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A challenge in antibiotic stewardship: detection of vancomycin-variable *Enterococcus faecium* (VVE) in human clinical and commensal samples (2009-2022)

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Abstract

Background: Vancomycin-variable-enterococci (VVE) are *van*A+ enterococci expressing a vancomycin-susceptible phenotype that can revert to a resistant phenotype (VRE) after vancomycin exposure. **Objective:** We aimed to screen and characterize VVE in a large collection of *Enterococcus faecium* (Efm) [1]. **Methods:** We performed a *van*A-PCR screening on an extensive Efm collection (2009-2022), including hospital (*n*=255) and healthy-human (*n*=161) isolates, followed by disk-diffusion susceptibility testing. Vancomycin MICs (Etest) were performed in *vanA*+ isolates with a susceptible phenotype. VVE were sequenced (Illumina-MiSeq/Eurofins-Germany) and representatives of each clonal-complex-CT were sequenced by Nanopore (Plasmidsaurus/USA). cgMLST, antimicrobial resistance and plasmid-replicases (*rep*;Resfinder/PlasmidFinder-CGE-tools) were evaluated. *van*A-transposons and plasmids were characterized and compared to references using Geneious-Prime tools, alongside NCBI blastn/blastx.
Results: We identified seven VVE (7/416; 2%), six causing infections (3-urine, 1-pus, 1-blood from 2009 and 1-tissue from 2011) and one healthy-human (2022), indicating daily contact with non-treated water and no hospitalization in the previous 12-months. All VVE were vancomycin susceptible (MIC:1.5-4mg/ml), resistant to ampicillin, erythromycin, ciprofloxacin and identified as ST78: five CT230 (4-clinical;1-commensal) and two clinical CT330. Hybrid assemblies of two clinical isolates, CT230 and CT330, showed a homologous Tn*1546* structure with 18,211bp (*van*H-*van*A-Δ*van*X-IS*1216*-*van*Y-*van*Z-other_genes-IS*1216*-Δ*tnp*A-*tnp*B-*van*R-Δ*van*S) flanked by *IS1216*. The presence of Δ*van*X and Δ*van*S by IS*1216*-insertions might explain the lack of resistant phenotype. The healthy-human isolate apparently carries an identical Tn*1546* (nanopore-sequencing is ongoing). Closed genomes carried two different plasmids with Tn*1546*. One is a mosaic plasmid (~150kb) presenting Inc18-like-*rep*_pRE25, Rep1 (*rep*_pTT39_p3) and Rep3 (Δ*rep*_pVRE1-*Van*A). The other (~107kb) carried a Rep3-like (*rep*_pZY2). No homologous plasmids have been described. The healthy volunteer isolate had similar *rep* content to hospital isolates, possibly indicating plasmid similarities or recombined plasmids. **Conclusions:** We firstly report identical strains and Tn*1546*-VVE platforms in human clinical and commensal samples across distant years. This indicates potential colonization leading to VVE selection upon hospital admission and/or antibiotic administration. Continuous surveillance of VVE is crucial for optimizing antibiotic stewardship and ensure effective treatments.

Keywords: vancomycin-variable enterococci; *Enterococcus faecium*; *van*A; Tn*1546*

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