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Investigation of a successful *vanA* *Enterococcus faecium* clonal group in the capital region of Denmark, 2012-2015, using short-read and long-read sequencing

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Background: Vancomycin-resistant *Enterococcus faecium* (VRE_{fm}) has emerged as an increasingly important pathogen. There has been a tremendous increase of *vanA* VRE_{fm} in the Capital Region of Denmark (1.7 million inhabitants) since 2012. A previous study of VRE_{fm} isolates from the Capital Region of Denmark, 2012-14 identified a polyclonal outbreak investigated by WGS-based typing. However, a dominating clonal group comprising 40% of the isolates was identified. This clonal group was also responsible for the first local hospital outbreak. To understand the success of this clonal group, we investigated the genetic content of isolates belonging to this group identified from 2012-2015. The pan-genome was identified and a complete genome from an isolate belonging to this group was generated.

Material/methods: All VRE_{fm} isolates were sequenced on the Illumina MiSeq platform. Two x 150 bp paired-end-reads were produced. Reads were assembled *de novo* using Velvet and contigs were annotated by Prokka. The pan-genome was identified using Roary on default settings.

One isolate (V24) was selected for PacBio sequencing. V24 was assembled using a hybrid assembly methodology using both short, low error rate Illumina reads and PacBio long reads. The reads were assembled by SPAdes. Scaffolding of contigs was performed with SSPACE-longRead. Sequence

reads of all isolates were mapped to the closed chromosome of V24 using SMALT and single nucleotide polymorphisms (SNPs) were called using samtools.

Results: From 2012-15, we identified 361 VREfm isolates belonging to the largest clonal group. The mean number of SNP differences within the group was 16 SNPs. The pan-genome contained 5,905 genes of which 1,684 were core genes (present in $\geq 99\%$ of all VREfm isolates), 2,223 were soft core genes (present in $\geq 95\%$) and 2,960 were cloud genes (present in $< 15\%$). Assuming that an *E. faecium* genome contains approx. 3,000 genes, we can conclude that approx. 75% of the genome belongs to conserved soft core genes (2,223 genes/3,000 genes) and 25% (approx. 800 genes) belongs to the accessory genome. The gene pool for the accessory genome contained 3,682 genes.

The genome of V24 comprised a chromosome of 2,7 Mb and ten plasmids with sizes ranging from 4,304 bp to 172,811 bp. Fourteen percent of the genome was located on plasmids. Three plasmids contained antibiotic resistance genes, including one with *vanA*.

Conclusions: The dominating VREfm clonal group in the Capital Region of Denmark 2012-15 contained a highly flexible genome with 14% of the genome located on plasmids. We also identified a highly variable accessory genome with a large gene pool, acquired over four years. This characterizes a clone that rapidly can adapt to new selective pressures in the hospital environment and in the gastrointestinal tract which could explain part of the success of this dominating clonal group.