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Detection of Vancomycin Resistance (van Genes) in Clinical Isolates of Enterococcus A review study

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ABSTRACT

Vancomycin-resistant enterococci (VRE), primarily Enterococcus faecium and E. faecalis, are high-priority healthcare related pathogens that cooperation empiric therapy, prolong hospitalization, and increase mortality. Resistance is most often facilitated by acquired van gene clusters—especially vanA and vanB—which remodel the peptidoglycan target from D-Ala–D-Ala to D-Ala–D-Lac (or D-Ala–D-Ser), reducing vancomycin binding. Mobile elements (e.g., Tn1546) and plasmids facilitate horizontal spread within and between lineages and species. Phenotypic detection uses consistent MIC methods (broth microdilution; careful use of automated systems) guided by CLSI, while molecular detection targets van operons by PCR or WGS. In India, surveillance advises data shows rising VRE proportions in tertiary centers with E. faecium predominance, reflecting global trends reported by CDC. Therapeutic options include linezolid and high-dose daptomycin (often with synergy), while infection-prevention and antimicrobial-stewardship remain basic controls.

Keywords: *Enterococcus faecium, Enterococcus faecalis, VRE, vanA, vanB, Tn1546, CLSI, EUCAST, linezolid, daptomycin, infection control*

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1. INTRODUCTION

The genus Enterococcus comprises more than 50 lactic acid bacteriaspecies , some of them help in fermenting food and dairy items. However, certain species—particularly E. faecalis and E. faecium—are significant human pathogens responsible for infections such as bacteremia, urinary tract infections, sepsis, and meningitis [1–3]. Their ability to survive under harsh physicochemical conditions, including desiccation, low temperatures, and exposure to disinfectants, facilitates their persistence on hospital surfaces and the hands of healthcare personnel, thereby contributing to transmission in clinical environments [4]. Among nosocomial pathogens, enterococci rank third overall (12%) after coagulase-negative staphylococci and Staphylococcus aureus, and are the second most frequent isolates from intensive care unit (ICU) settings [5].

Vancomycin-resistant enterococci (VRE) were first reported in Europe in the late 1980s [6]. Since then, they've come up as a significant global reason behind healthcare-related infections (HAIs). In particular, vancomycin-resistant E. faecium (VREfm) is responsible for the majority of cases [7,8]. The remarkable success of VREfm in clinical settings is attributed to its high genomic plasticity, recombination rate, and extensive horizontal gene transfer, all of which promote rapid acquisition of resistance traits [9].

At the genetic level, 9 vancomycin resistance determinant types are described in enterococci: vanA, vanB, vanC, vanD, vanE, vanG, vanL, vanM, and vanN. Of these, vanA and vanB are most frequently associated with human infections globally [10]. In enterococci, some strains carry silent or cryptic van gene clusters such as vanC, vanD, vanE, vanG, vanL, vanM that are not actively transcribed but can be activated under selective pressure or antibiotic exposure.

In China, however, epidemiological investigations reveal that vanA, vanB, and vanM are the predominant genotypes [11]. The vanA gene cluster forms part of the Tn1546 transposon,comprising a seven-gene operon that can be plasmid-borne or integrated into the chromosome [12,13]. Transfer of vanA and/or vanB operons from other enterococci or anaerobes enables vancomycin-susceptible E. faecium (VSEfm) to evolve into resistant strains [14,15].

Molecular epidemiology of VREfm has advanced with the use of core genome multilocus sequence typing (cgMLST), a high-resolution, allele-based approach that provides greater discriminatory power compared with pulsed-field gel electrophoresis (PFGE) and conventional MLST [16]. Integration of cgMLST with characterization of mobile genetic elements, such as transposons, enhances outbreak investigations by enabling distinction between closely related clonal VREfm isolates [17].Enterococcus spp. are intrinsically hardy, colonizing the human gastrointestinal tract and persisting on hospital surfaces, medical devices, and the hands of healthcare workers. Over recent decades, selective pressure that originate in the broad-spectrum antibiotics has driven emergence of VRE as a major healthcare-associated threat. VRE infections—most notably bloodstream, intra-abdominal, surgical-site, device-associated, and complex UTIs—are linked with higher mortality and costs compared with vancomycin-susceptible strains. Public-health agencies highlight VRE as a serious threat, emphasizing robust surveillance, standardized laboratory detection, and stringent infection-prevention practices[18,19].

2. TAXONOMY AND CLINICAL RELEVANCE

Enterococcus spp. are Gram-positive, facultative anaerobic cocci which form part of the commensal gastrointestinal microbiota of both animals & humans. Although more than a dozen Enterococcus species have been associated with human disease, two species—E. faecalis and E. faecium—account for the majority of clinically significant infections. E. faecalis has historically been the predominant cause of infections that are acquired from the hospitals and community, but in recent decades, E. faecium has emerged as the principal pathogen in the nosocomial setting. This shift is attributed to its greater capacity for antimicrobial resistance acquisition, stress adaptation, and survival in hospital environments.Vancomycin-resistant enterococci (VRE) are particularly enriched in hospital-adapted clonal lineages of E. faecium, most notably the clonal complex CC17. These lineages are characterized by multidrug resistance, carriage of van operons, enhanced biofilm formation, and tolerance to desiccation and disinfectants. Collectively, these traits confer a strong selective advantage, facilitating persistence in healthcare environments, cross-transmission between patients, and rapid expansion during outbreaks [20,21].

3. EPIDEMIOLOGY AND BURDEN OF VRE IN INDIA AND WORLDWIDE

According to the European Antimicrobial Resistance Surveillance Network (EARS-Net), the proportion of vancomycin-resistant E. faecalis invasive isolates increased from 10.4% in 2014 to 17.3% in 2018, and controlling their spread remains challenging in many European countries due to the limited availability of effective treatment options [22].

In India, VRE displayed a steady positive trend in the last two decades. First documented case was submitted by Mathur P. et al. in New Delhi in 1999. Since then, the prevalence of VRE infections has ranged between 1% and 8.7% across different studies from 1999 to 2021 [23].

A similar rise has been noted in Germany, particularly for vancomycin-resistant E. faecium. Reports indicate an increase from less than 5.0% in 2001 to 14.5% in 2013 [24]. The German Antimicrobial Resistance Surveillance (ARS) system further documented rising VRE rates in hospitals (from 16.2% in 2008 to 18.5% in 2012) and in out-patient settings (from 9.3% in 2008 to 19.4% in 2012), signaling a serious public health concern linked to antimicrobial resistance [19].

Colonization of the gastrointestinal tract (GIT) by VRE is particularly problematic as it predisposes patients to invasive infections &promotes intra-hospital transmission. Therefore, carrier detection &strict infection control practices are crucial

within healthcare facilities. In Asia, VRE prevalence is also on the rise. A meta-analysis by Sreshtha et al. (2021) reported a pooled prevalence of 8.1% across Asian countries, with regional variations: Western Asia (11.4%), South Asia (7.7%), East Asia (3.1%), and Southeast Asia (1.8%) [25].

In the Indian context, the frequent use of vancomycin and third-generation cephalosporins has contributed significantly in the emergence of VRE in tertiary care hospitals. Implementation of stringent antibiotic stewardship programs along with strict adherence to infection control protocols may help reduce the prevalence [26]

VRE have become established as a critical cause of healthcare-associated infections (HAIs) worldwide. Across Europe, surveillance through EARS-Net indicates that the population-weighted mean prevalence of vancomycin resistance among invasive E. faecium isolates remains high, at approximately 20% in 2023. This represents an overall increase compared with 2019, despite modest declines in a few countries during the most recent reporting period. Outbreaks of VRE continue to be reported across Europe, and they remain resource-intensive to contain due to environmental persistence and limited therapeutic options.In the US, the CDC classify VRE as a serious healthcare-associated threat, citing substantial morbidity and mortality associated with bloodstream and device-related infections. Updated CDC estimates highlight thousands of VRE cases annually, disproportionately affecting patients in critical care and oncology wards [27,28].

In India and other South Asian countries, the burden of VRE is increasing at an alarming rate. Systematic reviews and meta-analyses indicate a progressive rise in VRE prevalence over the past two decades, particularly in isolates from tertiary-care hospitals. E. faecium is consistently reported as the dominant VRE species, often exhibiting multidrug resistance including resistance to aminoglycosides, fluoroquinolones, and ampicillin.

ICMR Antimicrobial Resistance Surveillance Network has documented double-digit rates of vancomycin resistance among E. faecium bloodstream isolates in multiple tertiary centers, particularly in ICUs. Single-center reports across India have corroborated these findings, with periodic outbreaks found within high-risk settings including transplant units, oncology wards, &neonatal ICUs. These outbreaks underscore the pressing need for active screening programs, stringent contact precautions, and rigorous environmental cleaning protocols to curb transmission in healthcare facilities [29,30,31]. Vancomycin-resistant pattern of E. faecium and E. faecalis across India has been summarized in Table 1[24, 26, 32, 33].

Table 1. Studies showing Vancomycin-resistant pattern of E. faecium and E. faecalis across India [24, 26, 32, 33].

Author	**Year**	**Place**	**Vancomycin-resistant *E. faecium* (%)**	**Vancomycin-resistant *E. faecalis* (%)**
Sivaradjy et al.	2021	Pondicherry	81.0	8.0
Das et al.	2021	West Bengal	30.3	4.7
S Tripathi et al.	2016	Lucknow	39.0	61

Risk Factors and Transmission Ecology

The emergence and persistence of VRE are driven by a combination of host-related, treatment-related, and healthcare-environmental factors.

- Host-related factors: prolonged hospitalization, severe underlying comorbidities (such as malignancy, diabetes, or organ failure), immunosuppression, and the invasive devices' presence.
- Treatment-related factors: prior exposure to broad-spectrum antibiotics, particularly cephalosporins, carbapenems, anti-anaerobic agents (e.g., metronidazole), and especially vancomycin, which selects for resistant strains.
- Healthcare-environmental factors: high colonization pressure in wards, ICU admission, inadequate hand hygiene, and contamination of medical equipment and hospital surfaces.

Transmission occurs predominantly via contaminated fomites' and healthcare workers' hands. VRE are remarkably resilient in hospital environments, surviving for weeks on surfaces such as bed rails, doorknobs, and monitoring equipment. Colonization of the gastrointestinal (GI) tract often precedes invasive infection, with asymptomatic carriers acting as reservoirs during outbreaks. This makes active surveillance of stool or rectal swabs an important strategy in outbreak control and in high-risk populations [18, 34].

Mechanisms of Vancomycin Resistance

4. THE VAN OPERONS

The hallmark of glycopeptide resistance in enterococci lies in the acquisition of van operons, which remodel the terminal dipeptide of the peptidoglycan precursor. Normally, peptidoglycan chains end in D-Ala–D-Ala, the high-affinity binding site for vancomycin. The van operons encode enzymes that substitute this with D-Ala–D-Lac or D-Ala–D-Ser, thereby reducing vancomycin's binding affinity by approximately 1,000-fold and 7-fold, respectively.

- vanA: confers high-level, inducible resistance to both vancomycin & teicoplanin. It is typically located on Tn1546, a transposon often harbored on transferable plasmids, which enables inter- and intra-species dissemination across E. faecium and E. faecalis.
- vanB: mediates variable-level vancomycin resistance, while isolates generally remain susceptible to teicoplanin. It is usually found on chromosomal islands or conjugative transposons.
- Other clusters—including vanD, vanE, vanG, vanL, vanM, and vanN—are described but account for only a minority of clinical cases worldwide. Some confer low-level resistance, while others are restricted to particular geographical regions or species [35,36].

5. GENETIC PLATFORMS AND MOBILITY

Among mobile genetic elements, Tn1546 is the most extensively studied vanA transposon. Its modular architecture, flanked by insertion sequences (IS elements), facilitates rearrangements and diversification. The diversity of Tn1546 variants—through IS1216, IS1542, and IS1251 insertions—contributes to differences in horizontal transfer efficiency and associated fitness costs. These differences influence whether resistance spreads primarily by clonal expansion of a successful VRE lineage or by horizontal transfer of van operons to unrelated backgrounds. The combination of clonal expansion and plasmid exchange underlies the persistence of VRE in hospitals worldwide [12, 37].

Vancomycin-Variable Enterococci (VVE)

A clinically important but diagnostically challenging phenomenon is vancomycin-variable enterococci (VVE). These isolates harbor intact or partially disrupted van loci but may initially appear phenotypically susceptible in standard MIC testing. Upon exposure to vancomycin, however, resistance can be induced, leading to treatment failure and unrecognized transmission. If laboratories rely solely on automated systems without confirmatory molecular testing, VVEs can evade detection and fuel silent outbreaks, complicating infection-control efforts [38]

6. CLINICAL IMPACT

VRE infections are associated with significant clinical consequences compared to infections caused due to vancomycin-susceptible enterococci (VSE). Bacteremia, endocarditis, intra-abdominal infections, &device-related infections caused by VRE carry increased rates of mortality, extended stays at the hospital, and inflated hospital expenses. Therapeutic challenges arise because VRE frequently exhibit co-resistance to other antibiotic classes, including ampicillin, fluoroquinolones, and aminoglycosides (often high-level resistance).

In India, several multicenter and single-center studies have demonstrated a rising incidence of VRE bacteremia, particularly in ICUs and immunocompromised cohorts (oncology, transplant). Similar trends were seen within North America &Europe, where VRE is now considered one of the leading causes of multidrug-resistant bloodstream infections. These clinical challenges underscore the importance of rapid detection and precise antimicrobial stewardship [27, 31].

Laboratory Detection and Characterization Phenotypic Detection and Standards

Accurate detection of VRE in clinical microbiology laboratories requires strict adherence to international reference standards.

- CLSI (M100, latest edition) and EUCAST guidelines provide breakpoints and methodology for vancomycin susceptibility testing in Enterococcus.
- Broth microdilution is considered the reference standard. Automated MIC systems may be used but require cautious interpretation, particularly for values close to breakpoints.
- Gradient diffusion methods (E test, MTS) are discouraged for vancomycin in enterococci, as they may underestimate MICs, leading to false susceptibility reports.
- Agar-screen methods (using vancomycin-containing plates) can be useful for outbreak investigations and screening but should not replace MIC-based categorization [39].

Practical notes for tertiary-care laboratories:

- Always rely on MIC-based methods for vancomycin against Enterococcus. Confirm unusual or borderline results using broth microdilution.
- Interpret automated system results cautiously near critical breakpoints; verify with reference methods when treatment

decisions are impacted.
- A resistance pattern where both vancomycin and teicoplanin are resistant suggests vanA, while vancomycin resistance with retained teicoplanin susceptibility points toward vanB—useful in triaging subsequent molecular tests [36, 39].

Molecular Detection of van Genes

Molecular testing complements phenotypic assays and is essential in outbreak settings or when results are ambiguous.
- Conventional or multiplex PCR targeting vanA and vanB is the most widely used method. Expanded panels can detect rarer clusters (vanD, vanE, vanG, vanL, vanM, vanN).
- Whole-genome sequencing (WGS) provides a comprehensive understanding of the resistance landscape. It identifies whether van operons are plasmid-borne or chromosomally integrated, distinguishes Tn1546 variants, and determines clonal relatedness of isolates—critical for infection-prevention teams [35, 40].

Future Outcome

The finding of van genes in clinical isolates of Enterococcus provides an essential foundation for establishment hospital infection control strategies and guiding empirical therapy. In the future, such molecular screening could be combined into routine diagnostic systems to ensure early identification of vancomycin-resistant enterococci (VRE) and timely application of preventive measures. Continuous monitoring will also allow the evaluation of emerging resistance patterns and the appearance of novel van gene variants, which may influence therapeutic options. Furthermore, large-scale multicentric studies could help in mapping the genetic epidemiology of VRE across regions, thus supporting the development of antimicrobial stewardship programs and more effective treatment strategies. The outcomes of this work may also stimulate the exploration of novel drugs, synergistic antibiotic combinations, and non-antibiotic replacements for managing VRE infections.

7. CONCLUSION

This study climaxes the growing problem of vancomycin resistance among Enterococcus isolates within tertiary care settings & confirms presence of van genes as the molecular basis of resistance. The findings highlight the need for routine molecular surveillance, early detection, and strict practices for infection control for limiting VRE's spread. The identification of precisevan genotypes further provides understanding into the local epidemiology and resistance mechanisms, which can directly inform clinical decision-making. Overall, the study emphasizes that molecular detection of van genes is a rapid, reliable, and clinically relevant tool for controlling therapy, reducing treatment failures, and limiting the distribution of multidrug-resistant enterococci in healthcare facilities.

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