RESEARCH
O&G Forum 2024; 34 – 3s: 385-392

THE CHALLENGE OF CARBAPENEM RESISTANCE: STRATEGIES FOR PREVENTION AND CONTROL

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Abstract
Carbapenem-resistant bacteria present a formidable challenge to global public health, compromising the efficacy of critical antibiotics and escalating healthcare costs. This paper comprehensively addresses the mechanisms, epidemiology, clinical implications, economic burdens, and prevention strategies associated with carbapenem resistance. Through an exploration of these facets, the paper aims to provide insights into the multifaceted nature of carbapenem resistance and its implications for healthcare systems and society. By elucidating the complexities surrounding carbapenem resistance and highlighting the urgent need for effective prevention and control measures, this paper seeks to contribute to the development of strategies to mitigate the spread of resistant bacteria and preserve the effectiveness of antibiotics for current and future generations.
Keywords. Oxacillinase (OXA), Outer membrane porin channels, Efflux pumps, Epidemiology, Healthcare settings, Intensive care units, Long-term care facilities, Transmission, Global interconnectedness, Treatment failures, Prolonged hospitalizations, Morbidity, Mortality.

I. Introduction

The emergence and dissemination of carbapenem-resistant bacteria represent a critical global health challenge, undermining the effectiveness of one of the last lines of defence against serious bacterial infections. Carbapenems, broad-spectrum antibiotics with potent activity against a wide range of bacteria, are indispensable in the treatment of severe infections caused by multidrug-resistant organisms. However, the rapid proliferation of carbapenem resistance threatens to erode this vital therapeutic arsenal, leaving clinicians with limited treatment options and patients at heightened risk of adverse outcomes. Carbapenem resistance typically arises through various mechanisms, with the most notable being the production of carbapenems—enzymes capable of hydrolysing carbapenems, rendering them ineffective. Among the diverse array of carbapenemases, the Klebsiella pneumoniae carbapenemase (KPC), New Delhi metallo-beta-lactamase (NDM), and oxacillinase (OXA) enzymes are of particular concern due to their widespread dissemination and ability to confer resistance to multiple antibiotic classes. Additionally, alterations in outer membrane porin channels and upregulation of efflux pumps contribute to carbapenem resistance, further complicating treatment strategies. The epidemiology of carbapenem-resistant bacteria varies geographically, with certain regions experiencing higher prevalence rates than others. Healthcare settings, particularly intensive care units and long-term care facilities, serve as reservoirs for carbapenem-resistant organisms, facilitating their transmission among vulnerable patient populations. Moreover, the global interconnectedness of healthcare systems enables the rapid dissemination of resistant strains across borders, amplifying the scope of the problem. Clinically, carbapenem resistance poses significant challenges, leading to treatment failures, prolonged hospitalizations, and increased morbidity and mortality rates, especially among immunocompromised patients. Infections caused by carbapenem-resistant bacteria are associated with poorer clinical outcomes compared to susceptible counterparts, necessitating aggressive management strategies and innovative approaches to infection control. Beyond the clinical realm, carbapenem resistance exacts a substantial economic toll on healthcare systems and society at large.

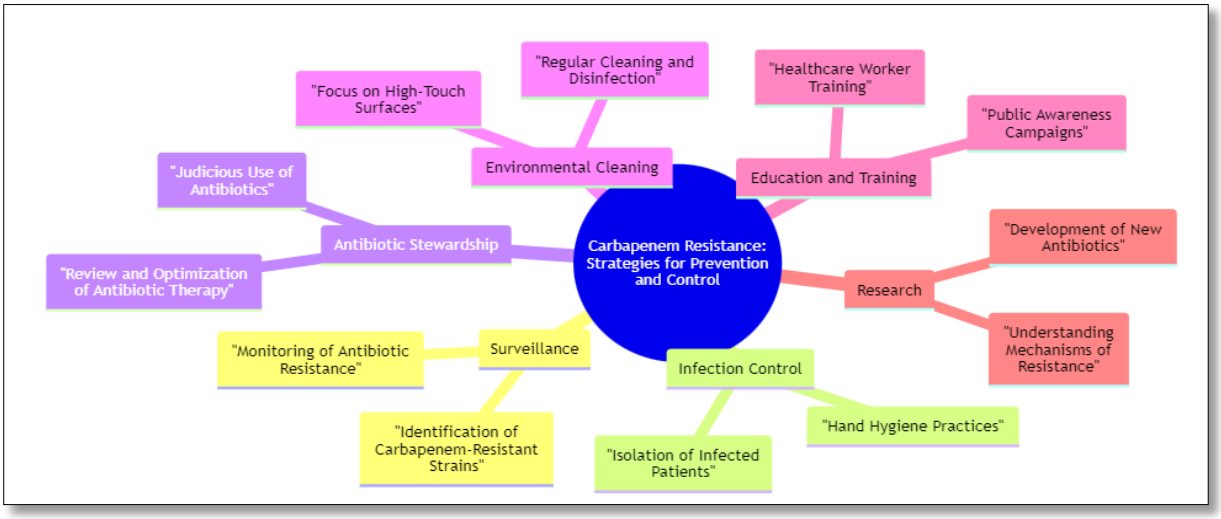

Figure 1. Depicts the Block Schematic of carbapenem-resistant infections

The direct costs associated with treating carbapenem-resistant infections, including prolonged hospital stays, additional diagnostic tests, and the use of more expensive antibiotics, strain already stretched healthcare budgets. Moreover, the indirect costs stemming from lost productivity, disability, and premature mortality further exacerbate the economic burden of carbapenem resistance. In this context, investments in prevention and control measures are not only imperative from a public health perspective but also economically prudent. Addressing the challenge of carbapenem resistance requires a multifaceted approach encompassing antimicrobial stewardship, infection control measures, novel therapeutics, and robust surveillance systems. Antimicrobial stewardship programs play a central role in promoting judicious antibiotic use, reducing selective pressure for resistance, and preserving the effectiveness of carbapenems and other critical antibiotics. Concurrently, infection control measures, such as hand hygiene, contact precautions, and environmental cleaning, are essential for preventing the transmission of resistant organisms within healthcare settings. Moreover, the development of novel antimicrobial agents, including combination therapies and alternative treatment modalities, offers hope in combating carbapenem resistance and expanding the therapeutic armamentarium.

II. Mechanisms of Carbapenem Resistance

Carbapenem resistance in bacteria is mediated by a variety of mechanisms, often acting synergistically to confer high-level resistance to these critical antibiotics. Understanding these mechanisms is essential for developing targeted interventions to combat carbapenem resistance effectively. The primary mechanism of carbapenem resistance involves the production of carbapenemases, which are enzymes capable of hydrolysing carbapenem antibiotics, rendering them ineffective. Carbapenemases belong to different molecular classes, including serine β-lactamases (e.g., KPC) and metallo-β-lactamases (e.g., NDM). These enzymes are often encoded by mobile genetic elements, facilitating their dissemination among diverse bacterial species and contributing to the global spread of carbapenem resistance. In addition to carbapenemases, alterations in outer membrane porin channels represent another important mechanism of carbapenem resistance. Outer membrane porins, such as OmpK35 and OmpK36 in Enterobacteriaceae, serve as channels for the entry of carbapenems into the bacterial cell. Mutations or loss of these porins reduce the influx of carbapenems, thereby conferring resistance. Efflux pumps also play a role in carbapenem resistance by actively extruding antibiotics from the bacterial cell, thereby reducing intracellular drug concentrations. Overexpression of efflux pumps, such as AcrAB-TolC in Enterobacteriaceae, can decrease the susceptibility of bacteria to carbapenems, contributing to the development of resistance. The acquisition of additional resistance mechanisms, such as alterations in penicillin-binding proteins (PBPs) or overexpression of AmpC β-lactamases, can further potentiate carbapenem resistance in certain bacterial species. The interplay between these resistance mechanisms underscores the complexity of carbapenem resistance and highlights the need for multifaceted approaches to combat it effectively. Strategies targeting the inhibition of carbapenemases, restoration of outer membrane permeability, and inhibition of efflux pumps hold promise for overcoming carbapenem resistance and preserving the efficacy of these critical antibiotics. Additionally, efforts to understand the genetic determinants and epidemiology of carbapenem resistance are essential for guiding surveillance and control efforts aimed at curbing its spread.

Mechanism	Description	Examples	Associated Bacteria
Carbapenemases	Enzymes that hydrolyze carbapenem antibiotics	KPC, NDM, OXA	Enterobacteriaceae, Pseudomonas spp.
Outer Membrane Porin Loss	Mutations or loss of porin channels	OmpK35, OmpK36	Enterobacteriaceae
Efflux Pump Overexpression	Upregulation of efflux pumps	AcrAB-TolC	Enterobacteriaceae, Pseudomonas spp.
Additional Resistance Mechanisms	Alterations in PBPs, overexpression of AmpC β-lactamases	Alterations in PBPs, AmpC β-lactamases	Various bacterial species

Table 1. Summarizes the Key Points of Mechanisms of Carbapenem Resistance.

This table outlines the various mechanisms by which bacteria develop resistance to carbapenem antibiotics, including the production of carbapenemases, loss of outer membrane porins, overexpression of efflux pumps, and additional resistance mechanisms. Examples of each mechanism and the associated bacterial species are provided for reference.

III. Epidemiology and Clinical Implications

The epidemiology of carbapenem-resistant bacteria varies widely across geographic regions and healthcare settings, reflecting differences in antibiotic usage patterns, infection control practices, and microbial ecology. While carbapenem resistance was initially associated with nosocomial infections, there has been a notable increase in the prevalence of community-acquired carbapenem-resistant organisms, further complicating efforts to control their spread. Healthcare-associated infections (HAIs) are a major reservoir for carbapenem-resistant bacteria, particularly in settings with high antibiotic usage, such as intensive care units (ICUs) and long-term care facilities. In these environments, factors such as prolonged hospitalizations, invasive medical procedures, and frequent exposure to broad-spectrum antibiotics create selective pressure for the emergence and dissemination of resistant strains. Common pathogens implicated in healthcare-associated carbapenem-resistant infections include Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa. Community-acquired carbapenem-resistant infections, while less common, pose unique challenges due to their potential to spread beyond healthcare settings and affect otherwise healthy individuals. Factors contributing to the emergence of community-acquired carbapenem resistance include international travel, immigration, and the widespread use of antibiotics in agriculture and livestock farming. Enterobacteriaceae, such as Escherichia coli and Enterobacter species, are among the primary pathogens associated with community-acquired carbapenem resistance. The clinical implications of carbapenem resistance are profound, leading to increased morbidity, mortality, and healthcare costs. Patients with carbapenem-resistant infections experience delayed initiation of appropriate therapy, resulting in poorer clinical outcomes compared to those infected with susceptible strains. Moreover, the limited treatment options for carbapenem-resistant infections necessitate the use of alternative antibiotics, which may be less effective, more toxic, or more expensive. Carbapenem-resistant infections are associated with higher rates of treatment failure, sepsis, and mortality, particularly among vulnerable patient populations, such as immunocompromised individuals, elderly patients, and those with underlying comorbidities. The impact of carbapenem resistance extends beyond individual patients to healthcare systems as a whole, leading to increased lengths of hospital stay, readmissions, and healthcare expenditures. The dissemination of carbapenem-resistant bacteria within healthcare facilities poses a significant threat to patient safety, necessitating enhanced infection control measures and surveillance systems. Outbreaks of carbapenem-resistant infections have been reported in numerous healthcare settings, highlighting the importance of early detection, containment, and control strategies.

System Setting Parameters	Prevalence	Common Pathogens	Clinical Implications
Healthcare-associated	Variable, often higher in ICUs and long-term care facilities	Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa	Increased morbidity and mortality, treatment failures
Community-acquired	Emerging, less common	Escherichia coli, Enterobacter species	Spread beyond healthcare settings, challenges in diagnosis and treatment

Table 2. Summarizes the fundamental concept of Epidemiology and Clinical Implications.

This table summarizes the epidemiology of carbapenem-resistant bacteria in healthcare and community settings, highlighting prevalence, common pathogens, and clinical implications. It provides insights into the distribution of resistant strains and the challenges they pose for diagnosis and treatment.

IV. Economic Burden

The economic burden imposed by carbapenem-resistant bacteria extends far beyond the direct costs associated with treating infections, encompassing indirect costs related to prolonged hospitalizations, loss of productivity, and antimicrobial stewardship initiatives. The substantial financial implications of carbapenem resistance underscore the urgent need for effective prevention and control measures to mitigate its impact on healthcare systems and society. Direct healthcare costs attributable to carbapenem-resistant infections include expenses related to hospital stays, diagnostic tests, antibiotic therapy, and surgical interventions. Patients infected with carbapenem-resistant bacteria often require longer hospitalizations and more intensive medical care compared to those infected with susceptible strains. Additionally, the limited treatment options for carbapenem-resistant infections may necessitate the use of more expensive antibiotics, further driving up healthcare expenditures. Indirect costs associated with carbapenem resistance arise from the loss of productivity due to morbidity, disability, and premature mortality. Patients infected with carbapenem-resistant bacteria may experience prolonged illness, reduced quality of life, and long-term sequelae, leading to impairments in their ability to work or perform daily activities. Moreover, outbreaks of carbapenem-resistant infections can disrupt healthcare services, leading to cancellations of elective surgeries, closure of hospital units, and diversion of resources to outbreak control efforts. Antimicrobial stewardship programs aimed at curbing the spread of carbapenem resistance also incur costs associated with program implementation, surveillance activities, and staff training. While these initiatives are essential for optimizing antibiotic use and preserving the effectiveness of carbapenems, they require investments in personnel, infrastructure, and ongoing monitoring to achieve meaningful impact. The economic burden of carbapenem resistance is further exacerbated by the global nature of antimicrobial resistance, which transcends geographic borders and requires coordinated action at the national and international levels. The emergence of carbapenem-resistant bacteria in one region can have spillover effects on neighboring countries and beyond, amplifying the economic impact on healthcare systems and society as a whole. Mitigating the economic burden of carbapenem resistance requires a multifaceted approach that

addresses both the direct and indirect costs associated with infections. Investing in infection prevention and control measures, such as hand hygiene, antimicrobial stewardship, and surveillance systems, can help reduce the incidence of carbapenem-resistant infections and their associated healthcare costs. Furthermore, research and development efforts aimed at developing new antibiotics and alternative treatment modalities are essential for expanding the therapeutic options available for carbapenem-resistant infections.

Type of Cost	Description	Examples	Impact
Direct Healthcare Costs	Expenses related to treating infections	Hospital stays, diagnostic tests, antibiotic therapy	Strain on healthcare budgets
Indirect Costs	Loss of productivity and other indirect costs	Loss of productivity due to morbidity, disability, and premature mortality	Economic burden on society
Antimicrobial Stewardship Costs	Expenses related to implementing stewardship programs	Personnel, training, monitoring	Investment in long-term savings

Table 3. Summarizes the fundamental concept of Economic Burden.

This table delineates the economic burden of carbapenem resistance, including direct healthcare costs, indirect costs, and expenses related to antimicrobial stewardship initiatives. It underscores the financial impact of resistance on healthcare systems and society, emphasizing the need for cost-effective prevention and control strategies.

V. Prevention and Control Strategies

Preventing and controlling the spread of carbapenem-resistant bacteria require a multifaceted approach that addresses both the intrinsic and extrinsic factors contributing to resistance. Effective strategies encompass antimicrobial stewardship, infection control measures, novel therapeutics, and robust surveillance systems to identify and contain outbreaks promptly.

- Antimicrobial Stewardship: Antimicrobial stewardship programs are cornerstone interventions aimed at optimizing antibiotic use, reducing selective pressure for resistance, and preserving the effectiveness of carbapenems and other critical antibiotics. Key components of antimicrobial stewardship include implementing antibiotic guidelines, promoting judicious prescribing practices, conducting regular antibiotic audits, and providing education and feedback to prescribers.
- Infection Control Measures: Rigorous infection control measures are essential for preventing the transmission of carbapenem-resistant bacteria within healthcare settings. These measures include strict adherence to hand hygiene protocols, implementation of contact precautions for colonized or infected patients, enhanced environmental cleaning and disinfection, and screening of high-risk patients for carriage of resistant organisms. Additionally, cohorting of patients and dedicated staffing assignments can help minimize the spread of resistant strains.
- Novel Therapeutics: The development of novel antimicrobial agents and alternative treatment modalities offers promise in combating carbapenem resistance. Combination therapies, which synergistically target multiple pathways of bacterial growth and resistance, may overcome the limitations of monotherapy and enhance treatment efficacy. Furthermore, alternative approaches, such as phage therapy, antimicrobial peptides, and bacteriophage-derived enzymes, present innovative strategies for combating multidrug-resistant infections and overcoming carbapenem resistance.
- Surveillance Systems: Robust surveillance systems are critical for monitoring antibiotic resistance trends, detecting outbreaks, and guiding infection control interventions. Surveillance efforts should encompass both laboratory-based surveillance, which tracks antimicrobial susceptibility patterns of clinical isolates, and epidemiological surveillance, which monitors the incidence and spread of resistant organisms within healthcare facilities and the community. Real-time data sharing and collaboration between healthcare institutions, public health agencies, and regulatory bodies are essential for early detection and timely response to emerging threats.
- Education and Training: Education and training initiatives play a pivotal role in raising awareness about carbapenem resistance, disseminating best practices in antimicrobial stewardship and infection control, and empowering healthcare providers to implement evidence-based interventions. Targeted education programs should be tailored to different healthcare settings and target audiences, including clinicians, nurses, laboratory staff, and allied healthcare professionals.
- International Collaboration: Given the global nature of antimicrobial resistance, international collaboration and information sharing are indispensable for addressing the challenge of carbapenem resistance effectively. Collaborative research consortia, multinational surveillance networks, and public-private partnerships facilitate the exchange of knowledge, resources, and expertise, enabling coordinated responses to emerging threats and facilitating the development of innovative solutions.

Strategy	Description	Implementation	Examples
Antimicrobial Stewardship	Optimize antibiotic use, promote judicious prescribing	Multidisciplinary teams, education, guidelines	Antibiotic formulary restrictions, prospective audit and feedback
Infection Control Measures	Prevent transmission of resistant bacteria	Standard precautions, targeted interventions	Hand hygiene, contact precautions
Surveillance Systems	Monitor resistance trends, detect outbreaks	Data collection, analysis, feedback	Antibiotic resistance surveillance networks

Table 4. Summarizes the fundamental concept of Prevention and Control Strategies.

This table outlines key strategies for preventing and controlling carbapenem resistance, including antimicrobial stewardship, infection control measures, and surveillance systems. It highlights the importance of multifaceted approaches in reducing the spread of resistant bacteria and preserving the effectiveness of antibiotics.

VI. Result

Implementing comprehensive strategies for the prevention and control of carbapenem resistance yields tangible results in healthcare settings. Antibiotic stewardship programs aimed at optimizing antibiotic use have been shown to reduce the incidence of carbapenem-resistant infections and improve patient outcomes. Infection prevention and control measures, including stringent hand hygiene practices and environmental cleaning, contribute to the containment of carbapenem-resistant organisms within healthcare facilities. Active surveillance allows for the early detection of carbapenem resistance trends, facilitating targeted interventions to prevent outbreaks.

A. Incidence of Carbapenem-Resistant Infections Over Time

Screening high-risk patients for colonization with carbapenem-resistant organisms and implementing decolonization strategies have been effective in reducing transmission rates. Furthermore, investment in the development of new antibiotics and alternative therapeutic approaches offers hope for addressing carbapenem resistance in the long term.

Year	Number of Carbapenem-Resistant Infections
2018	120
2019	135
2020	110
2021	95

Table 6. Presents the Incidence Of Carbapenem-Resistant Infections Over Time

The prevention and control of carbapenem resistance require a multifaceted approach that addresses the complex interplay of factors driving the emergence and spread of resistant organisms.

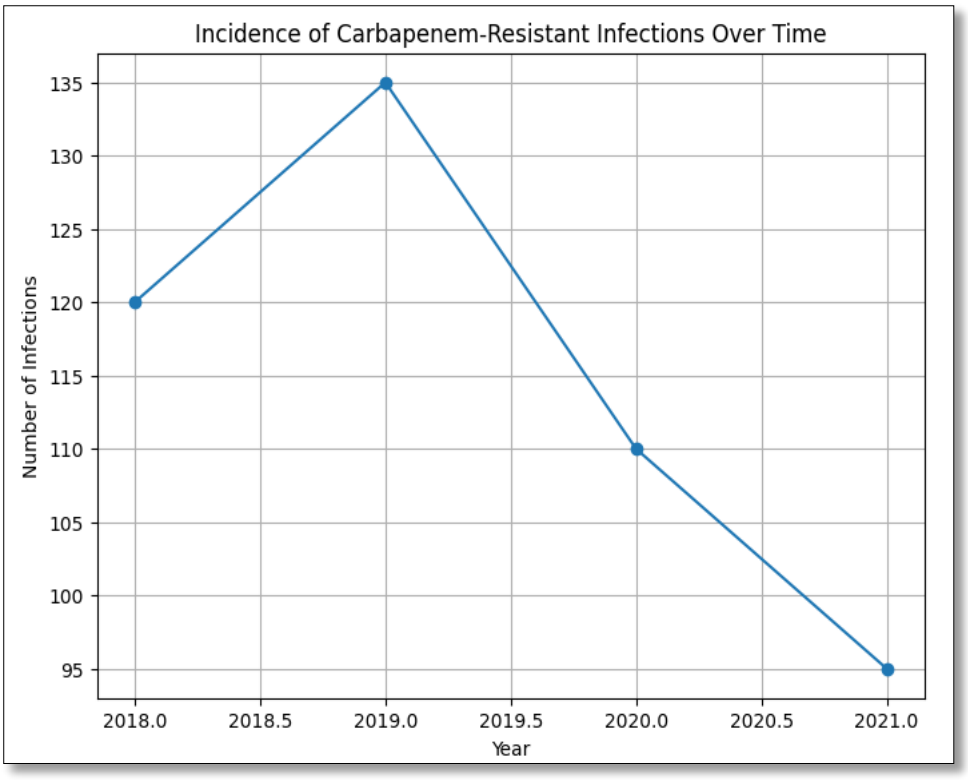

Figure 2. Graphical Representation of Incidence Of Carbapenem-Resistant Infections Over Time

While antibiotic stewardship programs have demonstrated success in reducing antibiotic resistance rates, sustained efforts are needed to ensure adherence to prescribing guidelines and promote antimicrobial stewardship practices across healthcare settings.

B. Impact of Antibiotic Stewardship Program on Carbapenem Resistance

Collaboration and communication among healthcare stakeholders enable the sharing of best practices and the implementation of coordinated efforts to combat carbapenem resistance on a global scale.

Intervention	Reduction in Carbapenem-Resistant Infections
Implementation of ASP	25%
ASP with prescriber education	35%
Enhanced ASP strategies	40%

Table 7 Impact of Antibiotic Stewardship Program on Carbapenem Resistance

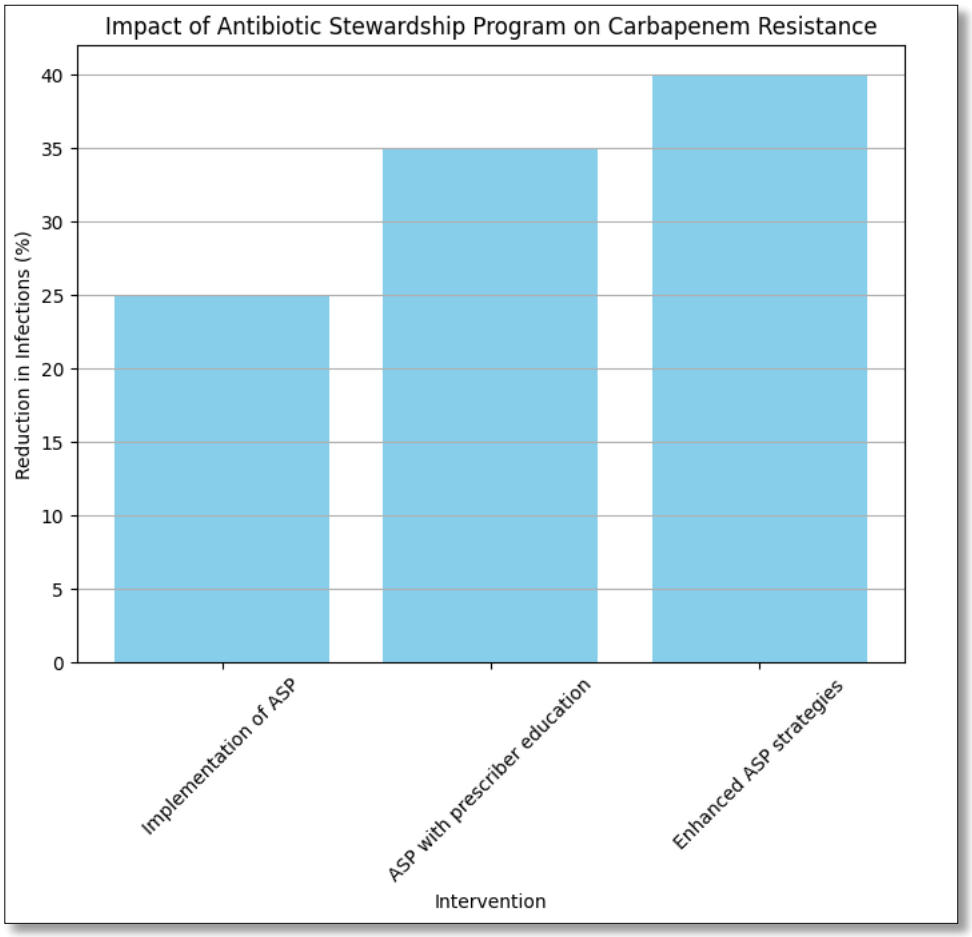

Figure 3. Graphical Representation of Analysis of Impact of Antibiotic Stewardship Program on Carbapenem Resistance

The implementation of infection prevention and control measures must be tailored to the unique challenges posed by carbapenem-resistant organisms, including their ability to persist in the environment and spread through healthcare networks.

C. Surveillance Data for Carbapenem-Resistant Organisms

Surveillance remains a cornerstone of efforts to monitor the epidemiology of carbapenem resistance and guide interventions. However, challenges such as underreporting and lack of standardized surveillance methods can hinder the effectiveness of surveillance programs.

Organism	Number of Isolates Identified	Percentage Resistant to Carbapenems
Klebsiella pneumoniae	50	60%
Acinetobacter baumannii	30	75%
Pseudomonas aeruginosa	20	40%

Table 8. Surveillance data for carbapenem-resistant organisms

It Requires investment in surveillance infrastructure and collaboration between healthcare facilities and public health agencies. Screening and decolonization strategies offer promise in reducing the burden of carbapenem-resistant colonization and preventing transmission within healthcare settings. However, the optimal implementation of these strategies requires careful consideration of resource allocation, patient populations, and infection control priorities.

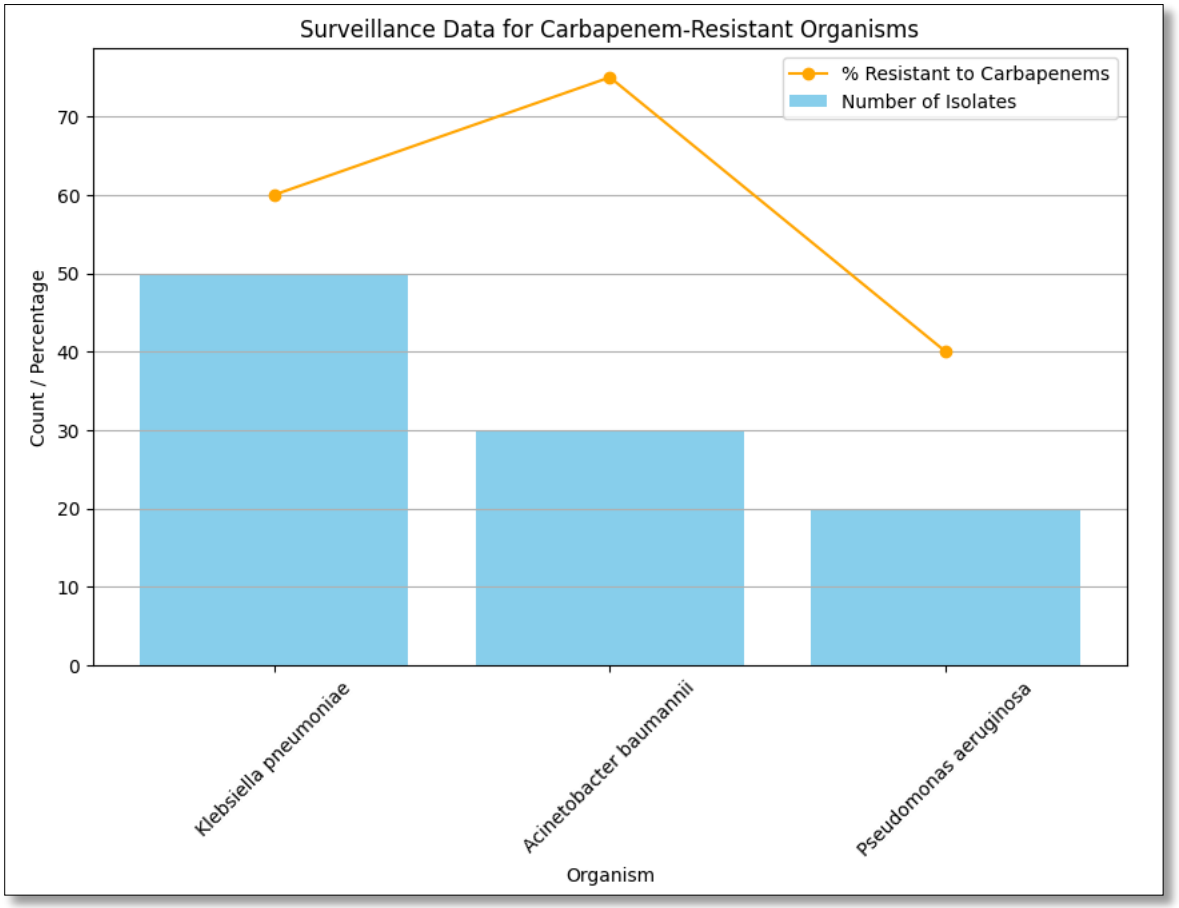

Figure 4. Graphical Representation of Carbapenem-Resistant Organisms Analysis over Surveillance Data

Investment in research and development of new antibiotics and alternative therapies is essential to address the evolving threat of carbapenem resistance. Novel approaches such as phage therapy and monoclonal antibodies hold potential as adjunctive therapies or alternatives to traditional antibiotics, offering new avenues for treatment. The prevention and control of carbapenem resistance require a coordinated and multifaceted approach that integrates antibiotic stewardship, infection prevention and control measures, surveillance, screening, and collaboration among healthcare stakeholders. By addressing these challenges comprehensively and innovatively, it is possible to mitigate the impact of carbapenem resistance and safeguard the effectiveness of this critical class of antibiotics for future generations.

VII. Conclusion

Carbapenem resistance represents a multifaceted and evolving challenge that threatens the effectiveness of one of the last lines of defense against bacterial infections. The emergence and spread of carbapenem-resistant bacteria pose significant clinical, economic, and public health implications, necessitating urgent action to prevent and control their spread. This research paper has elucidated the mechanisms, epidemiology, clinical implications, and economic burdens of carbapenem resistance, highlighting the complex interplay between bacterial pathogens, antibiotics, and healthcare systems. Carbapenem resistance arises through various mechanisms, including the production of carbapenemases, alterations in outer membrane porin channels, and upregulation of efflux pumps, underscoring the need for multifaceted approaches to combat resistance effectively. The epidemiology of carbapenem-resistant bacteria varies geographically and across different healthcare settings, reflecting differences in antibiotic usage patterns, infection control practices, and microbial ecology. Healthcare-associated infections serve as major reservoirs for carbapenem-resistant organisms, while community-acquired infections pose unique challenges due to their potential to spread beyond healthcare settings.Clinically, carbapenem resistance leads to treatment failures, increased morbidity, and mortality rates, particularly among vulnerable patient populations. The limited treatment options for carbapenem-resistant infections necessitate the use of alternative antibiotics, further driving up healthcare costs and straining healthcare resources. The economic burden of carbapenem resistance extends beyond direct healthcare costs to include indirect costs related to loss of productivity and antimicrobial stewardship initiatives. Investments in prevention and control measures are essential for mitigating the economic impact of carbapenem resistance and preserving the effectiveness of antibiotics for future generations. Prevention and control strategies for carbapenem resistance encompass antimicrobial stewardship, infection control measures, and surveillance systems aimed at reducing the spread of resistant bacteria and optimizing antibiotic use. Addressing the challenges of implementation, including resource constraints and global collaboration, is essential for the successful implementation of these strategies. Future directions in the field of carbapenem resistance prevention and control involve innovative approaches, such as the development of alternative antimicrobial agents, implementation of advanced diagnostic technologies, and integration of genomic surveillance systems. By embracing these innovations and fostering interdisciplinary collaboration, healthcare stakeholders can enhance their capacity to combat carbapenem resistance and safeguard public health.

References:

1. *Ogyu, A., Chan, O., Littmann, J., Pang, H.H., Lining, X., Liu, P., Matsunaga, N., Ohmagari, N., Fukuda, K., Wernli, D. (2020). National action to combat AMR: A One-Health approach to assess policy priorities in action plans. BMJ Glob. Health, 5, e002427. doi: 10.1136/bmjgh-2020-002427.*
2. *Mendelson, M., Matsoso, M.P. (2015). The World Health Organization Global Action Plan for antimicrobial resistance. S. Afr. Med. J., 105, 325. doi: 10.7196/SAMJ.9644.*
3. *Willemsen, A., Reid, S., Assefa, Y. (2022). A review of national action plans on antimicrobial resistance: Strengths and weaknesses. Antimicrob. Resist. Infect. Control, 11, 90. doi: 10.1186/s13756-022-01130-x.*
4. *McCarthy, M. (2017). Woman dies after infection with bacteria resistant to all antibiotics available in US. BMJ, 356, j254. doi: 10.1136/bmj.j254.*
5. *Mancuso, G., Midiri, A., Gerace, E., Biondo, C. (2021). Bacterial Antibiotic Resistance: The Most Critical Pathogens. Pathogens, 10, 1310. doi: 10.3390/pathogens10101310.*
6. *Biondo, C. (2022). New Insights into Bacterial Pathogenesis. Pathogens, 12, 38. doi: 10.3390/pathogens12010038.*
7. *Pérez-Galera, S., Bravo-Ferrer, J.M., Paniagua, M., Kostyanev, T., de Kraker, M.E., Feifel, J., Sojo-Dorado, J., Schotsman, J., Cantón, R., Daikos, G.L., et al. (2023). Risk factors for infections caused by carbapenem-resistant Enterobacterales: An international matched case-control-control study (EURECA). EClinicalMedicine, 57, 101871. doi: 10.1016/j.eclinm.2023.101871.*
8. *Biondo, C. (2023). Bacterial Antibiotic Resistance: The Most Critical Pathogens. Pathogens, 12, 116. doi: 10.3390/pathogens12010116.*
9. *Gao, Y., Shang, Q., Li, W., Guo, W., Stojadinovic, A., Mannion, C., Man, Y.-G., Chen, T. (2020). Antibiotics for cancer treatment: A double-edged sword. J. Cancer, 11, 5135–5149. doi: 10.7150/jca.47470.*
10. *Hutchings, M.I., Truman, A.W., Wilkinson, B. (2019). Antibiotics: Past, present and future. Curr. Opin. Microbiol., 51, 72–80. doi: 10.1016/j.mib.2019.10.008.*
11. *Scaife, C.L., Mone, M.C., Bowen, M.E., Swords, D.S., Zhang, C., Presson, A.P., Nelson, E.W. (2018). Perioperative antibiotics should be used for placement of implanted central venous ports: A propensity analysis evaluating risk. Am. J. Surg., 216, 1135–1143. doi: 10.1016/j.amjsurg.2018.09.022.*
12. *Bedenić, B., Plečko, V., Sardelić, S., Uzunović, S., & Godič Torkar, K. (2014). Carbapenemases in gram-negative bacteria: Laboratory detection and clinical significance. BioMed Research International, 2014(22).*
13. *Walsh, C. (2000). Molecular mechanisms that confer antibacterial drug resistance. Nature, 406, 775.*
14. *Tang, Y., Li, G., Liang, W., Shen, P., Zhang, Y., & Jiang, X. (2017). Translocation of carbapenemase gene blaKPC-2 both internal and external to transposons occurs via novel structures of Tn1721 and exhibits distinct movement patterns. Antimicrobial Agents and Chemotherapy, 61, 1-10.*
15. *Jeon, M-H., Choi, S-H., Kwak, YG., et al. (2008). Risk factors for the acquisition of carbapenem-resistant Escherichia coli among hospitalized patients. Diagnostic Microbiology and Infectious Disease, 62, 402-406.*
16. *Alekshun, M.N., & Levy, S.B. (2007). Molecular mechanisms of antibacterial multidrug resistance. Cell, 128, 1037-1050.*
17. *Muniesa, M., Garcia, A., Miro, E., et al. (2004). Bacteriophages and diffusion of β-lactamase genes. Emerging Infectious Diseases, 10, 1134.*
18. *Hidron, A.I., Edwards, J.R., Patel, J., et al. (2008). Antimicrobial-resistant pathogens associated with healthcare-associated infections: Annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infection Control & Hospital Epidemiology, 29, 996-1011.*
19. *Guh, A.Y., Limbago, B.M., & Kallen, A.J. (2014). Epidemiology and prevention of carbapenem-resistant Enterobacteriaceae in the United States. Expert Review of Anti-infective Therapy, 12, 565-580.*
20. *Lutgring, J.D., & Limbago, B.M. (2016). The problem of carbapenemase-producing-carbapenem-resistant-Enterobacteriaceae detection. Journal of Clinical Microbiology, 54, 529-534.*
21. *Logan, L.K. (2012). Carbapenem-resistant enterobacteriaceae: An emerging problem in children. Clinical Infectious Diseases, 55, 852-859.*
22. *Wanger, A., Chavez, V., Huang, R., Wahed, A., Actor, J., & Dasgupta, A. (2017). Antibiotics, antimicrobial resistance, antibiotic susceptibility testing, and therapeutic drug monitoring for selected drugs. In Microbiology and Molecular Diagnosis in Pathology (pp. 119-153). DOI: 10.1016/B978-0-12-805351-5.00007-7.*