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# Dissemination of hospital-adapted lineages of vancomycin-resistant Enterococcus faecium in raw and treated wastewater across the East of England revealed by whole-genome sequencing

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**Background:** Vancomycin-resistant *Enterococcus faecium* (VREfm) causes an increasing number of healthcare associated infections in the United Kingdom. A hospital-adapted lineage of *E. faecium* accounts for almost all of these infections, however its prevalence outside hospitals, and the contribution of hospital wastewater to the dissemination of this lineage are understudied. Our objective

was to quantify hospital-adapted lineages of *E. faecium* in raw and treated wastewater from municipal wastewater treatment plants (WWTPs) in the East of England, and compare them to invasive *E. faecium* isolates using whole-genome sequencing.

**Material/methods:** A cross sectional survey was conducted in 2014-15 to isolate *E. faecium* from raw and treated wastewater in 20 municipal WWTPs, of which 10 were located downstream of acute hospitals and 10 did not receive hospital waste. In addition, wastewater from the main sewer of Cambridge University Hospitals NHS Foundation Trust (CUH) was sampled (2014-15). Quantitative cultures for total enterococci, ampicillin-resistant *E. faecium* and VREfm were performed for each sample. We sequenced 446 isolates from municipal wastewater (n=383), CUH sewer (n=40), and bacteraemia isolates from CUH from 2014-16 (n=23) using the Illumina HiSeq2000. The data was supplemented with 164 genomes of *E. faecium* bacteraemia isolates sourced in the East of England between 2010 and 2012 (85% from CUH) and 10 reference strains. Phylogenetic and bioinformatics analyses were performed using open-access tools.

**Results:** *E. faecium* cultured from municipal wastewater under no antibiotic selection belonged almost exclusively to lineages previously associated with human commensal and animal origin. By contrast, VREfm belonged to the hospital-adapted lineage and, whilst only a small subset of the total enterococcal population, was disseminated in all sampled locations (20/20 raw, 17/20 treated wastewater samples). The majority of invasive and CUH sewage isolates belonged to the hospital-adapted lineage. Analysis of this lineage (481 *E. faecium* isolates, including all VREfm from wastewater, n=188) demonstrated closely related strains (within 0-20 core genome single nucleotide polymorphisms) between raw and treated wastewater, and between different WWTP locations. Multiple clusters containing genetically related invasive and wastewater isolates were identified and involved WWTPs located both downstream of and unrelated to hospitals. The largest cluster of isolates was widely disseminated (15/20 WWTPs) and included the highest proportion of contemporaneous invasive isolates (5/23), suggesting rapid emergence and clonal expansion in this region. Genes encoding antimicrobial resistance and virulence factors were shared amongst wastewater and invasive isolates throughout the hospital-adapted lineage.

**Conclusions:** The hospital-adapted lineage of VREfm is widely disseminated in both hospital and non-hospital-related wastewater in the East of England indicating that hospital effluent is not its sole source and suggesting widespread VREfm carriage in the community. Wastewater treatment is insufficient to prevent downstream environmental spread of *E. faecium* and further research is needed to develop more effective treatment processes.