J. Pharm. Tech. Res. Management Vol. 11, No. 2 (2023), pp.133–141

CHITKARA

Journal of Pharmaceutical Technology Research and Management

Journal homepage: https://jptrm.chitkara.edu.in/

Antibiotic Resistance: Retrospective, Concurrent, and Prospective Data

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ARTICLE INFORMATION

Received: 11 June, 2023
Revised: 04 August, 2023
Accepted: 20 September, 2023
Published Online: 10 November, 2023

Keywords:
Antibiotic Resistance; Rationale Use; Pollution; Antibiotics Use

DOI: 10.15415/jptrm.2023.112006

ABSTRACT

Background: Over decades, antimicrobial medicines have been extensively used in industries such as agriculture and cattle husbandry, not only for the treatment of illnesses but also as preventative measures. Because of this extensive usage, bacteria have unintentionally developed antibiotic resistance (ABR), sometimes without the host's knowledge. It has made treating infectious infections more unclear and difficult.

Purpose: This review examines the patterns of antibiotic use and the types of bacteria that have developed resistance. It also explores their therapeutic mechanisms of action and the mechanisms behind resistance development. Additionally, the review discusses retrospective and concurrent data on ABR and proposes a prospective approach for the surveillance and monitoring of ABR globally.

Method: The review analyses both historical and current data on the global use of antimicrobial agents and their impact on antibiotic resistance. It assesses various strategies for the rational use of antibiotics, considering past patterns and current trends in ABR. The study also evaluates ongoing efforts to monitor and prevent the spread of ABR.

Result: Here, findings highlight the widespread and growing issue of antibiotic resistance, driven by both human and agricultural use of antibiotics. The review underscores the significance of continuous surveillance, monitoring, and the rational use of antimicrobial agents to combat the global threat of ABR, ensuring more effective management of infectious diseases.

Conclusion: Urgent global action is needed against antibiotic resistance because of both human and agricultural use. Improved surveillance and rational use of antibiotics are a prerequisite for preserving the efficacy of treatments available today and for maintaining public health. Strategic planning ahead will be the best management of infectious diseases.

1. Introduction

Beginning with the fact that S. Waksman, the person who discovered the streptomycin, was also the first one who gave the description of the term "antibiotic," which is simply a description of a use, a laboratory effect, or an activity of a chemical compound, that has been seriously overinterpreted (Waksman, 1973). Its intrinsic function and sort of chemical are not defined; only its application is explained (Benzian *et al.*, 2023). The term "antibiotic" here used to describe any class of organic chemicals that precisely connect with microorganism targets to either slow down or eliminate microorganisms, at the risk of upsetting our purist colleagues. No consideration is paid to the chemical's or class's origin (Alekshun & Levy, 2007). Therefore, entirely synthetic medicines are categorised as antibiotics because they engage in receptor interaction, elicit certain cell responses, and initiate biochemical processes of cross-resilience in case of infections. Such as, Fluoroquinolones (FQs), trimethoprim, and sulphonamides are a few good leads (Ben *et al.*, 2019). Although underappreciated, the failure of the effective discovery platform developed by S. Waksman in the year, 1940s was origin of the antibiotic problem. The system was straightforward: zones on an overlay plate where development was inhibited were used to screen soil-derived Streptomyces for antibacterial action in opposition to a test bacterium that was sensitive to it (Waksman, 1973). The process is comparable to Alexander Fleming's accidental discovery of penicillin. However, Waksman's use of a systematic screen was with distinguished approach of identifying antibiotics from chance and helped him win the Nobel Prize (Ben *et al.*, 2019). Streptomycin, the first drug to effectively treat TB and the first aminoglycoside, was found because of the screening of Streptomyces. Over the following 20 years, the pharmaceutical industry rapidly embraced this "Waksman platform" to create the primary families of antibiotics. However, after 20 years of success, the platform was abandoned since the profits from

ISSN No.: 2321-2217(Print) ISSN No.: 2321-2225(Online); Registration No. : CHAENG/2013/50088

mining soil-derived Streptomyces had decreased due to the disclosure of known chemicals (Dehbashi *et al.*, 2020).

Antibiotic resistance is a unique issue for science and medicine due to its emergence and dissemination. The proliferation of the multidrug-resistant 'ESKAPE' pathogens, is now the crisis' most defining feature. In fact, there exist strains of some Gram-negative bacteria, including A. baumannii, which are immune to every antibiotic now in use.

Antibiotics disrupt or alter vital cellular processes, and resistance mechanisms seem to take advantage of every trick in the book to stop an antibiotic from working. These include drug degradation (for instance, linezolid is effluxes by the Acrobatic multidrug pump), target modification (for instance, changes in the 30S ribosomal protein PRs confers resistance to streptomycin), and restriction of drug penetration and/or efflux (Friedrich, 2019). Regarding tolerance, the same cannot be stated. A specialised survivor called a persisted is the major offender accountable for the germs' tolerance towards antibacterials. Persisters are not mutants; rather, they are phenotypic variations of actively dividing cells created stochastically in the population. The processes behind the creation of persisters are still entirely unclear, even though all the viruses investigated so far create them. Toxin-antitoxin modules, have been found to be the main mechanism of persister creation in the model organism Escherichia coli (E. coli), and persister formation routes have been found to be highly redundant. This duplication makes it difficult to find a viable target for drug research. Infections generated by Candida albicans and P. aeruginosa have been found to select for increased levels of persisters during antimicrobial therapy, highlighting the importance between drug tolerance and persisters in the clinical presentation of illness (Keren *et al.*, 2004). Additionally, persisters play a crucial part in the origination of mutants which are normally resilient towards antibacterials. Only slowly, if at all persisters are destroyed, and as antibiotic concentrations drop, they start to proliferate again. (Figure 1)

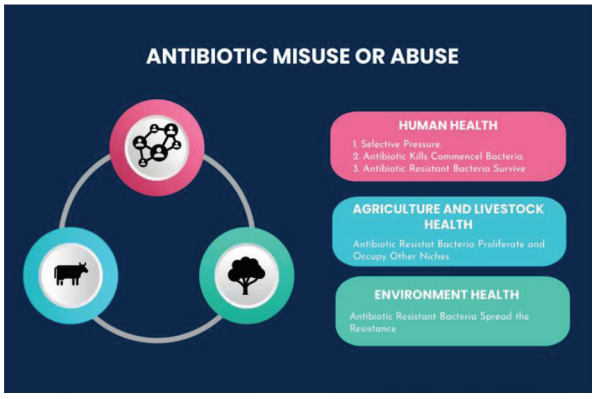

Figure 1: Antibiotic misuse or abuse with respect to human, agriculture and livestock, and environment health

2. Retrospective Data

In 1928, an accidental incident in a laboratory in London altered the trajectory of medical history. Speaking with a colleague after returning from vacation, St. Mary's Hospital bacteriologist Alexander Fleming saw a region surrounding an encroaching fungus on an agar dish where the germs were not developed. After extracting the mould, Fleming recognised its genus as Penicillium (Waksman, 1973). Fleming then extracted the Mold's active ingredient, which he named penicillin. He found that staphylococci and other gram-positive infections could be treated with penicillin due to its antibacterial qualities.

In 1929, Fleming reported the results of his investigation. In the meanwhile, his attempts to separate the extract from the unstable substance didn't turn positive. There was no progress in isolating penicillin as a medicinal agent for a period of 10 years. In order to isolate penicillin for use as a medication at the moment, Fleming gave his Penicillium mould to every person who demanded for the same (Keren *et al.*, 2004).

But as the 1930s got underway, the excitement around Paul Ehrlich's quest to find the miraculous treatment had diminished. The "Golden Age of Antibiotic Discovery" marked the discovery of nearly new antibiotic classes by the isolation of possible microorganism which are responsible for producing antibiotics from soil samples (Levin & Rozen, 2006). However, the limited number of NP classes from bacteria that are easy to produce fast presented challenges for compound rediscovery. Discovering novel strains that produce antibacterial agents in hitherto unexplored environments and the advancement of cutting-edge methods for genome mining and heterologous pathway expression have recently led to a revival in the field of NP discovery.

The abuse of antimicrobial agents in the past decades has been the significant concern in medicine, owing to different health related concerns and development of resistance (Figure 2). The key data and trends concerned with the same are mentioned below:

- Worldwide Antibiotic Intake: Specifically, between 2000 and 2015, low- and middle-income nations accounted for the majority of the 65% rise in antibiotic consumption globally.
- Methicillin-resistant staphylococcus aureus and multi-drug-resistant tuberculosis are examples of resistant bacteria that have emerged as a result of the AMR trend.
- Misuse in medical services: Studies have indicated that over 50% of outpatient settings prescribe antibiotics excessively often for viral diseases such as the flu, the common cold, and other conditions for which they are ineffective.

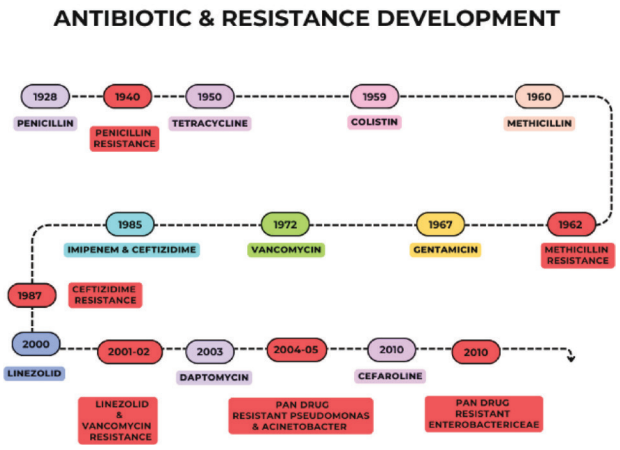

Figure 2: Comparison and timeline infographics of antibiotics development and their resistance development

3. Mechanisms of Antibiotic Resistance

Microorganisms can respond to a great range of living world threats, including the presence of antibiotic chemicals which can imperil their existence, because of remarkable genetic plasticity. Bacteria coexisting in the same biological niche as antibiotic producing species may be able to withstand the harmful antibiotic molecule because they have evolved methods to do so. The two different basic genetic approaches with an evolutionary perspective with respect to antibacterial attack are: (Lewis, 2013)

- Frequent gene mutation linked with the operation of compound action;
- HGT acquisition of foreign DNA coding for resistance determinants (Thomas & Nielsen, 2005).

The drug's effectiveness is modified by gene mutation in a subset of sensitive bacterial cells, maintaining cell viability in the antimicrobial chemical's presence (Mancuso *et al.*, 2021). As soon as a mutation resistant to the treatment appears, the vulnerable population gets wiped out with the use of antibacterials, allowing the resistant germs to remain in charge. Mutations that lead to resistance are often detrimental to cell homeostasis, resulting in a reduction in fitness, and are only maintained in the presence of the antibacterials (Thomas & Nielsen, 2005). The majority of antibacterial agents used in clinical settings originate from or are derived from chemicals found naturally in the environment, mainly dirt. Given that bacteria that coexist with these substances have innate genetic resistance indicators, there is compelling evidence that the "environmental resistive" is a primary source of antibacterial resilient genes in therapeutically relevant microorganisms (Malik & Bhattacharyya, 2019). Furthermore, it also depicts that this genetic exchange even marks significance towards the spread of ABR. Drug resistance to certain medications, such as the tetracycline mentioned above, has been known to be primarily attributed to drug active efflux. Recent reviews of the structures and potential processes of these transporters, and the later processes, such as hydrolysis, group transfer, and redox mechanisms, concentrate on the chemical method of antibiotic inactivation (Munita & Arias, 2016). The group transfer procedures are the most diverse and include the modification by acyl transfer, phosphorylation, glycosylation, nucleotidylation, ribosylation, and thiol transfer. Hydrolysis is particularly significant therapeutically, and particularly when used to beta-lactam antibiotics (Mancuso *et al.*, 2021). While these techniques by themselves actively reduce the concentration of medications in the surrounding environment, enzymes that alter antibiotics physically have a unique quality that presents a unique challenge to scientists and medical professionals considering new approaches to anti-infective therapy (Thakur *et al.*, 2020; Sharma *et al.*, 2020).

Table 1: Antimicrobials with their mechanism of action (basic) and their resistance mechanism developed by bacteria against those respective antibiotics

S.NO.	Group of Antimicrobials	Mechanism of Action	Resistance Mechanism
1.	Beta-lactams	By preventing the synthesis of cell walls, the action is generated.	The production of beta-lactamases generates the resistance mechanism.
2.	Carbapenems	By preventing the synthesis of cell walls, the action is generated.	The production of Carbapenemase generates the resistance mechanism.
3.	Penicillin	By preventing the synthesis of cell walls, the action is generated.	The production of Penicillinase generates the resistance mechanism.
4.	Cephalosporins	By preventing the synthesis of cell walls, the action is generated.	Production of Cephalosporinase

5.	Fluoroquinolone	DNA replication is inhibited to create the effect.	It is dependent on several variables, including target site gene mutation, modifying enzymes, efflux pumps, and many more.
6.	Sulphonamides	Folic acid metabolism is inhibited, which produces the effect.	Transposons and plasmids that express drug-insensitive versions of the target enzymes and allow resistance genes to propagate horizontally are the mediating agents of the resistance mechanism.
7.	Trimethoprim	Folic acid metabolism is inhibited, which produces the effect.	Transposons and plasmids that express drug-insensitive versions of the target enzymes and allow resistance genes to propagate horizontally are the mediating agents of the resistance mechanism.
8.	Tetracyclines	By attaching to the bacterial 30S or 50S, the action is generated by inhibiting ribosome assembly (inhibit protein synthesis).	It is dependent on several variables, including efflux pumps, target site alteration, and enzymatic modification.
9.	Chloramphenicol	Protein synthesis is inhibited, which results in the action.	It is dependent on several variables, including efflux pumps, target site alteration, and enzymatic modification.

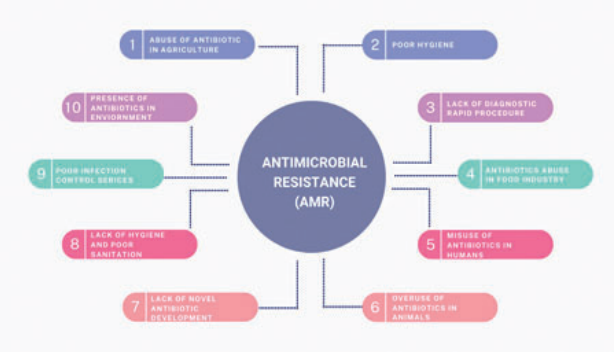

Figure 3: Factors contributing towards Antimicrobial Resistance

4. Key Pathogens of Concern

World Health Organisation states that, antibacterial resilience is a natural process which arise when microorganisms raise resistance to drugs that they were previously sensitive to and that were successful in treating diseases which are caused by these microorganisms. Drug resistance increases the likelihood of mortality and the spread of infectious diseases by making illnesses harder or impossible to cure. The idea that antibiotic overuse causes antimicrobial resistance (AMR) is inadequate because AMR is known to arise spontaneously over time through a multitude of methods. To put it another way, overuse of antibiotics in both people and animals speeds up this normal process, which encourages the spread of the resistance towards antimicrobials. Although we talk about germs growing resistant to antibiotics all the time, we almost ever consider what this implies (Sun *et al.*, 2019). The two categories of resilience are found that may be identified in this conflict: acquired and natural, that can further divided into intrinsic and induced resistance. Intrinsic resistance, which is unrelated to previous antibiotic exposure, is the term used to describe bacterial species that are naturally resistant to a class of antibiotics (e.g., resistance of ampicillin and vancomycin in E. coli, also 1st and 2nd-generation resistance of cephalosporin in P. aeruginosa) (Rehni *et al.*, 2008). In addition to causing natural resilience in bacteria, therapeutic dosages of antibiotics can also activate certain genes in those bacteria. Acquired resistance can arise from two distinct mechanisms: a mutation occurring in the DNA of cell during replication or transfer of genetic materials. Regarding the first approach, the particular mutant strains can transfer the mutation on to their progeny by the vertical route. There are few methods by which bacteria might acquire resilience: conjugation, transposition, and transformation (together known as horizontal gene transfer). At the time of transformation, the recipient microorganism takes up extracellular donor's Deoxyribonucleic Acid. During transduction, recipient bacteria become infected by donor's

Deoxyribonucleic Acid contained within the bacteriophage. The donor and recipient bacteria mate during conjugation in order to transmit DNA to them.

Subsequently, non-resistant bacteria acquire antibiotic resistance due to the pass on of antibiotic-resistant genetic material from the bacteria, which is already resistant to antibiotics (Levin & Rozen, 2006).

P. aeruginosa: Gram-negative, aerobic a common environmental pathogen, P. aeruginosa can cause number of hospitals acquired infection irrespective of acute or chronic nature, including serious respiratory infections in those with compromised host defences (Henrichfreise *et al.*, 2007). When it comes to hospital acquired bloodstream infections, the third most frequent gram-negative bacterium that is by P. aeruginosa (Jurado-Martín *et al.*, 2021). Many resilience mechanisms, both intrinsic and acquired from other species, have allowed this bacterium to demonstrate the respective resilience to a number of drugs falling in the antibacterial Category. As the main reasons of resilience include overexpression of efflux pumps, a deduction in the outer membrane's permeability, and the acquisition or resistant mutation genes which encode for proteins that control the passive diffusion of antibacterials over the external membrane (Poole, 2005). Ceftazidime and cefepime belong to the 3rd as well as 4th generations of cephalosporins, respectively, and are broad-spectrum antibacterials that cover this bacterium (Keren *et al.*, 2004).

P. aeruginosa was recently reported to harbour, with the main divisions of β-lactamases A, β-lactamases B, β-lactamases C, and β-lactamases D), just as A. baumanni. AmpC β-lactamase is an example of endogenous β-lactamase that may be produced by using β-lactam antibiotics such as imipenem and benzylpenicillin. Moreover, an excess of AmpC β-lactamases can result from a gene mutation in P. aeruginosa that confers resilience (Berrazeg *et al.*, 2015).Transferable aminoglycoside modifying enzymes (AMEs), which exhibit a decreased binding affinity for the target inside the bacterial cell, mediate pseudomonas resilience to aminoglycosides. To treat MDR P. aeruginosa, ciprofloxacin, imipenem, piperacillin, aztreonam, ceftazidime, or another anti-pseudomonas drug is combined with colostine. For drug-resistant P. aeruginosa strains, Fosfomycin has been shown to be a successful therapy when combined with aminoglycosides, cephalosporins, and penicillins (Hwang & Yoon, 2019).

4.1. Current Global Status of Antibiotic Resistance

4.1.1. Present-Day Statistics and Prevalence

As per World Health Organisation (WHO), ABR is increasing globally to levels that are unsafe. Up to 90% of Escherichia coli bacteria in some nations are resistant to drugs that are often prescribed, such as ampicillin and cotrimoxazole (Ben *et al.*, 2019). Antibiotic-resistant infections caused by bacteria were directly responsible for 1.27 million fatalities in 2019, and around 5 million deaths worldwide were linked to these diseases.

4.1.2. Geographic Distribution and Hotspots

South Asia, Southeast Asia, and Sub-Saharan Africa have the highest levels of antimicrobial resistance due to widespread antibiotic usage and misuse as well as potentially underfunded health services (Friedrich, 2019).

4.2. Contemporary Resistant Pathogens

4.2.1. Enterobacteriaceae Resistant to Carbapenems (CRE)

CRE infections, also referred to as "nightmare bacteria," can kill up to 50% of victims and are resistant to almost every antibiotic on the market (Gaynes, 2017).

4.2.2. Vancomycin-Resistant Enterococci (VRE)

VRE infections are frequently linked to healthcare-associated infections (HAIs), especially in individuals with impaired immune systems. They are very challenging to manage.

4.2.3. Methicillin-Resistant Staphylococcus Aureus (MRSA)

Although enhanced prevention strategies have led to a decline in MRSA frequency in certain areas, the pathogen still poses a serious risk to public health, especially in medical settings (Gaynes, 2017).

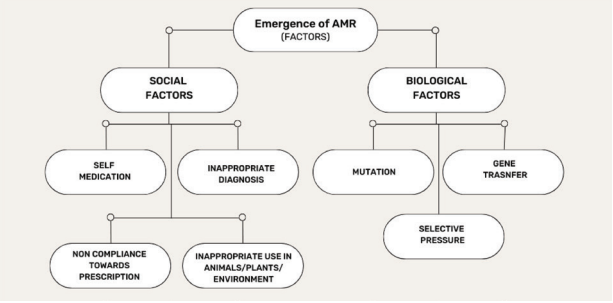

Figure 4: Leading factors causing emergence of AMR

5. Surveillance and Monitoring

Various nations have formed national and regional monitoring collaborations in response to the threats that antibiotic resistance poses to public health; others have not (Ontong *et al.*, 2021). Moreover, there is not a clear

structure in place for international monitoring programmes to work together (Iramiot *et al.*, 2020). The absence of an international framework for cooperative monitoring of antibiotic resistance hinders attempts to detect, characterise, and contain new threats, monitor growing resilience concerns, and methodically compare and assess the effectiveness of national resilience containment initiatives (Iramiot *et al.*, 2020). Thankfully, the essential elements of an international monitoring cooperation already exist, and far more has been achieved globally than is often recognised. This talk first centre on antibiotic resilience in common bacterial infections seen in hospital settings and the population, such as Escherichia coli, Staphylococcus aureus, and Streptococcus pneumonia.

5.1. Key Studies and Real-Time Data Analysis from the Last 5-10 Years

- Global Antimicrobial Resistance Surveillance System (GLASS) Report 2023: WHO's GLASS system provides real-time data on antibiotic resistance trends globally, showing significant increases in resistance to common antibiotics across multiple pathogens.

The 2021 Lancet Global Health Study: This study demonstrated that low- and middle-income nations, which have high mortality rates and restricted access to newer, more potent medicines, are disproportionately affected by antibiotic-resistant diseases.(Sun *et al.*, 2019)

6. Monitoring Antibiotic Resistance on a Nationwide Scale: A Prospective Strategy for reducing AMR.

Early WHO conferences advocated for the creation of regional/international, national, and local monitoring systems. Priority goals that have been highlighted at the national level include tracking patterns in infection and resilience, creating standard treatment guidelines, evaluating treatments for containing resilience, keeping an eye out for new resistant strains, and quickly identifying and controlling outbreaks (Hansen *et al.*, 2008). Benchmarking experiences by facility and geographic distribution is made possible by a national view, which is especially useful when combined with data on antibiotic usage, infection control strategies, pathogen population dynamics, and patient characteristics (Grundmann *et al.*, 2011).

Moreover, the coordinators nationwide are playing a crucial role in providing network members with mentorship in quality enhancement, data utilisation for local action, and treatment guideline decision-making (Hansen *et al.*, 2008). Since 1989, The WHONET software, developed and maintained by the WHO Collaborating Centre for Surveillance of Antibiotic Resilience in Boston, enables the interchange and management of laboratory test data related to microbiology at many surveillance levels. In order to assist national and/or local monitoring in more than 1700 clinical, veterinary laboratories, public health, food, and, more than 110 WHO Member States now make use of WHONET.

7. Conclusion

The review aims at the dramatic increase in ABR as a critical public health issue that also involves geographical and industrial boundaries. The emergence and spread of resistant strains of bacteria are largely associated with historical and contemporary patterns of antibiotic use, especially in agriculture and livestock. This is complicated by several interrelated factors and has brought attention to the need for a holistic understanding of both therapeutic action of antibiotics and the pathways through which bacteria develop resistance.

The results point to the necessity for the urgent implementation of overall surveillance mechanisms that monitor such changes in ABR dynamically in both time and across settings. Hotspots of resistance need to be detected so that prevention strategies to counteract their impact may be devised. The efforts already undertaken in the rational use of antibiotics must be strengthened even further by increasing education, policy reform, and stewardship activities focused on responsible prescribing and drug application practices.

Lastly, only a collaborative global approach can address multi-faceted issues presented by ABR, that is, by integrating data from human health and agricultural practices to come up with an integrated response to misuse of antibiotics. Interdisciplinary partnerships may enhance surveillance capabilities, while promotional innovative research into alternative therapies could pave the way for protection of antibiotics' effectiveness for tomorrow. Fighting ABR is no longer just a medical issue but rather a social issue that needs to be collectively addressed and dealt with by representatives from several sectors in order to preserve the incredibly valuable resource antibiotics hold for the treatment of infectious diseases.

Abbreviations

Abbreviation	Full Form
S. Waksman	Selman Waksman
FQs	Fluoroquinolones
HGT	Horizontal Gene Transfer

ESKAPE	Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species
DNA	Deoxyribonucleic Acid
E. coli	Escherichia coli
ESBLs	Extended Spectrum Beta-Lactamases
MDR	Multidrug-Resistant
AMR	Antimicrobial Resistance
WHO	World Health Organization
UN	United Nations
AMEs	Aminoglycoside Modifying Enzymes
HIV/AIDS	Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome
TB	Tuberculosis
NP	Natural Product
ABR	Antibiotic Resistance
CRE	Carbapenem-Resistant Enterobacteriaceae
VRE	Vancomycin-Resistant Enterococci
MRSA	Methicillin-Resistant Staphylococcus Aureus
HAI	Healthcare-Associated Infection
GLASS	Global Antimicrobial Resistance Surveillance System
WHONET	World Health Organization Network for Surveillance
AmpC	Ampicillin Class C

Acknowledgement

The authors extend their appreciation to the Chitkara University, Punjab for support.

Authorship Contribution

Designing of manuscript: Bhavesh Dharmani and Bisman Kaur; Analysis of the data: Sarita Jangra and Thakur Gurjeet Singh; Editing of the manuscript: Sarita Jangra and Thakur Gurjeet Singh; Critical review of the article: Thakur Gurjeet Singh; and Supervision: Thakur Gurjeet Singh.

Funding

There is no funding source for this article.

Conflict of Interest

There is no conflict of interest.

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

References

Alekshun, M. N., & Levy, S. B. (2007). Molecular mechanisms of antibacterial multidrug resistance. *Cell*, *128*(6), 1037–1050. https://doi.org/10.1016/j.cell.2007.03.004

Ben, Y., Fu, C., Hu, M., Liu, L., Wong, M. H., & Zheng, C. (2019). Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: A review. *Environmental research*, *169*, 483–493. https://doi.org/10.1016/j.envres.2018.11.040

Benzian, H., Beltrán-Aguilar, E., & Niederman, R. (2023). Global health threats are also oral health threats. *Journal of the American Dental Association (1939)*, *154*(5), 367–369. https://doi.org/10.1016/j.adaj.2023.01.007

Berrazeg, M., Jeannot, K., NtsogoEnguéné, V. Y., Broutin, I., Loeffert, S., Fournier, D., & Plésiat, P. (2015). Mutations in β-Lactamase AmpC Increase Resistance of Pseudomonas aeruginosa Isolates to Antipseudomonal Cephalosporins. *Antimicrobial agents and chemotherapy*, *59*(10), 6248–6255. https://doi.org/10.1128/AAC.00825-15

Boucher, H. W., Talbot, G. H., Bradley, J. S., Edwards, J. E., Gilbert, D., Rice, L. B., Scheld, M., Spellberg, B., & Bartlett, J. (2009). Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *48*(1), 1–12. https://doi.org/10.1086/595011

Cepas, V., & Soto, S. M. (2020). Relationship between Virulence and Resistance among Gram-Negative Bacteria. *Antibiotics (Basel, Switzerland)*, *9*(10), 719. https://doi.org/10.3390/antibiotics9100719

Dehbashi, S., Tahmasebi, H., Alikhani, M. Y., Keramat, F., & Arabestani, M. R. (2020). Distribution of Class B and Class A β-Lactamases in Clinical Strains of Pseudomonas aeruginosa: Comparison of Phenotypic Methods and High-Resolution Melting Analysis (HRMA) Assay. *Infection and drug resistance*, *13*, 2037–2052. https://doi.org/10.2147/IDR.S255292

Friedrich A. W. (2019). Control of hospital acquired infections and antimicrobial resistance in Europe: the way to go. *Wiener medizinische Wochenschrift*, *169*(1), 25–30. https://doi.org/10.1007/s10354-018-0676-5

Gaynes R. (2017). The Discovery of Penicillin—New Insights After More Than 75 Years of Clinical Use. *Emerging Infectious Diseases*, *23*(5), 849–853. https://doi.org/10.3201/eid2305.161556

Grundmann, H., Klugman, K. P., Walsh, T., Ramon-Pardo, P., Sigauque, B., Khan, W., Laxminarayan, R., Heddini, A., & Stelling, J. (2011). A framework for global surveillance of antibiotic resistance. *Drug resistance updates: reviews and commentaries in antimicrobial and anticancer chemotherapy*, *14*(2), 79–87. https://doi.org/10.1016/j.drup.2011.02.007

Hansen, S., Lewis, K., & Vulić, M. (2008). Role of global regulators and nucleotide metabolism in antibiotic tolerance in Escherichia coli. *Antimicrobial agents and chemotherapy*, *52*(8), 2718–2726. https://doi.org/10.1128/AAC.00144-08

Henrichfreise, B., Wiegand, I., Pfister, W., & Wiedemann, B. (2007). Resistance mechanisms of multiresistant Pseudomonas aeruginosa strains from Germany and correlation with hypermutation. *Antimicrobial agents and chemotherapy*, *51*(11), 4062–4070. https://doi.org/10.1128/AAC.00148-07

Hwang, W., & Yoon, S. S. (2019). Virulence Characteristics and an Action Mode of Antibiotic Resistance in Multidrug-Resistant Pseudomonas aeruginosa. *Scientific reports*, *9*(1), 487. https://doi.org/10.1038/s41598-018-37422-9

Iramiot, J. S., Kajumbula, H., Bazira, J., Kansiime, C., & Asiimwe, B. B. (2020). Antimicrobial resistance at the human-animal interface in the Pastoralist Communities of Kasese District, South Western Uganda. *Scientific reports*, *10*(1), 14737. https://doi.org/10.1038/s41598-020-70517-w

Jurado-Martín, I., Sainz-Mejías, M., & McClean, S. (2021). Pseudomonas aeruginosa: An Audacious Pathogen with an Adaptable Arsenal of Virulence Factors. *International journal of molecular sciences*, *22*(6), 3128. https://doi.org/10.3390/ijms22063128

Keren, I., Shah, D., Spoering, A., Kaldalu, N., & Lewis, K. (2004). Specialized persister cells and the mechanism of multidrug tolerance in Escherichia coli. *Journal of bacteriology*, *186*(24), 8172–8180. https://doi.org/10.1128/JB.186.24.8172-8180.2004

Lafleur, M. D., Qi, Q., & Lewis, K. (2010). Patients with long-term oral carriage harbor high-persister mutants of Candida albicans. *Antimicrobial agents and chemotherapy*, *54*(1), 39–44. https://doi.org/10.1128/AAC.00860-09

Levin, B. R., & Rozen, D. E. (2006). Non-inherited antibiotic resistance. *Nature reviews. Microbiology*, *4*(7), 556–562. https://doi.org/10.1038/nrmicro1445

Lewis K. (2013). Platforms for antibiotic discovery. *Nature reviews. Drug discovery*, *12*(5), 371–387. https://doi.org/10.1038/nrd3975

Malik, B., & Bhattacharyya, S. (2019). Antibiotic drug-resistance as a complex system driven by socio-economic growth and antibiotic misuse. *Scientific reports*, *9*(1), 9788. https://doi.org/10.1038/s41598-019-46078-y

Mancuso, G., Midiri, A., Gerace, E., & Biondo, C. (2021). Bacterial Antibiotic Resistance: The Most Critical Pathogens. *Pathogens (Basel, Switzerland)*, *10*(10), 1310. https://doi.org/10.3390/pathogens10101310

Munita, J. M., & Arias, C. A. (2016). Mechanisms of Antibiotic Resistance. *Microbiology spectrum, 4*(2). https://doi.org/10.1128/microbiolspec.VMBF-0016-2015

Ontong, J. C., Ozioma, N. F., Voravuthikunchai, S. P., & Chusri, S. (2021). Synergistic antibacterial effects of colistin in combination with aminoglycoside, carbapenems, cephalosporins, fluoroquinolones, tetracyclines, fosfomycin, and piperacillin on multidrug resistant Klebsiella pneumoniae isolates.*PloS one*, *16*(1). https://doi.org/10.1371/journal.pone.0244673

Poole K. (2005). Efflux-mediated antimicrobial resistance. *The Journal of antimicrobial chemotherapy*, *56*(1), 20–51. https://doi.org/10.1093/jac/dki171

Rehni, A. K., Singh, T. G., Jaggi, A. S., & Singh, N. (2008). Pharmacological preconditioning of the brain: a possible interplay between opioid and calcitonin gene related peptide transduction systems. *Pharmacological reports: PR*, *60*(6), 904–913.

Sharma, A., Mittal, A., Puri, V., Kumar, P. and Singh, I. (2020). Curcumin-loaded, alginate–gelatin composite fibers for wound healing applications. *3 Biotech*, *10*, 464. https://doi.org/10.1007/s13205-020-02453-5

Sun, D., Jeannot, K., Xiao, Y., & Knapp, C. W. (2019). Editorial: Horizontal Gene Transfer Mediated Bacterial Antibiotic Resistance. *Frontiers in microbiology*, *10*, 1933. https://doi.org/10.3389/fmicb.2019.01933

Thakur, A. K., Chellappan, D. K., Dua, K., Mehta, M., Satija, S., & Singh, I. (2020). Patented therapeutic drug delivery strategies for targeting pulmonary diseases. *Expert opinion on therapeutic patents*, *30*(5), 375–387. https://doi.org/10.1080/13543776.2020.1741547

Thomas, C. M., & Nielsen, K. M. (2005). Mechanisms of, and barriers to, horizontal gene transfer between bacteria. *Nature reviews. Microbiology*, *3*(9), 711–721. https://doi.org/10.1038/nrmicro1234

Waksman, S. A. (1973). History of the word 'antibiotic'. *Journal of the history of medicine and allied sciences*, *28*(3), 284-286. https://doi.org/10.1093/jhmas/xxviii.3.284

Journal of Pharmaceutical Technology, Research and Management

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Volume 11, Issue 2 **November 2023** **ISSN 2321-2217**