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The Medical Implications of Multidrug Resistance and its Influence on Healthcare. How can Future Developments Improve Treatments against Bacterial Infections?

Bacteria has the capacity to acquire multidrug resistance (MDR). This occurs when a bacterium becomes unresponsive to antibiotics, due to mutations in its deoxyribonucleic acid (DNA). Cases of MDR have a prevalent influence on healthcare, as they lead to ineffective treatments of bacterial infections, potentially having a direct influence on human mortality and increasing the danger of infectious diseases. This can have a consequential rise in healthcare expenses, influencing economic implications, leading to negative outcomes for those who are from low and lower-middle income countries *(McDonnell, A., Countryman, A., Laurence, T., et al., 2024).* Researchers and organisations continue to increase the awareness of MDR, through improving public knowledge and the importance of correct antibiotic dosage. New technologies are in development to produce techniques better suited for precision base treatments of bacterial infections. Studies by researchers at Tulane University, have provided this, through the development of a mutational signature in MDR prone bacteria. With this breakthrough, predicting the susceptibility of a bacteria developing resistance is a possibility. Informuta Inc. continues to utilise this research, in addition to their own developments, to produce a machine learning model able to scan bacteria and predict their likelihood to develop resistance.

Bacteria are prokaryotic, unicellular organisms. A small number of bacteria are pathogenic, meaning they cause infectious disease. Pathogenic bacteria reproduce rapidly and release toxins to damage or enter the body's cells. Antimicrobials are substances that kill microbes *(Microbiology Society, 2020).* Antibiotics specifically function to target bacteria by inhibiting their growth or killing the organism. DNA in bacteria is organised into one circular chromosome which resides in the nucleoid region of the cytoplasm. Bacteria also often contain plasmids, which are accessory chromosomes separated from the rest of the DNA. Many plasmids contain genes with the capacity to cause the host bacterium to become resistant to antibiotics. MDR is when bacteria mutate over time and no longer respond to antibiotics, thus making the treatment ineffective. Antimicrobial resistance (AMR) is a similar term, but it is non-specific and refers to a pathogen developing resistance, whereas MDR only refers to bacteria. Mutations are a change in the structure or amount of DNA in an organism, which often result from DNA replication errors *(Gilchrist, D., 2019)*. Point mutations are a type of mutation where a single nitrogen base in the DNA is altered. DNA mismatch repair (MMR) has a role in DNA replication, mutation avoidance and genome stability; it is crucial to the viability of cells. In DNA replication, the ladder-like structure of DNA is unzipped by helicase, so the genetic code is exposed. This allows the template strand to be replicated by DNA polymerase, which adds a complementary nucleotide to each base, doubling the amount of genetic material. Occasionally, errors are made, and base pairs are placed in an incorrect position *(Metzler, K., 2025)*. MMR machinery then operates to detect errors, and exonuclease removes the incorrect nucleotide. DNA polymerase then replaces it with the correct nucleotide. If this repair process does not occur, a mutation can arise.

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MDR is a pressing concern in healthcare. The World Health Organization estimates that antimicrobial resistance could surpass heart disease and cancer as the leading cause of death by 2050 *(Yawn, A., 2025)*. Figure 1 shows the predominance of deaths associated with AMR compared to other health ailments in 2019. It is the third greatest of the aliments provided, with it directly causing 1.27 million deaths globally, and it being associated with many more (see figure 1) *(Institute for Health Metrics and Evaluation, 2023)*. The less predominant ailments are close in the number of deaths they cause. However, there is a large gap between the number of deaths caused by pulmonary disease and those associated with AMR. This demonstrates the significance of AMR in society, with its convincing predominance in causation of deaths compared to other diseases. This validates the cruciality of implementing research in this area to reduce its influence on human mortality. The Centre for Global Development estimates that treatments of antibiotic-resistant infections increase healthcare costs by US$ 66 billion, and if historical trends continue, could rise to US$ 159 billion by 2050 *(McDonnell, A., Countryman, A., Laurence, T., et al., 2024).* These rise in costs will heavily impact low and lower-middle income countries and further impact broader economic stability. Resources are highly constrained in these countries, highlighting their disadvantage if the effects of AMR continued to increase. NPS MedicineWise in 2014 found that 57% of general practitioners involved in their research, reported that they would prescribe antibiotics for upper respiratory tract infections to meet patient expectations. Furthermore, 20% of the surveyed consumers reported that they would expect doctors to prescribe antibiotics for a cold or flu *(NPS MedicineWise, 2021).* These findings are vital, as MDR has rapidly developed due to the excessive and improper use of antibiotics. The consequential influence of MDR results in infections lasting longer, complications becoming more likely, and probability of spread increasing. MDR is a relevant and concerning issue in healthcare, requiring solutions and advancement in medicinal practices.

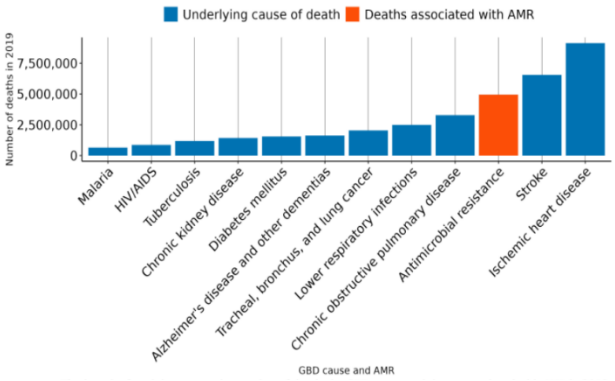

Figure 1: the global number of deaths caused by various health ailments, including AMR *(Institute for Health Metrics and Evaluation, 2023).*

The demands to reduce the dangers of AMR has led to efforts toward minimising this issue. The communication between countries to collaborate in their response is vital, as AMR affects every individual, and with combined goals, improvement is promising. A meeting was held in September 2024 with the United Nations General Assembly, as an "important opportunity for world leaders to collectively address the looming threat AMR poses" *(United Nations, 2024)*. The Global Leaders Group works to accelerate political momentum, leadership, and action on AMR. The World Health Organization's 'World AMR Awareness Week' has contributed to the improved awareness and understanding of AMR to those most influential; One Health stakeholders, policymakers and the public. It encourages appropriate practices to reduce the spread and prevent emergence of AMR.

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Research and development of technologies to support MDR solutions has been the focus of Tulane University researchers, through the analysis of mutational signatures. *(Hall, K.M., Williams, L.G., Smith, R.D., et al., 2025)*. The bacteria *Pseudomonas aeruginosa* (*P. aeruginosa*) was heavily researched, as it is a common cause of infection in hospitals and is known to be susceptible to MDR *(Catalano, A., Iacopetta, D., Ceramella, J., et al., 2022)*. Initially, the university's researchers endeavoured to discover the full trinucleotide mutational signature that develops in MMR-deficient *P. aeruginosa* following its acquisition of MDR. Single base substitution patterns have previously been extracted from human tumours associated with MMR-deficiency. The needs of society utilised this pre-existing technique in a new context to analyse *P. aeruginosa*. Single clone analysis provided insufficient results to generate a robust signature, therefore the combined observed mutations from each clone was composed into one composite spectrum. This process found that the mutational signature is dominated by C-to-T and T-to-C transitions. These findings leave the possibility for the development of a "promising diagnostic tool that may predict MDR and guide precision-based medical care" *(Hall, K.M., Williams, L.G., Smith, R.D., et al., 2025)*. Tools like this are not available in medicine currently. A breakthrough like this will enable precision-based treatments that are more effective to protect against bacteria. Ultimately, mortality rates and the effects of MDR on patients and healthcare have the potential to decrease by applying these developments. Informuta Inc. is a company that aims to develop a machine learning model that can scan bacteria samples and predict their susceptibility to develop resistance *(Informuta, 2024)*. Tulane University also researched the link between MMR-deficiency and MDR, to help better understand the issue at hand. The role of antibiotic treatment and MMR-deficiency in the development of MDR in bacteria is not yet fully understood. Figure 2 demonstrates the correlation of MDR with MMR-deficient isolates of bacteria compared to wild type *(Hall, K.M., Williams, L.G., Smith, R.D., et al, 2025)*. As demonstrated by figure 2, the isolates which are MMR-deficient have a higher percentage with MDR by approximately 40%. If knowledge can be developed on why this is the case, information could uncover how to make treatments on bacterial infections more informed and precise.

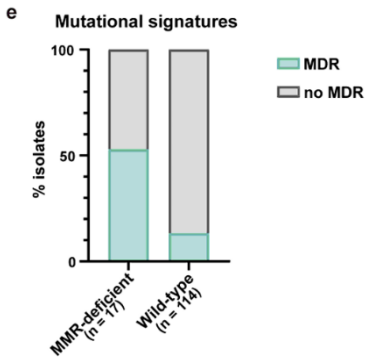

Figure 2: correlation of MMR-deficiency and MDR of bacterial isolates *(Hall, K.M., Williams, L.G., Smith, R.D., et al., 2025)*.

In 2019, AMR was the direct cause of 1.27 million deaths globally and was associated with many more fatalities *(Institute for Health Metrics and Evaluation, 2023)*. The treatment of antibiotic-resistant infections increases healthcare costs, contributing to the disadvantages which low and lower-middle income countries face. With the treatment and development of MDR having significant expenses, it is not viable for these countries to have upmost quality and efficiency in their MDR-related healthcare. MDR causes infections to become increasingly dangerous, as they last longer, have an increased probability of complications and are probable to spreading to the wider community. These concerns

have led to the need for research in developing precision-based treatments which are more effective at protecting patients against bacteria. Tulane University has recently developed a mutational signature in MDR-prone bacteria, which in time will hopefully lower the negative impacts MDR has on society.

The acquisition of resistance in bacteria to antibiotics is an increasingly relevant issue in healthcare. The consequences of MDR raise cause for concern, with its influence on human fatalities, increased healthcare costs, and the spread of harmful infectious diseases. The demands to reduce the negative effects of MDR on society has led to the Global Leaders Group taking action to raise awareness and accelerate political movement regarding MDR. In addition, there have been recent developments in knowledge of bacterial resistance. The application of existing technologies in new contexts has enabled the finding of a mutational signature in MDR-prone *P. aeruginosa* to be found by Tulane University researchers. This finding has the potential to improve the effectiveness of treatments against antibiotic-resistant infections. These developments have the possibility to reduce the negative influence MDR currently has on healthcare.

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