Surveillance and Impact of Antibiotic Resistance in Emerging Food Borne Pathogens

Ravikant V. Vinchurkar[1*], Kumari M.[2], Somveer[3], Deshmukh RR[1] and B. Lakshmaiah[1]

[1]Ph.D. Scholar, Dairy Microbiology Division, National Dairy Research Institute, Karnal

[2]Teaching Associate, Dairy Engineering Division, CoDST, RAJUVAS, Bikaner

[3]Ph.D. Scholar, Dairy Engineering Division, National Dairy Research Institute, Karnal

*Corresponding Author: ravikantvinchurkar97@gmail.com

Recent research conducted in various regions of India has discovered traces of antibiotics in livestock products such as chicken meat and dairy. This finding indicates widespread antibiotic use in the production of food animals (Boeckel et al., 2015). Gandra et al.'s study in 2016 revealed that *Pseudomonas aeruginosa* exhibited an antibiotic resistance rate exceeding 50%, while *E. coli* and *Klebsiella pneumonia* demonstrated resistance rates of over 70% to the broad-spectrum antibiotics fluoroquinolones and third-generation cephalosporin. In 2010, Kumarasamy et al. investigated Enterobacteriaceae isolates from two significant Indian centers, Chennai (South India) and Haryana (North India). Furthermore, Dixit and other co-authors (2011) highlighted a concerning trend of resistance to novel antimicrobial medicines like carbapenems across various Gram-positive and Gram-negative microorganisms since their release in 2010. They predicted that by 2050, antimicrobial resistance (AMR) would lead to 2 million fatalities annually in India (Laxminarayan *et al.*, 2012). Additionally, their research found that 70-80% of India's Enterobacteriaceae harbored extended-spectrum beta-lactamases (ESBLs). Collectively, these studies underscore the rapid expansion of the antimicrobial resistance issue in India, emphasizing the urgent need for decisive action by various organizations to control AMR.

Epidemiology

Antimicrobial-resistant bacteria are found across the globe, posing a growing challenge in the treatment of common infections. An illustrative case is the increased difficulty in managing urinary tract infections (UTIs) due to the prevalence of resistant *E. coli*, compromising the effectiveness of the Fluoroquinolones on a global scale. Treatment failures for gonorrhea, using 3rd generation Cephalosporins, have been documented in at least 10 countries. In the US alone, over 2.8 million cases of antibiotic resistant infections have been emerging annually, resulting in more than 35,000 deaths. Moreover, the incidence of resistant pathogens directly correlates with sepsis related outcomes, as demonstrated in a current investigation analyzing hospitalized patients from 2011 to 2014. This study identified the highest sepsis rates against Fluoroquinolone resistant *E. coli*, 3rd generation Cephalosporins, Carbapenem resistant *Klebsiella* species, and Vancomycin-resistant *Enterococcus* (VRE).

Mechanisms of Resistance

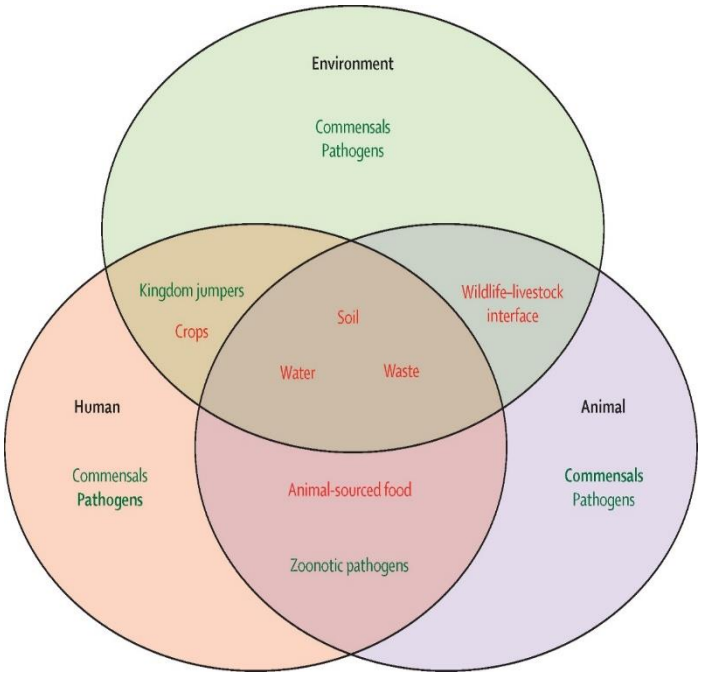

Fig. 1 Different sources of AMR pathogens

There are two types of bacterial resistance: intrinsic and acquired. Intrinsic resistance occurs when the antibiotic has no impact on the pathogen from the beginning. Acquired resistance is gained through the transmission of genetic material that imparts resistance. Specific bacterial genes are situated on plasmids, which are small, circular, double-stranded DNA molecules distinct from chromosomal DNA. These plasmids are transferred from one bacterium to another through a process known as conjugation, and this transfer can occur between bacteria of different species. The mechanisms that

bacteria utilize to develop acquired resistance are encoded on plasmids and can be categorized into four groups.

1) reduced permeability of the cell wall to antibiotics;

2) modification of enzymes to deactivate antibiotics;

3) changes in the drug target site; and

4) efflux pumps that eliminate antibiotics from the cell.

The primary mechanism used by bacteria is drug inactivation through enzymes, and the genes responsible for encoding these types of enzymes might be persuaded by specific medications or constantly expressed.

Multidrug-Resistant *Enterococcus*

Enterococci, which are primarily benign bacteria found in the gut, are a widely recognized group of microorganisms that demonstrate both inherent and acquired resistance to antibiotics. Particularly concerning are *E faecium* and *Enterococcus faecalis*, as they may possess various acquired resistance mechanisms, leading to multidrug resistance (Kumari et al., 2023). These organisms can display a significant level of resistance to beta-lactams (through beta-lactamase enzymes and modified binding proteins), vancomycin (involving alterations in peptidoglycan synthesis, known as VRE), and aminoglycosides (via enzymatic degradation). Ampicillin remains the preferred treatment for susceptible Enterococcus infections; however, options for addressing systemic infections caused by multidrug-resistant Enterococcus are limited, with drugs like linezolid, daptomycin, and tigecycline being among the available alternatives.

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

MRSA first appeared in the early 1960s, shortly after the introduction of methicillin. Like most gram-positive organisms, the cell wall serves as a primary target for antimicrobial agents, leading to the development of acquired antimicrobial resistance. For a bacterium to be categorized as MRSA, it must harbor the mecA gene, responsible for a structural alteration in penicillin-binding protein 2a (PBP2a). This modification hinders the binding of beta-lactam antibiotics to the cell wall. Although laboratory testing for methicillin susceptibility in S aureus is infrequent due to the instability of methicillin plates, MRSA is identified using a similar beta-lactam, oxacillin. According to the Clinical Laboratory Standards Institute, methicillin resistance is defined as an oxacillin mean inhibitory concentration of at least 4 mcg/mL, and oxacillin-resistant isolates also exhibit resistance to all beta-lactams, with a few exceptions such as ceftaroline.

Table 1: List of pathogens and their intrinsic resistance

Organism	Intrinsic resistance
Bacteroides (anaerobes)	aminoglycosides, many β-lactams, quinolones
All gram positives	aztreonam
Enterococci	aminoglycosides, cephalosporins, lincosamides
Listeria monocytogenes	cephalosporins
All gram negatives	glycopeptides, lipopeptides
Escherichia coli	macrolides
Klebsiella spp.	ampicillin
Serratia marcescens	macrolides
Pseudomonas aeruginosa	sulfonamides, ampicillin, 1st and 2nd generation cephalosporins, chloramphenicol, tetracycline
Stenotrophomonas maltophilia	aminoglycosides, β-lactams, carbapenems, quinolones
Acinetobacter spp.	ampicillin, glycopeptides

Extended-Spectrum Beta-Lactamase (ESBL)-Producing Organisms

Many gram-negative bacterial species have developed acquired resistance to beta-lactam antibiotics through the production of beta-lactamase. This enzyme works by deactivating the antimicrobial properties of the antibiotic, specifically by hydrolyzing its beta-lactam ring. The first beta-lactamase identified was a penicillinase found in *E. coli* in 1940, predating the medical use of penicillin. Over time, new antibiotics were created to counteract this enzyme, such as broad-spectrum cephalosporins. However, the introduction of these antibiotics led to resistance against even broader-spectrum agents, resulting in the emergence of the ESBL enzyme. Currently, more than 150 ESBLs have been identified in various species of Enterobacteriaceae and in Pseudomonas aeruginosa.

Pseudomonas aeruginosa

Pseudomonas aeruginosa, a gram-negative opportunistic pathogen, is a common cause of nosocomial infections. Treatment typically involves the use of beta-lactams, fluoroquinolones, and aminoglycosides. However, Pseudomonas often exhibits various mechanisms of resistance. Inherently, *Pseudomonas* has a lower membrane permeability

compared to *E. coli*, making it less susceptible to certain antimicrobials. The resistance mechanisms in *Pseudomonas* include mutations in genes encoding enzymes targeted by fluoroquinolones and the production of aminoglycoside-modifying enzymes for aminoglycoside resistance. Beta-lactam resistance is attributed to modifications in penicillin-binding proteins, efflux pump overexpression, and enzymatic drug inactivation. Exposure to antipseudomonal beta-lactam antibiotics increases the risk of resistance development. A retrospective study with 7,118 patients revealed a 4% increased risk of new resistance for each additional day of antipseudomonal beta-lactam therapy. To mitigate resistance, it is crucial to limit the duration of beta-lactam exposure effectively.

Enterobacteriaceae and ampC Enzyme

Enterobacteriaceae comprise over 100 species, with certain pathogens like *Serratia marcescens, Morganella morganii, Proteus vulgaris, Citrobacter species,* and Enterobacter species possessing the inducible beta-lactamase enzyme ampC. While not initially expressed, ampC can activate in response to certain antibiotics, leading to resistance. Culture and sensitivity reports may not detect ampC, but if resistance to cefoxitin is observed, it can serve as a surrogate marker for ampC. In such cases, avoiding penicillins and narrow-spectrum cephalosporins is advisable to prevent further resistance development.

Impact of Antibiotic Resistance in Food Borne Pathogens

Antibiotic resistance poses a significant threat to public health, particularly when it comes to foodborne pathogens. The widespread use of antibiotics in agriculture, including in livestock for growth promotion and disease prevention, has contributed to the emergence of antibiotic-resistant strains of bacteria. This phenomenon is alarming, as it diminishes the effectiveness of commonly used antibiotics in treating infections caused by these pathogens. When antibiotic-resistant strains of foodborne bacteria, such as *Salmonella* or *E. coli*, proliferate, it not only complicates the treatment of infections in humans but also raises the risk of severe and potentially life-threatening illnesses. Moreover, the transmission of antibiotic-resistant genes from foodborne pathogens to other bacteria further exacerbates the problem. Addressing antibiotic resistance in foodborne pathogens requires a multifaceted approach, including prudent antibiotic use in agriculture, surveillance of resistant strains, and the development of alternative strategies for disease control in both humans and animals. Failure to address this issue comprehensively could lead to a future where treating common infections becomes increasingly challenging and may have dire consequences for global public health.

Conclusion

This article focuses on pathogens and mechanisms directly related to the global challenge of antimicrobial resistance. Bacteria, being ancient organisms, possess inherent survival skills within their environment, including the host undergoing antibiotic treatment. The widening gap between escalating resistance and the development of effective drugs emphasizes the crucial need for enhanced Antimicrobial Stewardship (AMS) and a comprehensive understanding of how bacteria can elude even the most potent antibiotics. Despite efforts to create new antibiotics capable of countering the latest resistance mechanisms, such endeavors have proven futile. The active participation of pharmacists in drug selection and AMS can significantly enhance patient outcomes and curb the further advancement of bacterial resistance. It is imperative to recognize that developing new medications alone does not offer a solution to this crisis; instead, the preservation of existing agents is paramount.

Reference

Kumarasamy, K. K., Toleman, M. A., Walsh, T. R., Bagaria, J., Butt, F., Balakrishnan, R., Chaudhary, U., Doumith, M., Giske, C. G., Irfan, S., Krishnan, P., Kumar, A. V., Maharjan, S., Mushtaq, S., Noorie, T., Paterson, D. L., Pearson, A., Perry, C., Pike, R., Rao, B., Woodford, N. (2010). Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *The Lancet. Infectious diseases*, *10*(9), 597–602.

Kumari M, Vinchurkar RV, Somveer and Deshmukh RR (2023). Mathematical model-based comparative storage study of dahi at refrigeration and room conditions. *International Journal of Statistics and Applied Mathematics, 8*(3), 603-605.

Muloi, D. M., Jauneikaite, E., Anjum, M. F., Essack, S. Y., Singleton, D. A., Kasudi, M. R., ... & Zadoks, R. N. (2023). Exploiting genomics for antimicrobial resistance surveillance at One Health interfaces. *The Lancet Microbe*, *4*(12), e1056-e1062.

Reygaert W. C. (2018). An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS microbiology*, *4*(3), 482–501.

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

* * * * * * * *