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Vancomycin-resistant *Enterococcus faecium*: impact of ending screening and isolation in a Danish University hospital

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SUMMARY

Background: Substantial resources are used in hospitals worldwide to counteract the ever-increasing incidence of vancomycin-resistant and vancomycin-variable *Enterococcus faecium* (VREfm and VVEfm), but it is important to balance patient safety, infection prevention, and hospital costs.

Aim: To investigate the impact of ending VREfm/VVEfm screening and isolation at Odense University Hospital (OUH), Denmark, on patient and clinical characteristics, risk of bacteraemia, and mortality of VREfm/VVEfm disease at OUH. The burden of VREfm/VVEfm bacteraemia at OUH and the three collaborative hospitals in the Region of Southern Denmark (RSD) was also investigated.

Methods: A retrospective cohort study was conducted including first-time VREfm/VVEfm clinical isolates (index isolates) detected at OUH and collaborative hospitals in the period 2015–2022. The intervention period with screening and isolation was from 2015 to 2021, and the post-intervention period was 2022. Information about clinical isolates was retrieved from microbiological databases. Patient data were obtained from hospital records.

Findings: At OUH, 436 patients were included in the study, with 285 in the intervention period and 151 in the post-intervention period. Ending screening and isolation was followed by an increased number of index isolates. Besides a change in *van* genes, only minor non-significant changes were detected in all the other investigated parameters. Mortality within 30 days did not reflect the VREfm/VVEfm-attributable deaths, and in only four cases was VREfm/VVEfm infection the likely cause of death.

Conclusion: Despite an increasing number of index isolates, nothing in the short follow-up period supported a reintroduction of screening and isolation.

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Introduction

Enterococcus faecium is a part of the intestinal microbiota and associated with nosocomial infections — especially in the urinary tract, abdomen, and bloodstream [1,2].

E. faecium infections have been treatable using glycopeptides such as vancomycin, but resistance appeared in the 1980s [3—5]. Based on phenotypic susceptibility and the presence of different *van*-resistance genes, *E. faecium* can be classified as vancomycin-susceptible *E. faecium* (VSEfm), vancomycin-resistant *E. faecium* (VREfm), and vancomycin-variable *E. faecium* (VVEfm) [5,6].

In Denmark, VREfm were rarely found before 2012, and VVEfm was detected for the first time in 2015. Both have since spread throughout the country and caused several outbreaks. In 2022, VREfm/VVEfm comprised 9% of Danish *E. faecium* bacteraemia isolates, and 0.4% of the Danish population were colonized [5,7]. To counteract the development, a variety of different screening and isolation strategies are used in Danish hospitals. However, screening and isolation increase hospital workload and costs, and studies indicate that isolation increases the patient's overall risk of complications and death, due to fewer tests of vital parameters, delayed examinations, and fewer contacts with hospital staff. In addition, patients report social stigmatization and reduced physical contact with family members [8—12].

When screening and isolation are ended, studies from countries with high incidences of VREfm have reported that the number of patients with VREfm rises to a steady level within a year or two [13—17]. The consequence of ending screening and isolation has not been studied in a low-prevalence setting, but knowledge on the topic is important to balance patient safety, infection prevention, and hospital costs.

During 2019—2021, the yearly mean number of patients detected with VREfm/VVEfm at Odense University Hospital (OUH) was 260 [5]. In this period, we observed only few infections caused by VREfm/VVEfm, despite frequent colonization and empiric antibiotic regimes not active against VREfm/VVEfm. Studies report a 24—66% 30-day mortality after *E. faecium* bacteraemia despite adequate antibiotic treatment. Mortality is correlated to severe underlying illness, but no study has investigated whether *E. faecium* was the actual cause of death [18—22]. In a recent study we found that only 6% of the 30-day mortality in patients with VSEfm bacteraemia was attributable to infection *per se* [23]. Therefore, OUH ended screening and isolation against VREfm/VVEfm at the end of 2021.

The aim of this study was to examine the impact of ending VREfm/VVEfm screening and isolation at OUH by investigating changes in the VREfm/VVEfm patients: age, gender, treatment departments, site of infection, treatment, bacteraemia within 30 days of primary infection, 30-day mortality, VREfm/VVEfm-attributable death, and burden of bacteraemia at OUH. To investigate a possible increased transmission to the collaborative hospitals we investigated the burden of VREfm/VVEfm bacteraemia in all hospitals in the Region of Southern Denmark (RSD).

Methods

This study was conducted as a retrospective cohort study in RSD.

Setting

RSD covers approximately one-fifth (1.2 million) of the Danish population. There are four hospitals in the region with frequent inter-hospital referrals. OUH is the largest (~1000 beds and 90,000 admissions/year) and has a number of highly specialized clinical functions. The three non-OUH hospitals — Lillebaelt Hospital, Esbjerg and Grindsted Hospital, and Hospital Sønderjylland — are regional collaborative hospitals with a total of ~1240 beds and 135,000 admissions per year.

Each hospital has its own Department of Clinical Microbiology (DCM) and Infection Prevention and Control (IPC), and a high proportion of two- and four-bed rooms.

Inclusion criteria

All patients with their first-time clinical VREfm/VVEfm isolate (index isolate) detected by culture at a DCM in the RSD from January 2015 through December 2022 were included. Clinical isolates were defined as all VREfm/VVEfm isolates excluding isolates from rectal swabs. We included both inpatients and outpatients regardless of symptoms and prescribed antibiotics.

The four DCMs did not use the same diagnostic methods to detect vancomycin resistance, nor the same thresholds for including *E. faecium* from different sample categories. However, diagnostic algorithms for blood cultures were identical and the analysis of the non-OUH hospitals was therefore restricted to the number of index isolates from blood culture.

Investigation periods

The study was divided into an intervention period (January 1st, 2015 to December 31st, 2021) with specific precautions and a post-intervention period (January 1st to December 31st, 2022) with standard precautions.

VREfm/VVEfm-specific precautions

Screening was performed as a single rectal swab on patients admitted to the hospital in case of:

- hospitalization outside the Nordic countries within the last six months
- positive VREfm/VVEfm sample (clinical or screening) within the last six months

- detection of VREfm/VVEfm in another inpatient located in the same hospital room
- suspicion of an outbreak in the ward.

Wards with repeated outbreaks performed periodic screening of all patients on admission and submission.

All VREfm/VVEfm-positive patients were isolated (single or cohort) when admitted to hospital, until six months after the last positive finding.

Infection precautions were continuously adjusted to deal with local outbreaks, including enhanced cleaning frequency and hydrogen peroxide decontamination.

Bacterial identification and susceptibility testing

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Microflex LT; Bruker Daltonik Gmb, Bremen, Germany) was used for bacterial identification.

Susceptibility to vancomycin was determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST (www.eucast.org). In-house polymerase chain reaction (PCR) was used for detecting the vancomycin-resistance genes *vanA*, *vanB*, and a deletion in the *vanX* gene [24]. An isolate was registered as VREfm if *vanA* and/or *vanB* were detected without a deletion in *vanX*, and as VVEfm if a deletion was found. The combination of the *vanA* gene and the *vanX* deletion was designated *vanAXd*.

Whole-genome sequencing

Clinical VREfm and VVEfm isolates were referred for whole-genome sequencing at Statens Serum Institut (SSI), Denmark, as part of a national surveillance programme. Results of multi-locus sequence typing (MLST) and core-genome MLST (cgMLST) were available to the DCMs as sequence types (ST) and complex types (CT).

Data sources

All Danish residents have a unique identification number that holds information on age and sex and enables unambiguous identification in administrative and healthcare systems [25].

Number of admissions was provided by the Departments of Data and Automation.

At OUH, data on samples containing *E. faecium* were retrieved from the Microbiology Department Database System (MADS, Aarhus, Denmark) and The Danish Microbiology DataBase (MiBa) and included sample date, requesting ward, specimen, anatomical location, presence of arterial and/or central lines, urinary tract catheters, and abdominal drains [26,27].

Information about date of death, clinical parameters, antibiotic treatment, and removal of indwelling catheters was extracted from electronic hospital records (Cambio COSMIC; https://www.cambiogroup.com) and EPJ SYD [28].

Blood culture data (number, number of patients, and results) were extracted from MADS at both OUH and non-OUH.

Samples

The first sample containing VREfm/VVEfm was defined as the index sample. If more than one sample with VREfm/VVEfm were collected at the same date from different locations, the index sample was categorized as mixed and further subdivided; if the mixed sample-set included a VREfm/VVEfm-positive blood culture, the sample-set was grouped as 'blood', otherwise as 'other'.

If samples collected within two days of the index sample contained both VREfm/VVEfm and other bacterial species, the index sample was categorized as polymicrobial.

Coagulase-negative staphylococci in a single blood culture were regarded as contamination and were not included.

Treatment

Linezolid, daptomycin, and tigecyclin were regarded as active against VREfm/VVEfm. Teicoplanin and quinopristin–dalfopristin were not available in our hospital.

Antibiotic treatment was registered if started within seven days after the index sample was obtained. Duration was counted as number of days where at least one dose of antibiotic was administered.

Catheter removal or replacement was registered within seven days after the index sample.

Mortality

Mortality within 30 days after the index sample date was registered. For patients who died within 30 days, death attributable to VREfm/VVEfm was categorized as 'likely', 'possible', 'unlikely', and 'unknown', based on data from hospital records and a previously described algorithm [23].

Statistical analyses

The two periods were compared using χ^2-statistics for categorical and Student's *t*-test for continuous variables in the univariate analyses, and logistic regression with odds ratios (ORs) and 95% confidence intervals (CIs) in the multivariate analyses. The multivariate analyses were adjusted for *van* genes and requesting ward. We reiterated all the analyses by including only 2021 in the intervention period. Stata/SE, vs 17 (StataCorp., College Station, TX, USA) was used for statistical analyses. *P*-Values were two-sided and $P < 0.05$ was considered statistically significant.

Ethics approval

The Danish Patients Safety Authority has approved the collection of data from the hospital records (ref. no.: 3-3013-2554/1).

Results

A total of 436 patients with a VREfm/VVEfm index isolate detected at OUH were included; 285 (65.4%) were detected in the intervention period and 151 (34.6%) in the post-intervention period (Table I).

A total of 471,975 blood cultures were obtained at OUH in the periods; 38,881 (8.2%) with bacterial growth, 2135 with *E. faecium* (929 patients), and 105 with VREfm/VVEfm (47 patients; 35 with an index isolate at OUH).

Table I
Clinical and microbiological characteristics for VREfm/VVEfm index isolate patients at Odense University Hospital in the intervention period (2015–2021) vs post-intervention period (2022) ($N = 436$)

Variable	Total	Intervention 2015–21	Post-intervention 2022
No. of patients	436	285	151
Van gene			
vanA	59 (13.5%)	54 (18.9%)	5 (3.3%)
vanB	169 (38.8%)	43 (15.0%)	126 (83.4%)
vanAXd	206 (47.2%)	186 (65.2%)	20 (13.2%)
vanA + *vanB*	2 (0.5%)	2 (0.7%)	0
Sex			
Men	203 (46.6%)	134 (47%)	69 (45.7%)
Age (years)			
<18	3 (0.7%)	1 (0.3%)	2 (1.3%)
≥18	433 (99.3%)	284 (99.7%)	149 (98.7%)
Mean	72.75	73.1	72.1
Median (interval)	75 (0; 99)	75 (0; 99)	75 (11; 96)
Place of detection			
General practitioner	46 (10.6%)	28 (9.8%)	18 (11.9%)
Hospital	390 (89.4%)	257 (90.2%)	133 (88.1%)
Intensive care units	56 (14.4%)[a]	46 (17.9%)	10 (7.5%)
Internal medicine: total	178 (45.6%)	115 (44.7%)	63 (47.4%)
Abdominal	16 (4.1%)	9 (3.5%)	7 (5.2%)
Nephrology	24 (6.1%)	15 (5.8%)	9 (6.8%)
Haematology/oncology	49 (12.5%)	33 (12.8%)	16 (12.0%)
Other	89 (22.8%)	58 (22.5%)	31 (23.3%)
Surgery: total	89 (22.8%)	57 (22.2%)	32 (24.0%)
Abdominal	25 (6.4%)	16 (6.2%)	9 (6.8%)
Urology	26 (6.7%)	18 (7.0%)	8 (6.0%)
Orthopaedic/plastic/wound	38 (9.7%)	23 (8.9%)	15 (11.3%)
Paediatric	1 (0.2%)	1 (0.4%)	0
Other	66 (16.9%)	38 (14.8%)	28 (21.1%)
Specimen			
Blood culture	35 (8.0%)	27 (9.5%)	8 (5.3%)
Urine	335 (76.8%)	212 (74.4%)	123 (81.5%)
Abdominal fluid	29 (6.7%)	21 (7.4%)	8 (5.3%)
Skin/soft tissue/bone/visceral	24 (5.5%)	14 (4.9%)	10 (6.6%)
Other, e.g. sputum	13 (3.0%)	11 (3.9%)	2 (1.3%)
Patients with positive VREfm/VVEfm blood culture within 30 days, excluding index blood VREfm/VVEfm isolates	12 (2.8%)	12 (4.2%)	0
Microbiological culture results			
VREfm/VVEfm mono-microbial	256 (58.7%)	167 (58.6%)	89 (58.9%)
Polymicrobial total	180 (41.3%)	118 (41.4%)	62 (41.1%)
Enterobacterales	66 (36.7%)[b]	40 (33.9%)	26 (41.9%)
Non-fermentative Gram-negative rods	31 (17.2%)	21 (17.8%)	10 (16.1%)
Gram-positive, catalase-negative cocci	16 (8.9%)	14 (11.9%)	2 (3.2%)
Staphylococcus aureus	4 (2.2%)	3 (2.5%)	1 (1.6%)
Coagulase-negative staphylococci	15 (8.3%)	10 (8.5%)	5 (8.1%)
Yeast	55 (30.6%)	36 (30.5%)	19 (30.6%)
Anaerobe	9 (5.0%)	6 (5.1%)	3 (4.8%)
Other	9 (5.0%)	5 (4.2%)	4 (6.5%)
VREfm/VVEfm active antibiotic treatment initiated ≤7 days from the index sample			
No	378 (86.7%)	248 (87%)	130 (86.1%)
Yes	33 (7.6%)	28 (9.8%)	5 (3.3%)
Unknown	25 (5.7%)	9 (3.2%)	16 (10.6%)
VREfm/VVEfm active antibiotic treatment length (days), median (range)			
Total	4 (1; 28)	3.5 (1; 28)	10 (4; 14)
	$N = 33$	$N = 28$	$N = 5$

(*continued on next page*)

Table I (*continued*)

Variable	Total	Intervention 2015–21	Post-intervention 2022
Blood cultures	6 (1; 17) $N = 18$	3 (1; 17) $N = 13$	10 (4; 14) $N = 5$
Urine samples	2.5 (1; 17) $N = 8$	2.5 (1; 17) $N = 8$	–
Abdominal samples	11 (4; 17) $N = 3$	11 (4; 17) $N = 3$	–
Catheter present at the anatomical location of the positive VREfm/VVEfm sample, and removal/change ≤7 days after the index sample			
Yes: total	194 (44.5%)	131 (46.0%)	63 (41.7%)
Removal/change ≤7 days	100 (51.5%)	62 (47.0%)	38 (60.3%)
Arterial and/or intravenous	20 (57.1%)[c]	15 (55.6%)	5 (62.5%)
Removal/change ≤7 days	17 (85%)[d]	12 (80%)	5 (100%)
Urinary tract	150 (44.8%)[c]	98 (46.2%)	52 (42.3)
Removal/change ≤7 days	76 (50.7%)[d]	47 (48%)	29 (55.8%)
Abdominal	24 (82.8%)[c]	18 (85.7%)	6 (75.0%)
Removal/change ≤7 days	7 (29.2%)[d]	3 (16.7%)	4 (66.7%)
30-day mortality and cause of death ≤30 days from the index sample			
Dead ≤30 days	97 (22.2%)	65 (22.8%)	32 (21.2%)
Likely dead due to VREfm/VVEFm	4 (4.1%)	4 (6.2%)	0
Possibly dead due to VREfm/VVEFm	7 (7.2%)	1 (1.5%)	6 (18.8%)
Unlikely dead due to VREfm/VVEFm	82 (84.5%)	57 (87.7%)	25 (78.1%)
Unknown dead due to VREfm/VVEFm	4 (4.1%)	3 (4.6%)	1 (3.1%)

VREfm/VVEfm vancomycin-resistant/vancomycin-variable *Enterococcus faecium*.
[a] Percent of hospital isolates.
[b] Percent of the number of polymicrobial samples.
[c] Percent of the number of the equivalent VREfm/VVEfm specimens.
[d] Percent of the total number of patients with a catheter present at the anatomical location for the positive VREfm/VVEfm sample.

Differences in patient, clinical, and microbiological characteristics between the two periods were, with few exceptions, minor (Table I). Men:women ratios were identical: 0.87 for all cases, and 1.9 for bacteraemia cases only. Distribution of departments did not differ between the two periods, except for intensive care units (ICUs) with 46 (17.9%) patients in the intervention period vs 10 (7.5%) in the post-intervention period ($P < 0.01$).

Of the 35 patients with a blood index sample, 12 (34.3%) were treated at the ICU, and eight (22.9%) at the Departments of Haematology/Oncology, while the rest were treated in a variety of other departments.

Overall 30-day mortality was 22.2% ($N = 97$) and there was no significant difference ($P = 0.70$) between the periods (Table I and Figure 1). VREfm/VVEfm was the 'likely' cause of death in 4.1% of the patients ($N = 4$). Of the 35 bacteraemia patients, 16 (45.7%) died within 30 days, and in two patients (12.5%), VREfm/VVEfm was the 'likely' cause of death.

VRE/VVEfm active antibiotic treatment was associated with increased 30-day mortality ($P < 0.01$). Thirteen (39%) of the 33 treated patients died within 30 days, whereas 83 (22%) of the 378 patients not treated died. Nine of the 18 treated bacteraemia patients died within 30 days.

Thirty-day mortality was not related to the presence, removal, or replacement of intra-abdominal or intra-vascular catheters. Patients with VREfm/VVEfm in the urine had a higher 30-day mortality ($P < 0.01$) if a urinary tract catheter was present. The mortality was not related to change or removal of the urinary tract catheter.

There was no difference in the number of polymicrobial samples in the two periods. Yeast was detected in 18.6% and Enterobacterales spp. in 13.4% of patients who died within 30 days.

The distributions of *van* genes in the two periods were significantly different ($P < 0.01$). *vanA* (18.9%) and *vanAXd* (65.2%) dominated the intervention period, whereas *vanB* (83.4%) dominated the post-intervention period. In addition, there was a shift from *vanA* to *vanAXd* and *vanB* within the intervention period (Table I and Figure 2). The distribution of characteristics was therefore assessed in relation to the two periods for each *van* gene separately (Table II). Most of the numbers in these groups were too small for meaningful statistical assessment, but there were no conspicuous differences between the periods or *van* genes when focusing on percentages for the larger numbers. The multivariate analyses corroborated these results as only the *van* genes differed between the two periods (OR: 0.04, 95% CI: 0.01–0.10 for *vanA*; 0.03, 0.02–0.06 for *vanAXd*) whereas there were no differences between any of the wards, including ICUs.

Whole-genome sequencing was performed on 74.1% ($N = 323$) of the isolates. Types and distribution during the years can be found in Supplementary Table A1.

To account for possible heterogeneity in the seven-year intervention period, the last year (2021) of the intervention was compared with the post-intervention period (2022) (Supplementary Table A2). No significant difference was detected in any parameter between the two periods except for *van*-gene types ($P < 0.01$).

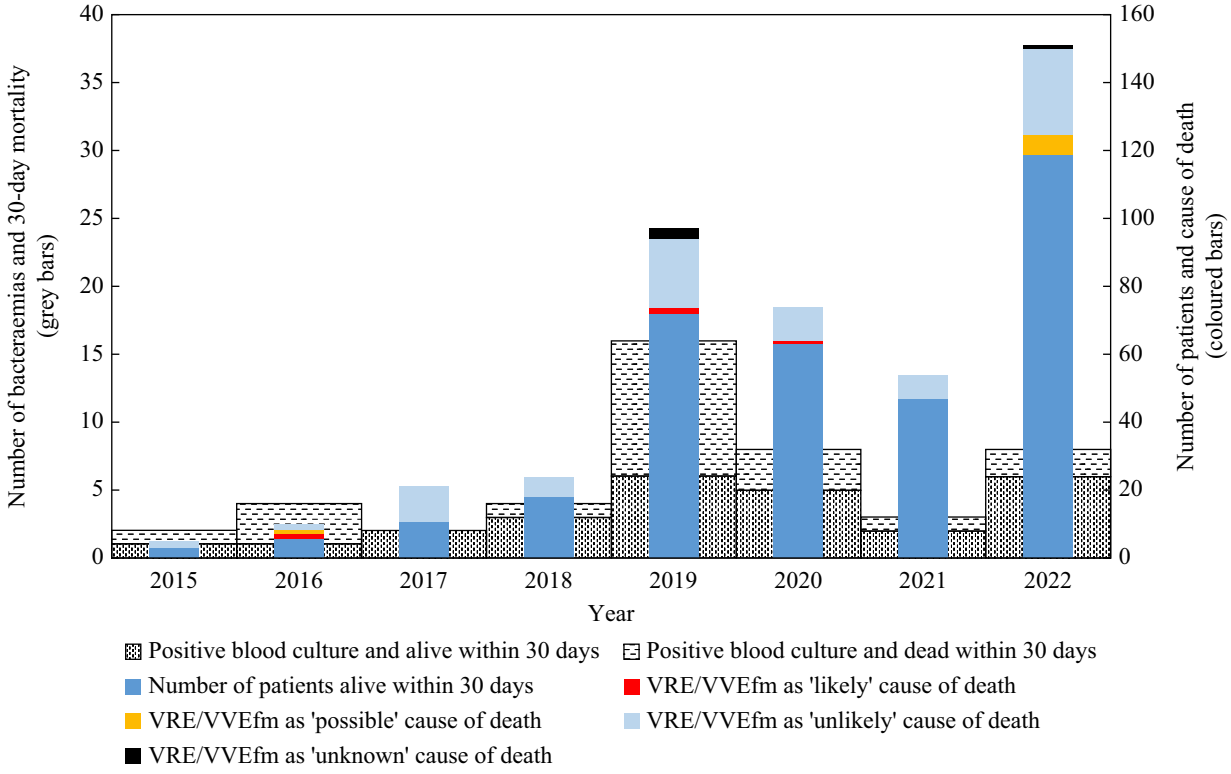

Figure 1. Distribution of 30-day mortality and vancomycin-resistant/vancomycin-variable *Enterococcus faecium* (VREfm/VVEfm) as the cause of death for VREfm/VVEfm index isolate patients, at Odense University Hospital in the period 2015–22 ($N = 436$).

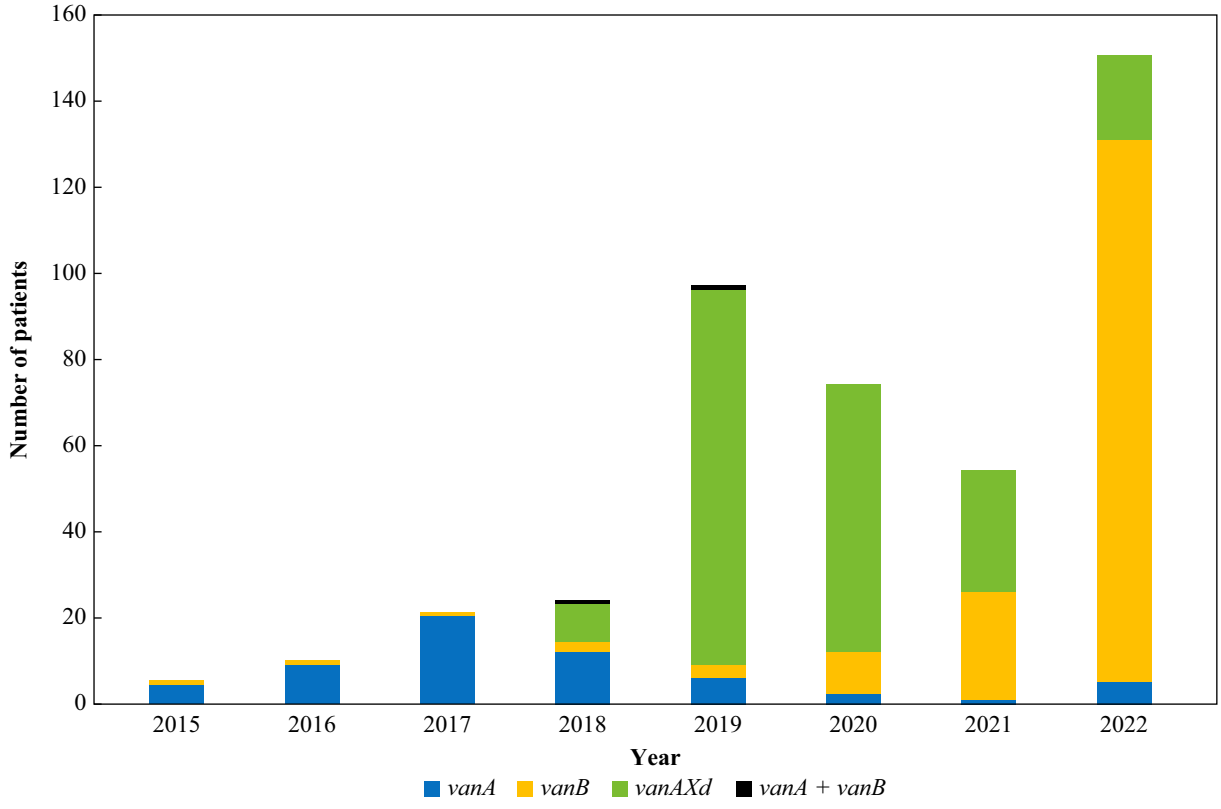

Figure 2. Distribution of *van* genes in vancomycin-resistant/vancomycin-variable *Enterococcus faecium* (VREfm/VVEfm) index isolates detected at Odense University Hospital in the period 2015–22 ($N = 436$).

Table II
Association between clinical, microbiological information, and *van* genes detected in the VREfm/VVEfm index isolates at Odense University Hospital in the period 2015–21 vs 2022 ($N = 436$)

Variable	*vanA*		*vanB*		*vanAXd*	
	2015–21	2022	2015–21	2022	2015–21	2022
Total no.[a]	54	5	43	126	186	20
Specimen						
Blood culture	5 (9.3%)	0	4 (9.3%)	7 (5.6%)	18 (9.7%)	1 (5%)
Urine	35 (64.8%)	4 (80%)	29 (67.4%)	101 (80.2%)	147 (79%)	18 (90%)
Abdominal fluid	9 (16.7%)	1 (20%)	5 (11.6%)	7 (5.6%)	6 (3.2%)	0
Skin/soft tissue/bone/visceral	2 (3.7%)	0	4 (9.3%)	9 (7.1%)	8 (4.3%)	1 (5%)
Other, e.g. sputum	3 (5.6%)	0	1 (2.3%)	2 (1.6%)	7 (3.8%)	0
Microbiological culture results						
VREfm/VVEfm monomicrobial	30 (55.6%)	4 (80%)	23 (53.5%)	71 (56.3%)	114 (61.3%)	14 (70%)
Polymicrobial total	24 (44.4%)	1 (20%)	20 (46.5%)	55 (43.7%)	72 (38.7%)	6 (30%)
Enterobacterales	6 (25%)[b]	0	7 (35%)	24 (43.6%)	27 (37.5%)	2 (33.3%)
Non-fermentative Gram-negative rods	3 (12.5%)	1 (100%)	4 (20%)	8 (14.5%)	14 (19.4%)	1 (16.7%)
Gram-positive, catalase-negative cocci	1 (4.2%)	0	2 (10%)	2 (3.6%)	11 (15.3%)	0
Staphylococcus aureus	0	0	2 (10%)	1 (1.8%)	1 (1.4%)	0
Coagulase-negative staphylococci	5 (20.8%)	0	1 (5%)	5 (9.1%)	4 (5.6%)	0
Yeast	9 (37.5%)	0	4 (20%)	15 (27.3%)	23 (31.9%)	4 (66.7%)
Anaerobe	1 (4.2%)	0	1 (5%)	3 (5.5%)	4 (5.6%)	0
Other	0	0	3 (15%)	4 (7.3%)	2 (2.8%)	0
VREfm/VVEfm active antibiotic treatment initiated ≤7 days from the index sample						
No	45 (83.3%)	5 (100%)	39 (90.7%)	107 (84.9%)	162 (87.1%)	18 (90%)
Yes	9 (16.7%)	0	4 (9.3%)	5 (4%)	15 (8.1%)	0
Unknown	0	0	0	14 (11.1%)	9 (4.8%)	2 (10%)
Median (range) VREfm/VVEfm active antibiotic treatment length in days						
Total	3 (1; 18)	–	6.5 (1; 11)	10 (4; 14)	2 (1; 28)	–
	$N = 9$		$N = 4$	$N = 5$	$N = 15$	
Blood cultures	8 (3; 10)	–	5.5 (1; 10)	10 (4; 14)	1.5 (1; 17)	–
	$N = 3$		$N = 2$	$N = 5$	$N = 8$	
Urine samples	2 (1; 4)	–	3	–	2 (1; 17)	–
	$N = 4$		$N = 1$		$N = 3$	
Abdominal samples	4	–	11	–	17	–
	$N = 1$		$N = 1$		$N = 1$	
Catheter present at the anatomical location of the positive VREfm/VVEfm sample, and removal/change ≤7 days after the index sample						
Yes: total	31 (57.4%)	1 (20%)	18 (41.9%)	51 (40.5%)	81 (43.5%)	11 (55%)
Removal/change ≤7 days	15 (48.4%)	0	10 (55.6%)	31 (60.8%)	37 (45.7%)	7 (63.6%)
Arterial/intravenous	3 (60%)[c]	0	2 (50%)	4 (57.1%)	10 (55.6%)	1 (100%)
Removal/change ≤7 days	1 (33.3%)[d]	0	2 (100%)	4 (100%)	9 (90%)	1 (100%)
Urinary tract	20 (57.1%)[c]	1 (25%)	11 (37.9%)	41 (40.6%)	67 (45.6%)	10 (55.6%)
Removal/change ≤7 days	14 (70%)[d]	0	5 (45.5%)	23 (56.1%)	28 (41.8%)	6 (60%)
Abdominal	8 (88.9%)[c]	0	5 (100%)	6 (85.7%)	4 (66.7%)	0
Removal/change ≤7 days	0	0	3 (60%)	4 (66.7%)	0	0
30-day mortality and cause of death ≤30 days from the index sample						
Alive ≤30 days	31 (57.4%)	1 (20%)	38 (88.4%)	102 (81%)	149 (80.1%)	16 (80%)
Dead ≤30 days	23 (42.6%)	4 (80%)	5 (11.6%)	24 (19%)	37 (19.9%)	4 (20%)
Likely dead due to VREfm/VVEfm	1 (4.3%)	0	0	0	3 (8.1%)	0
Possibly dead due to VREfm/VVEfm	1 (4.3%)	1 (25%)	0	3 (12.5%)	0	2 (50%)
Unlikely dead due to VREfm/VVEfm	20 (87%)	3 (75%)	5 (100%)	20 (83.3%)	32 (86.5%)	2 (50%)
Unknown dead due to VREfm/VVEfm	1 (4.3%)	0	0	1 (4.2%)	2 (5.4%)	0

VREfm/VVEfm vancomycin-resistant/vancomycin-variable *Enterococcus faecium*.
[a] The two isolates containing a *vanA* and a *vanB* gene are not included in the table.
[b] Percent of the number of polymicrobial samples.
[c] Percent of the number of the equivalent VREfm/VVEfm specimen.
[d] Percent of the total number of patients with a catheter present at the anatomical location for the positive VREfm/VVEfm sample.

At all four hospitals, from 2015 to 2022, the number of admissions decreased, whereas both the total number of obtained blood cultures and the number of patients who had at least one blood culture taken increased.

A total of 20 blood index isolates was included from non-OUH. During the entire period, at OUH, there was an overall increase in the number of index isolates per 10,000 blood-cultured patients (Figure 3). The numbers were small, but the number of blood index isolates per 10,000 blood-cultured patients seemed to be stable since 2019 – both at OUH and non-OUH.

Discussion

There was an increased number of index isolates after ending screening and isolation precautions against VREfm/VVEfm. No differences in age, gender, site of infection, number of bacteraemia cases within 30 days of primary infection, 30-day mortality, death attributable to VREfm/VVEfm, and burden of bacteraemia at hospitals in RSD were detected between the two periods.

There were significant changes in the *van* gene distribution in the investigation period, but no obvious differences in the patient characteristics in relation to each *van* gene separately between the two periods.

The increased number of index isolates in the post-intervention period is in agreement with findings from high-incidence countries ending screening and isolation regimes [13,16,29]. In most studies from high-incidence countries the incidence stabilized within 34 months, but due to our short post-intervention period it is unknown whether this will happen in our low-incidence setting [13]. Measures to contain the COVID-19 pandemic may have reduced the VREfm/VVEfm transmission in the intervention period. The COVID-19 restrictions were partially lifted during the post-intervention period. It is possible that fewer VREfm/VVEfm first-time cases would have been detected in the post-intervention period if only the VREfm/VVEfm precautions had been ended.

As demonstrated in other studies, VREfm/VVEfm bacteraemia was mostly found in men – a finding for which there is still no definitive explanation [30]. However, more women had an index isolate, especially from the urinary tract system. This might be explained by Danish women living longer than men, and by bacteriuria being more common in women and older patients [31,32].

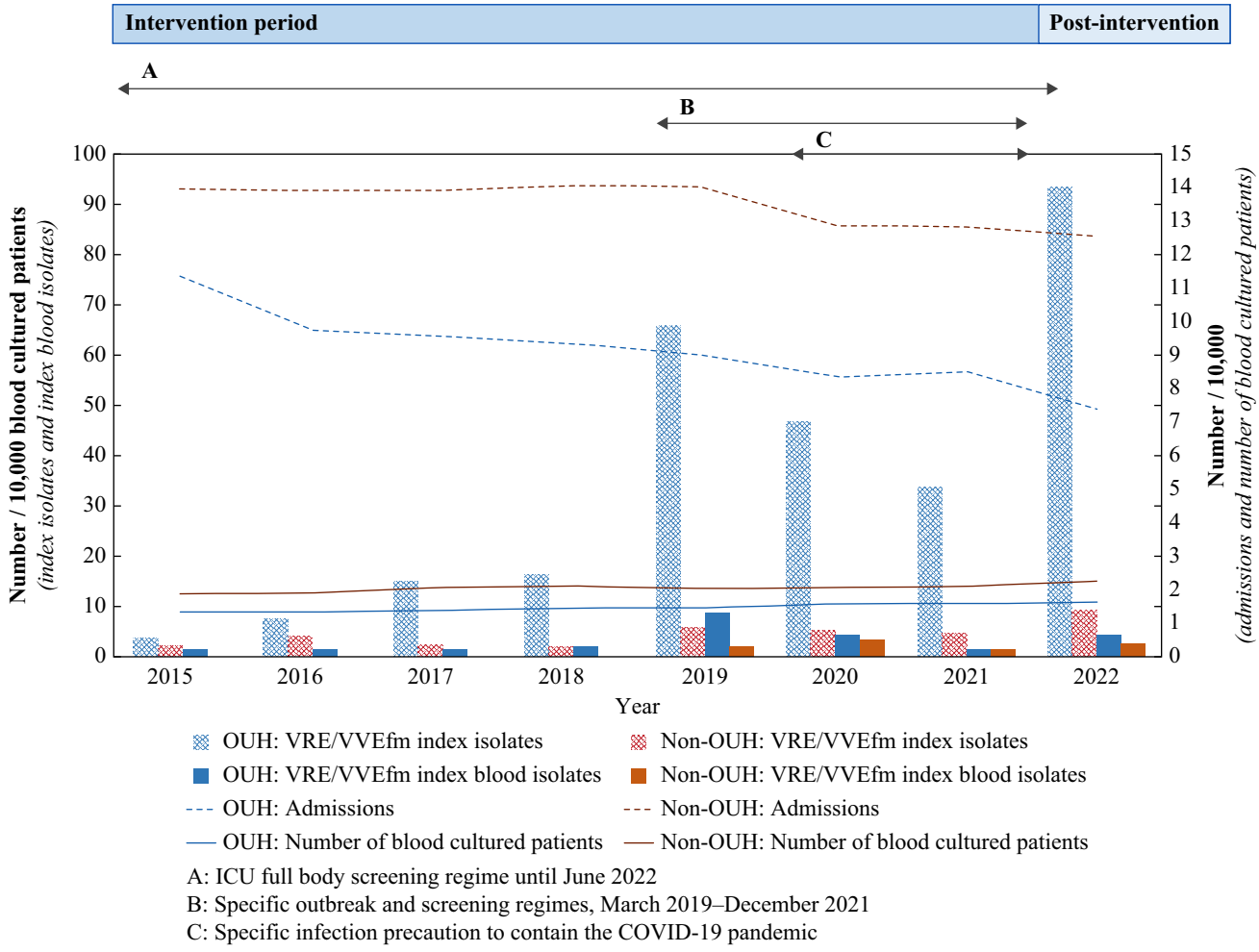

Figure 3. Number of vancomycin-resistant/vancomycin-variable *Enterococcus faecium* (VREfm/VVEfm) index isolates at Odense University Hospital (OUH) (all-case and bacteraemia) and at non-OUH (only bacteraemia) in the period 2015–22, related to number of blood cultured patients and infection control interventions.

The high number of ICU and haematology/oncology inpatients matches earlier findings, and is probably linked to various risk factors, e.g. high age, severe disease, immunosuppression, use of catheters and drains, long duration of hospitalization, and prolonged use of broad-spectrum antibiotics [4,18,22,33,34].

There was a significant reduction in index isolates detected at the ICU in the post-intervention period, which may have been due to ceasing a regimen of full-body microbiological screening three times a week in mid-2022.

In both periods, most samples were from the urinary tract and may reflect the number of colonized patients. The observed non-significant decrease in blood isolates from the intervention to the post-intervention period could be due to the change in the ICU full-body screening as described above or to other uninvestigated factors.

The low number of patients treated with VREfm/VVEfm active antibiotics was comparable to a recent German study [35]. Fewer patients were treated in the post-intervention period, and treatment was mainly given for VREfm/VVEfm bacteraemia and in longer duration. Although there were no changes in the recommended empiric antibiotic regimen at OUH, more patients had their catheters changed without a supplementary antibiotic treatment in the post-intervention period. This practice is supported by earlier findings of recovery taking place without use of antibiotics, but with removal of the infected foreign devices [36].

The higher 30-day mortality in relation to antibiotic treatment is probably due to a higher likelihood of treating critically ill patients. Treatment of VREfm/VVEfm could therefore indicate severe underlying disease and risk of death.

The number of index isolates fell from 2019 to 2021 and rose in 2022. The changes were non-significant, and may be related to a bundle of infection control interventions and their cessation at OUH, and are coincident with the COVID-19 pandemic.

The risk factors mentioned above for patients at ICU and Departments of Haematology/Oncology are associated with both a poor prognosis and an increased risk of being colonized with antibiotic-resistant micro-organisms, that may or may not contribute to the poor outcome [33,34].

The 30-day mortality was high, but VREfm/VVEfm was only the 'likely' cause of death in a few cases. This discrepancy between 30-day mortality and 'likely' cause of death is in accordance with our recent study on VSEfm bacteraemia [23].

For collaborating hospitals, the prevalence of resistant bacteria is affected by carryover from the hospital with the highest prevalence [37]. In all the hospitals in RSD, the number of admissions decreased during the period while the number of patients having a blood culture increased. This could be due to the changes in the Danish Public Health Services, where more and more patients are treated by the general practitioner or as outpatients, and only patients with relatively severe illness are admitted to hospital. Despite this, the number of VREfm/VVEfm first-time bacteraemia cases per 10,000 blood-cultured patients did not increase at non-OUH hospitals.

The strengths of this study are that all clinical cases regardless of sample material were included.

All cases were investigated and evaluated by examination of the hospital records. The same systems and procedures were used for recording data in the before-and-after period. Data were not affected by the hypothesis of this study, as this was unknown at the time of data registration.

One limitation of the study is that routine PCR for detecting the *van* genes at OUH was not introduced until 2018. We therefore used this method retrospectively on stored VREfm/VVEfm isolates. One consequence may be reduced detection of VREfm/VVEfm before 2018. Major limitations were the short duration of the post-intervention period and the small numbers of bacteraemia cases.

The before-and-after study design without a control group in general makes definitive conclusions about causal relationship difficult. The results may not be generalizable to other healthcare settings or populations.

During the last decade, patients admitted to hospital have become older, more comorbid, and more ill. Technological improvements entail more patients receiving advanced treatments and intensive care. They are often treated with broad-spectrum antibiotics resulting in a changed microbiota [38]. Together with a non-normal functioning immune system, this may cause difficulties in isolating the clinical impact of low-pathogenic, resistant bacteria such as VREfm/VVEfm. Treatment and specific infection control interventions against VREfm/VVEfm should be used with caution. It may be more efficient to use efforts to improve adherence to standard precautions and antibiotic stewardship — to reduce not only VREfm/VVEfm, but also other nosocomial pathogens [3,17,39,40].

In conclusion, this study investigated the impact of ending VREfm/VVEfm screening and isolation in a Danish university hospital. The number of patients with a first-time clinical VREfm/VVEfm isolate increased, but we found no changes that could support the need for reintroducing screening and isolation. The follow-up period was short and the development must be monitored closely in the years to come. Further research on the consequences of and need for continued screening and isolation in low-incidence countries is highly relevant.

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Author contributions

Conceptualization, methodology: S.G.K.H., K.O.G., M.N.S., A.H., F.S.R.; software: S.G.K.H., K.G.O., C.O., M.C., R.D., F.S.R.; data collection: S.G.K.H., K.K., A.N., L.A., K.O.G., J.L.-T., C.O., M.C., R.D., F.S.R.; data curation, formal analysis, validation, interpretation, visualization: S.G.K.H., K.O.G., F.S.R.; investigation: F.S.R.; project administration, funding acquisition, resources, supervision: S.G.K.H., M.N.S., A.H., F.S.R.; writing — original draft: S.G.K.H., K.O.G., F.S.R.; writing — review and editing: S.G.K.H., K.K., L.A., K.O.G., J.L.-T, C.O., M.C., R.D., M.N.S., A.H., F.S.R.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2024.01.019.

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