Egyptian Journal of Animal Health

P-ISSN: 2735-4938 On Line-ISSN: 2735-4946
Journal homepage: https://ejah.journals.ekb.eg/

Article Review

An Overview on Bacterial Antimicrobial Resistance

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Received in 18/6/2025
Received in revised from 9/7/2025
Accepted in 17/8/2025

Keywords:

Antimicrobial Resistance
Types
mechanisms

ABSTRACT

Background: Antibiotic resistance among bacteria represents a critical challenge to global public health and food safety. Pathogenic bacterial strains are increasingly exhibiting resistance to widely used antimicrobial agents, thereby complicating treatment outcomes. Antibiotic-resistant bacteria are defined as those that can tolerate the inhibitory or bactericidal effects of antibiotics, maintaining viability and proliferative capacity despite exposure. These organisms employ diverse molecular and physiological mechanisms to evade the action of antibiotics. Development and antimicrobial resistance (AMR) propagation are primarily driven by the irrational and non-evidence-based use of antimicrobial agents in human clinical settings, food-producing animal agriculture, veterinary medicine, environmental contamination with antimicrobial compounds, and inadequate infection control measures within healthcare settings. Laboratory-based antimicrobial susceptibility testing (AST) remains essential for characterizing the resistance profile of bacterial isolates and guiding effective therapeutic interventions.

Aim: Elucidating the molecular mechanisms by which bacteria evade antimicrobial action is essential for identifying global resistance trends, optimizing the clinical application of existing therapeutics, and informing the development of novel agents with reduced susceptibility to resistance. Such insights also underpin innovative approaches targeting the mitigation of the spread and impact of antimicrobial resistance.

Conclusion: Antibiotic resistance contributes to prolonged hospitalizations, elevated healthcare expenditures, and Elevated mortality burden. Mitigating This worldwide public health challenge requires a multifaceted approach, including judicious antibiotic prescribing, the development of novel antimicrobial agents, stringent infection control protocols, adherence to hygiene standards, regulatory oversight, and robust surveillance systems for both antimicrobial resistance and antibiotic consumption.

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DOI: 10.21608/ejah.2025.448557

INTRODUCTION

Antibiotics, once hailed as 'wonder drugs,' have been widely used for treatment and prevention in medicine, agriculture, and animal husbandry. Resistance occurs when bacteria survive and multiply despite therapeutic antibiotic levels, rendering the drugs ineffective **(Zaman et al. 2017).**

Antibiotics serve as a cornerstone in controlling bacterial infections, such as community-acquired pneumonia induced by *Streptococcus pneumoniae*, as well as being integral to modern healthcare systems **Annual Report of the Chief Medical Officer (2011)**.

Resistance to antibiotics is considered a global health threat driven by the dissemination of resistant microorganisms and genetic elements among animals, humans, and environmental reservoirs, leading to substantial morbidity and mortality worldwide (**Joakim & Carl-Fredrik, 2022; Blair et al. 2015).**

Widespread antibiotic resistance could make infections harder to treat, potentially deterring patients from undergoing procedures like joint replacement surgery. As a true One Health concern, antibiotic resistance requires coordinated monitoring and control across human medicine, animal husbandry, agriculture, and aquaculture (**Annual Report of the Chief Medical Officer, 2011).**

Antibiotic resistance imposes substantial societal costs, including higher mortality, morbidity, healthcare utilization, and productivity loss. A report from Iceland, the EU, and Norway estimated 25,000 deaths annually and €1.5 billion in combined hospital and societal expenses due to resistant infections (**CDC, 2013)**.

Both WHO reports and the Lancet underscore the Multiple contributing elements of AMR and emphasize One Health approaches **(CDC, 2022)**, which acknowledge the integrated relationship among human, animal, and environmental health, as in Figure 1.

Historically, veterinarians relied on clinical experience to select antimicrobials for treating bacterial infections. However, rising resistance to commonly used agents has made empirical selection increasingly challenging (**White et al. 2001**).

Antibiotics exert cytotoxic or cytostatic effects on microorganisms, aiding the immune system of the host to eliminate infections. These agents are predominantly small molecules synthesized by microorganisms, capable of exerting biological effects at low doses. However, some classes as oxazolidinones and sulfonamides, are synthetic and not derived from natural products **(Martens & Demain, 2017)**

Antibiotic-resistant bacteria pose a major global health concern arising from their resistance to both natural and synthetic antibiotics **(Coates et al. 2002)**. Multi-drug-resistant bacteria (MDRB), which exhibit resistance to three or more antibiotics, are increasingly encountered in clinical settings **(Kuenzli et al. 2014)**. Resistance may be intrinsic or acquired, often driven by irrational antibiotic use. Key mecha-

nisms include reduced antibiotic uptake, target site modification, and enzymatic degradation of active compounds **(Blair et al. 2015)**.

The antibiotic resistance crisis stems from widespread overuse and misuse of antibiotics, compounded by limited pharmaceutical investment in new drug development due to economic disincentives and regulatory hurdles **(Michael et al. 2014**). The CDC's threat categorization highlights bacterial pathogens that not only challenge clinical management but also impose significant economic and emotional burdens on affected individuals and healthcare systems **(Rossolini et al. 2014**).

Antibiotic resistance is not confined to hospital settings. As healthcare delivery has expanded, the boundaries between community and the clinical facilities have blurred, with residential and nursing homes also emerging as important vehicles of resistant pathogens (**Sabtu et al. 2015**).

Excessive usage of antibiotics in medicine and/or agriculture accelerates the emergence of resistance mechanisms, undermining the effectiveness of clinically important antimicrobials. Antimicrobial resistance (AMR) contributes to treatment failures, increased mortality and morbidity, and rising medical expenditures (**Avesar et al. 2017**).

For certain pathogens-mainly Gram-negative bacteria, particularly as Enterobacteriaceae family, Pseudomonas aeruginosa, and Acinetobacter baumannii therapeutic options become increasingly limited (**Livermore, 2009**).

This article will demonstrate:

1- What is antibiotic resistance?

2- Methods for detection of Antimicrobial Resistance.

- The conventional approach of screening for AMRs.
- Disk diffusion method
- Broth and agar dilution methods .
- Molecular Methods for Detection of Antimicrobial Resistance.

3- Bacterial Resistance Mechanisms

a) Efflux Pumps
b) Antibiotic Inactivation
c) Target Modification
d) Reducing Entry of Antimicrobial Agents
e) Mutation
f) Biofilm Formation

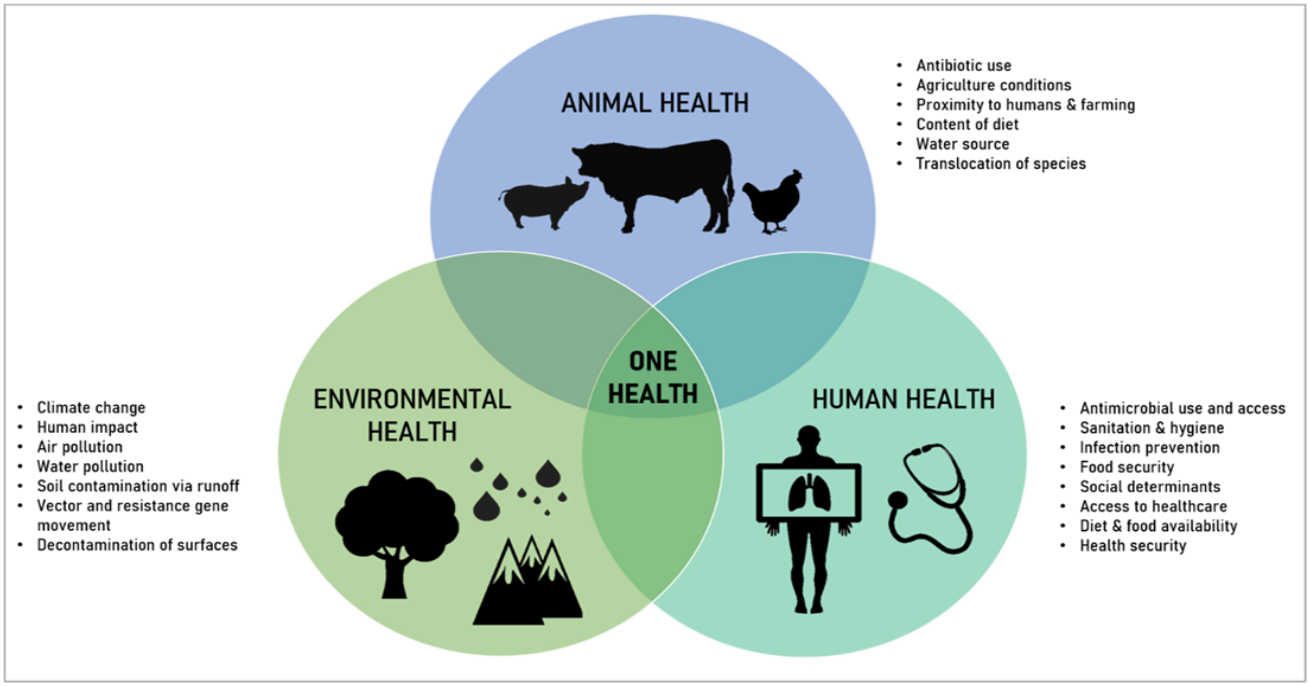
4- Examples for Antibiotic-Resistant Bacteria**.**

Methicillin-Resistant *Staphylococcus aureus*
ESBL-Producing *E. coli*
Pseudomonas aeruginosa

5- Strategies to Minimize and control the antibiotic Resistance

a) Strategy to protect antibiotics and prevent further resistance.
b) Reinvigorating drug development pathways and bringing new antibiotics into markets.

Figure 1. One Health Diagram



Source: Prinzi *et al.* (2022)

1- What is antibiotic resistance?

Antibiotic resistance occurs when a microorganism can grow or survive despite exposure to therapeutic concentrations of an antibiotic that would typically inhibit or eliminate the same species of microorganisms. In clinical practice, the classifications 'susceptible' or 'resistant' are used in predicting the likelihood of treatment effectiveness versus suboptimal therapeutic response. Resistance is particularly concerning when the effective drug concentration exceeds the therapeutic window permitted by safety margins (**Sabtu et al. 2015**).

Microorganisms may exhibit intrinsic resistance to certain antibiotics or acquire resistance following exposure. Acquired resistance arises from genetic mutation or horizontal gene transfer. Dissemination of Resistance genes can be via transduction (bacteriophage-mediated transfer), conjugation (plasmid-mediated transfer) or transformation (uptake of free DNA). These mechanisms enable efficient spread of resistance genes across bacterial populations, including between unrelated species (**Livermore, 2004**).

The spread of resistant phenotypes within previously susceptible species is variable and often changeable. For instance, the β-lactamase gene has disseminated widely in *S.aureus*, *Haemophilus influenzae*, and many *Enterobacteriaceae*, yet has not become prevalent in enterococci. Conversely, vancomycin resistance genes such as *vanA*, though present in enterococci, remain rare in *S. aureus* (**Sabtu et al. 2015**).

Antibiotic resistance is rising at an alarming pace, rendering infections such as pneumonia, tuberculosis, and gonorrhea increasingly difficult or impossible to treat. Antibiotic-resistant infection prevalence is closely related to the antibiotic consumption (**Zaman et al. 2017**).

2- Methods for the detection of Antimicrobial Resistance:

Antimicrobial susceptibility testing is a laboratory technique for assessing resistance in isolated bacteria. It determines an isolate's susceptibility to therapeutic agents and is also valuable for tracking emerging and disseminating the resistant microorganisms within populations (**Jorgensen & Turnidge, 2015**).

Guidelines for antimicrobial susceptibility testing are regularly updated by international organizations. Key bodies specifying testing and interpretation criteria for veterinary microorganisms include the Clinical and Laboratory Standards Institute (CLSI) in the USA, the World Organisation for Animal Health (OIE) in the EU, and the CDS-AST in Australia **(Guetaba, 2015).**

a) The conventional approach of screening for AMRs

The process comprises inoculating clinical specimens on antibiotic-selective agar, isolating separate bacterial colonies, and applying methods such as broth dilution or disk diffusion, gradient strip testing to assess the minimum inhibitory concentration (MIC) for antibiotic groups **(Randall et al. 2014).** MIC values are then interpreted using clinical breakpoints provided by organizations such as the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI) **(Matuschek et al. 2014).**

Conventional phenotypic antibiotic susceptibility techniques remain fundamental in regular diagnostics, as they assess directly bacterial growth in the presence of antibiotics on liquid or solid media. Solid media-based tests, as disk diffusion and E-test assays, typically need 18–22 hours for visible bacterial growth to allow evaluation of inhibition zones (**Veses Garcia et al. 2018**). In contrast, molecular analysis can be used to detect specific antimicrobial resistance genes, offering faster and more targeted insights (**Anjum et al. 2017**).

Agar disk diffusion and broth microdilution are the most dominant antibiotic sensitivity testing techniques in veterinary laboratories. Other approaches include broth and agar dilution, E-test, automated systems, and genotypic assays (**Balouiri et al. 2016**).

b) Disk diffusion method: In the disk diffusion method, a standardized volume of antimicrobial compound diffuses from disks, tablets, or gradient strips in the surrounding agar medium inoculated with a pure bacterial inoculum. The resulting inhibition zone reflects the organism's susceptibility, with its diameter correlating to the MIC of the bacterium–antibiotic pair. Generally, a larger zone indicates greater susceptibility, though this depends on the antibiotic's concentration and diffusion properties. Although manual zone measurement is labor-intensive, automated readers are commercially available and can be seamlessly integrated into laboratory information systems **(OIE Terrestrial Manual, 2012).**

c) **Broth and agar dilution methods:** they are employed for determining the MIC defined as the lowest concentration of an antimicrobial agent visibly suppressing bacterial growth, typically reported in µg/mL or mg/L. Importantly, the MIC isn't an exact value but rather falls between the lowest concentration that inhibits growth and the next lower concentration tested. To ensure accurate interpretation, the range of antimicrobial concentrations should encompass the established clinical breakpoints (susceptible, intermediate, resistant) specific to each bacterium–antibiotic pairing, and must include appropriate quality control reference strains to validate assay performance **OIE Terrestrial Manual (2012).**

The broth dilution method: it is accomplished using either macrodilution (in tubes with ≥2 mL) or microdilution (in microtiter plates with smaller volumes). Commercially available microtiter plates often contain lyophilized, pre-diluted antibiotics in individual wells. Using standardized plate lots helps minimize inter-laboratory variation caused by manual preparation and dilution of antimicrobials. These plates should be used in conjunction with a validated and documented test protocol to ensure consistency and reliability **OIE Terrestrial Manual (2012).**

Agar dilution involves incorporating serial

twofold concentrations of an antimicrobial agent into agar media, followed by inoculating the surface with a standardized bacterial suspension. This method is considered one of the most reliable for determining the MIC of a specific bacterium-antimicrobial combination. Key advantages include the capability to test numerous bacterial isolates simultaneously on the same testing plates-excluding swarming organisms, which may interfere with interpretation **OIE Terrestrial Manual (2012).**

Other bacterial AST and specific antimicrobial resistance tests:

Minimum inhibitory concentrations (MICs) may be determined utilizing commercially available gradient strips, which release a predefined amount of antibiotics along a gradient. While convenient, these strips are relatively expensive and may yield inconsistent MIC results for certain bacterium–antimicrobial combinations when compared to agar dilution methods (**Rathe et al. 2009**).

Regardless of the antimicrobial susceptibility testing technique employed, procedures must be meticulously recorded to confirm accuracy, reproducibility, and data validity. Routine inclusion of appropriate reference strains is essential for quality control during each AST run. The choice of AST method should be guided by growth characteristics of the target bacteria. In specific cases, specialized assays may offer superior sensitivity or specificity for detecting particular resistance mechanisms.

Beta-lactamase detection: Chromogenic cephalosporin-based assays, such as nitrocefin tests, can provide rapid and reliable identification of beta-lactamase activity in some bacterial isolates (**CLSI, 2008**).

Inducible clindamycin resistance: In *Staphylococcus* spp., the D-zone test-using adjacent erythromycin and clindamycin disks-can reveal inducible resistance by observing blunted inhibition zones (**Zelazny et al. 2005**).

Extended-spectrum beta-lactamase (ESBL) activity: ESBL production in organisms such as *Enterobacteriaceae* can be detected via disk diffusion assays incorporating cephalosporins (e.g., cefotaxime, ceftazidime) with and without clavulanic acid, a beta-lactamase inhibitor (**CLSI, 2008**). **OIE Terrestrial Manual (2012)**

d) Molecular Methods for Detection of Antimicrobial Resistance

Advanced DNA-based assays have revolutionized AMR by targeting genetic determinants directly. The most advanced methodologies for predicting antimicrobial resistance phenotypes rely on identifying and characterizing genes associated with defined resistance mechanisms. Approaches such as comparative genetic probes, microarrays, genomics, nucleic acid amplification techniques (such as polymerase chain reaction [PCR]), and DNA sequencing provide enhanced rapid detection, sensitivity, and specificity of well-established Resistance-related genetic markers (**Cai et al. 2003**).

Genotypic methods have proven valuable in complementing traditional phenotypic AST approaches, particularly for:

- **Methicillin-resistant staphylococci (MRSA)**: Detection of *mecA* and related resistance genes (**Cai et al. 2003)**
- **Vancomycin-resistant enterococci (VRE)**: Identification of *vanA*, *vanB*, and other resistance loci **(Chen et al. 2005)**

Fluoroquinolone resistance: Characterization of mutations in *gyrA*, *parC*, and other quinolone resistance-determining regions (**Perreten et al. 2005)**

Cutting-edge DNA-based diagnostics now support multiplex detection of clinically relevant resistance genes and their variants in a single assay, offering rapid, comprehensive insights that inform targeted antimicrobial therapy.

The integration of rapid pathogen identification with genotypic resistance profiling holds promise for curbing antimicrobial resistance by guiding early, targeted therapy with the most appropriate antimicrobial agents.

Nonetheless, genotypic methods must be

validated as complementary to conventional AST, ensuring that genetic findings align with phenotypic susceptibility profiles. Emerging platforms also offer the potential in screening bacterial isolates for extensive panels of antibiotic resistance genes both rapidly and cost-effectively, enhancing the utility of these tools for public health surveillance and antimicrobial stewardship programs (**Frye et al. 2010**).

Emerging diagnostic techniques are enabling earlier detection of infections and antimicrobial resistance compared to traditional techniques and sensitivity testing. In addition, biomarkers as procalcitonin and C-reactive protein (CRP) have shown potential in guiding antibiotic stewardship by helping clinicians differentiate bacterial from non-bacterial infections, thereby reducing inappropriate antibiotic prescriptions (**Schuetz et al. 2012**).

Molecular methods, particularly polymerase chain reaction (PCR), have significantly improved the speed and accuracy of resistance detection. For example:

- **MRSA identification**: PCR enables accurate and rapid detection of methicillin-resistant *Staphylococcus aureus* directly from clinical specimens.

Rifampicin resistance in *Mycobacterium tuberculosis*: Genetic assays can identify mutations associated with resistance, facilitating timely initiation of appropriate therapy (**Drobniewski et al. 2000**).

Advanced molecular and analytical technologies are increasingly being employed to accelerate the detection of antibiotic resistance and pathogen identification. Multiplex PCR assays and next-generation sequencing (NGS) allow instant detection of multiple resistance genes, earlier as well as more comprehensive insights into resistance profiles.

Mass spectrometry-based identification methods, such as Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF), have significantly decreased the time required for identifying cultured bacteria in comparison to conventional biochemical techniques.

In parallel, automated susceptibility testing platforms are emerging as valuable tools for expediting antimicrobial susceptibility results, potentially improving clinical decision-making and patient outcomes (**Greatorex et al. 2014**).

Bacterial Resistance Mechanisms

Understanding how bacteria resist antibiotics is key to combating antimicrobial resistance. Misuse—especially incomplete antibiotic courses—can promote survival of resistant strains. Mechanisms of resistance include:

a) Efflux Pumps

Efflux transport proteins actively extrude antibiotics from the cell, thereby reducing intracellular drug concentrations. These pumps often exhibit broad substrate specificity, enabling them to eject a wide range of antimicrobial agents (**Giedraitienė et al. 2011).**

b) Antibiotic Inactivation

Bacteria employ multiple strategies to render antibiotics inactive, including the transfer of functional groups, redox-based modifications, and enzymatic hydrolysis. A classic example is the production of β-lactamases, which hydrolyze the ring of β-lactam of penicillins, thereby neutralizing their antimicrobial activity. These enzymes are often secreted extracellularly, allowing bacteria to inactivate antibiotics before they reach their intracellular targets.

Another prominent mechanism comprises enzyme-mediated structural modification of antibiotics through functional groups transference, such as ribosyl, acyl, phosphoryl, or thiol moieties. These alterations result in irreversible changes to the drug's structure, preventing effective binding to its target site **(Kumar & Varela, 2013).**

c) Target Modification

Modification of target sites of antibiotic impairs the drug's ability to bind effectively, thereby reducing its antimicrobial activity. Because these targets are often essential for vital

cellular functions, bacteria cannot simply eliminate them. Instead, they evolve mechanisms to structurally alter the target molecules, diminishing drug affinity while preserving function. A well-characterized example is the staphylococcal alteration of Penicillin-Binding Proteins (PBPs), which are the main targets of β-lactam antibiotics. These modifications reduce the binding efficiency of the drug, contributing to resistance **(Davies & Davies, 2010).**

Reducing Entry of Antimicrobial Agents

Frequently, antimicrobial compounds require access into the bacterial cell to reach their target site. Porin channels are the passageways by which antibiotics cross the outer membrane of the bacteria. Some bacteria protect themselves by preventing these antimicrobial compounds from entering their cell walls (**Poole, 2002).**

e) Mutation

Mutation refers to a spontaneous alteration in the sequence of DNA of a gene, potentially leading to changes in the trait it encodes (**Ali et al. 2018**). Even a single base-pair substitution can result in replacing one or more amino acids, thereby modifying the structure or function of enzymes and cellular components. Such changes may alter the binding affinity or activity of targeted antimicrobial agents, contributing to resistance

In prokaryotic genomes, mutations commonly arise from base substitutions induced by exogenous factors, errors by DNA polymerase, or structural changes such as deletions, insertions, and duplications (**Martínez & Baquero, 2000**).

f) Biofilm Formation

Biofilms are structured microbial communities composed of bacteria and fungi, encased within a self-produced extracellular matrix. This matrix-rich in polysaccharides, proteins, and nucleic acids- anchors the biofilm to both biotic and abiotic surfaces, forming a dense, protective barrier.

Within biofilms, microorganisms are embedded in a thick, slimy layer that shields them from environmental stressors, including antimicrobial agents. The physical barrier limits drug penetration, while the high cell density promotes genetic exchange and increases the likelihood of resistant mutants emerging under antimicrobial pressure (**Soto, 2013**).

Examples for Antibiotic-Resistant Bacteria:

1) Methicillin-Resistant Staphylococcus aureus (MRSA)

Staphylococcus spp. is among the most prevalent bacteria affecting both humans and animals, commonly implicated in skin and mucosal infections. Their clinical significance is amplified by their ability to acquire resistance to multiple antimicrobial agents **(Guo et al. 2020).** Over time, *Staphylococcus aureus* has accumulated diverse resistance traits, rendering it refractory to several antibiotic classes **(Avorn et al. 2011).**

Mechanisms include chromosomal mutations, impaired aminoglycoside uptake, and enzymatic drug modification **(Lowy, 2003).**

MRSA strains are defined by the acquisition of the mecA gene, that encodes penicillin-binding protein 2a (PBP2a)- a transpeptidase of low affinity for β-lactam antibiotics. This confers resistance not only to methicillin but also to virtually all β-lactams, posing a worldwide public health threat **(Arsic et al. 2012).** MRSA strains, including those associated with livestock, were frequently isolated from several dairy products such as raw milk and raw-milk products **(Peton & Le Loir, 2014**).

The primary mechanisms of β-lactam resistance in *S. aureus* include:

β-lactamase production, conferring resistance to natural penicillins and extended-spectrum agents.

PBP2a expression, which prevents β-lactam binding and disrupts cell wall synthesis.

Resistance is encoded by mecA or its homologue mecC, both placed on the staphylococ-

cal cassette chromosome mec (SCCmec). These genes render penicillins, cephalosporins (except ceftaroline), carbapenems, and monobactams ineffective. The mecC variant (e.g., *mecALGA251*) has been identified in isolates from humans, pets, and wildlife across Europe, with cattle recognized as a major reservoir (**Gómez et al. 2016).**

MRSA strains often harbor additional resistance genes, conferring multidrug resistance (MDR) to sulfonamides, aminoglycosides (gentamicin, kanamycin, streptomycin), macrolides, fluoroquinolones, and tetracyclines **(Kizerwetter-Świda et al. 2016).** Fluoroquinolone resistance, for instance, is frequently mediated by mutations in topoisomerase II (gyrA, gyrB) and topoisomerase IV (parC, parE)—enzymes essential for DNA replication. Concerning mutations in the quinolone resistance-determining region (QRDR) alter active sites, reducing drug binding and leading to cell survival under antimicrobial pressure.

Another major resistance mechanism involves plasmid-mediated gene acquisition, enabling horizontal transfer of resistance determinants across bacterial populations **(Jacoby et al. 2014).**

This facilitates rapid adaptation and dissemination of resistance traits, especially in environments with high antibiotic exposure.

ESBL-Producing *E.coli*

Escherichia coli (*E. coli*) is a prevalent inhabitant of the intestinal microbiota in both mammals. Within this species, strains may be broadly classified into non-pathogenic commensals and pathogenic variants. The pathogenic forms include intestinal pathogenic *E. coli* (IPEC), which are associated with gastrointestinal infections, and extraintestinal pathogenic *E. coli* (ExPEC), that implicated in systemic diseases such as urinary tract infections and septicemia.

Among IPEC strains, several distinct pathotypes were identified according to their virulence profiles and clinical manifestations. These include **(Kotłowski et al. 2020)**

- Enterotoxigenic E. coli (ETEC)
- Diffusely adherent E. coli (DAEC)
- Enteropathogenic E. coli (EPEC)
- Enterohaemorrhagic E. coli (EHEC)
- Enteroinvasive E. coli (EIEC)
- Enteroaggregative E. coli (EAEC)
- Adherent invasive E. coli (AIEC)

A major antimicrobial resistance mechanism in *Enterobacteriaceae* is the production of extended-spectrum β-lactamases (ESBLs)-enzymes that hydrolyze and inactivate a broad range of β-lactam antibiotics, including monobactams, cephalosporins, and penicillins. These enzymes are typically encoded on plasmids, facilitating horizontal gene transfer and rapid dissemination among bacterial populations. Importantly, ESBL-producing *E. coli* strains often exhibit co-resistance for several antibiotic classes such as quinolones, aminoglycosides, and sulfonamides. This multidrug resistance significantly complicates treatment, as therapeutic options become increasingly limited, posing a serious challenge to effective clinical management **(Rawat & Nair, 2010**).

4)Pseudomonas aeruginosa Resistance Mechanisms

Pseudomonas aeruginosa exhibits remarkable adaptability in developing resistance to antimicrobial agents. This resistance can arise either through the acquisition of foreign genetic material as plasmids and other mobile elements, or via spontaneous chromosomal mutations that modify the expression or function of intrinsic resistance pathways. One of the predominant mechanisms by which P. aeruginosa becomes resistant to aminoglycosides is through enzymatic modification, which chemically inactivates the antibiotic.

Beyond the broad spectrum of aminoglycoside-modifying enzymes, high-level resistance has also been linked to methylation of the 16S ribosomal RNA, a process that interferes with drug binding at the ribosomal target site. This methylation mechanism was initially identified in *P. aeruginosa* in 1993, with the responsible gene named rmtA. Since then, five methyltransferase enzymes RmtA, RmtB, RmtC, RmtD, and ArmA - have been characterized and reported in some clinical isolates of *P. ae-*

ruginosa as well as various Enterobacteriaceae species worldwide **(Lister et al. 2009).**

P. aeruginosa is the most frequent cause of both community-acquired and hospital-acquired pneumonia. It accounts for approximately 10% of all nosocomial infections globally (**Matta et al. 2018**). The global rise in antibiotic resistance among P. aeruginosa strains is mainly due to the widespread and often inappropriate use of antimicrobial agents (**Yayan et al. 2015**).

Fluoroquinolones resistance (FQs) in *P. aeruginosa* is primarily driven by three mechanisms: (1) point mutations in the genes encoding DNA gyrase (gyrA and gyrB) and topoisomerase IV (parC and parE), which are the molecular targets of FQs; (2) the plasmid-mediated quinolone resistance (PMQR) determinants that can be horizontally transferred; (3) mutations in regulatory genes that influence the expression of efflux pumps and reduce the expression of outer membrane porins, thereby limiting drug uptake (**Yang et al. 2015**).
Additionally, *P. aeruginosa* possesses the ampC gene, which encodes an inducible chromosomal β-lactamase. Mutations in the regulatory gene ampR can lead to overexpression of this β-lactamase, particularly under antibiotic pressure. These mutants are more likely to be selected in clinical settings where monotherapy is employed, further contributing to treatment failure and resistance development (**Ramanathan et al. 2017**).

2) Strategies to Minimize and Control Antibiotic Resistance

Antibiotic resistance is one of multifaceted global challenge requiring coordinated efforts across healthcare, agriculture, research, and policy. Key strategies include appropriate antibiotic use, vaccination, public education, surveillance, regulatory reform, and the development of novel therapeutics (**Laxminarayan et al. 2013**)

A) Protecting Existing Antibiotics and Preventing Further Resistance

The effectiveness of current antibiotics is declining due to rising resistance and a lack of new drugs. Prudent antibiotic use in human medicine, veterinary care, and agriculture is essential to slow resistance and preserve drug efficacy (**Lee et al. 2013**).

Key Measures:

- **Antibiotic Stewardship**: Develop and implement formal prescribing guidelines to prevent misuse and overuse.
- **Rapid Diagnostics**: Invest in molecular tools for early detection and surveillance of resistance genes.
- **Agricultural Reform**: Reduce antibiotic use in food animals through bans, restrictions, and incentives for livestock-specific alternatives.
- **Policy and Regulation**: Enforce stricter licensing, impose penalties for misuse, and promote responsible antibiotic distribution.
- **Education and Vaccination**: Raise public awareness and promote immunization to reduce infection rates and antibiotic demand.

Surveillance Systems: Monitor resistance patterns and antibiotic usage to inform policy and clinical practice (**Tillotson, 2015**).These principles were central to the **One Health** initiative, which promotes stewardship of existing antibiotics and the development of novel diagnostics. In the 2013 annual report, England's Chief Medical Officer suggested placing antibiotic resistance on the national risk register and outlined seven strategic urgencies:

Optimize prescribing practices
Improve prevention and control of infection.
Raise awareness as well as change public behavior
Strengthen research and evidence-based.
Develop new drugs, vaccines, and diagnostics
Enhance surveillance systems
Foster national and international collaboration

B) Reinvigorating Drug Development and Market Access

Despite the urgent need for new antibiotics, development is hindered by regulatory complexity, inconsistent clinical trial standards, and lack of global harmonization. Many promising agents fail to reach the market due to bureaucratic barriers and ineffective communica-

tion between industry, regulators, and research institutions.

Political engagement is growing, and global initiatives are underway to address these challenges. Notably, the Infectious Diseases Society of America (IDSA) hurled the *Bad Bugs, No Drugs* campaign in 2003, advocating for reforms in drug approval processes and increased funding for antimicrobial research (**Boucher et al. 2009**).

CONCLUSION

In conclusion, the escalating threat of antimicrobial resistance demands a multifaceted response that integrates scientific innovation, responsible antibiotic use, and coordinated global action. Understanding bacterial resistance mechanisms—from efflux pumps and enzymatic inactivation to genetic mutations and biofilm formation—is essential for guiding effective diagnostics and treatment. Advances in molecular diagnostics, rapid testing, and surveillance tools offer promising avenues for early detection and containment. Meanwhile, strategic efforts to preserve existing antibiotics, reform agricultural practices, and reinvigorate drug development pipelines—supported by education, policy, and international collaboration—are critical to safeguarding public health and ensuring the continued efficacy of antimicrobial therapies Fig. 2

Figure 2. Elements of Global AMR Collaboration:

Source: Prinzi *et al.* (2022)

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