were the primary causes of bacteremia [2].

Although bacterial resistance to antibacterials has existed long before the antibiotic era, even in remote environments not exposed to drugs, the increase in resistance has escalated with the rising consumption of antibacterials and the development of new drugs. Genetic changes, such as mutations, can trigger resistance, as observed in *Mycobacterium tuberculosis* which shows resistance to multiple drugs, and in quinolone resistance in *Enterobacteriaceae*. Other genetic mechanisms like transposons and integrons can also facilitate the transfer of resistant genes via plasmids, integrating them into bacterial chromosomes and passing them down to subsequent generations [14].

In Indonesia, almost all types of *Shigella*, particularly *S. flexneri*, have shown resistance to first-line antibiotics for treating diarrhea, necessitating the use of more expensive alternative medications, which poses a significant economic burden [14].

This article presents a contemporary approach by exploring the molecular and genetic mechanisms of antibacterial resistance, which have not been extensively addressed in the Indonesian context. Emphasis on genetic elements such as horizontal gene transfer, integrons, and plasmids offers a fresh perspective on the causes and spread of resistance.

Although many studies have assessed antibacterial resistance from clinical and pharmacological viewpoints, there is still a lack of research that thoroughly examines the involvement of genetic mechanisms in the spread of resistance in Indonesia. Additionally, few studies have linked genetic data with policies for controlling antibiotic distribution at the community level. The purpose of this article is to deepen the understanding and highlight the molecular and genetic mechanisms underlying the evolution of antibacterial resistance, with the hope of contributing meaningful scientific insight toward sustainable resistance control efforts.

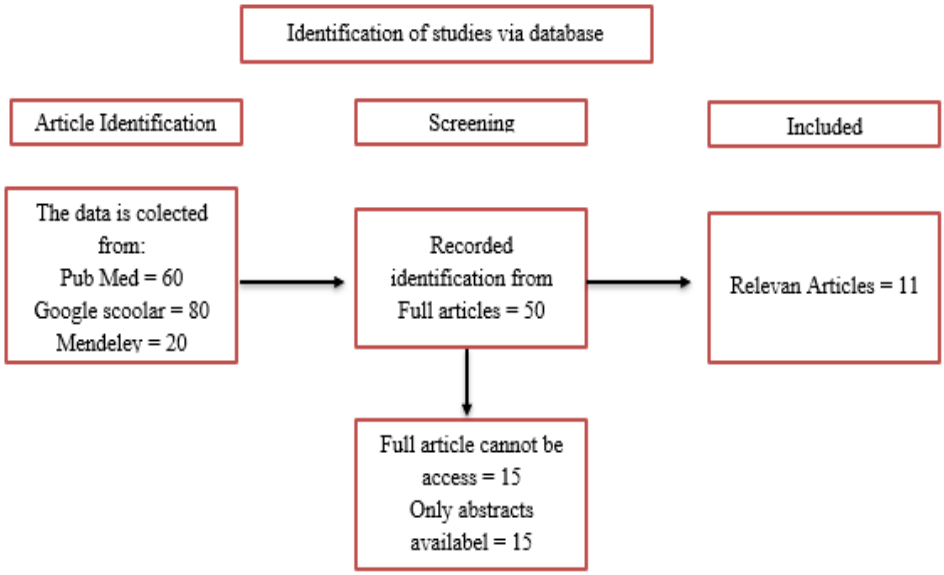


Figure 1. PRISMA Flowchart for the Review Methodology

2. Result and Discussion

To gain a deeper understanding of the molecular and genetic mechanisms underlying antibacterial resistance, a review of several relevant scientific articles was conducted. These articles were analyzed based

on their research focus, methodologies, and key findings that contribute to the understanding of the development of antibacterial resistance, particularly in relation to clinical and public health contexts. The table below presents a summary of the articles reviewed in this study.

Table 1. Review article

No.	Title	Author and Year	Research Method	Results
1	Antibiotic Resistance: Turning Evolutionary Principles into Clinical Reality	Andersson et al., (2020)	Review Article	Antibiotic resistance is one of the major challenges facing modern medicine worldwide. The past few decades have seen rapid advances in our understanding of the various factors that influence the emergence and spread of antibiotic resistance at the population level and individual patient level. However, the process of implementing these advances into health policy and clinical practice has been slow.
2	Genetic and In-Silico Approaches for Investigating the Mechanisms of Ciprofloxacin Resistance in *Salmonella Typhi*: Mutations, Extrusion, and Antimicrobial Resistance	Noman Khan et al., (2024)	The mechanism of ciprofloxacin resistance was investigated by sequencing the quinolone resistance-determining regions (QRDRs) and identifying the presence of the qnrS1 gene.	Ciprofloxacin resistance in *S. Typhi* is essentially related to mutations and the presence of extrinsic factors. Mutation-induced factors include mutations in the QRDR, while extrinsic factors involve the presence of transport channels that aid in antibiotic extrusion. Docking studies showed a significant impact of these mutations on the binding affinity of ciprofloxacin with gyrA and parC. The lack of direct interaction at the mutation site, along with altered solvent accessibility, suggests a structural basis for the drug's reduced effectiveness. In addition to mutation-induced resistance, the presence of transport channels plays an important role in the extrusion of antibiotics from cells, contributing to resistance.
3	Genetic Diversity, Virulence Profiles, and Antimicrobial Resistance of *Salmonella enterica* Serovar Typhi Isolated from Typhoid Fever Patients in Baghdad, Iraq	Muna Sabah Dawood, Nadheema Hammood Hussein, and Khetam Habeeb Rasool (2024)	VITEK-II and confirmed by polymerase chain reaction (PCR) to detect the 16S rRNA gene.	Antimicrobial resistance is a considerable threat to public health, and many local studies in Iraq have reported the uncontrolled spread of antimicrobial-resistant bacteria. This study supports the observation that *S. typhi* presents with a wide variety of virulence genes among Iraqi patients, detecting the presence of viaB, staA, cdtB, and orfL virulence genes, which play an important role in the pathogenicity of local isolates, in almost all samples tested.
4	Resistance of enteric bacteria: global aspects of antimicrobials	Yenny and Elly Herwana (2007)	Studi Literatur	Antimicrobial resistance to enteropathogens is ongoing in both developing and developed countries. Especially in developing countries, this situation is supported by many factors.
5	Review Article: Antimicrobial Resistance in	Putu Ayu Sisyawati Putriningsih amd I Putu	Review Article	*Staphylococcus pseudintermedius* has many types of resistant genes and their respective

	Staphylococcus pseudintermedius	Gede Yudhi Arjentinia (2023)		resistance mechanisms, which are obtained through mutation or HGT.
6	Education on the Appropriate Use of Antibiotics in an Effort to Prevent Resistance at the Air Dingin Health Center	Elvionita, C., Ferilda, S., and Putra, R. Y. (2023).	Extention method	The counseling session showed that the community in Air Pacah Subdistrict, Koto Tangah District, Padang City, demonstrated an increased understanding of pathogenic bacterial resistance, including its definition, criteria, contributing factors, and the importance of prudent use of medications.
7	DAGUSIBU Antibiotic Counseling in Efforts to Prevent Bacterial Resistance in Tlobo Sempon Hamlet, Karangsari Village.	Asmawan, M. C., Oktavia, R., Fadilah, U., Saputra, M. B., Nisa, M. P. A., Fadilah, M. I., and Arradhin, A. A. (2024)	Test, seminar, and Q&A	The results showed that, on the pre-test, 27 participants (45%) were aware of DAGUSIBU Antibiotics, whereas the post-test demonstrated a significant increase, with 41 participants (68.3%) being aware of DAGUSIBU Antibiotics. This indicates that the counseling was effectively conducted and successful.
8	DAGUSIBU Antibiotic Counseling in an Effort to Prevent Bacterial Resistance in Tlobo Sempon Hamlet, Karangsari Village.	Sari, dkk Tahun 2023	Education is delivered using a 4.5-minute animated video.	The results of this study showed that less than 60% of participants knew that fever does not always require antibiotics and the correct definition of antibiotic resistance.
9	Literature Review: Incidence of Resistance in Antibiotic Use	Putri, et al., (2023)	Literature Review	Overall, the studies found and analyzed reported the incidence of resistance to antibiotic use. Almost all studies described the percentage incidence of antibiotic resistance to certain bacteria. The increasing use of antibiotics has created high evolutionary pressure for the emergence of antibiotic resistance for bacterial survival.
10	Antibiotic resistance in the food supply chain: trends, resistance mechanisms, and prevention measures	Kurnianto, and Syahbanu (2022)	Literature Review	Antibiotic resistance is a public health challenge because it has significant health and socio-economic impacts influenced by the use of antibiotics in the food chain, posing an important threat to human health and food security.

11	16s rRNA Sequencing Analysis in the Field of Microbiology	Rianda T Tahun 2011	Literature Review	16S rRNA sequencing analysis is the answer to the need for a diagnosis method in the field of microbiology quickly and accurately. sequencing analysis can also identify organisms that cannot and are difficult to be cultured identified and can not be phenotyped (due to resistance to certain antibiotics).

The discussion section should include the following components:

a) A tabulated presentation of the research findings, aligned with the methods and variables used in the study;
b) An analysis and evaluation of the data based on the theoretical framework and formulas derived from the literature review;
c) For greater clarity, the discussion may incorporate comparative analysis, mathematical equations, graphs, images, and tables;
d) Interpretation of the analytical results to generate insights, added value, and practical relevance in relation to the research problems and objectives;
e) The findings must address the research questions and objectives; and
f) The discussion should be concise and focused on interpreting the results rather than repeating the data already presented in the results section.

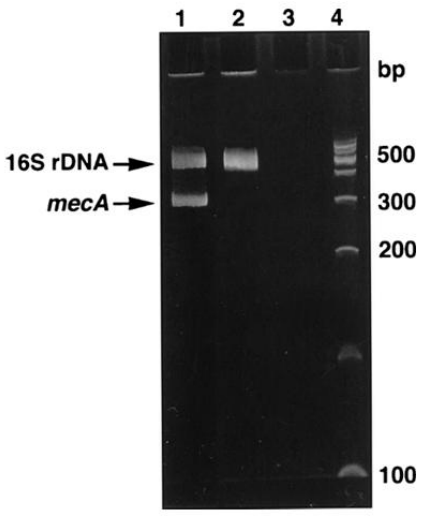
2.1 Antimicrobial Resistence

Antibacterial resistance refers to the ability of microorganisms such as bacteria, viruses, fungi, or parasites to withstand the effects of antimicrobial agents that were previously effective in treating infections. This phenomenon occurs when microorganisms undergo genetic changes or acquire resistance genes from other microbes, rendering antibacterial drugs less effective or even ineffective at inhibiting their growth or eliminating them [11]. Resistance can occur naturally through genetic mutations or be acquired via horizontal gene transfer between microorganisms. One of the main drivers of this resistance is the inappropriate use of antibiotics, including self-medication without a doctor's prescription or failure to complete the prescribed dosage.

2.2. Testing Method

From a time-efficiency perspective, sequencing analysis offers a significant advantage, as it can be performed in a relatively short period. Clarridge (2004) conducted an analysis summarizing the time required to identify a single clinical sample using sequencing methods. Molecular identification techniques based on nucleic acid amplification and sequencing have demonstrated superior performance in terms of speed, sensitivity, and accuracy [12].

One such example is the detection of the mecA gene in Staphylococcus species. The mecA gene encodes a penicillin-binding protein known as PBP2a or PBP2', which has reduced affinity for methicillin and



related compounds. However, since methicillin resistance can also arise through mechanisms other than the presence of mecA—such as the hyperproduction of β-lactamase—conventional susceptibility testing is still necessary for mecA-negative Staphylococcus isolates.

Figure 1. Multiplex PCR and Gel Electrophoresis for the Identification of the mecA Gene in Staphylococcus spp.

Two separate PCRs were conducted: one to amplify a segment of the 16S rDNA unique to *Staphylococcus* spp., and the other to amplify a portion of the mecA gene. Lane 1 represents a *methicillin-resistant Staphylococcus aureus* (MRSA) strain; electrophoresis bands corresponding to both 16S rDNA and mecA are present. Lane 2 contains *methicillin-sensitive Staphylococcus aureus* (MSSA); a band appears for 16S rDNA, but no band is observed for mecA. Lane 3 is the negative control (reagents only), and Lane 4 contains DNA fragment size standards. bp = base pairs.

The multiplex PCR method illustrated in Figure 1 was used in the laboratory to detect the mecA gene from isolated *Staphylococcus* colonies that had been cultured using standard methods. Two distinct PCR amplicons were simultaneously generated in the same reaction tube, hence the term *multiplex PCR*. In one reaction, a specific segment of the mecA gene was amplified. In the other, a nucleotide sequence from the 16S rRNA gene, which is unique to *Staphylococcus*, was amplified. The second PCR serves to confirm that the amplified organism is indeed a *Staphylococcus* species.

The PCR products (amplicons) were electrophoresed through an agarose gel, and their sizes were determined by comparison with DNA size standards. If no band appears, it may indicate that the organism tested is not a *Staphylococcus* species or that the PCR failed. A positive result should yield amplicons of the expected sizes for both mecA and 16S ribosomal DNA (16S rDNA), based on the oligonucleotide primers used in the PCR.

Additional confirmatory steps (not shown in Figure 1) may be carried out. For example, the mecA amplicon may undergo signal hybridization with a labeled probe, restriction fragment length polymorphism (RFLP) analysis using restriction endonucleases, or DNA sequencing [4].

2.3 Mechanisms of Antibacterial Resistance

The evolution of antibacterial resistance (AMR), particularly antibiotic resistance, can be influenced by antibiotic exposure, based on fundamental biological principles and the fact that it correlates well with the frequency of resistance. It is also possible that additional factors, such as heavy metals and other biocides, play a role. This may include co-selection between biocides and antibiotic resistance genes (ARGs), where multi-resistance genetic elements (such as MGEs) provide resistance to both or through cross-resistance mechanisms between biocides and antibiotics [1].

Several factors determine the rate at which antibiotic resistance evolves due to complex driving forces. First, the mutation supply rate, or the rate at which resistance mutations appear, is determined by the population size, mutation rate, horizontal gene transfer (HGT), the level of resistance conferred by resistance mechanisms, the growth of resistant mutants at different drug concentrations, and the strength of various selective pressures. The variation in neutral alleles in the population can also influence the likelihood of mutations to a resistant genotype, as neutral nucleotide substitutions may reduce the steps required to produce a target protein resistant to antibiotics [1].

Second, for most human pathogens, resistance mechanisms involve the horizontal acquisition of pre-existing resistance genes, and the frequency of HGT is difficult to assess using in vitro experiments. Secondary factors include compensatory mutations at other loci that reduce the fitness cost associated with resistance and epistatic interactions between different resistance mechanisms that affect overall resistance and fitness. Additionally, co-selection, where one resistance gene is inherited alongside another due to their genetic relationship, can have a significant impact on the rate and trajectory of resistance evolution. Resistance to multiple antibiotics is acquired through a complex adaptation process that develops through the acquisition of ARGs and/or mutations that may occur across various niches (humans, animals, and external environments) [1].

An important mechanism that microbial populations use to survive in the face of threats is through genetic mutation, activation of previously inactive resistance genes, or genes that produce resistance factors. These three mechanisms can overlap within a single bacterium. Excessive use of antibiotics can impose selective pressure, promoting the reproduction of resistant microorganisms [14].

There is compelling evidence that bacteria exhibited resistance to antibiotics long before the advent of what is known as the "antibiotic era." A significant surge in the number of antibiotic-resistant bacteria occurred during the "antibiotic era." The extraction, purification, synthesis, and widespread use of antibacterial agents by humans has accelerated the evolutionary process of bacteria by imposing selective pressure, forcing bacteria to adapt to survive—either by becoming resistant or facing death. Microbes that were previously sensitive to specific antibacterials can undergo genetic changes, leading them to become insensitive (resistant) or less sensitive [14].

Factors influencing microbial resistance characteristics to antibacterials are linked to elements with genetic properties. Some types of bacteria are naturally resistant to certain antibacterials. For example, gram-positive bacteria, which lack an outer cell membrane layer, are naturally resistant to polymyxins, which work by disrupting the microbial cell membrane after interacting with phosphates in the microbial membrane's phospholipids [14].

Antibacterial resistance can be triggered by two aspects: internal factors and external factors. Internal factors arise from changes in the chromosomal genes or processes within microbial cells that make them resistant to antibacterials, while external factors occur when microorganisms acquire resistance genes from the environment, which may come from other organisms via horizontal gene transfer (HGT). Exposure to antibiotics stimulates antibacterial resistance in various ways: mutations in chromosomal genes or modifications to antibacterial targets (e.g., reduced affinity for the drug), decreased drug absorption capacity, activation of efflux mechanisms, and complete modification of essential metabolic pathways. On the other hand, horizontal gene transfer induces antibiotic resistance through three methods: transformation, transduction, and conjugation. Generally, conjugation utilizes mobile genetic elements (MGEs) as "tools" to distribute crucial genetic information, although direct chromosome-to-chromosome transfer is also possible. The most significant mobile genetic elements are plasmids and transposons. Both play crucial roles in the emergence and spread of antibacterial resistance among clinically relevant organisms [11].

Most antibiotic resistance arises from genetic mutations or horizontal gene transfer that carries resistance traits. These genetic changes occur randomly, happen spontaneously, and do not depend on the presence of antibacterial drugs. Changes occur when there is an error in the DNA replication mechanism that is not repaired by the DNA repair system. Mutations occur at varying rates (10^(-4) to 10^(-10) per cell division) and involve processes such as deletion, substitution, or addition of one or more nucleotide base pairs, which ultimately lead to the replacement of amino acids [14].

The genetic alteration process, known as single-step mutation, results in very high resistance in a short time and quickly. For example, changes in the system regulating the chromosome that codes for the production of β-lactamase by Enterobacter and Citrobacter species [14].

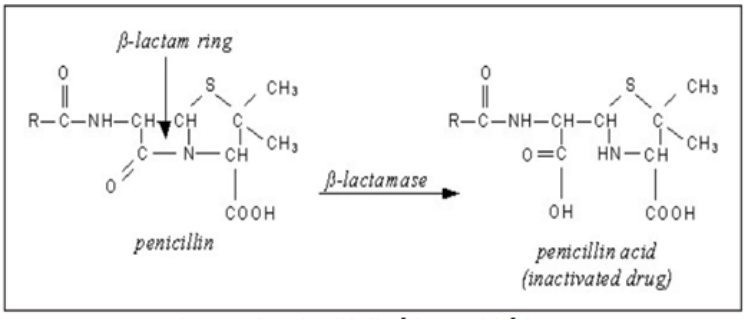


Figure 2. Resistance to β-lactam antibiotics by β-lactamase

As a result, there is a rapid increase in the production of β-lactamase within a short period, which can break down antibacterial agents, including those resistant to β-lactamase such as ceftazidime and cefotaxime. In contrast, multi-step mutations result in a gradual increase in resistance. One example is the mutation in DNA gyrase (gyrA and parC) that occurs in bacteria such as Salmonella sp. or Staphylococcus aureus, which leads to clinical resistance to fluoroquinolones. Most genetic information in bacteria is stored in chromosomes, but there are exceptions. Some microbes possess genes located outside the chromosomes, such as plasmids (a circular double-stranded DNA ranging in size from 2 to 200 kilobases per pair) or bacteriophages (viruses that infect bacteria and can integrate into the bacterial chromosome) [14].

These genetic elements outside the chromosome can be transferred vertically, meaning from bacteria to their offspring through binary fission, and more intriguingly, horizontally, crossing species and genus boundaries. The resistance factors that are transferred can move from the chromosome to the plasmid or vice

versa through transposons and integrons. However, not all plasmids have the ability to be transferred. Only plasmids known as R factors (resistance factors) can be transferred, which are also called transmissible plasmids. The R factor is divided into two parts: the resistance transfer factor (RTF) and the resistance-determinant unit (r). The RTF section facilitates the movement of the R factor [14].

Each unit-r has the ability to resist one type of antibacterial. Therefore, multiple unit-rs within a single R plasmid provide resistance to various antibacterials simultaneously. These R factors are primarily inherited among enterobacterial bacteria. A transposon is a single gene or a small group of genes that can remain attached in reverse or directly repeat DNA sequences. An integron consists of two DNA fragments, where one part carries a gene resistant to antibiotics. Bacterial resistance to various antibiotics is caused by plasmids that carry multiple resistances or by genes in the chromosome that provide resistance traits [14].

2.4 Prevention Efforts

M According to the World Health Organization (WHO) (2015), various strategies have been introduced to address the spread of antibacterial resistance, particularly as a result of excessive antibiotic use. These efforts are designed within a global action plan aimed at inhibiting the development of resistant microorganisms, especially emerging ones [9].

Prevention of antibacterial resistance can be carried out through various efforts, including the judicious use of antibiotics, raising public awareness, preventing infections, and strengthening health surveillance and policy development. Antibiotics should be used according to a doctor's prescription, not taken indiscriminately, and finished as recommended to prevent bacteria from developing resistance.

Several studies have proven that the public needs to be educated about the dangers of antibacterial resistance through health campaigns and information media. In addition, infection prevention is also essential and can be achieved by maintaining personal hygiene, such as regularly washing hands, consuming clean food, and implementing hygiene standards in healthcare facilities. The government should also tighten regulations on antibiotic use, both in the medical and agricultural sectors, to prevent excessive and uncontrolled use. Furthermore, research on the development of new antibiotics and alternative therapies, such as bacteriophages and natural compounds, should continue to be promoted to find more effective solutions in addressing microbial resistance. By implementing these measures comprehensively, it is hoped that antibacterial resistance can be controlled and the effectiveness of treatments can be maintained [3,7,13].

3. Conclusion

Antibacterial resistance (AMR) is a serious threat to global health, including in Indonesia. The misuse and improper use of antibiotics have accelerated the emergence of microorganisms that are resistant to treatment, making infections more difficult to manage. Several pathogenic bacteria, such as *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*, have shown high levels of resistance, especially in hospital settings.

This resistance occurs due to genetic mutations and gene transfer between bacteria through plasmids, transposons, and integrons. The impacts include increased morbidity and mortality rates, prolonged illness duration, and rising treatment costs. Therefore, effective control strategies are needed, such as prudent antibiotic use, raising public awareness, and further research on resistance mechanisms and the development of alternative therapies.

With coordinated efforts from various stakeholders, including healthcare professionals, government, and the public, antibacterial resistance can be controlled to preserve the effectiveness of treatments in the future.

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