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Review article

Simultaneous detection of vancomycin- and linezolid-resistant genes in *Enterococcus* spp.: A literature review

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Abstract: Antibiotic resistance has become a critical global health concern, particularly with the rise of multidrug-resistant *Enterococcus* spp., including strains resistant to last-resort antibiotics such as vancomycin and linezolid. These resistances are mediated by transferable genes (e.g., *vanA*, *vanB*, *cfr*, *optrA*, and *poxtA*) and chromosomal mutations, contributing to limited treatment options and increased clinical burden. Therefore, this review aims to summarize the key mechanisms of vancomycin and linezolid resistance and to focus on the importance of simultaneous molecular detection of these resistance genes. Such approaches, including multiplex polymerase chain reaction and advanced genomic techniques, are essential for rapid and accurate diagnosis, enabling timely therapeutic decisions, improving infection control strategies, and ultimately reducing the spread and impact of resistant enterococcal infections.

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Introduction

Antibiotic resistance is now recognized as one of the biggest health crises globally. It is not only causing hundreds of thousands of deaths every year but also making even the most potent antibiotics, like vancomycin, ineffective [1, 2]. Bacteria can evolve very quickly and spread resistance genes among themselves, which has made the situation worse. It has resulted in worldwide alarm, and several countries have enacted stricter measures to control the inappropriate use of antibiotics in human health as well as in animal farming. Besides relying on their natural resistance, bacteria acquire resistance in two ways: through random mutations that are then selected, or by acquiring new genes from other bacteria via mechanisms such as plasmids, transposons, and integrons. Moreover, these genetic exchanges make it possible for resistance features to be widely distributed, leading to the emergence of superbugs that are resistant to multiple drugs and thus posing a greater challenge for health worldwide [3-5].

Among the resistant pathogens, the *Enterococcus* spp. has received attention as an important hospital-acquired organism, part of the ESKAPE group. These bacteria, normally dwelling in the gut, have, through time, become one of the top causes of nosocomial infections such as urinary tract infections, bacteraemia, and endocarditis [6]. According to epidemiological studies, there is a rise in the number of resistant strains, with *E. faecium* being the most resistant one that can resist ampicillin and vancomycin significantly more than *E. faecalis*. The discovery and transmission of vancomycin-resistant enterococci (VRE) in various areas, including the Middle East and North Africa, demonstrate their increasing significance in clinical and public health, especially in healthcare facilities like Intensive Care Units (ICUs) [7].

Basically, Vancomycin resistance in this group of bacteria is predominantly gained through changes in the bacterial cell wall precursors, especially with the acquisition of van gene clusters like *vanA* and *vanB* that weaken the interaction of the drug with the bacteria [7]. VRE infections lead to greater complications, death, longer hospitalisations, and higher healthcare expenses. Identifying VRE uses culture-based methods and the latest molecular techniques like PCR and real-time PCR that give better sensitivity and specificity [8,

9]. On the other hand, linezolid, which is also a last-resort antibiotic, has over time been associated with resistance development largely due to chromosomal mutations in the 23S rRNA and also the uptake of transferable resistance genes like *cfr*, *optrA*, and *poxtA*. The participation of mobile genetic elements in spreading these resistance determinants is facilitating their distribution across bacterial populations [10, 11]. In general, these issues stress the necessity for efficient molecular methods, especially simultaneous detection techniques, to promptly identify resistance genes and to enhance infection control and the effectiveness of therapies [10].

Antibiotic resistance

Every year, hundreds of thousands of fatalities are attributed to growing antibiotic resistance in microorganisms. The most significant issue is the steadily increasing number of microorganisms that are resistant to widely used antibiotics, even last-resort medications like vancomycin [10, 12]. The alarming increase of an issue that impacts public health globally and necessitates international cooperation is confirmed by the speed at which resistant genes are evolving around the globe [13]. The World Health Organisation (WHO) identified multidrug-resistant strains as an important global health concern in 2014 due to the notable global growth in their population [14, 15].

Legislative frameworks have been widely implemented to establish guidelines to limit or abolish the use of antibiotics, particularly those belonging to shared classes with human medicine. This includes the misuse of antibiotics in livestock feed, which remains widespread malpractice, especially in developing countries. Moreover, the use of antibacterial agents in meta-phylaxis and treatment has been subjected to strict European Regulation 2019/6 [16].

Mechanisms of Acquisition of Drug Resistance Among Bacteria

Innate resistance, which is the most basic kind of resistance, is an inherent lack of vulnerability. This is a consistent characteristic of a species, strain, or entire bacterial group [17]. Because of its "innate" resistance to specific antibiotic groups, a particular bacterium is insensitive to an antibiotic. It could be related to low affinity, cell wall impermeability, the lack of an antibiotic receptor, or the synthesis of enzymes [18].

Changes in the bacterial susceptibility could be classified as either primary or secondary resistance. Primary resistance can develop even in the absence of direct drug exposure due to a spontaneous genetic mutation. This kind of resistance is chromosomally encoded and does not spread to other species of bacteria [19].

After being exposed to antimicrobial treatments, previously sensitive bacteria develop secondary resistance, sometimes referred to as acquired resistance [20]. Through horizontal gene transfer processes like conjugation, transformation, or transduction, this kind of resistance arises from the acquisition of genetic material, such as plasmids, transposons, or integrons, that carry resistance genes from other resistant bacteria [21]. Antibiotic overuse or misuse creates selective pressure that encourages the survival and spread of resistant strains. As a result, bacteria can develop various resistance determinants, which can result in multidrug resistance and provide serious obstacles to infection management and treatment methods [22].

Multiple investigations have shown that bacteria employ two primary genetic techniques to enable natural defence against antibiotics: acquisition of foreign deoxyribonucleic acid (DNA) encoding factors determining resistance via horizontal gene transfer and gene mutation, which is frequently linked to the mechanism of action of an antibacterial compound **(Table 1)** [23-29].

Enterococci

First identified in the human gastrointestinal tract in 1899, *enterococci* are gram-positive, facultative anaerobic cocci in short and medium chains. In 1984, 16S rRNA sequencing and DNA hybridisation identified them as a distinct species from *streptococci* [30]. They are among the earliest of the ESKAPE strains (*Enterobacter spp*., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Enterococci spp*.) that the WHO has identified as increasingly common nosocomial and antibiotic-resistant infections that pose an imminent danger to public health recently [31]. The first reports of VRE in animals date back to 1933, when avoparcin—an analogue of vancomycin—was added to animal feed. Yet, a few years later, in 1988, they were first documented in people in England [32, 33].

Table 1. Previous investigations have elucidated the mechanisms underlying the acquisition of drug resistance in bacteria.

Type of study	Year	Main findings	Reference
Review article	2014	Summarizes evidence that bacterial populations in the human gut acquire resistance via spontaneous mutation and horizontal gene transfer (transformation, transduction, conjugation); discusses ecological niches and conditions promoting horizontal gene transfer (HGT).	[23]
Review article	2016	Emphasise the molecular and pharmacological causes of bacterial resistance, highlighting particular scenarios that frequently arise in clinical settings.	[24]
Review article	2019	Reviews mechanisms by which HGT spreads antibiotic resistance genes among diverse species, and contrasts HGT-driven rapid multidrug-resistant (MDR) acquisition with slower mutation-driven adaptation.	[25]
Mathematical modelling / theoretical study	2021	Models' thresholds for resistant mutants to replace wild-type strains and for coexistence; includes HGT via conjugation and shows criteria where HGT or mutation dominate resistance emergence.	[26]
Review / experimental models	2022	Summarizes in vivo evidence showing antimicrobial resistance genes (ARGs) acquisition via mutation and HGT, mechanisms promoting transfer in gut and environmental contexts, and implications for ARG dissemination.	[29]
Review / systematic narrative	2023	Documents rapid transfer of ARGs, higher rates in biofilms, and role of mobile genetic elements (plasmids, integrons, transposons) in disseminating resistance across species.	[27]
Research / review on genetic mechanisms	2024	Discusses how resistance arises via HGT (transformation/transduction/conjugation) and de novo mutations, including gene amplifications and small indels/ single nucleotide polymorphisms (SNPs) as mutation types leading to resistance.	[28]
Review article	2014	Summarizes evidence that bacterial populations in the human gut acquire resistance via spontaneous mutation and horizontal gene transfer (transformation, transduction, conjugation); discusses ecological niches and conditions promoting horizontal gene transfer (HGT).	[23]

From an epidemiological perspective, enterococci have become one of the leading causes of nosocomial infections worldwide, particularly in intensive care settings, where they account for a large proportion of infections [33, 34]. They are commonly implicated in bloodstream infections [35], endocarditis, and urinary tract infections [36], with hospital-acquired urinary tract infections (UTIs) representing a significant burden. Among the species, *E. faecalis* is generally more susceptible to antibiotics, whereas *E. faecium* shows high levels of resistance, especially to ampicillin and vancomycin [37]. In the Middle East and North Africa (MENA) region, which includes the Gulf region (GCC, Gulf Cooperation Council), rising levels of antibiotic resistance in both healthcare and non-healthcare settings are also being recognised as a threat [38, 39]. Numerous reports from MENA and GCC nations show how VRE is emerging and gaining popularity, including Morocco [40], Algeria [41-43], Tunisia [44, 45], Libya [46], Egypt [47-52], Saudi Arabia [53, 54], Qatar [55], Bahrain [56], Iran [57], and others. Unfortunately, there is little and out-of-date reported epidemiological research on *Enterococcus spp*. and VRE at the national and regional levels from the MENA area. While *E. faecium* accounted for 16% of nosocomial infections in Jordan, *Enterococcus faecalis* was the most often isolated species, accounting for 83% of infections [58], **Table 2**.

Table 2. Epidemiological studies of *Enterococci*.

Year	Study site	Prevalence / Main Findings	Reference
2015–2023	Egypt	*VRE* prevalence rose from 10% to ~35%; meta-analysis confirms upward national trend.	[47, 49, 51]
2022	Qatar	10-year study: rising *Enterococcus* bloodstream infections; 20% vancomycin-resistant isolates.	[55]
2011–2022	Saudi Arabia	*Enterococcus spp*. common in UTIs; growing *VRE* resistance trends.	[53, 54]
2021	UK	*Enterococci* responsible for 15–20% of hospital-acquired UTIs.	[36]
2020	Libya	First whole-genome sequenced *VRE faecium* isolates; presence of *vanA/vanB* genes confirmed.	[46]
2019	USA	*E. faecalis*: 10% vancomycin-resistant and typically ampicillin-sensitive; *E. faecium*: 80% vancomycin-resistant and 90% ampicillin-resistant.	[37]
2016–2019	Tunisia	Detection of novel vancomycin-resistant *E. faecium* clones in hospitals.	[44, 45]
2018	Algeria	Healthcare-associated infections with *vanA E. faecium* reported.	[41]
2018	Middle East (GCC region)	Rising antimicrobial resistance levels; VRE emergence documented in MENA countries.	[39]
2016	Morocco	First report of community intestinal carriage of VRE; increasing prevalence in *Casablanca.*	[40]
2016	Iran	Systematic review: *VRE* prevalence between 9–12%; increasing resistance patterns.	[57]
2012	Algeria	Emergence of MDR *E. faecium* in hospitals; early VRE cases confirmed.	[42]
2011	Bahrain	Detected co-colonization with MRSA; early sign of *VRE* dissemination.	[56]
2009	Europe vs. USA	VRE prevalence lower in Europe; around 30% in USA; *E. faecium* represents 35% of nosocomial and 40% of bloodstream isolates in transplant patients.	[35]
2008	Jordan	*E. faecalis* 83% and *E. faecium* 16% of nosocomial infections; *VRE* uncommon but emerging.	[58]

Vancomycin-Resistant *Enterococci* (VRE)

Vancomycin-resistant *enterococci* bacteria have become a major nosocomial infection worldwide since the late 1980s, and they are frequently transmitted through inadequate hospital hygiene practices. This raises the cost of care, lengthens hospitalisations, and increases the mortality incidence [59]. Genes that are resistant to a broad range of antibiotics, including glycopeptides (Teicoplanin and vancomycin), trimethoprim-sulfametoxa, cephalosporin, and beta-lactam, are carried by VRE bacteria. Vancomycin-resistant *enterococci* bacteria may contribute to a serious health emergency because of their strong resistance to a variety of antibiotics. In order to get around this, glycopeptides like vancomycin must serve as the primary antibiotics utilised in the final line of treatment [60]. In principle, resistance is predicated on changed targeting for antibiotic–drug interactions, and vancomycin hinders the bacteria's cell wall expansion [61]. Vancomycin-susceptible *enterococci* produce cell wall precursors that have a strong attraction for vancomycin and terminate in D-Ala-D-Ala. These precursors are unable to contribute to the formation of cell walls once they are bound [62]. Vancomycin thus eliminates the microorganisms. When vancomycin is added to a resistant cell, VRE infections produce precursors with different termini, like D-Ala-D-Lac, which have a low affinity for interacting with vancomycin and can be used to synthesise cell walls [63]. The *VanA*, *B*, *C*, *D*, *E*, and *VanG* isolates are the six distinct patterns of vancomycin resistance to the VRE family. The VRE-*VanA* gene is responsible for the most severe form of VRE resistance to vancomycin. Additionally, it is teicoplanin resistant [64].

Since teicoplanin may be employed to manage it, the VRE-*VanB* gene is no longer commonly linked to resistance. *Van C* resistance is chromosomal and non-

transmissible to other bacteria, unlike transposon-based resistance mechanisms. It naturally arises in *Enterococci* that are thought to possess less virulent than *E. faecalis* and *E. faecium*, such as *E. casseliflavus* and *E. gallinarum*. There have occasionally been reports of resistance to *VanE* and *VanD* [65].

Emergence of Vancomycin-Resistant Enterococci

Since VRE *faecalis* and VRE *faecium* were initially isolated in England in 1988, they have spread quickly and are currently seen in numerous hospitals worldwide [66]. Vancomycin was initially prescribed in 1958 to treat gram-positive infection-causing bacteria [67]. By obtaining genes via plasmid or transposon that allow bacteria to avoid antibiotic-sensitive crucial stages in cell wall production, *enterococci* develop resistance to vancomycin [68].

Vancomycin works by preventing the production of cell walls by attacking their constituent parts [67]. It attaches to the amide linkage of the terminal segments of muramyl pentapeptide, such as D-alanyl-D-alanine of the elongating peptidoglycan, blocking the polymerase from prolonging the peptidoglycan backbone and preventing transpeptidase from cross-linking the expanding chains [32].

Morbidity and Mortality Rate of Vancomycin-Resistant Enterococci

In 2008, Saka et al. postulated that "exogenous" factors like allogenic bone marrow transplantation, chemotherapy drug exposure, hypoalbuminemia, and urinary catheter use were specifically responsible for VRE bacteremia [69]. In contrast, "endogenous" causes such as age, previous gastrointestinal illness, and abdominal surgery were the main triggers of pathogenicity for vancomycin-sensitive enterococci (VSE) bacteremia [70]. It has been demonstrated that all individuals experiencing bacteraemia had VRE colonisation. The higher death incidence by VRE is linked to vancomycin resistance. Therefore, in order to lower the incidence of VRE bacteremia, medical facilities need to be enhanced, infection control procedures should be modified, and overuse of antibiotics should be controlled [71].

Detection of Vancomycin-Resistant Enterococci (VRE)

There are several common techniques for detecting VRE, including conventional immunoassay and molecular techniques utilised in clinical laboratories. The traditional methods, such as disc diffusion, E-test, and minimum inhibitory concentration (MIC) in broth or agar, rely primarily on the cultivation of these microorganisms in particular methods [72]. The protocols are simple to follow; however, they aren't always useful. Certain microbes are difficult to cultivate or require a lengthy growth period before being suitable for use, which presents a challenge for certain investigators. Conversely, there are several kinds of molecular techniques, including multiplex PCR, real-time PCR, and PCR [73, 74]. They do, however, entail the target genes' amplification. They are crucial instruments for researching a wide variety of microorganisms due to their greater sensitivity and specificity for identification and measurement techniques compared to conventional approaches [61]. Each method also has drawbacks, such as a lengthy execution time and poor reproducibility of outcomes, and is more costly because it calls for pricey tools and chemicals [62]. Because of its instability, the RNA molecule requires specialised tools and knowledge of bioinformatics. Furthermore, the aforementioned techniques may produce high false-positive results since the sample contains both active and dead bacteria [63]. Immunoassays are another way to identify VRE; the most popular ones are lateral flow immunoassays and enzyme-linked immunosorbent assays (ELISA). The most popular method for diagnostic purposes is undoubtedly ELISA, a designated immunoassay known as the "gold standard of immunoassays" [75]. It is predicated on antigen-antibody reactions, which require an enzyme labelled on a secondary antibody. However, because the process is time-consuming and requires the manufacture of antibodies and enzymes, this method is expensive. Additionally, antibody instability is the most prevalent ELISA issue [76].

Biosensors have become a better method in recent years for supporting PCR and ELISA in the detection of biomolecule analytes such bacteria, viruses, and cancer-causing agents. Therefore, biosensors can be used to detect and measure microorganisms alongside PCR and ELISA [77]. The International Union of Pure and Applied Chemistry states that for a biosensor to function, a biorecognition component—such as an enzyme, DNA, or antibody—must come into close association with a transduction factor [78].

Linezolid-Resistant Genes in *Enterococcus spp*.

Enterococcus species exhibit a complex resistance profile that includes both intrinsic resistance and acquired resistance mechanisms, making them particularly challenging to treat [79]. Intrinsically, *enterococci* are resistant to several commonly used

antibiotics, such as low concentrations of aminoglycosides, cephalosporins, and clindamycin, due to inherent structural or functional features like low-affinity penicillin-binding proteins and limited permeability [80]. Over time, these organisms have also developed acquired resistance through mutation and horizontal gene transfer, conferring high-level resistance to aminoglycosides, beta-lactams, vancomycin, and, more recently, linezolid [81]. The conjunction of intrinsic barriers with quickly spreading acquired traits is what has led to the rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Enterococcus strains in clinical settings. This situation is causing serious worries around treatment failures and infection control [82].

Emergence of Linezolid Resistance

Linezolid is a manufactured antibiotic in the oxazolidinone family that was first released as a last-resort drug against Gram-positive multidrug-resistant bacteria, such as *Enterococcus* spp. , methicillin, resistant *S. aureus* (MRSA), and VRE [80]. Structurally, linezolid contains an oxazolidinone ring critical to its activity, and it exerts its antimicrobial effect by binding to the 50S ribosomal subunit, specifically the peptidyl transferase centre of domain V in the 23S rRNA [32, 81].

Initially, linezolid was considered to have a very low cross-resistance profile, but after several years of global clinical use, resistance has appeared, caused mainly by chromosomal mutations and acquired transferable resistance genes [83]. The propagation of these mechanisms is nowadays documented not only in hospitals but also in the community, thereby challenging the continued use of linezolid as a viable treatment option [84].

Mechanisms of Linezolid Resistance in Enterococcus Spp.

Resistance to linezolid in *Enterococcus* species arises through two major mechanisms: chromosomal mutations and the horizontal acquisition of resistance genes mediated by mobile genetic elements [85, 86].

Chromosomal Mutations of Linezolid Resistance in *Enterococcus*

The earliest recognized mechanism involves point mutations in the 23S rRNA gene, particularly the G2576T mutation within domain V, which reduces the binding affinity of linezolid to its ribosomal target [87]. The degree of resistance correlates with the number of mutated 23S rRNA gene copies present in the bacterial genome. Additionally, mutations in ribosomal proteins L3 and L4, which contribute to the structural configuration of the ribosomal binding site have been implicated in reduced susceptibility to linezolid [82].

Acquisition of Resistance Genes

One of the ways to become resistant to antibiotics is by acquiring mobile resistance genes such as *cfr*, *optrA*, and *poxtA*. These genes are most of the time found in plasmids, which makes it very easy for the bacteria to share these genes horizontally among themselves [80]. The *cfr* gene is a methyltransferase that methylates the 23S rRNA at adenine 2503, which results in a resistance that covers oxazolidinones as well as phenicols, lincosamides, and streptogramins, called PhLOPSA phenotype [79]. On the other hand, *optrA* and *poxtA* genes produce ATP-binding cassette F (ABC, F) ribosomal protection proteins that protect ribosomes from being bound by oxazolidinones, thus the antibiotics are displaced from the ribosome. Such genes have been found in clinical isolates as well as from the environment and in combination with other resistance genes, they largely contribute to multidrug resistance and the difficulty of therapy [85].

Role of Mobile Genetic Elements

Several research works have highlighted the importance of insertion sequences (IS) such as IS1216E and transposons such as Tn6674, Tn554, like elements in the mobilization and dissemination of linezolid resistance genes [88, 89]. Moreover, these elements allow for integration, rearrangement, and horizontal transfer of resistance genes within plasmids and chromosomes, thus enhancing adaptability and persistence of resistant strains in clinical, agricultural, and environmental settings [90]. The existence of such mobile genetic elements contributes to the spread of resistance through the human animal environment interface at a high speed, thereby increasing the need for monitoring strategies that go beyond the usual ones [91].

Conclusion

Vancomycin and linezolid resistance in *Enterococcus* spp. Is spreading fast, thanks to chromosomal changes and gene swaps like *vanA*, *vanB*, *cfr*, *optrA*, and *poxtA*. These genes hop around on mobile elements, turning up in tough strains with few treatment choices. Patients face worse outcomes, and hospitals take on more strain. Old tests don't catch these mutations fast enough. New methods, like multiplex and real-time PCR, can find

multiple resistance genes at once. Surveillance needs to be tighter. Antibiotics must be used wisely. The system has to change how it tracks resistant bugs. Without better tools, the threat keeps growing.

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