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A REVIEW ON ANTIBIOTIC RESISTANCE

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ABSTRACT

Treatment failure and recurrent infections are linked to increased risk of antimicrobial resistance (AMR) and persistence. As a result, they play a significant role in the rising rates of morbidity and mortality that raise healthcare expenses. Standard microbiological assays may easily identify antibiotic resistance, and the threat that antibiotic resistance poses has long been understood. There are measures in place to stop the emergence of resistance and the dissemination of resistant bacteria. Antibiotic persistence, the phenomenon where bacteria survive antibiotic exposure even when they are completely susceptible, is still largely unrecognized. Antibiotic persistence, as opposed to antibiotic resistance, is more difficult to quantify and so frequently overlooked, which may result in treatment failures. In this review, we address the consequences of these bacterial pathways for antibiotic resistance and human health. We address recent research that connects bacterial tolerance and persistence to the evolution of antibiotic resistance, and we explain the relationship between bacterial heterogeneity and antibiotic persistence. Lastly, we go into persister detection techniques, cutting-edge approaches to getting rid of bacterial persisters and the most recent developments in the creation of new antibiotics.

KEYWORDS

Antimicrobial resistance, Antibiotic persistence and Resistant bacteria.

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INTRODUCTION

The current state of medicine has been made possible by antibiotics. By the end of the previous century, infectious diseases were thought to have been eliminated and the mid-20th century was even dubbed the "antibiotic era." Antibiotics have also been essential for many other medical specialties as well as effective invasive and high-end procedures such as organ transplantation and immunomodulatory treatments in rheumatology and oncology[1]. The availability of antibiotic medication

has raised life expectancy overall by drastically lowering child mortality[2]. However, a growing number of bacteria are developing resistance to several of the antibiotics that are currently in use, leading to the emergence of multidrug resistant (MDR) bacteria[3]**.** Sir Alexander Fleming, who received the 1945 Nobel Prize in Medicine for discovering penicillin, cautioned against the possible consequences of overusing and abusing medicines, which could lead to the emergence of antibiotic resistance[4,5]. Antibiotic-resistant bacteria have emerged as a serious challenge to contemporary health care due to the lack of novel antimicrobial medications and the rising incidence of MDR bacteria that are leading to treatment failures[6]. In a race against time, numerous governments, the World Health Organization (WHO), and the United Nations (UN) have combined forces to lessen and prevent the development of resistance. One of the biggest challenges to human health, the "rapid and massive spread of infectious diseases," is highlighted in the most recent report from the World Economic Forum 2019 in Davos, Switzerland, as the reason why action must be taken (World Economic Forum, 2019). Antibiotic-resistant bacterial infections are estimated to be the cause of approximately 10 million fatalities annually by 2050, accounting for about 700,000 deaths globally each year[7,8]. The prevalence of infections and the dissemination of MDR bacteria are still on the rise, despite the fact that AMR is now widely recognized as a critical concern.

Moreover, an increased incidence of biofilm-related infections is caused by the growing number of implanted medical devices, including vascular endoprostheses, pacemakers, prosthetic heart valves, and joint prostheses. Antibiotic resistance is a prominent problem that results from this[9,10]. Antibiotic resistance enables microorganisms to resist antibiotic attacks even while they are fully susceptible in traditional microbiological tests[11]. Using *in vitro* research and mathematical modeling, Balaban and colleagues have recently shown that tolerance can evolve more quickly than resistance and that tolerance mutations can accelerate the evolution of antibiotic resistance[12,13]. Fighting antimicrobial resistance (AMR) requires an understanding of both antibiotic resistance and tolerance.

ANTIBIOTIC RESISTANCE MECHANISMS

When needed antibiotics are delayed due to antibiotic resistance, morbidity and death rates often rise. AMR refers to microorganisms that have a genetic predisposition to thriving at high antibiotic dosages[11]. The minimum inhibitory concentration (MIC) of an antibiotic is commonly used to measure it. This is the concentration at which resistant bacteria can multiply and flourish to a degree that is fatal to other strains of the same species. There are different types of antibiotic resistance. The presence or lack of particular structures can result in natural intrinsic resistance, which is one factor that makes antibiotics ineffective. Nevertheless, chromosomal gene alterations or horizontal gene transfer from plasmids or chromosomes can also cause bacteria to become resistant to antibiotics. Antimicrobial substances like triclosan, which inhibit fatty acid synthesis by targeting the enoyl-ACP reductase, are ineffective against Pseudomonas aeruginosa because the bacteria carries an insensitive homologue of fabI (enoyl-ACP reductase), fabV, which encodes an enzyme that is not inhibited by triclosan[14]. In general, Gram-negative bacteria are less permeable than Gram-positive bacteria and have an inherent resistance to several antibacterial agents, such as the cell wall-active glycopeptide vancomycin[15]. Since these large molecules are unable to pass through Gram-negative bacteria's outer bacterial barrier, they are unable to attack the cell wall. The pathogen that is Gram-positive Conversely, Staphylococcus aureus is recognized for its ability to quickly acquire resistance to antibiotics by acquiring specific genetic alterations (mutations or horizontal gene transfer), which results in infections that propagate in waves of epidemics[16]. This pathobiont, on the other hand, is naturally vulnerable to nearly all known antibiotics.

Reduced permeability of the bacterial cell membrane, such as by modifying or decreasing porins that would let antibiotic entrance into the cell, can be used to maintain low intracellular concentrations of antibiotics. Numerous Gram-negative bacteria, including *Escherichia coli, Klebsiella pneumoniae* and carbapenem-resistant Enterobacter species, have been well-documented to exhibit decreased porin expression or altered porins without expressing a carbapenemase[17-19]. Increasing the efflux of chemotherapeutics by the use of substrate-specific or multidrug resistance efflux pumps is another strategy for reducing intracellular antibiotic concentrations. Despite the fact that many bacteria have several MDR efflux pump genes on their chromosomes, some of these genes have been deployed onto plasmids. That microorganisms can exchange[20]. The antibiotic-targeting enzyme New Delhi metallo-blactamase 1 (NDM-1) was found to be carried on a plasmid coupled with genes encoding for a novel tripartite resistance nodulation division (RND) pump[20-21]. The fact that several resistance mechanisms can coexist on a single plasmid and be transmitted between bacteria makes this particularly concerning. It also emphasizes the significance of MDR efflux pumps as a key resistance mechanism. Patients with systemic infections have yielded several clinical isolates, such as *P. aeruginosa and S. aureus* that overexpress drug efflux pumps[22,23].

An antibiotic target molecule's spontaneous mutations or post-translational alterations may cause conformational changes that impair target binding and reduce antibiotic activity *S. aureus* can develop ciprofloxacin resistance due to single amino acid alterations that occur in close proximity to the active site tyrosine of the bacterial type II topoisomerase enzymes, DNA gyrase GyrA or DNA topoisomerase IV ParC[24,25]. As a result, the quinolone resistance determining region (QRDR) has been assigned to this domain[26]. Rifampicin is effective against the majority of clinical methicillin-resistant *S. aureus* (MRSA) isolates[27], but when rifampicin is administered as monotherapy, resistance develops quickly. Reduced affinity for rifampicin is the result of point mutations in the gene encoding the b-subunit of the DNA-dependent RNA polymerase (RpoB), which rapidly confers resistance[28]. Finally, directly altering antibiotics can result in the acquisition of resistance.

Antibiotics can be immediately destroyed by hydrolysis or rendered inactive by the transfer of chemical groups to places that are susceptible, preventing the target from attaching and functioning. Antibiotic resistance may arise from the inactivation of antibiotics by the addition of a chemical group, such as an acyl, nucleotidyl, phosphate, or ribitoyl group, which results in steric hindrance. Such an inactivation process is particularly vulnerable to the big molecules of aminoglycosides with numerous exposed hydroxyl and amide groups. A genomic island that confers resistance to aminoglycosides, including gentamicin, was discovered in Campylobacter coli isolated from chickens in China. This island contains genes for six aminoglycoside-modifying enzymes[29]. A wide variety of enzymes that may break down various antibiotics within the same class have evolved as a result of the creation of novel derivatives of previously identified antibiotic classes. For instance, extended-spectrum b-lactamases (ESBLs), which can hydrolyze extended-spectrum oxyimino cephalosporins like cefuroxime, cefotaxime, cefmenoxime, and ceftriaxone, succeeded the early b-lactamases, which were active against first-generation b-lactams[30].

In the past 20 years, the usage of carbapenems has expanded along with the number of bacteria bearing ESBL genes, which has resulted in the creation of strains that produce carbapenemase[31]. Many carbapenemase-genes are currently carried on plasmids and have been discovered in Enterobacteriaceae, K. pneumoniae, P. aeruginosa, and Acinetobacter baumannii[32] (Figure No.1A). Carbapenemases can degrade a variety of b-lactams, including extended-spectrum cephalosporins.

GENETIC BASIS OF ANTIMICROBIAL RESISTANCE

Because of their exceptional genetic flexibility, bacteria are able to adapt to a variety of environmental stressors, such as the presence of antibiotic compounds that could endanger their life. Because they have evolved ancient ways to survive the detrimental effects of antibiotics, bacteria that share the same ecological niche as organisms that produce antimicrobials are able to thrive in the presence of antibiotics due to their intrinsic resistance. From an evolutionary standpoint, bacteria employ two main genetic coping mechanisms in response to the antibiotic "attack":

Mutations in gene(s) frequently linked to the compound's mechanism of action and

Acquisition of foreign DNA through horizontal gene transfer (HGT) coding for resistance determinants.

MUTATIONAL RESISTANCE

In this case, a portion of bacteria taken from a vulnerable group experiences gene alterations that impact the drug's efficacy, preserving cell life in the presence of the antimicrobial chemical. The antibiotic destroys the susceptible population as soon as a resistant mutation appears, leaving the resistant germs in the majority. Resistance-causing mutations frequently have a negative impact on cell homeostasis, or reduced fitness, and are only preserved when the antibiotic is present. Generally speaking, the following pathways are used by mutations that lead to antimicrobial resistance to change the way antibiotics work:

Altering the antimicrobial target (reducing the drug's affinity; see below),

Reducing drug absorption,

Turning on efflux mechanisms to push out the toxic chemical, or

Causing widespread alterations in significant metabolic processes via modifying regulatory networks.

As a result, resistance resulting from acquired mutational alterations is varied in intricacy and variety.

We shall provide numerous instances of antibiotic resistance resulting from mutational alterations in this chapter (see below).

HGT

One of the main forces behind bacterial evolution is the acquisition of foreign DNA material by horizontal gene transfer (HGT), which is frequently the cause of the emergence of antibiotic resistance. The majority of antimicrobial drugs that are employed in clinical settings are either naturally occurring or derived from environmental sources, primarily soil. Intrinsic genetic resistance determinants are present in bacteria that coexist with these chemicals and a wealth of evidence indicates that these "environmental resistomes" are a major source of antibiotic resistance genes that are acquired by clinically relevant bacteria. Moreover, the spread of resistance to numerous commonly used antibiotics has been linked to this genetic exchange. Traditionally, there are three primary ways that bacteria take up foreign genetic material: (i) transformation (incorporating bare DNA), (ii) phage-mediated transduction and (iii) conjugation (bacterial "sex"). Only a few therapeutically relevant bacterial species are able to naturally integrate naked DNA to evolve resistance, making transformation possibly the most straightforward type of HGT.

Conjugation is a highly effective gene-transfer mechanism that occurs through cell-to-cell contact and is frequently linked to the emergence of resistance in hospital settings. It is also believed to occur frequently in the gastrointestinal tract of patients receiving antibiotic therapy. Mobile genetic elements (MGEs) are generally used during conjugation to transfer important genetic information between chromosomes, while direct chromosome-to-chromosome transfer has also been thoroughly studied[33]. The two most significant MGEs are transposons and plasmids, which are both essential for the emergence and spread of antibiotic resistance in organisms that are clinically relevant. Integrons, site-specific recombination systems that can recruit open reading frames in the

form of mobile gene cassettes, are finally one of the most effective methods for collecting antimicrobial resistance genes. One of the key forces behind bacterial evolution, integrons offer a reliable and relatively straightforward method for introducing new genes into bacterial chromosomes together with the required apparatus to guarantee their expression. The reader is referred to a recent state-of-the-art review[34] for more information on the mechanisms of HGT.

ESKAPE PATHOGENS

Nosocomial pathogenic microorganisms with increasing degrees of virulence and multidrug resistance are referred to by the abbreviation ESKAPE. They have a major negative impact on patient health, healthcare systems and financial stability. ESKAPE is an acronym representing the Gram-negative bacteria *K. pneumoniae, A. baumannii*, *P. aeruginosa* and Enterobacter species, as well as the Gram-positive bacteria *Enterococcus faecium and S. aureus*. They are all characterized by high levels of antibiotic resistance and frequently cause hospital-acquired infections that could be fatal for patients who are critically ill or have impaired immune systems[35]. The WHO identified twelve bacterial species against which new chemotherapy drugs are sorely needed, including all ESKAPE infections[36].

E. FAECIUM

Despite having a low virulence, the Gram-positive commensal E. faecium is challenging to remove from hospital environments. It is therefore much feared in the hospital system due to its propensity to produce nosocomial infections and outbreaks[37]. Drug-resistant enterococcal infections have been more common over the past few decades, with vancomycin-resistant enterococci (VRE) accounting for the majority of these infections with rates as high as 14.9% in the European Union (EU)[38] (Figure No.1B) and 30% in the United States of America (USA)[39]. Because of the resistance, treating these nosocomial VRE infections is extremely challenging and occasionally unfeasible.

S. AUREUS

Particularly in the nose, the Gram-positive bacterium *S. aureus* is a component of the typical skin microbiota. Around 50% of the population is either permanently or sporadically colonized, indicating significant carriage rates[40]. However, *S. aureus* is a major contributor to bacteremia, osteomyelitis, infective endocarditis, and infections of the skin and soft tissues. Prior to the development of antibiotics, S. aureus bacteraemia had fatality rates that exceeded 80%[41]. The 1940s saw the discovery of penicillin, which quickly improved patient outcomes. The first line of treatment for *S. aureus* infections was penicillin, but strains that produced b-lactamases (blaZ) swiftly evolved as a result of widespread use. Penicillin G resistance was present in over 80% of clinical isolates as early as 1948[42-44].

The b-lactam ring is hydrolyzed by the mostly extracellular enzyme B-lactamase, which makes the b-lactam inactive[45]. MRSA strains were identified about a year after semisynthetic penicillins were first introduced in 1961 and there is even proof that S. aureus acquired methicillin resistance prior to the medication's clinical application[46,47]. Before methicillin was developed, first-generation b-lactam antibiotics like penicillin were widely used, which led to the selection of strains with the mecA determinant, which confers resistance to methicillin[46]. These days, MRSA prevalence in Europe varies from less than 1 to over 40%. Invasive MRSA isolates are found at very low levels in Scandinavian nations like Iceland (0.0%) and Norway (0.9%), as well as at low levels in the Netherlands (1.2%), Switzerland (4.4%), Germany (7.6%), and France (12.1%), as well as at high levels of up to 34% in Italy, 38% in Portugal and 43% in Romania[48-50]. (Figure No.1C). Methicillin resistance is mediated by the gene mecA, which is transferred horizontally by the staphylococcal cassette chromosome mec (SCCmec) mobile genetic element[51]. The penicillin binding protein

(PBP2a), which the mecA gene encodes, is in charge of cross-linking peptidoglycans during the production of cell walls. PBP2a's poor affinity for b-lactams[52] causes resistance by making the antibiotics ineffective. The multilocus sequence type (MLST) MRSA-IV USA300 is a well-known pandemic and hypervirulent clonal lineage of community-acquired (CA)-MRSA that began spreading in the USA 20 years ago and is a major health danger and economic factor today[53]. MRSA colonization raises the chance of contracting an MRSA infection because, according to whole genome sequencing and other molecular typing techniques, 50-80% of isolated invasive strains are descended from colonizing bacteria[54,55]. It is a dynamic process in which certain strains evolve or are replaced by other strains within the same host, while others remain for extended periods of time[56]. Furthermore, *S. aureus* is frequently spread through hospital jackets, cell phones, and tablets-all of which are frequently used in clinics[57,47]. Glycopeptide antibiotics, like teicoplanin and vancomycin, are now utilized in clinics as the first line of treatment for MRSA infections. European MRSA strains with decreased teicoplanin sensitivity first surfaced shortly after vancomycin therapy was introduced in the 1980s[58]. The first vancomycin-resistant *S. aureus* (VRSA) was found in the USA in 2002[59] and in Europe eleven years later[60]. Vancomycin can be effectively substituted with linezolid, tigecycline, trimethoprim–sulfamethoxazole (TMP–SMX), daptomycin, a lipopeptide bactericidal antibiotic, or a 5th-generation b-lactam, such as ceftaroline or ceftobiprole. Similarly, a combined or single use of the streptogramin antibiotics quinupristin-dalfopristin, TMP-SMX, linezolid, or telavancin is advised if a decreased daptomycin susceptibility is seen in conjunction with a reduced vancomycin susceptibility[61].

K. PNEUMONIA

The rod-shaped, gram-negative pathogen K. pneumoniae is frequently linked to nosocomial infections. Many strains of K. pneumoniae have developed resistance to penicillin, cephalosporins and carbapenems through the use of diverse b-lactamases. Gram-negative bacterial infections are commonly treated with carbapenems; however, the emergence of K. pneumoniae strains that produce KPC and carry blaKPC makes treating these infections increasingly challenging[62] (Figure No.1D). Furthermore, NDM-1, the metallo-b-lactamase, is expressed by certain K. pneumoniae strains and is encoded by blaNDM-1[63]. The prevalence of carbapenem-resistant K. pneumoniae strains has grown due to the presence of NDM-1, necessitating the use of other antibiotics like aminoglycosides and fluoroquinolones more frequently. But using these antibiotics more often might also lead to an increase in drug resistance, which would make treating these infections much harder[64].

A. BAUMANNII

The opportunistic pathogen *A. baumannii*, which is Gram-negative, is linked to nosocomial infections in hospital stays longer than ninety days, mostly in patients with weakened immune systems[65]. Numerous illnesses, such as urinary tract and respiratory infections, are brought on by *A. baumannii*. *A. baumannii* presents a serious risk to patients, particularly in critical care units, because of the high prevalence of antibiotic resistances (Figure No.1E). Furthermore, isolates of *A. baumannii* resistant to carbapenem that possess blaIMP (imipenem metallo-b-lactamases) and blaOXA (oxacillinase serine b-lactamases) have been discovered. They are able to avoid the antimicrobial effects of the majority of conventional antibiotics due to the combination of resistance genes[66,67]. The World Health Organization (WHO) identified *A. baumannii* as crucial (in priority group 1) for the development of novel antimicrobial drugs due to the rising occurrence of multidrug-resistant strains of the bacteria worldwide[68].

P. AERUGINOSA

The Gram-negative bacterium *P. aeruginosa* has a strong inclination to become resistant to

antimicrobial medications and a low susceptibility to many of them. It is also included in the WHO priority group 1 of infections that urgently require novel treatment options. *P. aeruginosa* exhibits greater resistance to carbapenem as a result of reduced porin permeability and overproduction of AmpC[69]. Furthermore, P. aeruginosa has the ability to express imipenem metallo-b-lactamases, KPCs and ESBLs, which causes significant levels of carbapenem resistance (Figure No.1F). Successful treatments are becoming more difficult to treat due to the rising prevalence of multidrug-resistant isolates. While colistin, a last-resort antibiotic, is still effective in most cases, its widespread use in pig and poultry farming in the past has already led to the reporting of resistance due to genes like ESBLs and carbapenamases. AmpC b-lactamase, which is capable of hydrolyzing cephalosporins and broadspectrum penicillins, is hyperproduced in Enterobacter species[69-71]. B-lactams and carbapenems cause this overproduction, which is linked to higher death rates and the development of resistance during the course of treatment[72,73]. Many strains of Enterobacter spp. are only sensitive to a few last-resort antibiotics, as tigecycline and colistin, because of their propensity to quickly build resistances[74]. The urgent need for new antimicrobial drugs has been highlighted by the recent reports of even resistance to tigecycline and colistin, either via plasmid-mediated mobilized colistin resistance (mcr) genes or due to chromosomal mutations in genes of two-component systems (TCS) such as pmrA/B and phoP/Q and their regulators mgrB and pmrD[75-77].

In addition to the ESKAPE infections, another newly discovered human pathogen that is becoming more resistant to metronidazole is the spore-forming, Gram-positive bacterium Clostridioides difficile (formerly known as Clostridium difficile until 2016)[78]. Since beginning to track C. difficile infections (CDIs) in 2016, the European Centre for Disease Prevention and Control (ECDC) has identified metronidazole resistance in 26/569 (4.6%) of the cases[79]. Since a novel plasmid (pCD-METRO) granting metronidazole resistance has been discovered and is present in both animal and human isolates of C. difficile, the advent of metronidazole resistance is especially concerning[80]. Drug-resistant C. difficile should become less common and spread more slowly if broad-spectrum antibiotics are not used blindly and CDIs are closely monitored globally. Antibiotic resistance has already been the subject of numerous outstanding evaluations[81-89]. We want to continue concentrating on hard-to-treat infections, phenotypic variability, antibiotic persistence, and tolerance. We'll talk about how they can make treatment more difficult and potential preventative measures against bacterial infections in the future.

ANTIBIOTIC RESISTANCE IN THE ENVIRONMENT

Long before people began mass-producing antibiotics to cure and prevent infectious diseases, many bacterial species had the capacity to withstand the[90,91]. The pre-antibiotic era's dominant resistance mechanisms can be understood by examining isolated caves[91], permafrost cores[90] and other settings and specimens that have been preserved from anthropogenic bacterial contamination[92,93]. The constant competition between microorganisms for resources, including the natural production of secondary metabolites that are similar to many of the antibiotics used as pharmaceuticals today, is probably a major factor in the ancient and ongoing evolution of resistance mechanisms[94-96]. The relatively recent introduction of antibiotics as therapeutic agents drastically altered the conditions for the evolution and dissemination of resistance by posing previously unheard-of selection pressures, particularly on domestic animal and human microbiota members and in antibiotic-polluted environments. A wide variety of antibiotic resistance genes (ARGs) have been mobilized and horizontally transferred to numerous bacterial species, especially disease-causing ones, as a result of this selection pressure[97]. The ultimate, well-known result of these cumulative evolutionary processes is a progressive increase in the challenges associated with treating and

preventing bacterial illnesses. The linkages between the human, animal and environmental microbiota (the One Health Concept) must be understood and acknowledged since bacteria and genes frequently transcend habitats and species borders[98,99] to address this worldwide health concern[100-112].

In this Review, we outline our current understanding of how the environment contributes to the evolution of resistance and serves as a conduit for the spread of germs that are already common in human populations. We describe in detail how environmental resistance research could serve as a proxy for the local clinical resistance context, enhancing the role of traditional surveillance. In addition, we offer a critical analysis of the approaches taken in the investigation of environmental antibiotic resistance, especially as they relate to the evaluation of selection forces. Lastly, we pinpoint a few guiding principles for risk-reduction tactics, paying special attention to issues facing low- and middle-income nations and emissions resulting from the production of antibiotics.

RESISTANCE EVOLUTION IN THE ENVIRONMENT

Both the incorporation of foreign DNA by a bacteria and changes in its pre-existing genome can result in antibiotic resistance. When a patient or animal receives antibiotic treatment, mutations are easily caused and eventually repaired. It is uncommon elsewhere for viruses to face such a high selection pressure. Furthermore, the process operates independently of other species' genetic reservoirs. Therefore, for the majority of infections, external factors are generally less likely to play a significant role in the mutation-based development of resistance. Water, soil, and other habitats with highly varying ecological niches offer an unequaled gene pool with a variety that considerably surpasses that of the human and domestic animal microbiota with regard to the uptake of novel resistance factors[113,114]. The ambient microbiome's greatest remarkable characteristic is, in fact, its extreme variety, which offers a multitude of genes that pathogens may acquire and utilize to potentially offset the effects of antibiotics[115-119]. At least some of the pathogens targeted by all licensed antibiotic classes to date-whether they are synthetic, semi-synthetic, or natural compounds-have developed resistance to them. This implies that, unless we start having drastically new ideas about how antibiotics are made, external surroundings currently include resistance elements for any antibiotics that will ever be developed. Most ARGs have most likely progressively developed from genes with different functions throughout ages[120,121]. Their widespread appearance in pathogens can be attributed to more recent evolutionary processes, primarily to transfer events from ancestral species that changed the general functionality of the genes. A virus usually evolves sequentially toward acquired resistance from an initial chromosomal, stationary ARG (Figure No.2). Typically, the initial phase involves an ARG's capacity to migrate across the genome, which can be achieved by several means such as joining forces with insertion sequences[122,123] or creating gene cassettes and integrating them into integrons[124,125].

The gene must be moved to an autonomously moving element between cells, either a plasmid or an integrative conjugative element, in the second stage. Because of the presence of faecal bacteria, which are known to frequently carry these genetic elements, or because of conditions that may encourage frequent gene exchanges due to recurring stress, certain environments are probably more likely than others to provide the various genetic elements typically involved in mobilization and transfer of ARGs[126,127]. The horizontal transmission of a mobilized resistance gene to a pathogen, either directly or through a number of intermediate bacterial hosts, is the third stage. The physical transfer of the ARG-carrying bacterium to the human or domestic animal microbiota is the fourth phase, which can happen at any point in the process. This ability is referred to as "ecological connectivity"[128]. Large-scale cell-to-cell contact (as in biofilms) and high metabolic activity are most likely speeding up most processes. Antibiotics may

facilitate all of these processes, such as mobilization through integrons or insertion sequences[129,130], increases in donor cell abundance and consequent transfer chances, and the rate of horizontal gene transfer (HGT)[131,132]. Crucially, however, the majority of steps-if not all of them-also take place, albeit at varying rates, in the absence of antibiotics[133,134]. Therefore, it is critical to comprehend the locations of the bottlenecks in viruses' evolutionary transition towards resistance. The selection of uncommon genotypes with acquired resistance resulting from mobilization and/or HGT-genotypes that would otherwise become extinct-is probably going to be a crucial bottleneck[135]. Compensatory mutations may arise at any point in the bacterium's genome that carries the ARG, minimizing possible fitness costs by either enhancing competitiveness or decreasing niche overlap[136]. Only when all the events line up in terms of time and space may new ARGs appear in the clinic[137]. All, some, or none of the evolutionary stages might, in theory, take place in the outside world. 21 of the 22 ARGs with compelling evidence for their recent origin, down to the species level, originated from species that are occasionally linked to illnesses in domestic animals and/or humans[138].

This significant overrepresentation is consistent with the theory that, in the face of antibiotic selection pressure, domestic animals and/or humans provide the most significant settings for the development of resistance. Nevertheless, the vast majority of ARGs have an unknown recent origin, most likely due to their ancestry in as-yet-unsequenced environmental species. This alternative theory supports the external world playing a considerably larger influence. Changes in the genetic background around ARGs that impact resistance level, co-selection chances, pathogenicity, or transmission potential can compound the resistance challenge, even while the introduction of novel ARGs to pathogens is concerning. The outcomes of transmission events of genotypes that are already extensively circulating are very different from those of evolutionary events that result in the establishment of pathogens with novel, effective resistance genotypes through any of these pathways (as explained below). A new genotype that is more difficult to treat can propagate globally irreversibly[139] even from single incidents. Critical evolutionary events are harder to forecast than transmission since they are more uncommon and sometimes unique in nature. However, there can be significant advantages to being able to postpone or stop their onset.

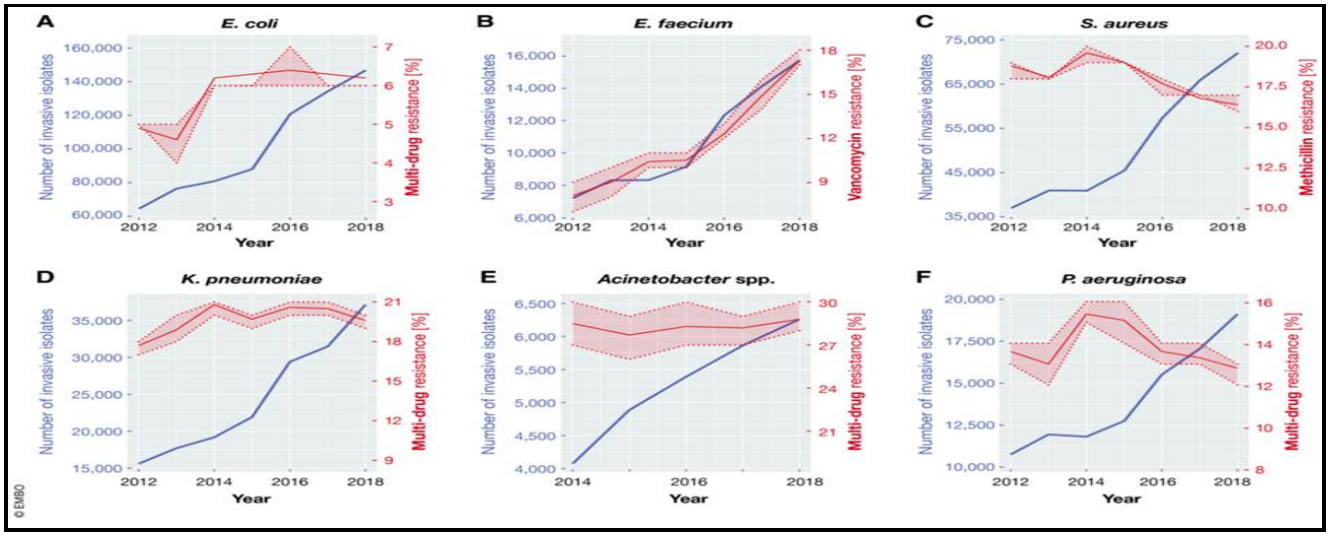

Figure No.1: A- The emergence of resistance to invasive bacterial isolates in the European Union (EU) and European Economic Area (EEA) throughout time

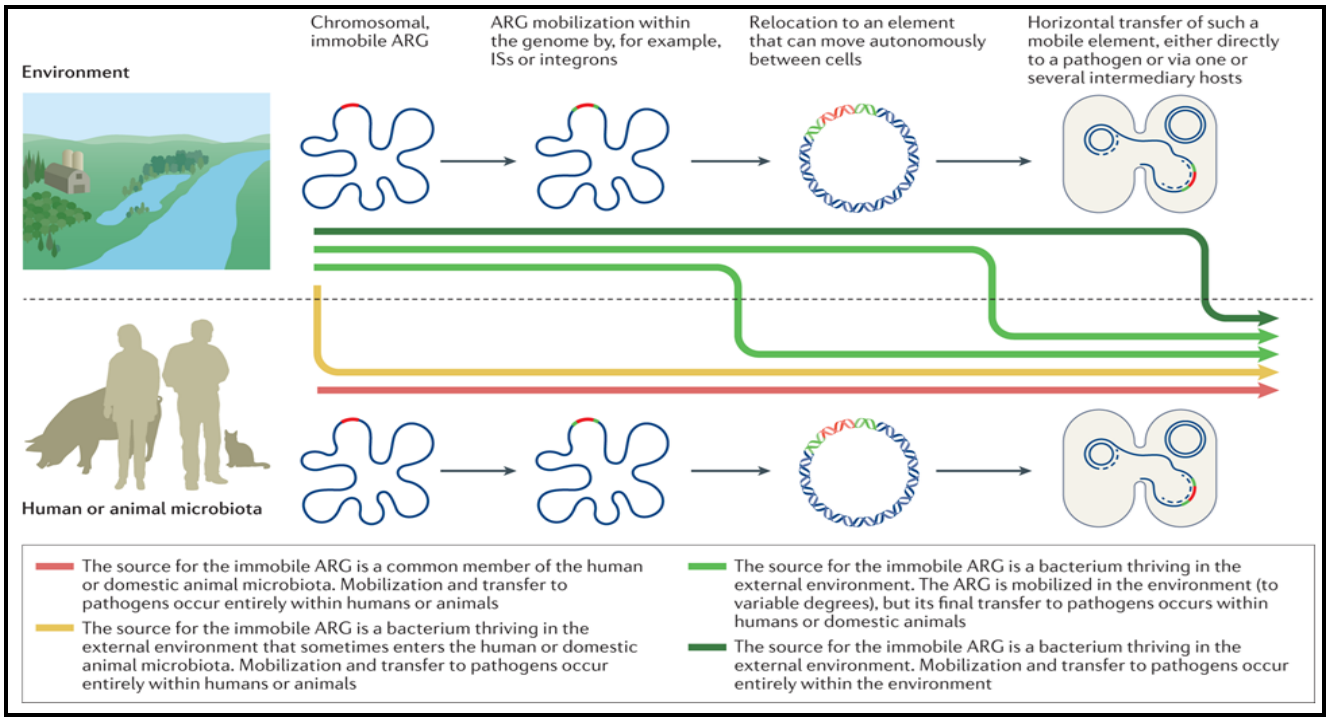

Figure No.2: The part that environmental factors play in the development of novel resistance genes in viruses

CONCLUSION

Antibiotics have enabled the condition of medicine as it is today. It was believed that infectious diseases had been eradicated by the end of the previous century and the middle of the 20th century was even referred to as the and quot; antibiotic era and quot; In addition, effective invasive and expensive operations like organ transplantation and immunomodulatory treatments in rheumatology and oncology have depended heavily on antibiotics. Antibiotics have also proven crucial for many other medical disciplines. The availability of antibiotics has significantly reduced child mortality, increasing life expectancy overall. Nevertheless, a growing number of bacteria are becoming resistant to a number of the currently available antibiotics, which is causing multidrug resistant (MDR) microorganisms to arise. Due to a shortage of new antimicrobial drugs and an increase in MDR bacteria that are causing treatment failures, antibiotic-resistant bacteria have become a significant threat to modern health care.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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