World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Antibiotic resistance: A literature review

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World Journal of Biology Pharmacy and Health Sciences, 2024, 19(02), 536–544

Publication history: Received on 17 July 2024; revised on 25 August 2024; accepted on 28 August 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.19.2.0555

Abstract

Antimicrobial resistance has grown to be a problem that affects not just the health of people and animals but also the economy and society. Because there are little preventative and control measures against antibiotic strains of bacterial infections, the Iraq area is most affected. There are two ways in which microbes might become resistant to drugs: either from other bacteria or from inside. Researching these resistance mechanisms is essential to creating effective illness therapies.

Keywords: Antibiotic resistance; Mechanisms of resistance; Strategy to combat antibiotic resistant

1. Introduction

The issue of antimicrobial resistance (AMR) poses a significant threat to public health, exerting a profound impact on humanity. In 2019 alone, it claimed the lives of an estimated 4.95 million people and is projected to result in considerable economic consequences by the year 2050, amounting to around $1 trillion annually. As of the GRAMME Global Burden Report in 2021 and the World Health Organization (WHO), AMR stands out as the leading cause of mortality worldwide. Among the 4.95 million fatalities in 2019, AMR from bacteria was directly responsible for 1 and a quarter of them. The analysis also identified the leading infection culprits, predicted 700,000 annual deaths from AMR, and discovered geographical trends in resistance-related mortality. According to a 2015 study based on EU/EEA statistics, AMR caused by bacteria was thought to have contributed to almost 33,000 fatalities in Europe that year [4].

Antimicrobial-resistant illnesses typically require longer hospital stays and more expensive or novel drug regimens. Additionally, they are more likely to experience severe health consequences, including certain cases of incurable anthrax infections [4]. Preterm infants and those with compromised immune systems in general are more susceptible to infection [5]. Additionally, AMR jeopardises patient outcomes from medical, dental, and surgical operations. Because of forms of gonorrhoea that are resistant to antibiotics, treatment is getting harder [5].

One of the main causes of antimicrobial resistance (AMR) is antibiotic pollution, sometimes known colloquially as the discharge of antibiotics into the environment. Antibiotic-resistant bacteria will arise if antibiotics are administered carelessly or indiscriminately, despite the fact that they are necessary medications for treating bacterial diseases. Antibiotics are metabolized by the body's enzymes into active compounds that destroy germs. However, certain antibiotics are released in the form of faeces or urine and get into the environment through wastewater treatment facilities. Eventually, these leftover antibiotics find their way into soil and water sources, where they encourage the emergence of new, resistant strains. (6)

Referred to as "superbugs," antibiotic-resistant bacteria have developed genetic mechanisms that enable them to withstand the impact of antibiotics. An illustrative example is Methicillin-resistant Staphylococcus aureus (MRSA),

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characterized by a mutated mecA gene that confers resistance to methicillin, a type of penicillin. Approximately 100,000 infections were brought on by MRSA in the US in 2019 (7). nevertheless poses a risk to people's health (8).

Superbugs are the microorganisms that have figured out how to withstand the medications we employ to eradicate them. They continuously change and adapt to new dangers, much like the villains in comic books. The most harmful bacteria and fungi are those that are multidrug-resistant (MDR) or pan-drug-resistant because they are able to withstand a broad variety of therapies. Patients who contract a superbug infection may not be able to recover, leaving them at the whim of these tiny enemies.

The six microbiological threats that make up ESKAPE are *Pseudomonas aeruginosa*, *Acinetobacter baumannii, Enterobacterales, Staphylococcus aureus,* and *Klebsiella pneumoniae*. These infamous microorganisms are so good at avoiding medicines and thriving in hospital environments that they have been given the moniker "ESKAPE."

The seven formidable foes in the microbial realm, identified as CRE, CRKP, MRSA, ESBL-producing enterobacterales, VRE, MDR Pseudomonas aeruginosa, and MDR Acinetobacter, stand as the most prevalent, challenging to combat, and substantial hazards to global health.

Multidrug-resistant bacteria did not arise until widespread and persistent usage of antibiotics caused them to become resentful of our previous misdeeds. Mycobacterium tuberculosis has developed into multidrug-resistant tuberculosis (MDR-TB) following decades of antitubercular drug treatment. Nowadays, MDR-TB is a common superbug in both developing and underdeveloped countries.

Microorganisms known as superbugs have developed a resistance to the antimicrobial medications that are frequently used to treat them. This includes both pan- and multidrug-resistant (MDR) bacteria and fungi (PDR). Superbug infections usually have little to no effective treatment.

ESKAPE, a formidable alliance comprising *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter, Staphylococcus aureus, Acinetobacter baumannii,* and *Enterobacteriales*, stands as a potent assembly of frequently encountered superbugs in medical facilities. Their possession of an array of antibiotic resistance genes makes MRSA, ESBL-producing Enterobacteriales, VRE, MDR Pseudomonas aeruginosa, MDR Acinetobacter, CRKP, and CRE some of the widely recognized ESKAPE pathogens, posing significant threats in healthcare settings. These superbugs pose a major risk to both patients and healthcare professionals since they are sometimes almost incurable due to their extreme antibiotic resistance. Our battle against superbugs demands vigilance, and the first step in that struggle is the prudent use of antibiotics. Antibiotics should only be taken when absolutely necessary, and we should always carefully follow our doctor's advice. Together, we can stop superbugs from spreading and safeguard our health as well as the health of those we love.

Multidrug-resistant bacteria did not appear until we released the dogs of antibiotic warfare, and they are now all impervious to our weapons, like a hydra with a hundred heads (7).

Superbugs are the masters of disguise among microorganisms; they hide in hospitals and other healthcare environments, waiting for an opportunity to attack. These crafty pathogens are nearly incurable because they have evolved to withstand our strongest medications. Hospital-acquired infections (HAIs) can originate from bacteria of both the gram-positive and gram-negative types such as *Citrobacter freundii, Clostridium difficile, Burkholderia cepacian, Staphylococcus epidermidis, Campylobacter jejuni,* and *Stenotrophomonas maltophilia.* Superbug infections frequently result in death since there are very few effective treatment options. Moreover, superbug-caused HAIs are linked to expensive medical care and extended hospital stays (10). The processes underlying antibiotic resistance and crucial strategies for preventing it are the main topics of this study.

2. Methods

2.1. Locating Data

The data for this literature review on antibiotic resistance was sourced from various scientific databases and search engines including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy involved utilizing keywords such as "antibiotic resistance," "mechanisms of resistance," and "strategy to combat antibiotic resistance." The searches were limited to peer-reviewed articles published in the past decade to ensure the inclusion of recent and relevant literature.

2.2. Selecting Data

Selection criteria were established to include articles that focused on the mechanisms of antibiotic resistance, epidemiology, implications of antibiotic-resistant infections on human health, and strategies for combating resistance. Articles were included based on their relevance to the scope of the review, quality, and credibility of the sources.

2.3. Extracting Data

Data extraction involved thoroughly reading and analyzing the selected articles to extract key information related to the mechanisms of antibiotic resistance, specific resistant bacteria, factors contributing to resistance, and strategies recommended to address this global health issue. Relevant data points, statistical information, and qualitative insights were extracted from each selected article.

2.4. Synthesizing Data

The synthesized data encompassed a comprehensive analysis of the extracted information, organizing it into thematic categories. Emphasis was placed on identifying patterns, common trends, and insights across the literature to provide a coherent overview of the subject matter. Comparative analysis and thematic synthesis were employed to present a holistic view of antibiotic resistance mechanisms and strategies to combat it.

2.5. Mechanisms of Drug Resistance

There are four primary ways that antibiotics affect bacteria: they can alter their cell walls, rupture their membranes, or halt the creation of proteins and DNA. Yet bacteria have found sophisticated strategies to evade these assaults. They either pump out most medications before they have any impact at all, limit the absorption of pharmaceuticals, or alter the target of the drug so that it cannot act (or alter its own structure so that a safe molecule can substitute for a harmful one).

Resistance to antibiotics in bacteria can arise through diverse mechanisms, including modifications to the drug target, the production of enzymes capable of breaking down the medication, or the development of pumps that actively eliminate the drug from the bacterial cell. On the other hand, intrinsic resistance is innate to the bacteria and usually arises from decreased drug uptake or efflux as well as chemical changes made to the antibiotic during metabolism.

Gram-positive bacteria exhibit a lower likelihood of developing resistance compared to their counterparts. This reduced susceptibility is attributed to the absence of an outer lipopolysaccharide (LPS) shell, a feature that often makes cells susceptible to medication-induced harm. Additionally, their capacity to actively pump out antibiotics is more constrained (11,12) (Figure 1,2).

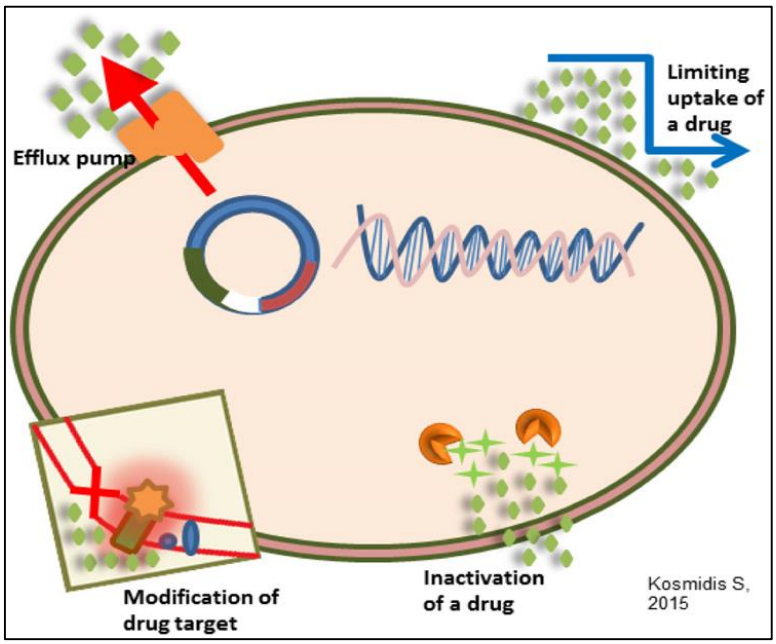

Figure 1 General antimicrobial resistance mechanisms

- **Limiting Drug Uptake** Lipopolysaccharide (LPS), a glycolipid characterized by numerous acyl chains, plays a crucial role as a key component in the outer membrane structure of gram-negative bacteria. Consequently, LPS acts as a barrier, impeding the entry of various chemicals into the cell. Making changes to the outer membrane's permeability, particularly with regard to porin proteins, is one method of lowering this innate barrier. Purines are the route via which hydrophilic antibiotics including beta-lactams, fluoroquinolones, tetracyclines, and chloramphenicol enter cells (13). Acquired antibiotic resistance can result from mutations that modify porin expression or function, leading to increased resistance when combined with other mechanisms like efflux pumps or enzymatic antibiotic degradation (14). Bacteria employ biofilm formation as an additional strategy to develop resistance to antibiotics. This involves bacteria adhering to surfaces and each other, resulting in the formation of slimy coatings known as biofilms. Notable examples of bacteria capable of creating biofilms *include Proteus mirabilis, Pseudomonas aeruginosa, E. coli, Klebsiella pneumoniae, Streptococcus viridans, Staphylococcus epidermidis, Staphylococcus aureus,* and *Enterococcus faecalis* (15).
- **Modification of Targets for Drug** Antibiotics can only attach to bacterial drug targets extremely weakly or not at all depending on the nature of the target molecule. The genes that encode the medication target proteins underwent spontaneous mutations, which is what led to this alteration.

Gram-positive bacteria have the ability to become resistant to β-lactam antibiotics through the formation of new, mutant forms of penicillin-binding proteins (PBPs). Changes in PBPs can impact the effectiveness and uptake capacity of β-lactam antibiotics by cancer cells, as they are the target of these antibiotics. Changing the quantity of PBPs in a cell is another. Some do this by adding a mecA gene or changing the PBPs' structural makeup (16).

Antibiotics that stop the development of the bacterial cell wall, such lipopeptides like daptomycin and glycopeptides like vancomycin, are helpful in treating this illness. Because of their thick lipopolysaccharide (LPS) outer layer, they are inherently resistant to Gram-negative bacteria.

The acquisition of vancomycin resistance is primarily observed in two major bacterial pathogens: Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). The development of van genes, which alter peptidoglycan precursors by making them less susceptible to vancomycin binding, is the cause of this resistance. Daptomycin cannot bind to this bacterial cell membrane in any manner at all without calcium. Gene mutations like mprF can increase the positive charge on the cell membrane's surface. It reduces daptomycin binding by decreasing calcium binding.

By altering their ribosomes, methylating their subunits, or shielding them, bacteria can become resistant to antibiotics. Bacteria may become resistant to oxazolidinones and aminoglycosides due to ribosomal alterations. Bacteria may become resistant to aminoglycosides, oxazolidinones, streptogramins, and macrolides (in gram-positive bacteria) if the subunit is methylated. Tetracycline resistance in bacteria can be attributed to ribosomal protection. These mechanisms disrupt the drug's ribosome-binding capacity and modify the degree of interference in various ways.

Fluoroquinolones, a notable class of antibiotics targeting synthesis enzymes, can be rendered ineffective by mutations in DNA gyrase (as seen in gyrA in Gram-negative species) or topoisomerase IV (present in Gram-positive species, exemplified by the gene grlA). This represents a mechanism through which bacteria develop resistance. Drugs cannot readily bind to gyrase and topoisomerase when these alterations alter their structural makeup (21).

- **Inactivation of Drug** Antibiotics can be rendered ineffective by bacteria through two methods: chemical modification or breakdown. The enzymes known as beta-lactamases hydrolyze beta-lactam antibiotics (22).
- **Efflux of Drug** Bacteria possess an energy-dependent efflux pump in their cytoplasmic membrane, enabling them to regulate the concentration of antibacterial substances, such as antibiotics, within bacterial cells. This pump plays a crucial role in expelling harmful substances, including metabolites, antibiotics, and signal molecules involved in quorum sensing. By getting rid of efflux pumps assist bacteria in maintaining their internal environment. Efflux pumps, classified according to their structure and energy source, fall into six distinct superfamilies: ATP-binding cassette (ABC), major facilitator superfamily (MFS), multidrug and toxic compound extrusion (MATE) superfamily, small multidrug resistance (SMR) superfamily, resistance-nodulation-division (RND) superfamily, and drug metabolite transporter (DMT) superfamily (22). Since efflux pumps are encoded on chromosomes, which means they are a component of the organism's DNA, they can confer antibiotic resistance on gram-positive bacteria.

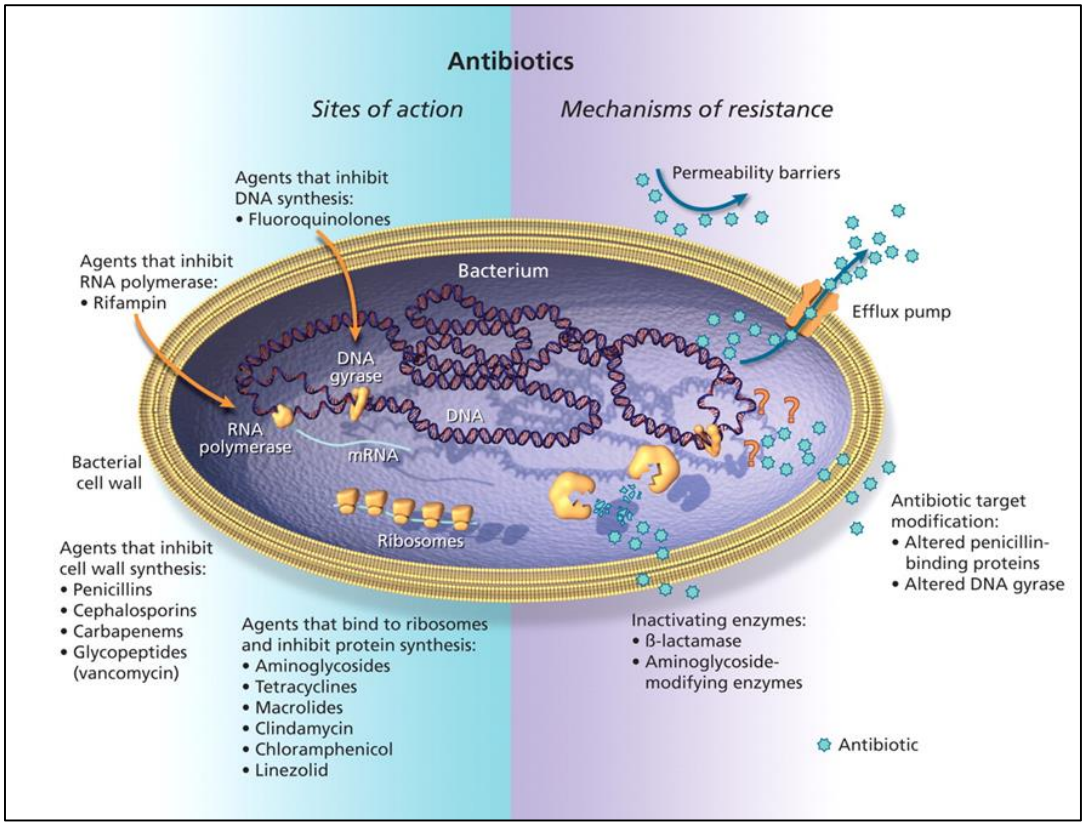

Figure 2 Sites of action and potential mechanisms of bacterial

2.6. Drivers to AMR

AMR stems from a variety of factors, encompassing environmental elements like inadequate sanitation, overcrowding, and ineffective infection prevention and control programs. Additionally, drug-related aspects, such as the availability of antibiotics over-the-counter and the prevalence of counterfeit and substandard medications, contribute to the problem. Patient-related factors, including ignorance, poverty, poor compliance, misconceptions, and self-medication, further exacerbate the challenges associated with antimicrobial resistance (AMR).

The emergence of antimicrobial resistance (AMR) has accelerated significantly, primarily attributed to the overuse and misuse of antibiotics (24). This trend is particularly pronounced in emerging nations, where the utilization of antibiotics has surged in tandem with economic growth (25).

Instances of inappropriate antibiotic prescribing encompass the prescription of antibiotics when unnecessary, the selection of inappropriate medications, and the administration of antibiotics at incorrect doses or durations (26). The widespread use of antibiotics in agriculture, livestock, and animal husbandry has led to antibiotic resistance among soil microorganisms (27).

Chemicals known as biocides are used in a variety of contexts, such as medical facilities, cosmetics, household cleansers, wipes, and furniture. They are substances that destroy microorganisms. In order to stop bacteria from growing in pipes and other equipment, they are also utilised in industry and agricultural (28)

Typical biocides are formaldehyde, ethanol, triclosan, chlorhexidine, and quaternary ammonium compounds (QACs), which include cetrimonium chloride/bromide, isothiazolium-benzalkonium chloride, stearyl trimethyl ammonium chloride, and alkyldimethylbenzyl ammonium chloride (ADBAC) (29). Misconceptions regarding antibiotics and a lack of knowledge about their application are major causes of inappropriate antibiotic use (30).

2.7. Strategy for Combating Antibiotic Resistant

The guidelines highlight six key areas for increased national and international monitoring to detect AMR issues and challenges and track antibiotic usage. Antimicrobial resistance (AMR) must be reduced by encouraging the appropriate use of antibiotics in both humans and animals, encouraging vaccination programs to prevent bacterial infections, raising

public awareness about AMR, enhancing hospital infection control measures, and backing national and international initiatives addressing AMR are crucial steps in addressing the issue (31) (Figure 3).

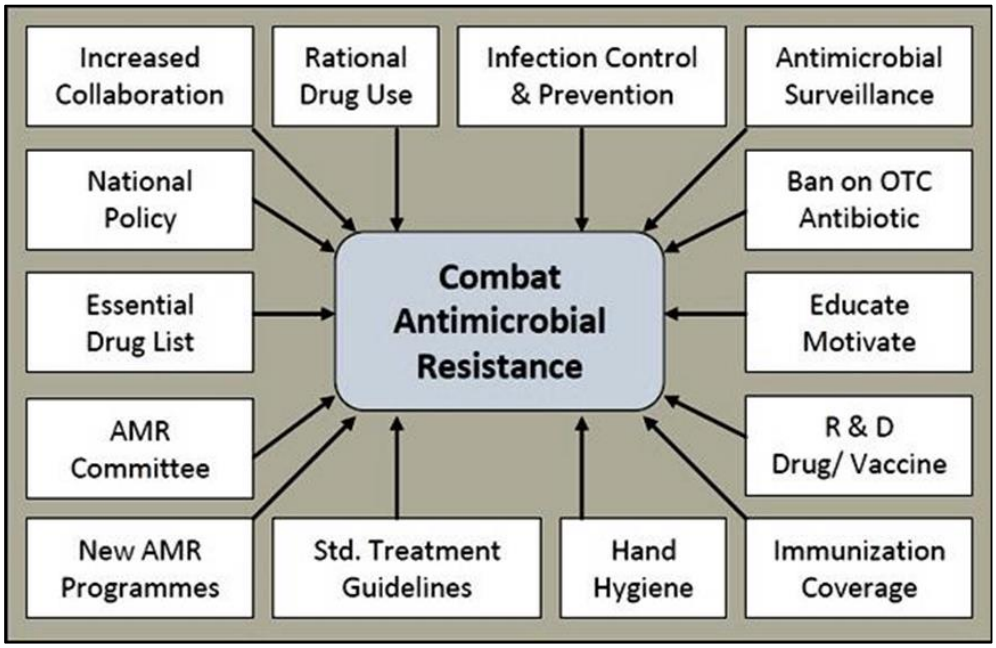

Figure 3 Combat antimicrobial resistance

Plan 1: Offering insights into the prevalence and trends of AMR, improved monitoring of AMR and antibiotic usage is vital for identifying existing challenges. Antimicrobial resistance (AMR) monitoring monitors shifts in microorganism populations, finds novel resistant strains that are critical to public health, and facilitates prompt reporting and outbreak investigation. Policy suggestions and clinical treatment decisions are dependent upon surveillance data. National AMR monitoring systems must be established as soon as feasible in every nation. Standardisation is required for microbiological laboratory procedures, data reporting systems, and data gathering system (32, 33).

Action plan 2: Countries cannot create thorough AMR plans if they lack awareness of and comprehension of AMR. It is also one of the main causes of the misuse of antibiotics. Most countries' general public and medical personnel lack a fundamental understanding of antimicrobial resistance (AMR) and the appropriate use of antibiotics, according to a recent survey. Conversely, a campaign seeks to communicate four key concepts to four main target audiences: 1. Only use antibiotics as directed by a physician.2. Adhere precisely to the doctor's antibiotic prescription guidelines, including dosage and frequency of administration.3. Antibiotics prescribed for someone else should not be taken.4. Antibiotics should not be taken for viral diseases like the common cold.

Action plan 3: Therefore, the most crucial strategy for preventing and managing antimicrobial resistance (AMR) is the appropriate use of antibiotics. The two primary causes of AMR are antibiotic overuse and misuse. Antibiotics that are now in use should be used carefully because no new ones have been produced in many years. Hospitals and governments should both practise antibiotic stewardship.

Antimicrobials and clinical practice stewardship initiatives should be integrated in hospitals. Therefore, it is crucial to collect data on the utilization of antibiotics by both humans and animals at the national level in Asian countries. Sales and distribution of antibiotics need to be controlled. To guarantee quality, standards for their production, licencing, and distribution should also be established.

The imperative development of new antibiotics capable of combating extensively drug-resistant (XDR) and pan-drug-resistant (PDR) bacteria is particularly crucial, given the global increase in these infections (34)

Action plan 4: Mitigating hospital infections is paramount in the battle against antimicrobial resistance (AMR). Healthcare-associated infections (HAIs), primarily triggered by antibiotic-resistant bacteria, stand out as a leading contributor to disease and mortality. Interrupting the transmission of resistant bacteria within hospital settings emerges as one of the most efficacious strategies to counter AMR.

Effective infection control in hospitals plays a pivotal role in managing antimicrobial resistance (AMR) within healthcare facilities. Additionally, it serves as a preventive measure against the emergence of AMR in the broader community, as resistant bacteria have the potential to disseminate from hospitals to the general population.

Establishing a solid foundation with backing from hospital administration, infection control specialists, thorough education, policy reinforcement, and initiatives, as well as sufficient support from the clinical microbiology laboratory, is crucial for enhancing infection control in Asian healthcare facilities.

Putting into practice antimicrobial stewardship programmes (ASPs), which are a crucial part of hospital infection control systems, can help lower hospital-acquired resistance (AMR).

Action plan 5: Encourage vaccination against bacterial infections. With the increasing global impact of antimicrobial resistance (AMR), the pool of effective antibiotics for combating resistant bacteria is diminishing. Promoting vaccination is a crucial step in addressing this challenge. By reducing the incidence of bacterial infections, vaccination can help decrease antimicrobial resistance (AMR) and the need for drugs. Many preventable bacterial diseases, such as tetanus, diphtheria, typhoid fever, pertussis, meningococci, Streptococcus pneumoniae, TB, cholera, and Haemophilus influenzae type B, can be averted through vaccinations. Additionally, vaccines against diseases like Pseudomonas aeruginosa and Staphylococcus aureus that are resistant to drugs are being developed.

The pneumococcal conjugate vaccination (PCV), which reduces the incidence of pneumococcal infections, is one example of a bacterial vaccine that can reduce AMR.

Action plan 6: From a clinical and financial standpoint, antimicrobial resistance (AMR) poses a greater threat to healthcare than any other infectious illness. Governments must thus give the fight against AMR first priority. If not, these ought to consist of public, legal, social, and economic actions as well as medical ones. Action plans and national control strategies (35).

3. Conclusions

AMR's global development and dissemination is a very concerning issue for animal health as well as human health. They are more difficult to treat, and they all result in worse results, higher expenses, and a heavier load on both the patients and society at large. Adopting sound microbiological practices, enhancing surveillance and monitoring, reducing antibiotic usage in food animals, particularly in livestock farming, improving access to high-quality vaccines and diagnostics—currently in high demand in the Vietnamese market—are crucial measures to address the issue of antimicrobial resistance (AMR). Also, it is vital that we implement regulations correctly so as to let persons who oppose control measures team.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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