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Antibiotic Resistance in Hospital Settings and Historical Trends in Misuse of Penicillin

Pavani Kottapalli[1*], Beluri Talari Ranjith Kumar[2]
[1]Indiana Wesleyan University
[2]Osmania Medical college
Corresponding Author Email: Pavanikothapalli28@gmail.com

Abstract
Background: The discovery of Penicillin by Alexander Fleming revolutionized the treatment of bacterial infections. However, antibiotic resistance has grown significantly, driven by genetic mutations, horizontal gene transfer, and biochemical defense mechanisms like β-lactamase production and efflux pumps. High prescription rates, poor infection control, and contaminated hospital environments have led to the rise of multidrug-resistant (MDR) bacteria such as MRSA, VRE, and CRE, threatening global health.
Objectives: This paper aims to explore the history and mechanisms of antibiotic resistance, highlighting the role of modifiable factors such as overuse of antibiotics, ineffective infection control measures, and hospital contamination. It also examines current interventions, including Antibiotic Stewardship Programs (ASPs), and evaluates the potential for alternative solutions like bacteriophage therapy and precision medicine.
Methods: The review analyzes existing research on antibiotic resistance, focusing on genetic and biochemical mechanisms, hospital-related factors, and current interventions. It examines the effectiveness of ASPs and infection control measures in reducing the burden of Hospital-Acquired Infections (HAIs).
Results: Hospital-Acquired Infections remain a significant burden, with high mortality rates and healthcare costs. Although interventions like ASPs have been implemented, the decline in new antibiotic development by the pharmaceutical industry has left few options for treating resistant infections.
Conclusions: To address antibiotic resistance, a multi-faceted approach is necessary. This includes improved antibiotic policies, better surveillance, and research that links human, animal, and environmental health. Without global cooperation and action, antibiotic resistance could render modern medicine ineffective, making once-treatable infections deadly.
Keywords: Antibiotic resistance, hospital-acquired infections, multidrug-resistant bacteria, antimicrobial stewardship, public health

Introduction

Antibiotics have been one of the greatest inventions of the twentieth century and have significantly lowered the incidence of morbidity and mortality due to bacterial infection (Muteeb et al., 2023). They have made complicated operations such as surgeries, organ transplants, and chemotherapy possible because they prevent and cure infections that would be lethal. Of these, Penicillin, discovered by Alexander Fleming in 1928, was the first antibiotic and revolutionized the world of medicine (Chhabra et al., 2024). Moreover, Penicillin was extensively used during the Second World War; it proved the value of antimicrobial treatment in saving many lives. However, this medical advancement was not without its drawbacks. Fleming became aware of the problems of antibiotic overuse and misuse and predicted the emergence of antibiotic-resistant bacteria if Penicillin is not used prudently. His concerns were largely ignored, and over time, Penicillin, which was once known as the wonder drug, became less effective due to bacterial resistance. According to Kleinbeck (2023), by the 1950s, some strains of *Staphylococcus aureus* exhibited resistance, which has risen over the decades. Currently, the World Health Organisation (WHO) estimates that antibiotic resistance directly leads to 1.27 million deaths per year and 4.95 million deaths related to bacterial Antimicrobial Resistance (AMR) globally, as a constant reminder of the ongoing problem.
Therefore, it has become a new problem in modern medicine: antibiotics, which were initially used to fight bacteria, are no longer effective. The more often they are applied, the more bacteria evolve, and many previously effective treatments become useless. This problem is well illustrated in the hospital context, where antibiotic resistance has emerged as a major public health threat (Broom et al., 2020). Hospitals are high-risk areas where patients who are immunocompromised due to chronic illnesses receive recurrent antibiotic administrations, which promotes the development of resistant microorganisms (Denissen et al., 2022). According to Blot et al. (2022), ICUs, surgical wards, and LTCFs are most vulnerable since patients receiving invasive procedures are spending more time in hospitals and are more likely to contract MDR infections. According to the CDC (2024), the Centers for Disease Control and Prevention antibiotic-resistant infections in the US are believed to occur at least 2.8 million annually but cause over 35,000 deaths, with hospital-acquired being among the leading causes. New strains of bacteria, for instance,

Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant *Enterococcus* (VRE), and Carbapenem-Resistant *Enterobacteriaceae* (CRE), are now producing antibiotics resistant ones and have become a significant source of HAIs, which increase the duration of hospital stays, costs, and mortality rates (Abban et al., 2023).

Examples of such resistance determinants include poor infection control procedures, improper use of antibiotics, and broad-spectrum antibiotics (Endale et al., 2023). There is the prescription of antibiotics based on assumed bacterial infections even when confirmatory tests are not conducted; this exposes bacteria to antibiotics, thus exerting selective pressures that cause the formulation of the resisting structures/models among bacteria (Larsson and Flach, 2021). Ignacio et al. (2019) observed that according to The Lancet Infectious Diseases, about 50% of antibiotics prescribed in hospitals are either inappropriate or not needed in any way and contribute to the increasing cases of antibiotic resistance. Other factors contributing to the problem include failure to adhere to various practices preventing infection spread, overcrowding, and poor antimicrobial stewardship programs. Due to inadequate preventive measures, the problem has raised the need for combined efforts to fight the issue in several nations. It is, therefore, necessary that we deliberate on the past abuses of the drug and the role that the hospital structures played in vindictive resistance to the said drug. This work will study the biochemistry of resistance, clinical and economic impacts of Multidrug-Resistant (MDR) bacteria, and challenges. It also evaluates the current strategies to address the problem, such as improved diagnostic techniques, policy measures, and novel therapies, according to Avershina et al. (2021), which also applies to the regular statement that it has been misused in the past lead to the present issues; there is a need to do it now. Continued failure to alter the current rate of antibiotic consumption, infection prevention, and healthcare policies means that all the medical progress made through the discovery of antibiotics may be overruled, and we end up living in a world where even an infection cannot be treated (Bhattacharya et al., 2023).

Historical Context of Penicillin Use and Misuse

Penicillin discovery is one of the most significant milestones in the medical field as it revolutionized the treatment of bacterial infections and saved millions of lives (Rehan, 2023). However, its popularity attracted the wrong use, which over time created the vice of antibiotic resistance. As pointed out by Ferraz (2024), there were red signals that bacteria could become resistant to Penicillin. Still, antibiotic overuse in the human population, the use in agriculture, and self-medication contributed to the development of resistant strains. This section explores the timeline of penicillin use, its discovery, systematic failures in drug administration, and the subsequent development of resistance.

Penicillin dates to 1928 when Fleming, a researcher, observed the ability of the mold to kill bacteria while researching Staphylococcus cultures in St. Mary's Hospital in London (Gaynes, 2017). These were discovered by Alexander Fleming in 1929. Still, they did not gain much attention until the late 1930s when Howard Florey, Ernst Boris Chain, and their colleagues at the University of Oxford developed ways of isolating and using them for clinical trials. In the early 1940s, the mass production of Penicillin began, especially during the Second World War, and the death rate from infections and diseases such as syphilis and pneumonia was significantly reduced (Gross and Sampat, 2025). This made Penicillin a near-miracle drug of the masses. Still, Fleming himself, when accepting his Nobel Prize in 1945, cautioned that the drug could be misused and, thus, lead to the emergence of resistant bacteria. However, this caution was lost in the demand for Penicillin and its misuse.

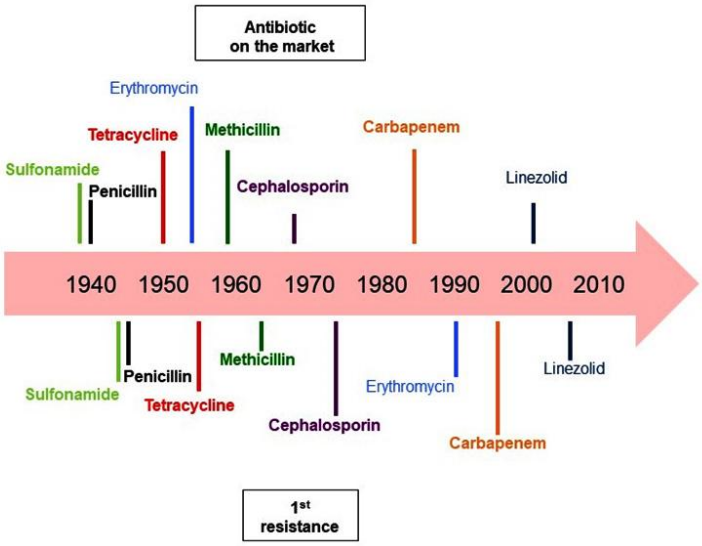

Figure 1: Antibiotic resistance (Abdallah et al., 2023)

Misuse of antibiotics began as early as the 1950s when Penicillin was rampant. According to Stivers and Timmermans (2021), due to pressure from pharmaceutical firms, physicians prescribed Penicillin for minor illnesses or conditions for which antibiotics were not helpful, such as viral infections. According to research conducted by the US Public Health Service, Ventola (2015) noted that 50-60% of the antibiotics prescribed were deemed unnecessary or not required. At the same time, the pharmaceutical industry contributed to the widespread use of antibiotics and often played down the issue of resistance. This problem worsened due to the poor regulation of antibiotic use, with physicians and other healthcare workers using the drugs as the go-to solution for various ailments.

In addition to human medicine, Penicillin was used in agriculture and animal health, and its misuse was common. The use of antibiotics in livestock as growth promoters was well on by the 1950s, leading to antibiotic resistance among bacteria (Low et al., 2021). In a study conducted by Uddin et al. (2021), the authors stated that antibiotic-resistant strains of bacteria from farm animals can easily be transmitted to humans through food, thereby causing hospital-acquired infections. While there is scientific evidence of the link between the use of antibiotics in agriculture and the emergence of resistance, the FDA and WHO failed to enact stringent measures. According to Rahman et al. (2022), the European Union finally prohibited antibiotic growth promoters in 2006, while the United States only implemented partial restrictions in 2017, well after the emergence of resistant strains.

Self-medication and over-the-counter drugs also contributed to the problem. In many countries, including Asia, Africa, and Latin America, some antibiotics are still easily accessible without prescription. Akande-Sholazi and Oyesiji (2023) revealed that 95.9% of antibiotic use in some parts of India and Nigeria was without prescription, which led to an underuse where patients were using antibiotics for a shorter time than they should, allowing bacteria to survive and develop resistance. As for prescription regulation, high-income countries had already implemented strict prescription policies by the end of the twentieth century, but global variations in the regulation of antibiotics continued to fuel resistance (McDonnell et al., 2024).

Since the 1940s, scientists have reported antibiotic-resistant Staphylococcus aureus strains, proving that bacteria adapt much faster than expected (Park and Ronholm, 2021). Methicillin-resistant *Staphylococcus aureus* (MRSA) appeared in the 1960s and was a significant problem in hospital infection control. In the 1980s and 1990s, multidrug-resistant bacteria emerged, especially in hospitals, due to the extensive use of antibiotics (Karthikeyan et al., 2022). Even as more proof of antibiotic resistance emerged, medical organizations took no precautions, such as the refusal of pharmaceutical companies to limit their production and prescription of antibiotics, which led to the continued misuse of these drugs well into the 2000s.

The lack of proper regulation of the use of antibiotics despite the various calls by different people has been a significant cause of this public health menace. The table shows that the resistance rates of these key bacteria have continuously risen over the years, indicating that the medical fraternity has not adequately addressed the issue of misuse.

Table 1: Resistance rates of bacteria

Year	% of *S. aureus* Resistant to Penicillin	% of MRSA Cases in Hospitals	% of Resistant *E. coli* Infections
1940s	<5%	0%	<1%
1960s	~50%	~5%	~10%
1980s	~80%	~20%	~30%
2000s	>90%	~50%	~50%
2020s	>95%	~60%	~60%

Medical institutions largely ignored early warnings from microbiologists, leading to today's crisis. The widespread overuse and misuse of Penicillin and other antibiotics have fueled an acceleration in resistance, leaving fewer effective treatment options (Dhami et al., 2024). This historical failure underscores the urgent need for more stringent antimicrobial stewardship, regulatory reforms, and global cooperation to mitigate the growing threat of antibiotic-resistant infections.

Mechanisms of Antibiotic Resistance in Hospital Settings

Antibiotic resistance in hospitals is genetic, biochemical, and organizational since it is the process through which pathogens can survive in clinical surroundings. Schinas et al. (2023) have stated that the Intensive care unit, surgical, and oncology wards are the most vulnerable wards that develop resistant infections because of frequent prescription of antibiotics. These settings also include immunocompromised patients; hence, the risk of developing severe resistant organism infections is also high. Thus, Wubetu Yihunie Belay et al. (2024) on bacterial resistance mechanism explain that resistance mechanisms include genetic changes, gene transfer and biochemical changes of β-lactamase, alteration of PBPs, and efflux pumps.

Genetic and Molecular Basis of Resistance

In the hospital, causative agents of antibiotic resistance include genetic mutation and Horizontal Gene Transfer (HGT) that allow movement of the factors in the bacteria within a short duration (Liu et al., 2021). There are different ways of mutation-driven resistance, such as altering the bacterial structure to evade the drug, reducing the inward transport of the drug, or enhancing the expulsion from bacteria cells. Such as mutation in the gyrA gene in *Escherichia coli* and *Pseudomonas aeruginosa* has been linked with fluoroquinolone resistance within a hospital setting (Heshmatipour et al., 2021). Infection caused by HGT is much more prevalent in hospital-acquired resistance cases than in community-acquired infections. Conjugative transfer of genes such as blaKPC, carbapenem resistance gene, and vanA, vancomycin resistance gene are identified in *Klebsiella pneumoniae* and *Enterococcus faecium* based on Paul et al. (2022). Wei et al. (2021) described a CR- K. pneumonia sp outbreak. In New York ICU in 2019, this study explained that a single plasmid with multiple genes can spread among patients within weeks. Capacitive-free DNA uptake has been noticed in *Streptococcus pneumoniae,* whereby transformation has led to the development of penicillin resistance, as posted by Gibson et al. (2022). It distinguished that horizontal gene transfer through bacteriophages is the process through which mecA (methicillin resistance) has spread through MRSA strains in the hospital.

Biochemical Resistance Strategies

Another clinically relevant resistance model is β-lactamase production, which is the ability of bacteria to synthesize enzymes that neutralize the β-lactam antibiotics. According to Guzmán-Blanco et al. (2014), Extended-Spectrum Beta-Lactamases (ESBLs) are most common in *Escherichia coli* and *Klebsiella pneumoniae,* which are associated with increased mortality of 58% for the cases of bloodstream infections acquired within the ICU. CRE is even more dangerous since they can synthesize carbapenemases like New Delhi metallo-β-lactamase (NDM-1) that neutralize even the last known antibiotics.

Another adaptation includes modification of PBPs, especially in MRSA, whereby they change the structure of PBPs to make them inaccessible to the drug. Methicillin-resistant *Staphylococcus aureus* (MRSA) possesses the mecA gene,

which codes for the alteration in the structure of the PBP to become PBP2a, which is not targeted effectively by β-lactam antibiotics (Ambade et al., 2023). Methicillin-resistant *Staphylococcus aureus* (MRSA) currently contributes to 20,000 deaths every year in the United States, which makes it a constant threat to patients in healthcare facilities (Kavanagh, 2019).

According to Jiang et al. (2023), multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* that are prevalent in ICUs eject the antibiotics via the AcrAB-TolC efflux pump system, reducing the treatment effectiveness. Similarly, outer membrane porin loss in *Klebsiella pneumoniae* limits the penetration of antibiotics into the bacterial cell, thus increasing the challenge of managing it. Biofilm formation exacerbates resistance in hospital-acquired infections. For instance, *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* attach themselves to catheters, ventilators, and prosthetic joints and cause chronic infection that is a hundred folds more resistant to antibiotics than the free-floating bacteria or planktonic bacteria (Thi et al., 2020).

Hospital-Specific Resistance Factors

Iqbal et al. (2025) revealed a study in UK hospitals that stated that 40% of the prescriptions of antibiotics in the ICU were either unnecessary or incorrect, which further fuels the evolution of resistance. Long-term antibiotic prophylaxis increases the risk of VRE or ESBL-KP infection, which is associated with high mortality (Nanayakkara et al., 2021). Likewise, long-term care facilities' elderly patients harbor multidrug-resistant Enterobacterales, which can immigrate to hospitals through patient' transfers.

Clinical Implications of Antibiotic Resistance in Hospitals

The Prevalence and Impact of Resistant Pathogens

MDR pathogens are associated with a considerable burden of HAIs, contributing to the development of severe complications in patients, especially in the ICUs, surgical wards, and LTCFs (Monegro et al., 2023). MRSA is one of the most widespread resistant bacteria in hospitals, and its manifestations include bloodstream infections, pneumonia, and surgical site infections. According to Kourtis et al. (2019), in the United States, MRSA infections are known to cause about 19,000 deaths per year. Likewise, vancomycin-resistant Enterococcus (VRE) infections have become prevalent, particularly in immunocompromised patients, with high mortality in bloodstream infections. CRE is known as "nightmare bacteria" due to its high level of resistance to most of the available antibiotics (Abdelaziz et al., 2021). Some other MDR organisms include Pseudomonas aeruginosa that causes ventilator-associated pneumonia and bloodstream infections and Acinetobacter baumannii, which is found in hospital settings and affects wound, lung, and urinary tract infections.

The cost of antibiotic resistance to healthcare organizations is enormous regarding finances and operations. Ho et al. (2024) observed that a study in The Lancet showed that antibiotic-resistant infections cost the US healthcare system more than $4.6 billion per year, while the situation in Europe and Asia was almost the same. Prolonged hospitalization, implementation of isolation measures, and increased number of tests further augment the cost burden, while human resources experience more pressure and stress in handling such complicated cases.

Is Treatment a Losing Battle?

Once believed to be an effective drug against CRE infections, Colistin has recently become resistant, making some infections virtually incurable (Raza et al., 2024). The first case of CR-Kp was reported in China, India, and, more recently, in the UK and other parts of the world, and this has led to concern since there are few treatment options available for this type of infection. One of the biggest problems associated with antibiotic resistance is the low rate of the development of new antibiotics. Pharmaceutical companies have shied away from antibiotic development because it is not commercially viable and costly to develop such drugs (Harald Brüssow, 2024). Unlike chronic diseases that require long-term treatment and ensure continuous cash inflows, antibiotics are prescribed for the short term and, thus, are not financially lucrative to pharmaceutical companies. This has led to what can be termed the innovation gap, whereby new mechanisms of resistance are developing at a faster rate than the development of new drugs.

As the use of conventional antibiotics proves to be ineffective, there is a switch to other therapies. Bacteriophage therapy, which uses viruses that infect bacteria, has been proven effective in case studies where *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were present (Kou et al., 2024). Also, efforts are being made using CRISPR genome editing to eliminate specific resistance genes from bacterial species (Palacios Araya et al., 2021). Probiotics and microbiome-based therapies are other possibilities for reintroducing healthful bacteria that can replace resistant ones.

Case Studies of Nosocomial Outbreaks

Some of the worst-known hospital epidemics have shown the potential of antibiotic resistance and the ineffectiveness of infection control measures. According to Conlan et al. (2016), one of the worst outbreaks of CRE was recorded in 2011 at the National Institutes of Health Clinical Centre in the United States; the carbapenem-resistant Klebsiella pneumoniae bacteria spread to 19 patients, out of which 11 died. Genetic sequencing later confirmed that the outbreak had originated from a patient transferred from another hospital; this showed that patient transfers are a significant source of resistant pathogens.

In 2015, an outbreak of colistin-resistant K pneumonia in a London hospital occurred and involved almost a hundred patients over 18 months (Otter et al., 2017). Several studies revealed poor hand washing and failure to observe correct infection control measures led to the spreading of pathogens within the hospital setting.

Asia has also experienced severe antibiotic-resistant outbreaks, especially in India, where the New Delhi metallo-β-lactamase (NDM-1) gene was first identified in 2008. This resistance gene, which makes the bacteria resistant to nearly all β-lactam antibiotics, has since spread worldwide. According to Sharma et al. (2023), high CRE infection rates in India have been reported in hospitals with crowding and poor infection control facilities; the mortality rates in ICU patients are above 50%.

There was a huge policy and preparedness blunder in 2019 when a Dutch hospital was hit by multidrug-resistant Acinetobacter baumannii. According to Yang et al. (2024), the outbreak impacted more than fifty patients in various wards, and the investigations showed that antibiotics used for ventilated patients were to blame for the resistance. The case highlighted the risks associated with broad-spectrum antibiotics, especially in the ICU, where VAP is common.

Factors Contributing to Antibiotic Resistance in Hospitals

Overprescription and Empirical Treatment Bias

The leading causes of this problem include the overuse of antibiotics in hospitals. It is a common practice among many healthcare providers to use broad-spectrum antibiotics as a precautionary measure without first testing the patient for bacterial infection. Fleming-Dutra et al. (2016) state that 30% of hospital antibiotic prescriptions are either inept or unnecessary. According to Llor and Bjerrum (2014), more than 250 million antibiotic prescriptions are written every year in the United States, with a large proportion of them being prescribed for presumed infections.

Another factor that has worsened the situation is the absence of Antibiotic Stewardship Programmes (ASPs) in most hospitals. Despite the intention to prevent broad-spectrum antibiotics, ASPs remain underutilized through promoting targeted therapy based on culture and sensitivity. According to the Pierre (2024) study in The Lancet, hospitals with active ASPs effectively reduced antibiotic-resistant infections by 20%. However, many healthcare facilities, especially in the developing world, do not possess the structures or staff capable of implementing such programs.

Hospital Hygiene, Cross-Contamination, and Healthcare Workers

Chavali et al. (2014) found that hand hygiene compliance rates are very low among hospital staff, and different studies have shown that only 40-60% of healthcare workers wash their hands properly. Medical devices and hospital equipment are also essential sources of antibiotic-resistant pathogens that get contaminated. Garvey (2024) explained that if ventilators, catheters, and surgical instruments are not sterilized well, they can host bacteria like MRSA, CRE, and *Acinetobacter baumannii,* leading to infections. For instance, in 2019, a large-scale outbreak of drug-resistant *Klebsiella pneumoniae* in an Italian ICU was attributed to contaminated bronchoscopes, which showed that inadequate sterilization processes can lead to adverse outcomes.

The Environmental Reservoir of Resistance

Hospital wastewater is also one of the essential sources of antibiotic residues and resistant bacteria since it contains concentrated antibiotics that patients excrete. In their study, Mutuku et al. (2022) identified fluoroquinolones, β-lactams, and tetracycline antibiotics in the hospital effluent, which exerts selective pressure that enhances the survival of resistant bacteria. Moreover, according to Kulik et al. (2023), it was estimated that 30–90% of the antibiotics consumed are not metabolized and are directly excreted into the wastewater systems.

Sewage systems also enhance the spread of resistance by promoting HGT among bacteria. Hospital effluents introduce resistant genes into the environment and disperse them with other environmental microorganisms in wastewater treatment plants through plasmids and transposons. Sambaza and Naicker (2023) found from Nature that there is a higher concentration of resistance genes in wastewater treatment plants in urban areas than in natural water sources, thus contributing to the spread of AMR. Precarious and inadequate disposal of medical waste is another factor that leads to the emergence of resistance. It was also found that antibiotics and other pharmaceutical waste are improperly disposed of in some regions and pollute the soil and water. This is especially the case in countries with poor regulatory policies on the disposal of pharmaceutical waste. For instance, Arun et al. (2022), in their study on water contamination

in India, discovered that water samples taken from pharmaceutical industries had antibiotic residues that were a thousand times the recommended limit, hence promoting the development of resistant bacteria strains like NDM-1.

Strategies for Mitigating Antibiotic Resistance in Hospitals

Antimicrobial Stewardship Programmes (ASP): The Triumphs and the Setbacks

Antimicrobial Stewardship Programmes (ASPs) are among the most effective interventions to prevent hospital antibiotic resistance. These programs seek to reduce antibiotic misuse through proper prescription, the right antibiotic choice, and the correct therapy length. Implementation of ASPs has been previously reported to be effective in the Scandinavian countries, characterized by stringent antibiotic policies, effective surveillance, and educational interventions that have resulted in lower rates of resistance (Christensen et al., 2022). For example, in Sweden, which has very strict antibiotic prescribing standards and a focus on infectious disease specialists, the MDR infection rate is among the lowest in Europe. Molstad et al. (2017) stated that the ASPs used in Sweden have led to a 25% decrease in the usage of antibiotics within five years, further proving the efficiency of this strategy.

On the other hand, ASPs in low-income countries face many challenges, such as inadequate funding, limited access to diagnostic equipment, and poor healthcare infrastructure. The availability of antibiotics without prescription in many African and South Asian countries is another factor that leads to misuse. In Nigeria, Ogunleye et al. (2021) established that over 80 percent of hospital patients received antibiotics without diagnosis, increasing the resistance rates. One of the most contentious issues in ASP implementation is minimizing or maximizing antibiotic usage.

Infection Control and Surveillance

In this case, strong infection prevention and control measures are critical in preventing the emergence and spread of resistant bacteria in healthcare facilities. Vancomycin-resistant Enterococci (VRE), Methicillin-resistant *Staphylococcus aureus* (MRSA), and carbapenem-resistant Enterobacteriaceae (CRE) are some of the MDR organisms that have been implemented in countries such as the UK and the Netherlands (Noster et al., 2021). Hospitals that conduct screening on admission have seen a 40% decrease in nosocomial infections, thus showing the efficiency of screening in preventing outbreaks (Douglas et al., 2023). Other measures that have been suggested include the use of ultraviolet (UV) light disinfection and nano-coating with antimicrobial properties, which have demonstrated the potential of lowering pathogen survival rates (Mandal, 2024). Maugeri et al. (2025) conducted a study in hospitals in the United States. They established that UV light disinfection lowered the incidence of C. difficile by 70%, showing its effectiveness in infection control. The WHO's Global Action Plan on Antimicrobial Resistance will entail enhanced hygiene measures, surveillance, and regulation of antibiotic usage (Essack, 2021). However, the level of compliance with these guidelines differs across the regions. While high-income countries have effectively implemented these protocols into their healthcare systems, low and middle-income countries have a significant problem enforcing these protocols due to limited available resources and inadequate regulation. Enhancing global compliance with appropriate infection control measures is crucial to address hospital-based resistance.

Exploring Alternative Treatment Strategies

Due to the ineffectiveness of conventional antibiotics, scientists have considered other approaches in the fight against resistant infections. One of the most promising solutions is bacteriophage therapy, which includes viruses aimed at bacteria (Singh et al., 2022). While phage therapy has been practiced in Eastern European countries for decades, its acceptance in the Western world has been relatively slow because of bureaucratic issues and doubts about the effectiveness of the treatment. New studies, though, indicate that bacteriophages could be used as reliable substitutes for antibiotics to treat MDR infections. For instance, Van Nieuwenhuyse et al. (2022) found in Nature Medicine that phage therapy is effective in treating drug-resistant *Pseudomonas aeruginosa* infection in patients with cystic fibrosis, making it a promising treatment in the future.

Another promising approach to using AI is in precision medicine, which can potentially change how antibiotics are prescribed. Diagnostic tools can be implemented using artificial intelligence to analyze patient data and microbial genomes to prescribe the best-suited antibiotics for the patient, thus avoiding broad-spectrum antibiotics when they are not warranted (Branda and Scarpa, 2024). However, the widespread implementation of innovative technologies is hampered by the requirements for high-quality digital networks and skilled personnel.

Besides phage therapy and artificial intelligence, other approaches are being explored to develop non-antibiotic compounds, including antimicrobial peptides and quorum-sensing inhibitors. These new agents target bacterial signaling and pathogenicity and are less likely to lead to bacterial resistance. The current treatments are still in the early stages of clinical trials, and additional studies and approval are necessary for the treatments to become standard in hospitals.

Policy and Legislative Interventions

Antibiotic prescriptions are generally controlled by policies and legislation, which are vital in the fight against antibiotic resistance. However, the variation of policies worldwide has been a significant setback. For instance, Sulis et al. (2021) noted in India that despite the government's measures to control antibiotic availability, research indicates that as much as 70% of the population buys antibiotics without a prescription, thus encouraging resistance. On the other hand, countries like Germany and the Netherlands have been able to implement prescription-only policies on antibiotics, which has helped reduce Antibiotic resistance.

The problem of antibiotic resistance requires international cooperation to be effectively solved globally. The WHO has recently suggested a global approach to regulating and monitoring antibiotics. However, there are some issues about how this can be implemented in different areas of the world. Public-private partnerships and financial incentives for antibiotic research and development have to be adopted to stimulate the stalled market for antibiotic development.

Future Directions and Research Gaps

New antibiotics have not been discovered in the past few decades because of scientific, economic, and regulatory issues. Pharmaceutical companies have pulled out of antibiotic development mostly because they cannot make sufficient profits compared to drugs for chronic diseases, and there is a severe scarcity of new antimicrobial compounds (Altarac et al., 2021). Governments and global health organizations must provide funding and policy changes to encourage the development of antibiotics (Dutescu and Hillier, 2021). Government incentives such as public-private collaborations, financial incentives, and market access incentives help encourage pharmaceutical companies' research. Also, faster regulatory processes for new antibiotics can enhance their usage in hospitals. Without these reforms, they will remain pinned to ineffective and less effective antibiotics that fuel resistance.

According to Jeżak and Kozajda (2021), hospitals are not the isolated environment where such bacteria can develop and disseminate; they can be imported from livestock, agriculture, and contaminated environments. Incorporation of One Health into the infection control plans in hospitals will enable the assessment and management of external factors contributing to the development of resistance. For instance, limiting antibiotic use in food processing and enhancing the methods of handling waste can minimize the admission of resistant bacteria into hospitals (McCarthy et al., 2021). Effective coordination between doctors, veterinarians, and environmentalists will help improve the monitoring and containment of resistant strains to avoid spreading across sectors.

The recent developments in genomic sequencing and artificial intelligence have provided new ways of identifying and studying antibiotic resistance. Molecular typing helps hospitals detect specific resistance genes in bacterial strains, which would help to reduce the time to prevent their spread (Struelens et al., 2024). Using AI and big data analytics, large quantities of genomic data can be analyzed to identify the trends toward resistance and forecast the probable outbreaks (Zhao et al., 2024; Jangid, 2020). Predictive modeling can help in the early detection of AMR hotspots in the hospital to prevent their spread. Further, with machine learning techniques, it is possible to identify the risk factors of resistance based on patient information, antibiotic prescription rate, and hospital characteristics. Such knowledge can be helpful for the hospital regarding resource management, identifying high-risk areas for infections, and implementing antibiotic stewardship programs at the ward or department level.

Conclusion

Hospital-acquired antibiotic resistance has become one of the major concerns in the world due to the misuse of antibiotics and poor regulation of use in the past few years. This review has also established how using Penicillin over the years has led to the development resistant pathogens due to misuse or overreliance on humans and animals. The genetic mutations, horizontal gene transfer, and biochemical defense systems have made it easier for bacteria to withstand all forms of antibiotics. High antibiotic prescription rates, insufficient infection control measures, and the contaminated environment of healthcare facilities contribute to the fast spread of resistance, which makes healthcare facilities the epicenter of MDR organisms.

Current strategies have been inadequate in managing resistance; hence, the intervention strategies have continued to improve. Current ASPs have proven effective in some areas, especially Scandinavian countries, but the implementation is still irregular. Screening methods and practical techniques of hospital disinfections have been implemented to prevent the spread of infections; however, healthcare organizations continue to grapple with the issue of compliance and implementation. However, the absence of new antibiotics due to economic factors that discourage research in the field of pharmaceuticals remains a challenge in available treatment. Inadequate investment in antibiotics innovation and the lack of a coherent policy in different countries have put hospitals in a more perilous position regarding MDR infections. There is a need to address antibiotic resistance in the hospital setting of concern. Officials should regulate the usage of antibiotics more stringently on a global level, increase funding for the discovery

of new antimicrobial agents, and facilitate the application of genomic surveillance with the help of artificial intelligence.

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