

First outbreak due to Vancomycin Resistant *Enterococcus* Epidemic Clone ST796 in Europe



Nasstasja Wassilew¹, Eveline Rolli¹, Yvonne Fietze¹, Carlo Casanova², Helena Seth-Smith³, Adrian Egli³, Jonas Marshall¹, Niccolò Buetti¹

¹Department of Infectious Diseases and Hospital Epidemiology, University Hospital Bern, Switzerland

²Institute for Infectious Diseases, University of Bern, Switzerland

³Division of Clinical Microbiology, University Hospital Basel and Applied Microbiology Research, Department of Biomedicine, University of Basel, Switzerland



Introduction

- Vancomycin-resistant enterococci (VRE) are multidrug-resistant microorganisms that can cause healthcare-associated infections and increase risk of mortality and length of hospital stay.
- An outbreak with VRE affected several hospitals within the Bern University Hospital group since the end of December 2017, due to a new VRE clone ST796 characterized by rapid intra- and inter-hospital dissemination.
- This clone has recently emerged in Australia and New Zealand and quickly spread between hospitals (1,2).
- Here, we describe a large outbreak of this clone in our hospital group and illustrate the genetic relationship of the Swiss and Australian isolates.

Table 1: Characteristics epidemic VRE clone versus others

	All patients* (n = 224)		Patients with VRE ST796 +/- other ST (n = 211**)		Patients with VRE ST other than 796 (n = 13***)	
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD
Mean age	66	±17	66	±17	65	±7
Female	80	35.7	77	36.5	4	30.8
Resistance type <i>vanB</i>	216	96.4	211	100	8	61.5
Invasive infection	12	5.4	12	5.7	1	7.8
Bacteremia	6	2.7	6	2.8	0	0

Description of VRE isolates during the outbreak from 26 December 2017 to 31 August 2018

*One patient was excluded from analysis, as we did not obtain the ST type; **Four patients carried two different ST, of which 1 was ST796; ***One patient carried two different non 796-ST; BSI – bloodstream infection

Outbreak management

The outbreak was characterized by two waves, between which the management strategy was adapted. After the outbreak was declared on 4 January 2018, the following outbreak investigation and management strategy was undertaken:

Strategy I

- VRE outbreak team formation
- Temporary admission stops in affected wards
- Cohorting of VRE-colonized or infected patients, contact precautions
- Ward staff cohorting
- Active contact tracing, targeted screening and preemptive contact precautions
- Tagging of outpatient contacts
- Cross-sectional screening of patients on high risk wards
- Environmental disinfectant cleaning on high risk wards
- Hand hygiene compliance reinforcement on all occasions

Strategy II

The outbreak seemed to near containment by April 2018, when another wave in VRE cases and transmissions was observed from May on. The management strategy was modified as follows:

- Discontinuation of preemptive contact isolation precautions of contacts
- Cohorting of patients and ward staff, managed by wards in their own responsibility
- Environmental disinfectant cleaning expanded to entire bed tower (with few exceptions)
- UV disinfection of rooms after discharge of VRE positive patients
- Expansion of weekly cross sectional screenings on high risk wards

Methods

Case work-up

- Assessment of epidemiological linkage by a line list and identifying contacts by chart review.

Microbiology

- Identification of *E. faecium* with (MALDI-TOF)* mass spectrometry⁵
- Screening for VRE and confirmation with detection of *vanA* and *vanB* resistance genes⁵
- Phenotypic susceptibility testing by CLSI⁶ disk diffusion and Etest⁸.

Whole genome sequencing

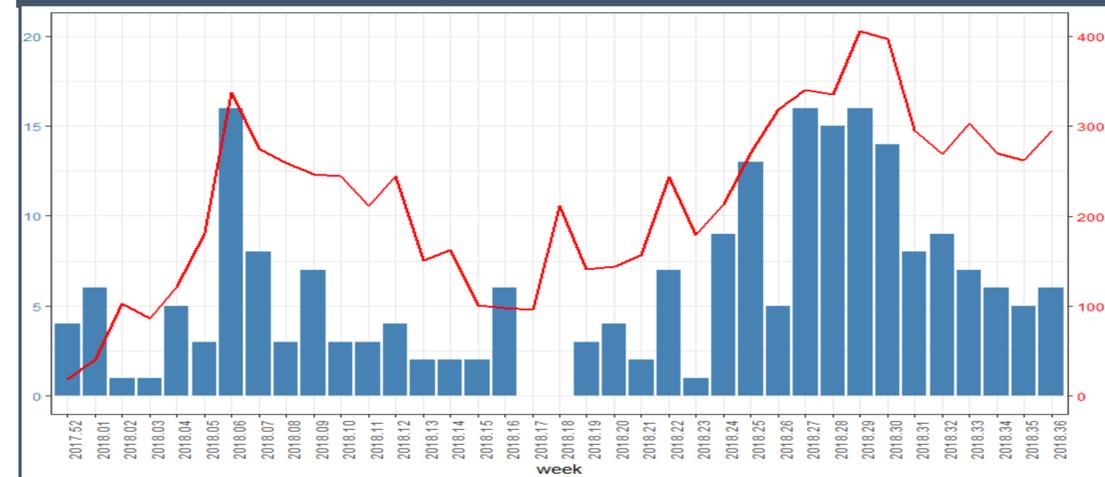
- VRE isolate analysis by whole genome sequencing (WGS) for epidemiological linkage.
- WGS sequencing was performed using a MiSeq Illumina platform** with 2 x 300nt paired-end sequencing after Nextera XT library preparation. Mean coverage of 60-fold)
- Read assembling and analysis by cgMLST^{9,10}
- Additional ST796 strain genome sequences were downloaded from databases for comparison (2).

*Matrix Assisted Laser Desorption/Ionisation Time-of-Flight; ⁵(Bruker Daltonics, Bremen, Germany); ⁶Xpert vanA/vanB, Cepheid, Sunnyvale, California (CA), United States (US); ⁸Clinical Laboratory Standards Institute; ⁹(bioMérieux, Marcy l'Étoile, France); ** (accredited with ISO/IEC 17025 norm at the Division of Clinical Microbiology, University Hospital Basel) ⁹Ridom SeqSphere+ 4.1.6, <https://www.ncbi.nlm.nih.gov/pubmed/26400782>

Outbreak description

Until 31 August 2018, three of six hospitals within the Bern University Hospital group had been affected. 7'500 screening samples were obtained from contact patients (Figure 1) and 224 patients were found to be colonized or infected with VRE (Table 1). Of these, 211 (94,2%) isolates were found to be virtually indistinguishable by cgMLST (separated by up to three alleles) and identified as MLST type ST796 (Figure 2). All of them carried the resistance type *vanB*. Of patients colonized with VRE ST796, 12 (5.4%) developed an invasive infection [six (2.7%) bacteremia, four (1.8%) abdominal infections and two (0.9%) deep wound infections/prosthetic infections]. Spatio-temporal links were found for almost all VRE patients. The remaining isolates were identified as MLST type ST117 (n = 7), ST555 (n = 2), ST78 (n = 5), ST17 (n = 1), ST80 (n = 1) and two new ST. The genomes of the Swiss outbreak isolates (ST796) all map to > 97% of the reference genome Ef_aus0233 from Australia, separated by ca 27 single nucleotide polymorphisms (SNPs), some of which cluster, indicative of recombination. The epidemic curve showed a biphasic course (Figure 1), with a decline of new VRE detections by the end of August.

Figure 1: Epidemic curve



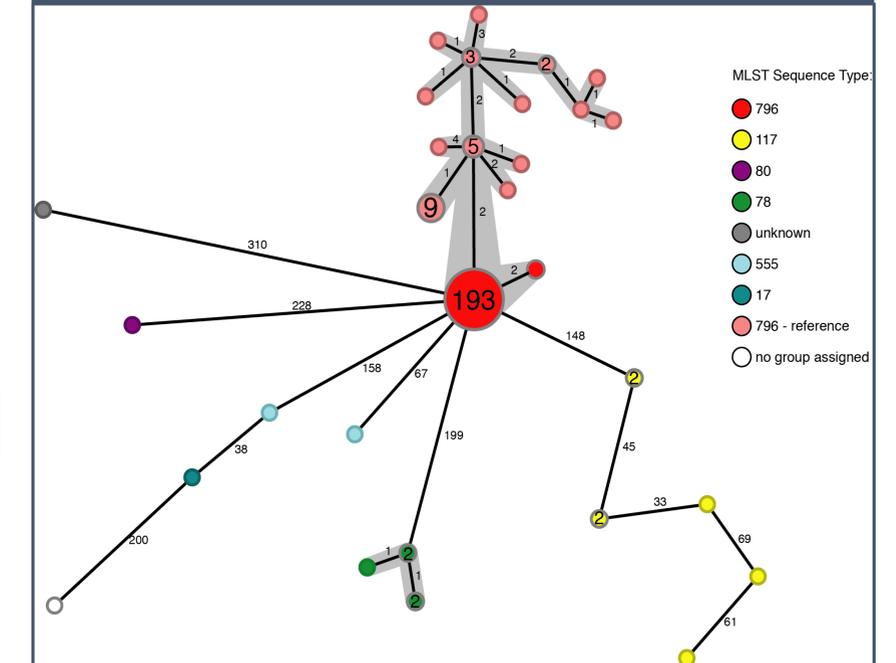
Epidemic curve of VRE cases (Bern University Hospital group, Switzerland). Blue bars: Number of patients; Red line: Number of screenings

Discussion

To the best of our knowledge, we report the first description of VRE ST796 clonal dissemination across several hospitals in Europe. *E. faecium* ST796 was first recognized at an Australian hospital during 2011 and spread rapidly throughout Australia and New Zealand, implying an effective transmission ability of this clone (1,2). The WGS analyses revealed a clear genomic relationship between isolates from the outbreak in the Bern University Hospital group described here and those from Australia. In Switzerland, VRE incidence is not systematically monitored for infection prevention purposes; national surveillance data are lacking. In collaboration with the National Center of Infection Control (Swissnoso), and the Swiss Centre for Antibiotic Resistance (ANRESIS) a national program on VRE epidemiology and the corresponding outbreak management has been launched on 29 June 2018.

Acknowledgements: Infection control team, Bern University Hospital

Figure 2: core genome Multi Locus Sequencing Typing



Core genome multi locus sequencing typing (cgMLST) analysis based on 1423 loci, performed in Ridom SeqSphere v4.1.6. Number of isolates belonging to each cluster is shown in the circles if more than one isolate and the number of allele differences between clusters is presented on the connecting lines. Outbreak strains are shown in red. Reference ST796 strains from Australia are shown in pink.

Conclusions

- We report the first VRE ST796 outbreak in Europe
- Close genetic relationship among VRE confirmed the epidemiologic links between patients
- Extended and rapid interventions are warranted on an interdisciplinary basis to control such an outbreak
- By the end of August 2018 the (biphasic) epidemic curve indicates a decline of new VRE detections
- The rapid spread of this multidrug-resistant clone warrants strengthening and synchronization of national infection control practices
- National guidance on the prevention and management of VRE transmissions has been issued on 12 September 2018

References:

1. Mahony AA, Buultjens AH, Ballard SA et al. Vancomycin-resistant *Enterococcus faecium* sequence type 796 - rapid international dissemination of a new epidemic clone. *Antimicrobial resistance and infection control*. 2018;7:44.
2. Leong KWC, Cooley LA, Anderson TL et al. Emergence of Vancomycin-Resistant *Enterococcus faecium* at an Australian Hospital: A Whole Genome Sequencing Analysis. *Scientific reports*. 2018;8(1):6274.