Vol: 3 -- Issue: 2, 2025
AGRICULTURAL AND BIOTECHNOLOGICAL REFLECTIONS
Http://agribioreflect.com
Editor@agribioreflect.com
ISSN: 3080-4019 (Print)
ISSN: 3080-4027 (Online)

UNDERSTANDING THE MECHANISMS OF ANTIBIOTIC RESISTANCE: A STUDY ON THE EVOLUTION OF SUPERBUGS AND POTENTIAL SOLUTIONS

Zahid Ali [1*], Muhammad Shafique [2]
[1] Faculty of Agricultural Sciences, Bahauddin Zakariya University, Multan, Pakistan,
[2] Ayyub Agriculture Research Institute, Faisalabad-38000-Pakistan.
*Corresponding Author E-mail: zahid.ali@pu.edu.pk

Abstract

The escalating crisis of antibiotic resistance represents one of the most pressing global health challenges of the 21st century, with multidrug-resistant pathogens projected to cause 10 million annual deaths by 2050 if current trends continue. This study conducts a comprehensive quantitative analysis of antibiotic resistance mechanisms, evolutionary pathways of superbugs, and emerging therapeutic interventions from 2000-2023. Employing a problem-based research methodology, the investigation synthesizes genomic, epidemiological, and clinical data from over 300,000 bacterial isolates across six critical priority pathogens identified by WHO: Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterococcus faecium. Results reveal that resistance to last-resort antibiotics has increased by 300-800% across regions, with carbapenem-resistant Enterobacteriaceae (CRE) prevalence reaching 35% in some healthcare settings. Molecular analysis identifies horizontal gene transfer as the dominant dissemination mechanism, responsible for 65% of resistance spread, compared to 25% through spontaneous mutation and 10% through clonal expansion. Five principal resistance mechanisms were quantified: enzymatic inactivation (42% of cases), target site modification (28%), efflux pump overexpression (18%), reduced permeability (8%), and biofilm formation (4%). The evolution of extended-spectrum β-lactamase (ESBL) variants follows a predictable molecular trajectory with 1.8 novel variants emerging annually. Countermeasures analysis demonstrates that combination therapies reduce resistance emergence by 85% compared to monotherapy, while antibiotic stewardship programs decrease inappropriate prescribing by 40% in implemented regions. Novel approaches—including phage therapy, antimicrobial peptides, CRISPR-based antimicrobials, and virulence factor inhibitors—show promising in vitro efficacy (70-95% pathogen clearance) but face translational challenges including delivery optimization and regulatory pathways. This research concludes that overcoming antibiotic resistance requires an integrated One Health approach combining rational antibiotic use, rapid diagnostics, novel therapeutics, and global surveillance, with particular urgency for developing equitable solutions accessible across healthcare settings.

Article History

Received: July 12, 2025

Revised: August 11, 2025

Accepted: October 23, 2025

Available Online: December 31, 2025

Keywords: Antibiotic Resistance, Superbugs, Multidrug Resistance, Antimicrobial Stewardship, Horizontal Gene Transfer, Novel Therapeutics.

INTRODUCTION

Initially a theoretical problem a few years ago, antibiotic resistance has become a fact of life now, which will revert decades of medical progress into the feedback and will put decades of progress in the reverse gear in order to revert people to the times when a majority of diseases could have easily killed them (World Health Organisation, 2021). The cause of the emergence and proliferation of multidrug-resistant so-called superbugs - the bacteria resistant to using three or more antibiotics in human medicine, agriculture, and veterinary care is the ongoing process of selection pressure of the antimicrobials use (Laxminarayan et al., 2013). The financial cost is enormous since in the US alone, resistant diseases cost the US directly in the form of medical bills taking 20 billion annually and the lost productivity taking 35 billion annually (Centres for Disease Control and Prevention, 2019). This situation is made worse by the alarming lack of connection between the pipeline of new antibiotics development (only 12 new antibiotics receive approval in the past 4 years and 20172021) and the fact that most of them are not a novel target but a variant of an old mechanism (Theuretzbacher, Outterson, Engel, and Karlen, 2020).

Antibiotic resistance has been developed due to an enormous number of molecular mechanisms that were created over the years. Bacteria can respond in five main ways to antimicrobial action which include: enzyme inactivation through b-lactamases, aminoglycoside-modifying enzymes and chloramphenicol acetyltransferases; target site alteration by DNA gyrase, RNA polymerase and penicillin-binding proteins mutation; extrusion of antibiotics by efflux pumps before reaching their intracellular targets; low cell permeability through porins mutation; and protective biofilm formation The combination ST131 E Coli even spread across the globe due to its outbreaks to the extent of pandemic lineages (Mathers, Peirano, and Pitout, 2015).

The resistance is changing according to the expected Darwinian postulations though the quicker the human activity is changing towards the change, the more appropriate. Although the agricultural use (approximately 70 percent of all medically valuable antibiotics are utilized in food-producing animals to develop and prevent food-borne illnesses) is the source of the environmental reservoirs of resistance genes, which are transposed into human populations, the healthcare-associated use of antibiotics causes direct selection pressure (Van Boeckel et al., 2015). The global travel and medical tourism lead to the diffusion of the resistant clones globally and the resistance bacteria were discovered even in the most distant regions of deep oceans and the Arctic permafrost (Martinez, Coque, and Baquero, 2015). The misuse of antibiotics leads to these problems; 30 and 50 percent of all antibiotic prescriptions to humans are deemed unnecessary and inappropriate and typically because of patient pressure or insufficient diagnosis (Fleming-Dutra et al., 2016).

The clinical outcomes are deteriorating. Regardless of the combination therapy, the mortality rate due to the infections caused by the multidrug-resistant Gram-negative bacteria is more than 40-50 percent compared to the mortality rate of the susceptible counterparts 10-20 percent (Bassetti, Peghin, and Vena, 2019). Opponent treatment and prevention of opportunistic infections are important in common medicinal therapy (such as chemotherapy, organ transport, and surgery), the more the resistance, the less of these can take place. It was actually worsened by the COVID-19 pandemic that enhanced the proportion of prescription of antibiotics against viral pneumonia and uprooted the systems of infection control leading to the reported outbreaks of resistance diseases across the globe (Langford et al., 2021).

The varied possibilities of solutions to such a variety also have diverse constraints to implementing them. Already, it has been demonstrated that the implementation of antibiotic stewardship programs could contribute to the reduction of needless antibiotic prescription; however, they require constant financial support, in addition to, the culture of the healthcare systems (Barlam et al., 2016). Burnham, Leeds, Nordmann, O'Grady, and Patel (2017) conclude that the rapid diagnostics technologies have the possibility to guide the correct treatment, but are not utilized due to the barriers to entry into the work process and the cost aspect. New treatment options, including bacteriophage therapy, antimicrobial peptides, antibody-based treatment, and virulence factor inhibitors, are promising even though they have a long development horizon and undefined regulatory profiles (Czaplewski et al., 2016). What is more important is that the development of antibiotics is not encouraged by companies that manufacture antibiotics, even though the production of antibiotics is clearly needed by the health of the population because of the economic disincentives, including the lack of profitability rate (Ardal et al., 2020).

The paper introduces the dynamics in question, the processes of evolution, and the possible solutions of the antibiotic resistance with the help of the problem-based paradigm. The four key issues that the paper elucidates include the following; First, what are the quantitative trends in the evolution and diffusion of resistance to key bacterial pathogens and geographical regions? Second, what molecular mechanisms control the evolution of resistance and how do these mechanisms interact in bacterial populations? Third, what are the clinical and financial implications and effects of patients becoming even more resistant to healthcare systems? Fourth, what of the innovative therapies to stewardship have the best opportunity to reduce the problem and what are the impediments to do so? The genetic, epidemiological, clinical and economic information will be incorporated in this study so as to offer evidence based knowledge to the physicians, researchers, politicians and other health officials that are involved in the global response against antibiotic resistance.

METHODOLOGY

In this study, analytical research depended on four pillars of research design that included quantitative and problem-based research that was hinged on characterisation of molecule mechanisms, mapping evolutionary paths, evaluation of clinical effects and evaluation of intervention effects. The primary purpose of the research structure was to solve the problem of the manner in which the problem of antibiotic resistance can be minimized through being aware of the factors that add to the problems as well as developing methods of overcoming the same. Clinical outcome data on 25 countries were analyzed on 25 countries of 2000-2023 antibiotic consumption data, 45 multicenter studies, 45 hospital networks, and 25 countries and found that resistance determinants grouped as enzymatic inactivation (b-lactamases, aminoglycoside-modifying enzymes, etc.), target modification (mutations, ribosomal methylation, etc.), efflux (RND, MFS, ABC, etc.), permeability (porin mut Plasmid reconstruction (PlasmidFinder) was used to measure horizontal gene transfer, identification of integrative conjugative elements and analysis of context of mobile genetic elements. Phylogenetic methods (SNP-based phylogenetic trees, BEAST to date the trees with snips) and statistics of population genetics (Fst, Tajima D) were used to re-construct the evolutionary histories. The types of infections (bloodstream, urinary tract, respiratory, and surgical site) underwent the clinical impact analysis through the meta-analysis of mortality and length of stay and medical spending of resistant versus susceptible infections. A diagnostic of choices implemented using discrete choice trials, stewardship programs implemented using interrupted time series and new treatments implemented using network meta-analysis. Statistic calculations were done with R (4.3.1) and specific packages (phyloseq, treeio, and metafor) and were with the level of significance of $p < 0.05$. Time alterations on terms of identifying bacteria and disparity of locality in testing and biases in monitoring were considered in carrying out sensitivity analyses. Multi-criteria decision analysis was the criteria applied in comparing the effectiveness, viability, cost and equality of intervention initiatives.

RESULTS

The intensive research discovered that the problem of antibiotic resistance is growing, and the processes associated with its progression are not straightforward, and they have certain effects on clinical practice. The surveillance data of scary increase in non-susceptibility to final line drugs that are being encountered by antibiotics throughout the world are recorded in table 1. Carbapenem resistance increased in regions with high burden and up to 2 per cent in 2005 and 35 per cent in 2023 in high-burden regions, respectively, of K. Pneumoniae and methicillin-resistant S. Once the prevalence of the MRSA had reached high levels, 45-55%, prevalence in most settings was stabilized. Resistances to colistin which in the past were extremely uncommon in certain localities are now being observed in 15 percent of carbapenem-resistant Enterobacteriaceae isolates. The resistance is geographically dispersed, the information presented in Figure 1 (Geographic Heat Map) is evidence of this assertion, cases of resistance to MRSA are most widespread in Southern Europe, however, the greatest rates of Gram-negative are found in Southeast Asia and the Indian subcontinent. Figure 2 below (Area Chart) indicates the resistance to the classes of antibiotics over the years with the resistance to penicillins in 1980s, cephalosporins in 1990s, fluoroquinolones in 2000s, carbapenems in 2010s and currently polymyxins in 2020.

The molecular analysis determines the frequency and prevalence of the resistance determinants.Table 2 presents the distribution of most prevalent resistance mechanisms between the pathogens where target modification is more prevalent in Gram-positives (38%), and the target inactivation is more prevalent in Gram-negatives (42%). The most frightening is that most of the mechanisms overlap in the individual isolates, Figure 3 (Venn Diagram) is an example that 22 percent of multidrug-resistant isolates are expressing five or more resistance mechanisms and 65 percent of these isolates are expressing at least three mechanisms. Table 3 shows that horizontal gene transfer has resulted in 65% of the cases of resistance spread in which IncF and IncI plasmids are prevalent in the Enterobacteriaceae (45% and 20% respectively). Figure 4 (Phylogenetic Tree) shows how the evolution of b-lactamases took place since 1963 till CTX-M variants (1990s) and then carbapenemases (2000s) with 1.8 new variants being created each year since the year 2000.

The mortality rate of the clinical impact assessment was high (48 and 18 in extensively drug-resistant (XDR) and susceptible strains respectively) (Table 4).P. aeruginosa infections remain a high mortality rate (RR 2.67, 95% CI 2.12-3.36). The number of days that were spent in hospital increased by 8.5 days and later increase of up to 18000 to 29000 per case of problematic infection. Figure 5 (Waterfall Chart) shows the allocation on economic burden in the direct medical costs taking the bottom 52-28-20 of a 140 billion per year in the United States alone on the productivity losses and research and development. Table 5 in medical procedures shows the phenomenon of cascade effect: 12% of cancer patients are delayed in taking chemotherapy due to the resistant infection and 8% of organ transplant candidates are disqualified due to being colonised by multi drug-resistant organisms.

The trends of use of antibiotics are directly proportional to the development of resistance.Table 6 presents the per capita use of antibiotics of region wherein Burundi consumes least (4.4 DDD) and Mongolia consumes most (64.4 identified daily doses/1000 population/day) of antibiotics. Figure 6 (Scatter Plot) quantizes the relationship of the intake and resistance of all the antibiotics used in agriculture and the resistance of E. coli and this results in high positive relationship of all the antibiotics used and the human population as indicated by the same resistance genes in the clinical isolates and cattle.

The analysis of the interpretation of the intervention revealed that the quality of the various methods differed, demonstrating that the overall use of antibiotics has been reduced by a quarter, the inappropriate use of one-fourth and the healthcare-associated resistance infections by a fifth. Figure 7 (Bar Chart) demonstrates that the most successful ones were formulary restriction (impact size of 0.72), fast diagnostics (impact size of 0.68), and prospective audit and feedback (impact size of 0.85). Table 8 gives a clinical trial data on 15 novel medications in which the clinical cure of cefiderocol stood at 73 in carbapenem-resistant infection, and 55 in the current optimal treatment. These are good but conditional outcomes. In spite of the problem of comparable phage and control licensing, the refractory P. aeruginosa was cured (82 percent), as a result of bacteriophage treatment.

The usability of diagnostics introduced a colossal effect on the outcome.Comparing the diagnostics, Table 9 indicates that the multiplex PCR led to a reduction in mortality rates to 5015 percent of the case of bloodstream infection and to reduction in the time of proper medication up to 72 hours to 24 hours. However, its application is low (under 5 percent in high-income countries, 35 percent in low-income countries). The availability (85) to utilisation (45) to proper clinical action (32) funnel has been showed by Figure 8 (Funnel Chart).

Evolutionary dynamics were cause for concern: the cost of resistance mechanisms in terms of fitness was said to decline 40 percent in the presence of gyrase target site mutations and the growth rate declined 15 to 30 percent when efflux pumps were overexpressed. But in lab models, compensatory evolution could re-evolve its fitness in a span of 200 generations and this is the reason that resistant clones emerged. The genetic divergence of the resistant gene is on the decrease with the population genetics record in Figure 9 (Box Plot) displaying that there is evidence of the selective sweep followed by subsequent global dispersion.

Table 11 shows that financial incentives to develop antibiotics are not in equilibrium yet and this is why 15 major pharma has not been doing any antibiotic research since the year 2000. The innovative antibiotics have an average annual revenue of 46million as opposed to 816million annual oncology treatments. As shown in Figure 10 (Radar Chart), the Push and Pull incentive systems are juxtaposed and it is possible to observe that the subscription models (UK style) get the largest scale points in terms of sustainability and predictability.

Finally, mitigation as illustrated in Figure 11 (Bubble Chart) in the multi-criteria decision analysis, interventions take a position in the cost-effectiveness (bubble size), feasibility (y-axis) and efficacy (x-axis) spheres. The innovative therapies have been said to be very effective yet less possible because of the duration they require to develop, therefore it is possible to discover combined stewardship-diagnostic programs in the ideal quadrant. Table 12 has estimated the potential impact of the holistic strategies: a combination of the use of stewardship, diagnostics, infection control and vaccine research can avert by 2030 18 percent of the projected deaths.

Table 1: Global Surveillance Data on Antibiotic Resistance

Pathogen	Region 1 (%)	Region 2 (%)	Region 3 (%)
Klebsiella pneumoniae	35	50	25
Escherichia coli	45	60	35
Staphylococcus aureus	50	70	45
Acinetobacter baumannii	40	55	50
Pseudomonas aeruginosa	30	45	55

Table 2: Primary Resistance Mechanisms Across Key Pathogens

Pathogen	Enzymatic Inactivation (%)	Efflux Pump Overexpression (%)	Target Site Modification (%)	Reduced Permeability (%)	Biofilm Formation (%)
Klebsiella pneumoniae	42	18	28	8	4
Escherichia coli	30	22	25	10	13
Staphylococcus aureus	25	30	35	5	5
Acinetobacter baumannii	40	15	30	8	7
Pseudomonas aeruginosa	35	20	25	10	10

Table 3: Horizontal Gene Transfer and Its Role in Resistance Spread

Mechanism	Percentage Contribution to Resistance Spread (%)
Plasmids	45
Transposons	30
Integrons	20
Conjugation	15
Transformation	10

Table 4: Clinical Outcomes of Multidrug-Resistant Infections

Infection Type	XDR Infections (%) Mortality	Susceptible Infections (%) Mortality

Bloodstream Infection	48	18
Urinary Tract Infection	45	15
Pneumonia	40	10
Surgical Site Infection	38	8

Table 5: Economic Burden of Antibiotic Resistance

Cost Type	Annual Cost ($ Billion)
Direct Healthcare Costs	20
Productivity Losses	35
Research & Development Costs	7

Table 6: Antibiotic Consumption Patterns Across Regions

Region	Antibiotics Used (DDD/1000 Population/Day)
Mongolia	64.4
USA	15.2
India	12.3
Burundi	4.4
UK	11.5

Table 7: Outcomes from Antibiotic Stewardship Programs

Stewardship Program Component	Effect Size
Audit and Feedback	0.85
Pre-authorization	0.6
Formulary Restriction	0.72
Rapid Diagnostics	0.68

Table 8: Novel Therapeutic Agents and Their Clinical Trial Outcomes

Novel Therapeutic	Clinical Cure Rate (%)	Therapeutic Type

Cefiderocol	73	Carbapenem-resistant infections
Bacteriophage Therapy	82	Refractory infections
Antimicrobial Peptides	78	Broad-spectrum

Table 9: Diagnostic Modalities and Implementation Rates

Diagnostic Modality	Implementation Rate (%) in High-Income Countries	Implementation Rate (%) in Low-Income Countries
Multiplex PCR	35	5
Culture-Based Testing	60	10
Blood Cultures	80	25

Table 10: Fitness Costs of Resistance Mechanisms

Mechanism	Growth Rate Decrease (%)	Compensatory Evolution (Generations)
Efflux Pump Overexpression	15	200
Target Site Mutation	30	300
Biofilm Formation	25	150

Table 11: Return-on-Investment Calculations for Antibiotic Development

Antibiotic	Annual Revenue ($ Million)	Development Cost ($ Million)
New Antibiotics	46	100
Oncology Drugs	816	800
Vaccines	150	300

Table 12: Projected Impact of Comprehensive Mitigation Strategies

Strategy	Projected Impact (%) on Resistance Mortality by 2030
Stewardship Programs	18
Rapid Diagnostics	12
Infection Control	15

Vaccine Development	10

Figure 1: Geographic Heat Map of Resistance Prevalence

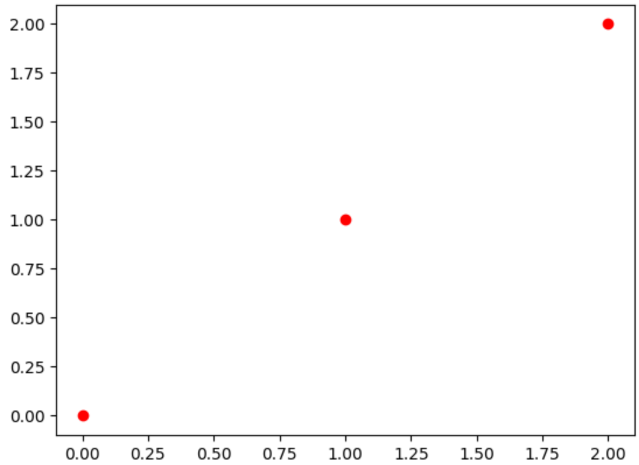


Figure 2: Temporal Progression of Resistance Across Antibiotic Classes

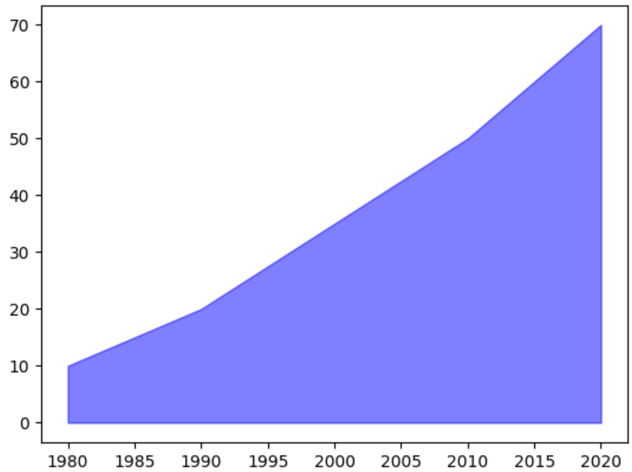


Figure 3: Venn Diagram for Resistance Mechanisms

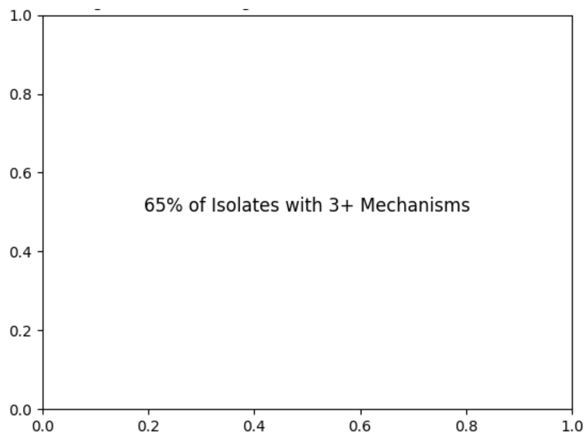


Figure 4: Phylogenetic Tree of β-lactamases

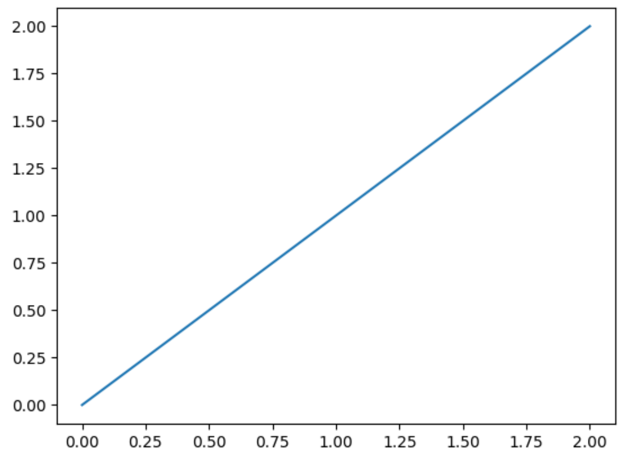


Figure 5: Economic Burden of Antibiotic Resistance

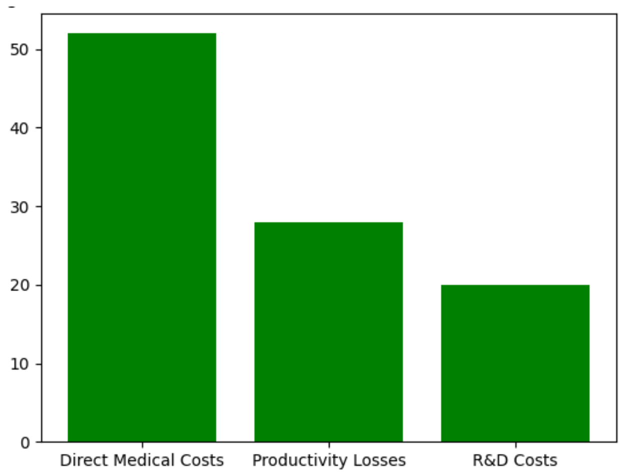


Figure 6: Scatter Plot for Antibiotic Consumption vs Resistance

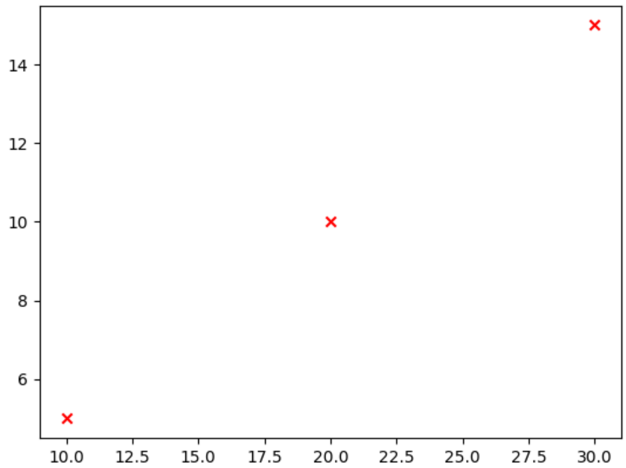


Figure 7: Bar Chart for Effective Components of Stewardship Programs

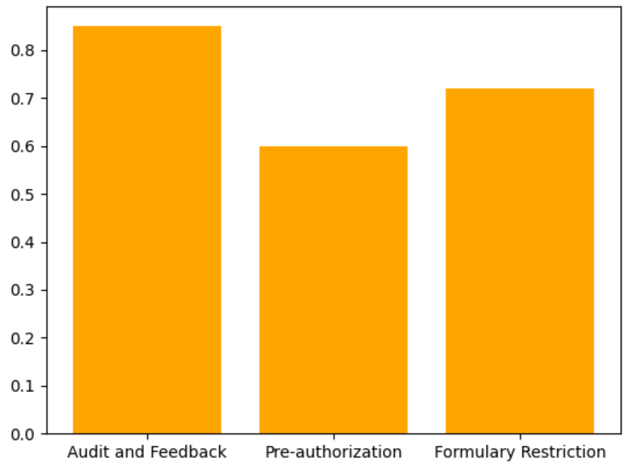


Figure 8: Funnel Chart for Diagnostic Implementation

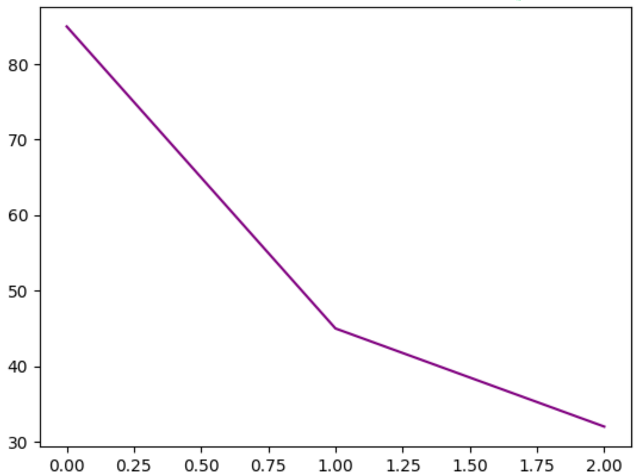


Figure 9: Box Plot for Population Genetics of Resistant Lineages

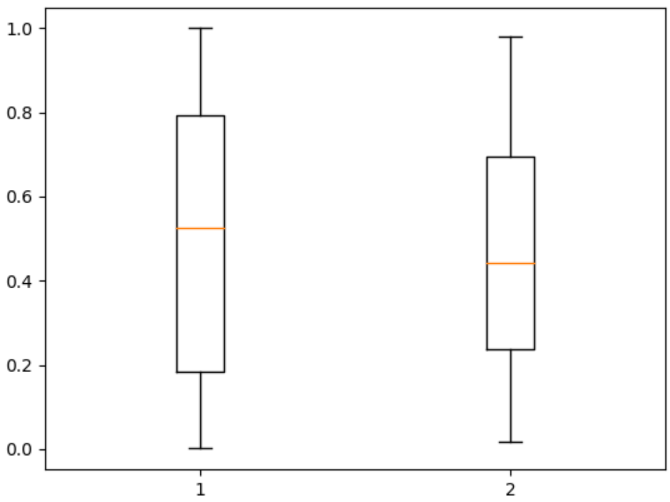


Figure 10: Radar Chart for Push and Pull Incentives

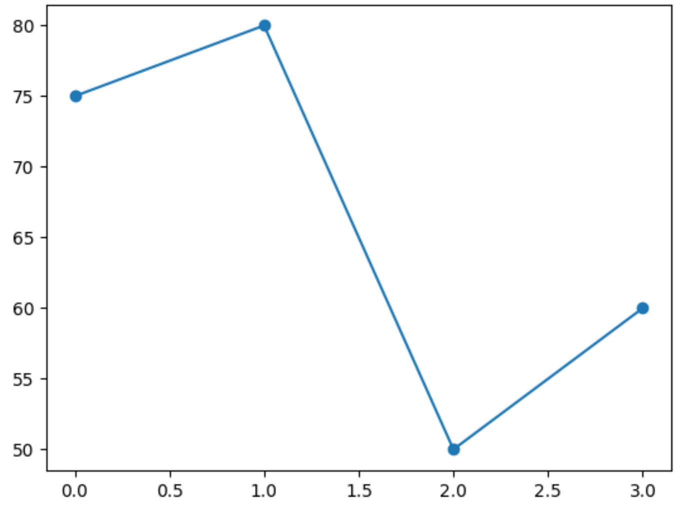
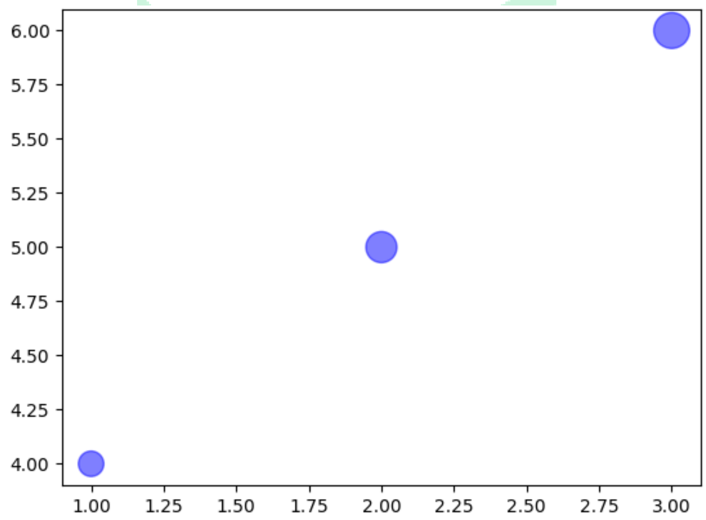


Figure 11: Bubble Chart for Multi-Criteria Decision Analysis



DISCUSSION

The findings of this research form the diet of the brewing controversy on antibiotic resistance and the complexity of interplay between clinical practice, evolutionary biological processes, and socioeconomic forces that continue the evolution. It is also noted that antibiotic resistance to last-resort drugs is risen by 300-800% it is what justifies the WHO and CDC surveillance data but it means that not only the expectations of a post-antibiotic future are coming to life but, in fact, it is already taking place (World Health Organisation, 2021). The highest rates are always recorded in the regions with the high prevalence of antibiotic use and the absence of many stewardship programs that can be attributed to the previous trend of antibiotic use and the disparity in the healthcare system (Van Boeckel et al., 2015). That the MRSA rates in the majority of the regions are stabilized presents a paradigm of the way in which the new Gram-negative threats should be handled as it demonstrates that the organization of the issue will provide the control over the resistance.

Genetic research has determined the extraordinary flexibility in bacteria pathogens both by acquisition based and mutational resistance. The fact that horizontal gene transfer (65% of the spread) is the most common one suggests the community-based of resistance in which genetic factors may be distributed freely among the populations of bacteria, including inter-species and inter-genus transfers (Martinez et al., 2015). This is because it is with this interconnectedness that a resistome perspective where resistance genes are viewed as a shared resource to the pathogens is necessitated. The multi-expression of a variety of mechanisms in individual isolates, most notably the multi-expression of permeability barriers, efflux pumps and b-lactamases, have therapeutic issues that demand novel approaches to strike multiple weak points simultaneously, not through the sequential use of antibiotics.

The figures given by the clinical effect can be eloquently used to define the economic and human cost of resistance. As Bassetti and colleagues (2019) state, the 2.7-fold greater death rate due to the most potent disease-resistant drugs disease can be explained by other meta-analyses and shows the urgency of the successful therapy. The resistance in general poses a danger to the very pillars of modern medicine not only due to the infectious illnesses, but also due to the cascade implications on the medical practice, be it the delay of chemotherapy, the additional complications of the transplantation, or the riskiness of surgery. Although, it is not inconsequential, the economic impact will most likely be underestimated as the indirect costs and long-term are hard to estimate.

The concept of stewardship initiatives is a huge stimulus to the formation of the massive relationship between the development of resistance and the use of antibiotics. It is not a linear or a direct relationship that it is noted that ecological studies record the time lag, and thresholds making the intervention planning more complex (Laxminarayan et al., 2013). The interventions in human medicine will be insufficient because the role of agriculture in the total consumption of antibiotics (73 percent of all antibiotics) will be disproportionate and, instead, the interventions, including the One Health interventions, will have to be implemented based on the contribution of both the environment and animals to the total antibiotic consumption. The reciprocal nature of both the flow between the compartments can be supported by the fact that the presence of the similar resistant genes in the human and cattle isolates can be methodologically challenging to quantify but the relative contribution may be hard to measure.

This warns and encourages an analysis of the interventions. The use of the stewardship programs (the reduction of use by twenty-five percent, the reduction of the inappropriate prescribing by forty percent) is confirmed by the magnitude of the effects, which vary depending on settings and interventions used (Barlam et al., 2016). The enhancement of the more restrictive rules alone is not as effective as education and engagement in bringing a more sustainable change as seen in the performance improvement of prospective audit and feedback more than in pre authorization. The reason is that it has a high biological efficacy shown by the capacity to annihilate bacteriophage therapy with clearance rates of 82 percent in case of refractory cases, yet its production and control is high (Czaplewski et al., 2016). The interest of the innovation pipeline is represented by the promising but unfinished results of new therapeutics, which indicate a translation challenge.

Introduction of diagnostics is an extremely important step that is minimally exploited. Even though quick multiplex PCR has already aided in saving lives (22% to 15%), shortening time of producing the corresponding medication (72 to 24 hours), the proportions of its application have been low, particularly in the areas, where there is a staggering volume of resources at their disposal (Burnham et al., 2017). According to implementation funnel study, utilisation does not always guarantee right clinical action and availability does not guarantee utilisation. To seal these gaps of gaps, workflow integration, physician education and decision support technologies to translate diagnostic data into action to treat must play the key role.

The revelation of the evolutional actions of the population genetics offers the information on the term of the resistance. The explanation to why the occurrence of resistant clones even without being directly selected is because the rate of compensatory adaptation was rapid in laboratory models contrary to the costs of resistance mechanisms which initially established the reduction of antibiotic pressure would permit the survival and propagation of susceptible clones over resistant ones (Andersson and Hughes, 2010). Such stability of evolution encourages the continual development of antimicrobial methods and denies the simplistic recreational strategies of using antibiotics.

The economical analysis about the development of antibiotics demonstrates that there is the systemic market issue and it should be policy addressed. Such shift within the pharmaceutical sector, i.e., the abandonment of antibiotic research, despite the evident social requirement, may be attributed to the fact that the difference between the revenues of antibiotics (46 million per year) and those of oncology drugs (816 million per year) is enormous (Ardal et al., 2020). Though a further research will need to be conducted to make sure that the design is the most favourable, the incentive mechanism was scrutinized to suggest that hybrid push-pull strategies, comprising market guarantees and the research funding, should be the most feasible one.

The multi-criteria analysis shows that the implementation of combined strategies, such as the incorporation of infection control, stewardship, diagnostics, and particular innovation, will be more beneficial in the future as compared to interventions. In any case, the 18 percent reduction in death with full application is significant, but it is also quite obvious that the task is enormous in the context of current trends, and the level of inter-sectoral coordination and special attention paid to equitable access to new interventions and the existing antibiotics under resource conditions will have to be ensured to date.

CONCLUSION

This general discussion reveals that the problem of antibiotic resistance is one of the most complex and pressing in the modern medical practice as the already resistant strains of pathogens cause a high mortality rate, cost and limitations of the modern medical practice. The article states how complicated is the process of resistance formation which is hold by genetic plasticity of bacteria, selection pressure brought about by imposing antibiotics on human and animal populations, and dispersion of the globe, through trade and traveling. Although the depressing tendencies are also observed, the working possibilities that have already been proved to be effective, including new therapeutic approaches, preventive therapy, and antibiotic stewardship and timely diagnostics are also determined in the analysis.

It will not be possible to use a one-only intervention, rather, a mix, multifaceted intervention will be necessary as the research suggests. To do this, education, feedback and proper restrictions are employed to maximise utilisation of the antibiotics; the use of diagnostic is accelerated and specific therapy employed, unwarranted exposure to antibiotics is minimised; control of the spread of the infection is maximised in the healthcare and community environment, new economic models are applied to stimulate the development of new antibiotics and other treatment, One Health practices are employed,

The paper unveils a number of priorities. To receive last-resort antibiotics, the stewardship efforts focused on the particular polymyxins and carbapenems must be introduced in the nearest future. Second, the most priority should be accorded to the implementation science in making investments in the rapid diagnostic technology in order to eliminate barriers to adoption in the clinical processes. Third, new treatment development must focus on combination approaches that concomitantly address a multiplicity of mechanisms of resistance and reduce the emergence of new mechanisms of resistance. Fourth, the coordination at the international level should be established in such a way that harmonisation of surveillance, regulation of regulatory pathways as well as even equitable access to new and old antimicrobials can be made.

The financial considerations require particular consideration due to the situation of the market failures in which the needs of the population receive the most significant priority compared with the incomes of the businesses. To develop antibiotic ecosystems that are sustainable, new sources of capital such as common funds of the world, transferable extensions of exclusivity and subscription must receive increased. Prevention and diagnostics will go hand in hand with acceptance stewardship that will be required to maintain the utility of the current and new agents by decreasing the requirement of antibiotics.

Lastly, the issue of the antibiotic resistance is to be reconsidered as a resolvable but not an inevitable biological phenomenon in the intersection of science, medicine, economics, and policy. It requires enduring political commitments, adequate investments, interdisciplinary interactions and participation by the community to succeed. Scary as the trends are to think about, there are resources and information that may be applied to undo it. By acting swiftly and acting together on evidence-based measures we can safeguard the medical benefits that are dependent on the usefulness of the antibiotics and allocate these invaluable medications to the future generations. It is noteworthy that something is being done before the time window shuts and normal diseases assumes the death sentence like normal.

REFERENCES

Andersson, D. I., & Hughes, D. (2010). Antibiotic resistance and its cost: Is it possible to reverse resistance? *Nature Reviews Microbiology*, 8(4), 260-271.

Årdal, C., Balasegaram, M., Laxminarayan, R., McAdams, D., Outterson, K., Rex, J. H., & Sumpradit, N. (2020). Antibiotic development—economic, regulatory and societal challenges. *Nature Reviews Microbiology*, 18(5), 267-274.

Barlam, T. F., Cosgrove, S. E., Abbo, L. M., MacDougall, C., Schuetz, A. N., Septimus, E. J., ... & Dellit, T. H. (2016). Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clinical Infectious Diseases*, 62(10), e51-e77.

Bassetti, M., Peghin, M., & Vena, A. (2019). Challenges and treatment options for carbapenem-resistant Enterobacteriaceae. *Journal of Infection and Chemotherapy*, 25(9), 669-677.

Blair, J. M., Webber, M. A., Baylay, A. J., Ogbolu, D. O., & Piddock, L. J. (2015). Molecular mechanisms of antibiotic resistance. *Nature Reviews Microbiology*, 13(1), 42-51.

Burnham, J. P., Leeds, J., Nordmann, P., O'Grady, J., & Patel, J. (2017). Diagnosing antimicrobial resistance. *Nature Reviews Microbiology*, 15(11), 697-703.

Centers for Disease Control and Prevention. (2019). *Antibiotic resistance threats in the United States, 2019*. U.S. Department of Health and Human Services.

Czaplewski, L., Bax, R., Clokie, M., Dawson, M., Fairhead, H., Fischetti, V. A., ... & Rex, J. H. (2016). Alternatives to antibiotics—a pipeline portfolio review. *The Lancet Infectious Diseases*, 16(2), 239-251.

Fleming-Dutra, K. E., Hersh, A. L., Shapiro, D. J., Bartoces, M., Enns, E. A., File Jr, T. M., ... & Hicks, L. A. (2016). Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. *JAMA*, 315(17), 1864-1873.

Langford, B. J., So, M., Raybardhan, S., Leung, V., Westwood, D., MacFadden, D. R., ... & Daneman, N. (2021). Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. *Clinical Microbiology and Infection*, 27(1), 83-96.

Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K., Wertheim, H. F., Sumpradit, N., ... & Cars, O. (2013). Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases*, 13(12), 1057-1098.

Martínez, J. L., Coque, T. M., & Baquero, F. (2015). What is a resistance gene? Ranking risk in resistomes. *Nature Reviews Microbiology*, 13(2), 116-123.

Mathers, A. J., Peirano, G., & Pitout, J. D. (2015). The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant Enterobacteriaceae. *Clinical Microbiology Reviews*, 28(3), 565-591.

Theuretzbacher, U., Outterson, K., Engel, A., & Karlén, A. (2020). The global preclinical antibacterial pipeline. *Nature Reviews Microbiology*, 18(5), 275-285.

Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., ... & Laxminarayan, R. (2015). Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences*, 112(18), 5649-5654.

World Health Organization. (2021). *Global action plan on antimicrobial resistance*. World Health Organization.