# ANTIBIOTIC RESISTANCE: TURNING EVOLUTIONARY PRINCIPLES INTO CLINICAL REALITY

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## ABSTRACT

Antimicrobial resistance (AMR) development in bacteria via chromosomal mutation or horizontal transmission of genes is a naturally occurring phenomena that may be detected even in the absence of human intervention. But it is the almost century-long widespread usage of antibiotics that has resulted in the current public health problem. Moreover, many bacteria exhibit a rise in antimicrobial resistance (AMR), which is frequently directed towards various antibiotic medicines (i.e., multidrug resistance, MDR). MDR pathogen infections are difficult, if not impossible, to treat with routinely used medications, necessitating the adoption of less effective and/or more hazardous regimens. More individuals are anticipated to die from MDR pathogen infections (10 million/year) by 2050 than from cancer (8.2 million/year) currently. Antimicrobial resistance is one of the most serious problems confronting contemporary medicine globally. Throughout the last few decades, we have made significant progress in our knowledge of the various variables that influence the establishment and spread of antibiotic resistance at both the population and individual patient levels. Unfortunately, integrating this achievement into health policy and clinical practise has been a long process. In this paper, we try to synthesise existing information regarding the evolution and ecology of resistance to antibiotics into a road map for future research as well as for environmental and clinical antibiotic resistance control. We investigate the emergence, transmission, and spread of antibiotic resistance at the population

level, and we investigate adaptability including microbial physiology and host resistance at the patient level. Lastly, we discuss novel techniques and technology for enhancing diagnosis and treatment while limiting resistance transmission.

**Keywords:** Antibiotic resistance; evolution; transmission; rapid diagnostics; prevention; new therapy; treatment; pathogens.

## INTRODUCTION

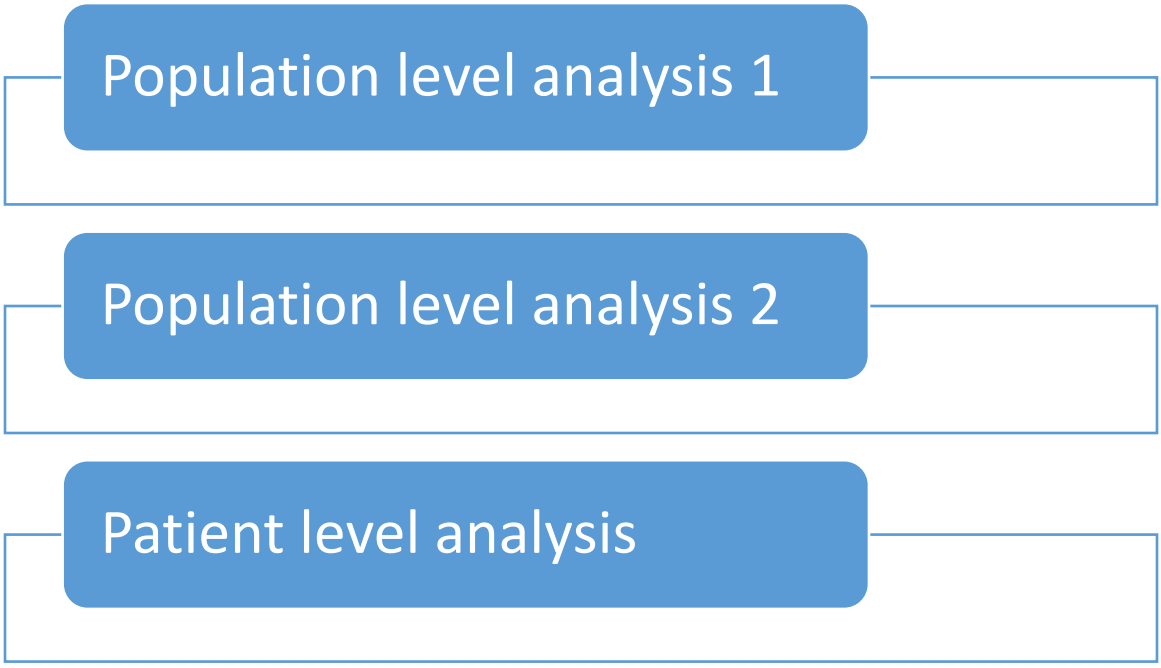
The field of Evolutionary Medicine seeks to combat growing rates of drug resistance by developing innovative treatment options based on evolutionary principles of resistance creation and spread. The aims are threefold: (I) to limit intra-patient resistance selection, which can lead to treatment failure; (ii) to offer individual patients with more rapid and less toxic therapies; and (iii) to reduce the danger of AMR development and transmission at the community level.

These objectives are particularly challenging to meet since specialised patient care and public health concerns do not usually coincide. Treatment techniques, in particular, that were originally designed to eliminate an illness as fast as possible, put a strong, frequently monotone selection pressure on the causative microorganisms. Depending on the bacteria's adaptation abilities, this can raise the likelihood of both short-term and long-term resistance development. Furthermore, the broad antimicrobial activity that is commonly required for effective empirical anti-infective treatment may disrupt the healthy microbiome, posing a risk for the development or worsening of secondary diseases. In this context, Evolutionary Medicine is intrinsically tied to Precision Medicine, which stratifies patients based on host, microbiome, and pathogen characteristics in order to provide the most effective and long-lasting medication for a given patient or group.

We have made great progress in understanding the numerous elements that contribute to the formation and spread of antibiotic resistance at both the community and individual patient levels during the last few decades. Unfortunately, incorporating this accomplishment into health policy and clinical practise has taken a long time. While policymakers have clearly stated that antibiotics should be used responsibly in clinical practise and agriculture, there has been little measurable change in clinical and agricultural practise to reflect the gravity of this public health crisis. With this in mind, the European Academy of Microbiology organised a special working

group tasked with defining a roadmap for future research as well as clinical and environmental antibacterial/antimicrobial management.

**THREE LEVEL OF ANALYSIS**:




**POPULATION LEVEL ANALYSIS 1**

**Emergence and transmission of antibiotic resistance:**

Many unanswered concerns about the development, transmission, and spread of antibiotic resista nce must be addressed in the near future.

The most pressing of these problems are: (i)How and where do antibiotic resistance genes (ARG s) and mobile genetic elements (MGEs) carrying ARGs evolve and emerge?

Is resistance more likely in people or animals during treatment, or in germs that live outside of a host organism, in an environmental niche?

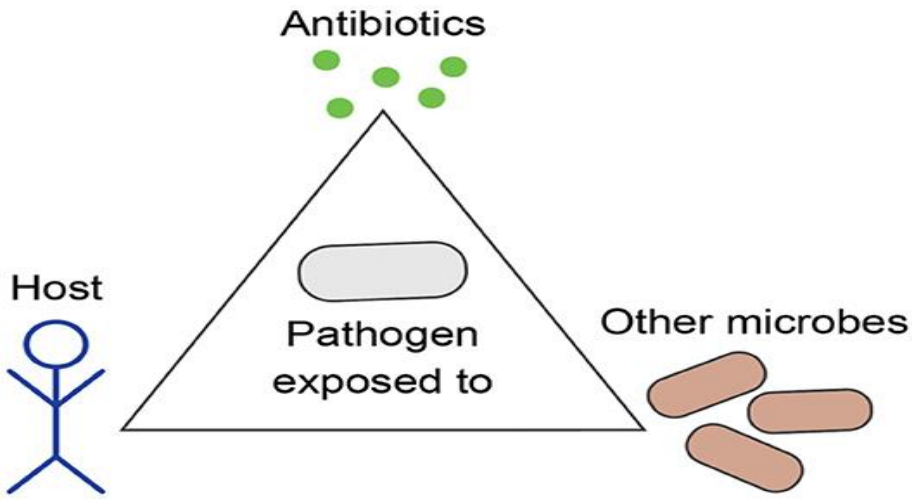
(ii) What selective pressures (antibiotics, biocides, heavy metals, or non-antibiotic treatments) promote resistance evolution?

(iii)Which bacterial features (for example, mutation rate, fitness cost of resistance and MGE carri age, pharmacodynamic response curves combined with treatment) are important determinants of resistance evolution?

(iv) What distinguishing features contribute to the global spread of antimicrobial drug- or multi-drug-resistant bacteria? And

(v) What role do host-related factors like as population density, host immunity and vaccination, travel, hygiene, and healthcare systems play in resistance creation and spread?

Experimentation with evolution, study into resistant phenotypes, mutation mapping, persistence, genetic mobility, and other issues should be included. To reduce the rates of resistance creation and spread, these research subjects must be extensively addressed, and appropriate evidence-based procedures must be used. A concerted effort will also be necessary to discover novel antibiotic treatments that will remain highly efficient bactericides in the future.




**Emergence of antibacterial resistance**

- **Where do resistant bacteria emerge?**

A resistant bacterium may exist in any environment, but its population frequency is likely to increase when it confers increased survival capacity under selective pressure. While there are

other types of selection processes, we will assume for the sake of this study that antibiotic prescription exposure is the dominant driver of antibiotic resistance evolution.

One example of how antibiotic use in animals is thought to have induced a resistance problem in humans is plasmid-borne colistin resistance caused by the mcr-1 (mobilised colistin resistance) gene. This gene has been discovered in clinical isolates of E. coli, Salmonella enterica, Klebsiella pneumoniae, and Enterobacter aerogenes/cloacae, and numerous lines of evidence show that the extensive use of colistin as a growth promoter in cattle is enriched for this gene.

- **Which selective pressures drive the evolution of antibiotic resistance?**

Given biological fundamental principles and the fact that growing antibiotic usage corresponds relatively well with resistance frequency, it is generally acceptable to suggest that antibiotic exposure is the major cause. This does not rule out the possibility of other factors, such as heavy metals and other biocides, playing a role through co-selection of biocide and antibiotic resistant strains (i.e. where a multi-resistance gene element (e.g. MGE) provides resistance to both) or cross-resistance between the biocide and antibiotic resistance mechanisms. Biocides may possibly reduce the colonisation resistance (the barrier effect) of that environment's naturally present microbiota, enabling the invasion of antibiotic-resistant bacteria, however such effects have yet to be thoroughly investigated.

- **Which bacterial factors are critical determinants of the rate at which antibiotic resistance evolves?**

Given this complication, it is also worth noting that current preclinical evaluations of the likelihood of resistance formation for novel antibiotic treatment potential frequently focus solely on de novo mutational resistance, typically using mutation rate measurements during serial passage processes under controlled laboratory conditions. This limited emphasis is significantly restricting, if not wholly incorrect, for two reasons. First, in vitro mutation rates do not match to clinical resistance emergence rates. The primary rationale for this mismatch is the fact that resistance growth and establishment of a resistant mutation within a patient are not considerably controlled by the rate of bacterial mutation supply. These variables generate a complicated web of options and selection pressures, making it difficult to untangle the relative contributions and importance of various aspects, or to discover which factors may be changed to our advantage.

**Dissemination and transmission of antibiotic resistance**

(i)What determines the global dissemination of specific clones?

(ii)What are the roles of human societal factors?

(iii)What role do complex microbiomes play in emergence and spread of antibiotic resistance?

**POPULATION LEVEL ANALYSIS**

**Future projections: Strategies to mitigate or prevent antibiotic resistance**

This level contains 12 various strategies, such as decreasing selection pressure, producing antibiotics with limited resistance potential, and so on. Reduce the availability of mutations and HGT. Narrow the selection window and take use of collateral sensitivity. Improve healthcare practises and implement evidence-based health policies to address antibiotic resistance. Antibacterial vaccination, antibiotic combinations Priority should be given to drug-resistant bacteria over resistant clones. Adjuvants, antibiotic activity enhancers, and new antibiotic resistance inhibitors can all be used to alter the microbiota.

In the latter half of the twentieth century, a global movement was initiated against the use of antibiotic combinations. When it comes to combination therapy, it may be time for more educated and diversified healthcare practitioners. Furthermore, for most infections, combination therapy is no more effective than single-drug monotherapy. Combination therapy, on the other hand, reduces the likelihood of resistant organisms arising since variants that are resistant to medication A remain susceptible to medication B, and vice versa. This is visible in some disorders, like as tuberculosis, but it is also important in infections in immunocompromised individuals. In actuality, antibiotic combinations should be viewed as a method for extending antibiotic life and reducing the development of antibiotic resistance. Based on a thorough understanding of the spectrum of resistance to different drugs, evolution-informed antibiotic combinations should enable the development of combinations that are not only effective but also less susceptible to resistance. Furthermore, in a number of cases, single antibiotics are ineffective in eradicating otherwise seemingly susceptible pathogens because these pathogens are only partially susceptible to them under in vivo conditions, frequently due to slow growth, heteroresistance, or persistence (see below), also known as a dormant stage. In these situations

(endocarditis, endovascular infections, cystic fibrosis pathogenic colonisation), specific antibiotics (such as aminoglycosides) targeting these latent populations are usually added, resulting in a combination therapy that is more effective than single drugs alone.

## PATIENT LEVEL ANALYSIS

### Bacterial physiology and within host resilience:

- **Limitations of antibiotic susceptibility testing**

The physiological condition of the bacteria as well as the environment of exposure affect antibiotic efficacy. Penicillin G is a textbook example since it kills replicating susceptible bacteria while not killing non-replicating susceptible microorganisms. This is because penicillin suppresses bacterial cell wall formation, which is only necessary in dividing cells. Rifampicin, on the other hand, inhibits bacterial RNA polymerase regardless of whether the bacteria are developing, which has lethal consequences in all bacterial cells. However, it is not surprising that the biological context or circumstances that exist in the laboratory, clinic, or in a human or animal host have a significant impact on bacterial susceptibility to antibiotics.

As a result, when predicting susceptibility in an infected patient, it is vital to be sceptical of the results of standardised laboratory tests for antibiotic sensitivity. We must recognise that the reported minimum inhibitory concentration (MIC) of any antibiotic is conditional, not absolute. Unfortunately, due to a lack of more relevant pharmacodynamics data, we rely heavily on MICs in praxis to prescribe antimicrobials. To compensate for this lack of knowledge, one technique is to dose the antibiotic far higher than the documented MIC, seeking to account for the influence of the bacteria's physiological state in the host organism.

- **Variation within and between hosts**

Bacterial responses to antibiotics differ based on the biological environment and physiological state, and the physiological condition of each individual cell in every bacterial population varies throughout time. This is especially true in the human body, which exhibits structural and physiological diversity in location (different tissues and organs), time (the ageing process), and function (impact of diseases, immunology, diet). Throughout the course of the disease, this heterogeneity changes the physiology and phenotype of the target pathogen in unpredictable and

ever-changing ways. It is well known that human life expectancy has grown over the last 150 years, and doctors may require specific methods of infection management in old and severely elderly patients. Because of a weaker immune system, the risk of repeated infections

- **Low antibiotic concentrations and selection for antibiotic resistance**

When antibiotics are used to treat a bacterial illness, the antibiotic dosage is often significantly larger than the MIC measured in the laboratory. Yet, the effective in vivo antibiotic concentration in specific body niches will be lower than average, allowing bacterial variations with low-level resistance to thrive. Because they are not deemed clinically resistant (resistance level below clinical break-points), such low-level resistant bacteria in the body enhance the chance of the formation of highly resistant clones, and treatment may be prolonged, increasing the selection pressure towards complete resistance. Consequently, despite the fact that antibiotic resistance is routinely monitored and procedures and clinical practise incorporate several efforts to prevent its establishment, resistant clones do emerge in patients who are receiving antibiotic therapy.

- **How can we improve prediction of possible failures in antibiotic therapy?**

A relevant susceptibility matrix summarising the findings of a series of MIC assessments under varied circumstances should be developed for each of the most significant bacterial pathogens. These settings should put to the test recognised parameters that impact bacterial growth and metabolism, such as nutritional availability, and should mimic the appropriate body niche as well as any other important environmental aspects. It is also critical to assess antibiotic effectiveness in situations of sluggish growth, dormancy, and the lag periods between dormancy and restart of growth. It is critical to include both reference strains and isolates of the relevant pathogens in these studies.

In summary, the foregoing debate concludes that currently available antibiotics, if utilised wisely and properly, have the potential to successfully eliminate bacterial infections. Additionally, employing shorter rounds of antibiotic therapy reduces the danger of fostering the formation of antibiotic-resistant bacteria or persisters. The technique outlined above is time and resource expensive. As a result, all study outputs and research and clinical data must be deposited and kept in publicly accessible databases. This includes information on disease/infection

development, treatment and outcome, genetic information on the infecting bacteria, and any other relevant molecular data.

**Precision medicine and antibiotic resistance**

Pathogens' complicated relationships with the host, local environment, and resident microbiota confuse their in vivo evolutionary responses to antimicrobial compounds. Precision Medicine is in action here. It is crucial to detect bacterial infections, including pathogen taxonomic identification, infection site(s), phenotypic and genotypic drug resistance profiles, as well as specific host and microbiome features, in order to develop better and more sustainable therapies. The development and execution of personalised therapies, on the other hand, presents Precision Medicine challenges that necessitate careful management of individual and public interests: vast sampling of microorganisms in an illness to support present exploratory research as well as future diagnostics or therapeutic monitoring, in combination with full patient characterisation in a system of medicine.

**“Omics”-based diagnostics in precision medicine**

Recent advances in "omics" technology and informatics have the potential to revolutionise and expand our understanding of AMR in the near future. WGS methods, in particular Nanopore and PacBio sequencing, provide extremely long reads and may detect DNA (and, in the case of Nanopore, RNA) modifications such as methylation. DNA methylation can generate population heterogeneity and epigenetic effects on gene expression in genetically sensitive bacteria, boosting adaptive resistance. Similarly, advanced proteomics can detect post-translational protein alterations that might contribute to antibiotic resistance. As current research continues, epigenetics, epitranscriptomics, and proteomics are anticipated to disclose previously unknown aspects of the complexities of antibiotic resistance.

Finally, a multifaceted "omics" approach that combines comprehensive pathogen and antibiotic resistance profiling with individualised patient data such as natural microbial community (metagenomics), genetic susceptibility to infections, immune response to infection, and PK/PD

modelling has the potential to enable optimised precision medicine for antimicrobial prescribing practises. Furthermore, such detailed analysis must be exact in order to avoid directing therapy away from contaminants and harmless colonists.

## CONCLUSION

The oft-repeated motto "prudent antibiotic usage" or "les antibiotiques ne sont pas automatiques" reflects the notion that any unwarranted rise in antibiotic use will lead to an increase in AMR prevalence. This is a proven reality that has been established at the individual, hospital, agricultural, national, and global levels of the environment. To us, the most serious possible global concern is cumulative "antibiotic pollution" of the environment, followed by "antibiotic-resistance pollution" of all living things' genes. Global issues necessitate global solutions, and only a committed and sustained worldwide effort can be successful in reversing current trajectories and trends. Sanitation and health management practise worldwide, in poorer and more prosperous nations and communities equally, will need to improve. As a result, it is in the direct interest of affluent nations to widely share and leverage all available resources on a global scale, because this is our most promising approach for winning the global war against antimicrobial resistance.

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