Journal of Hospital Infection 101 (2019) 264–271

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Reduction of nosocomial bloodstream infections and nosocomial vancomycin-resistant *Enterococcus faecium* on an intensive care unit after introduction of antiseptic octenidine-based bathing

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ARTICLE INFO

Article history:
Received 31 August 2018
Accepted 30 October 2018
Available online 5 November 2018

Keywords:
Vancomycin resistance
VRE
Enterococcus spp.
Antiseptic bathing
Octenidine

SUMMARY

Background: Vancomycin-resistant *Enterococcus faecium* (VRE) is emerging in German intensive care units (ICUs). On a 32-bed surgical ICU at a university hospital, increasing numbers of nosocomial cases occurred despite enforcement of hand hygiene and environmental disinfection.

Aim: To introduce universal octenidine-based bathing in order to reduce the burden of VRE.

Methods: Between January 2012 and March 2014, patients were screened for VRE on admission and twice weekly. Active surveillance was undertaken for VRE infections and colonizations, and for bloodstream infections (BSI) with any pathogen. Intervention in this before–after study comprised of standardized octenidine-based bathing. Distinct subgroups of VRE colonizations or infections were defined and used for statistical analysis of frequency, prevalence and incidence density.

Findings: In the pre-intervention period (January 2012 to April 2013), the admission prevalence of VRE was 4/100 patients and the mean incidence density of nosocomial cases was 7.55/1000 patient-days (PD). Pulsed-field gel electrophoresis analysis revealed prevalence of three *vanA* and two *vanB* clusters. In the post-intervention period (August 2013 to March 2014), the admission prevalence of VRE was 2.41/100 patients and the mean incidence density of nosocomial cases was 2.61/1000 PD [$P = 0.001$ (pre- vs post-intervention)]. Thirteen nosocomial VRE infections were identified in the pre-intervention period, compared with one nosocomial VRE infection in the post-intervention period. Incidence densities of BSI pre- and post-intervention were 2.98 and 2.06/1000 PD ($P = 0.15$), respectively.

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https://doi.org/10.1016/j.jhin.2018.10.023

Conclusion: The epidemiology of emerging VRE appeared as a complex mix of admitted cases and transmissions in small clusters, challenging infection control measures. The implementation of universal octenidine-based bathing combined with a standardized washing regime led to a significant reduction in nosocomial VRE.

Introduction

In recent years, vancomycin resistance of enterococci, mainly *Enterococcus faecium*, has increased in clinically relevant samples from patients in Europe [1]. Additionally, vancomycin-resistant *E. faecium* (VRE) detection in clinical specimens has shown a spatial distribution. In 2012, the percentage of vancomycin resistance of enterococci was between 1% and 5% in Spain, between 5% and 10% in Italy and Poland, between 10% and 25% in Germany and Great Britain, and between 25% and 50% in Ireland [1]. In Germany, the Krankenhaus-Infektions-Surveillance-System detected a dramatic increase in nosocomial VRE infections with a large variation in VRE proportions of all enterococcal infections from west (North Rhine-Westphalia) to east (Saxony) [2,3]. Cologne is sited within this belt, and the VRE proportion in blood cultures in a university hospital was 0% (0/20) and 35% (7/20) VRE/*E. faecium* in 2010 and 2011, respectively.

In 2011, three VRE infections emerged in a surgical intensive care unit (ICU) at the study hospital within two weeks. Therefore, infection control activities were intensified by introducing an active surveillance system for VRE, enforcing hand hygiene and additional environmental cleaning and disinfection; this system was fully implemented in December 2011. The National Reference Centre (NRC) for Staphylococci and Enterococci in Germany performed an analysis of all VRE isolates for the presence of pathogenicity markers *hyl* and *esp* and resistance genes *vanA* or *vanB*. This analysis showed primarily heterogenic epidemiology in the ICU. In 2012, VRE cases continued to increase despite all infection control measures. Therefore, in 2013, the decision was made to introduce a whole-body washing procedure for all patients.

Initial studies showed that antiseptic washing with chlorhexidine led to a reduction in VRE, and this appeared to be a promising option in the study setting [4—6]. At the time, chlorhexidine was not commercially available for antiseptic body washing in German hospitals. The alternative in Germany was octenidine, which was available as a body wash soap (Octenisan containing 0.3% octenidine), and had been in use for many years for decolonization of meticillin-resistant *Staphylococcus aureus* (MRSA)-positive patients. Octenidine has shown excellent activity against most relevant bacteria [6—8]. The primary aim of this intervention study was to control VRE colonizations and infections. A reduction in bloodstream infections (BSI) was included as a secondary outcome to enable comparability with other recently published studies using chlorhexidine for daily body washing [4,9,10].

Methods

Setting and VRE subgroups

A before—after intervention study was performed on an operative 32-bed surgical ICU (neuro, orthopaedic, visceral, vascular and trauma patients) in a 754-bed university hospital in Cologne. The intervention comprised a daily, structured, octenidine-based whole-body wash with Octenisan (octenidine 0.3%) (Schülke & Mayr, Sheffield, UK) for all patients.

The main study outcomes were nosocomial VRE acquisition, VRE infections and BSI with any pathogen. Infections were defined according to the criteria of the US Centers for Disease Control and Prevention [11]. Patients with a negative admission screen using a rectal swab, and subsequent detection of VRE either in rectal swabs or clinical specimens were defined as nosocomial cases.

In addition, VRE cases were divided into distinct patient subgroups as follows (see Supplementary Figure 1):

I: VRE colonization on admission, not resulting in VRE infection during hospital stay.
II: Nosocomial VRE colonization, not resulting in VRE infection during hospital stay.
III: VRE colonization at admission, followed by nosocomial VRE infection.
IV: Nosocomial VRE infection with or without prior nosocomial VRE colonization.
V: VRE infection on ICU admission.

Nosocomial VRE acquisition (colonizations and infections): Subgroups II and IV.
VRE infections: Subgroups III, IV and V.
Nosocomial VRE infections: Subgroups III and IV.
It was hypothesized that antiseptic body washing would reduce the incidence of VRE in Subgroups II, III (e.g. VRE BSI) and IV.

Bloodstream infections

Positive blood cultures taken after three days of admission were defined as nosocomial BSI. In the case of skin commensals, only repeated detection in at least two independent blood cultures was defined as BSI.

Study periods

Data from 2011 were excluded, as infection control policies were not fully implemented prior to December 2011. The pre-intervention period (PRE-IP) was January 2012 to April 2013. The intervention commenced in May 2013 and was fully implemented by July 2013. The post-intervention period (POST-IP) was August 2013 to March 2014.

Infection control measures

During all periods, hand hygiene was enforced and staff members were trained individually by an infection control nurse. Feedback of VRE and infection data was given

frequently. Environmental cleaning and disinfection of near-patient and contact surfaces was performed once per 8-h shift. Floors and contact surfaces in other rooms were cleaned and disinfected twice daily (glucoprotamine 0.5% or ethanol/isopropanol). All patients were cared for wearing single-use aprons and with bare forearms. Gloves were worn according to the recommendations of the World Health Organization. Contact precautions were applied to VRE-positive patients. All ICU patients were screened for VRE at admission and twice weekly with a rectal swab.

Epidemiology

Nosocomial VRE incidence rates were calculated per 1000 patient-days (PD). The prevalence of VRE on admission was calculated per 100 patient-admissions. VRE infection rates were calculated accordingly. BSI rates were calculated per 1000 PD. The epidemiological curve was updated weekly and depicted all nosocomial and community-acquired cases with respective Van types and virulence markers. This was given to ICU staff members for information.

Microbiological diagnostics

Rectal swabs were inoculated on selective chromogenic medium (ChromID VRE, BioMérieux, Marcy l'Etoile, France). Colonies suspicious for VRE were further analysed by Vitek2 (BioMérieux) for species identification and susceptibility testing. All isolated strains were sent to the German NRC for Staphylococci and Enterococci. Here, susceptibility testing was repeated by broth microdilution, and the minimal inhibitory concentrations (MICs) were evaluated according to the EUCAST MIC breakpoints. The isolates were analysed for the presence of the genes for hyaluronidase (*hyl*), enterococcal surface protein (*esp*) and *van*-resistance loci by multiplex polymerase chain reactions [12]. Once a patient had tested positive for VRE, they were not rescreened.

For transmission analysis, a set of strains was typed by *Sma*I macrorestriction analysis of genomic DNA resolved in pulsed-field gel electrophoresis (PFGE). To concentrate on the epidemiologically important cases, strains were selected according to the following principles: a set of isolates was typed which showed an identical *van* gene within an overlapping period of one to three weeks.

Antiseptic body washing

Octenidine-based body washing for all patients during their ICU stay was standardized by the use of single-use wash clothes for each body region. According to the manufacturer's recommendation, undiluted Octenisan was placed on the skin. After 2 min, it had to be removed with new wash clothes soaked with warm water. Hand disinfection was performed before contact at aseptic sites. Implementation of the structured body washing took four months. A standard operating procedure was written, and bedside instructions for all staff members were necessary to ensure implementation.

Statistics

The two-sided exact two-sample Fisher–Pitman permutation test was used to test the null hypothesis that frequency, incidence density and prevalence of each subgroup in the PRE-IP equalled the rates in the POST-IP. This test is also able to test for independence of seasonality. Linear regressions were analysed for both periods and each subgroup. For the analysis, the open source program 'R' was used [13]. *P*-values <0.05 were regarded as significant.

Ethics

Ethical approval was not required for the observational study as the authors were obliged to intervene by the German Infection Protection Act (Infektionsschutzgesetz §23) in order to control the high prevalence of VRE in the ICU.

Results

Epidemiological analyses in VRE subgroups

In total, 2485 and 1246 cases were treated in the ICU during the PRE-IP (16 months) and POST-IP (eight months), respectively. In the PRE-IP, a total of 100 VRE-colonized (4.00/100 patients) cases and 113 (7.55/1000 PD) nosocomial cases (Subgroups II + IV) were detected. In the POST-IP, 30 VRE-colonized (2.41/100 patients) and 19 (2.61/1000 PD) nosocomial cases were detected. The rate of VRE acquisition (Subgroups II + IV) was 65% lower in the POST-IP than in the PRE-IP. A summary of frequencies, prevalences and incidence densities of all analysed subgroups is given in Table I.

All subgroups were reduced in the POST-IP in comparison with the PRE-IP. Significance was reached in the group of nosocomial colonizations (Subgroup II), all admitted cases (Subgroups I + III + V), all nosocomial cases (Subgroups II + IV), nosocomial infections (Subgroups III + IV) and all VRE cases. Of the seven cases/patients with nosocomial infection (Subgroup IV) in the PRE-IP, five patients had nosocomial VRE colonization before infection. The one infected patient in the POST-IP was also colonized before infection.

The nosocomial infections (Subgroup IV) were one urinary tract infection (UTI) and six surgical site infections (SSIs) in the PRE-IP and one SSI in the POST-IP. In Subgroups III and V, three UTIs and 11 SSIs occurred in the PRE-IP and two SSIs in the POST-IP (data not shown).

In the PRE-IP, 33% of cases that were VRE positive at admission were those who had previously been re-admitted to the ICU. Eleven percent were known VRE-positive patients from the previous stay, and 22% were not known to be VRE positive. In the POST-IP, 33.3% of the admitted cases had a preceding stay on the ICU, and one (3.3%) had a previous detection of VRE.

Regarding linear regression analyses, VRE subgroups showed increasing trends in the PRE-IP (for slope estimates of incidence densities, see Table II). The trends were changed in the POST-IP. However, a significant change in trend could only be seen in nosocomial colonizations and all nosocomial cases (Supplementary Figure 2). Linear regressions of incidence densities of nosocomial infections in the PRE-IP and POST-IP are shown in Figure 1.

VRE molecular typing results

In the PRE-IP, of 100 admitted VRE cases, 61% carried the *vanA* gene and 39% carried the *vanB* gene. Of the 113

Table I
Change of incidence densities and prevalence of vancomycin-resistant *Enterococcus faecium* (VRE) subgroups from pre- to post-intervention period, and *P*-values analysed using the two-sided permutation test

	Cases (mean) pre-intervention[a]	Cases (mean) post-intervention[a]	Test statistic	*P*-value (two-sided)	Incidence density pre-Intervention[b]	Incidence density post-Intervention[b]	Test statistic	*P*-value (two-sided)	Prevalence pre-intervention[c]	Prevalence post-intervention[c]	Test statistic	*P*-value (two-sided)
Colonization on admission (I)	86 (5.375)	28 (3.500)	−1.818	0.083	5.694	3.939	−1.639	0.102	3.633	2.240	−1.724	0.083
Nosocomial colonization (II)	**106 (6.625)**	**18 (2.250)**	**−2.953**	**0.002**	**7.079**	**2.483**	**−2.928**	**0.002**	**4.572**	**1.438**	**−2.617**	**0.005**
NI following colonization on admission (III)	6 (0.375)	0 (0.000)	−1.425	0.315	0.384	0.000	−1.414	0.294	0.223	0.000	−1.454	0.241
NI (IV)	7 (0.438)	1 (0.125)	−1.278	0.277	0.470	0.127	−1.309	0.145	0.296	0.093	−1.134	0.344
Infection on admission (V)	8 (0.500)	2 (0.250)	−0.744	0.621	0.535	0.274	−0.724	0.587	0.314	0.158	−0.745	0.550
All admitted cases I + III + V	**100 (6.250)**	**30 (3.750)**	**−2.190**	**0.030**	**6.612**	**4.209**	**−2.049**	**0.039**	**4.170**	**2.398**	**−2.102**	**0.032**
All nosocomial cases II + IV	**113 (7.062)**	**19 (2.375)**	**−2.978**	**0.002**	**7.549**	**2.610**	**−2.961**	**0.001**	**4.867**	**1.531**	**−2.636**	**0.005**
NI III + IV	**13 (0.812)**	**1 (0.125)**	**−2.047**	**0.049**	**0.853**	**0.127**	**−2.065**	**0.030**	**0.519**	**0.093**	**−1.920**	**0.063**
All VRE cases	**213 (13.312)**	**49 (6.125)**	**−3.218**	**0.0006**	**14.161**	**6.819**	**−3.143**	**0.0007**	**9.038**	**3.929**	**−2.751**	**0.003**

Significant test statistics are highlighted in bold. NI, nosocomial infection.
[a] Mean frequency per month.
[b] Cases per 1000 patient-days (mean).
[c] Cases per 100 admissions (mean).

Table II
Linear regressions in the pre- and post-intervention period of incidence densities of vancomycin-resistant *Enterococcus faecium* (VRE) subgroups

Variable	Slope estimate pre-intervention	*P*-value	Slope estimate post-intervention	*P*-value
I. Community-acquired colonization	0.207	0.153	−0.339	0.223
II. Nosocomial colonization	0.542	0.001	0.0095	0.629
III. Nosocomial infection following community-acquired colonization	−0.014	0.748	0.0000	NaN
IV. Nosocomial infection	0.058	0.113	−0.085	0.134
V. Community-acquired infection	0.025	0.643	0.025	0.776
Community-acquired cases: I + III + V	0.219	0.147	−0.341	0.312
All nosocomial infections: III + IV	0.045	0.362	−0.085	0.134
Nosocomial cases: II + IV	0.600	0.0004	0.010	0.961
All VRE cases	0.819	0.0002	0.304	0.266

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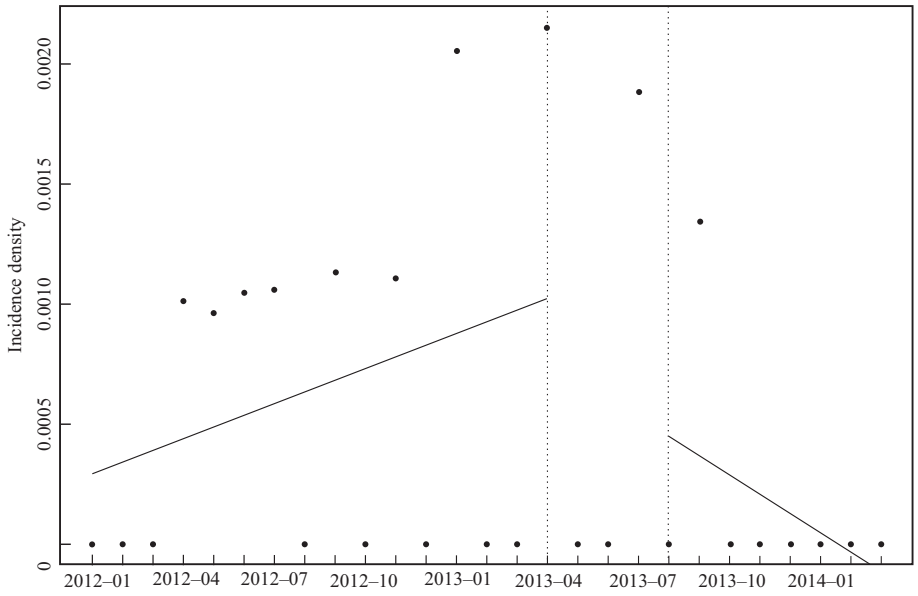

Figure 1. Linear regressions of all nosocomial vancomycin-resistant *Enterococcus faecium* (VRE) infections (Subgroups III and IV) in the pre- and post-intervention period. Slope estimates: pre-intervention 0.045; post-intervention: −0.085.

nosocomial cases, 60% were *vanA*-positive and 40% were *vanB*-positive. In the POST-IP, of 30 admitted VRE cases, 65% carried the *vanA* gene and 35% carried the *vanB* gene. Of the 19 nosocomial cases, 63% were *vanA*-positive and 37% were *vanB*-positive. PFGE patterns of the selected isolates are shown in Figure 2. In the PRE-IP, three VanA clusters and two VanB clusters were seen, as well as some singular strain patterns.

Bloodstream infections

In the PRE-IP, the BSI rate was 2.98/1000 [22 cases: nine Enterobacteriaceae, eight coagulase-negative staphylococci, two *Staphylococcus aureus* (one of which was MRSA), one *Candida albicans*, one enterococci (VRE) and one *Bacillus cereus*]. In the POST-IP, the BSI rate was 2.06/1000 [15 cases: four *Staphylococcus epidermidis*, four Enterobacteriaceae, three *S. aureus* (one of which was MRSA), two enterococci (no VRE) and two *Candida* spp.] ($P = 0.147$). (Supplementary Figure 3 shows linear regressions of all nosocomial BSI in the pre- and post-intervention period.)

No severe adverse events of daily octenidine-based body washes were observed during the intervention period.

Discussion

Well-designed and sufficiently powered multi-centre studies have demonstrated that antiseptic body washing reduces VRE, MRSA and BSI [4,9,10]. What can a single-centre study add? All infection control measures are only effective if the prevalence or incidence of pathogen colonizations or infections are high enough to be addressed by an intervention. In daily hospital infection control, different ICUs may be epidemiologically very distinct in terms of nosocomial infections or multi-drug-resistant organisms [4]. The infection

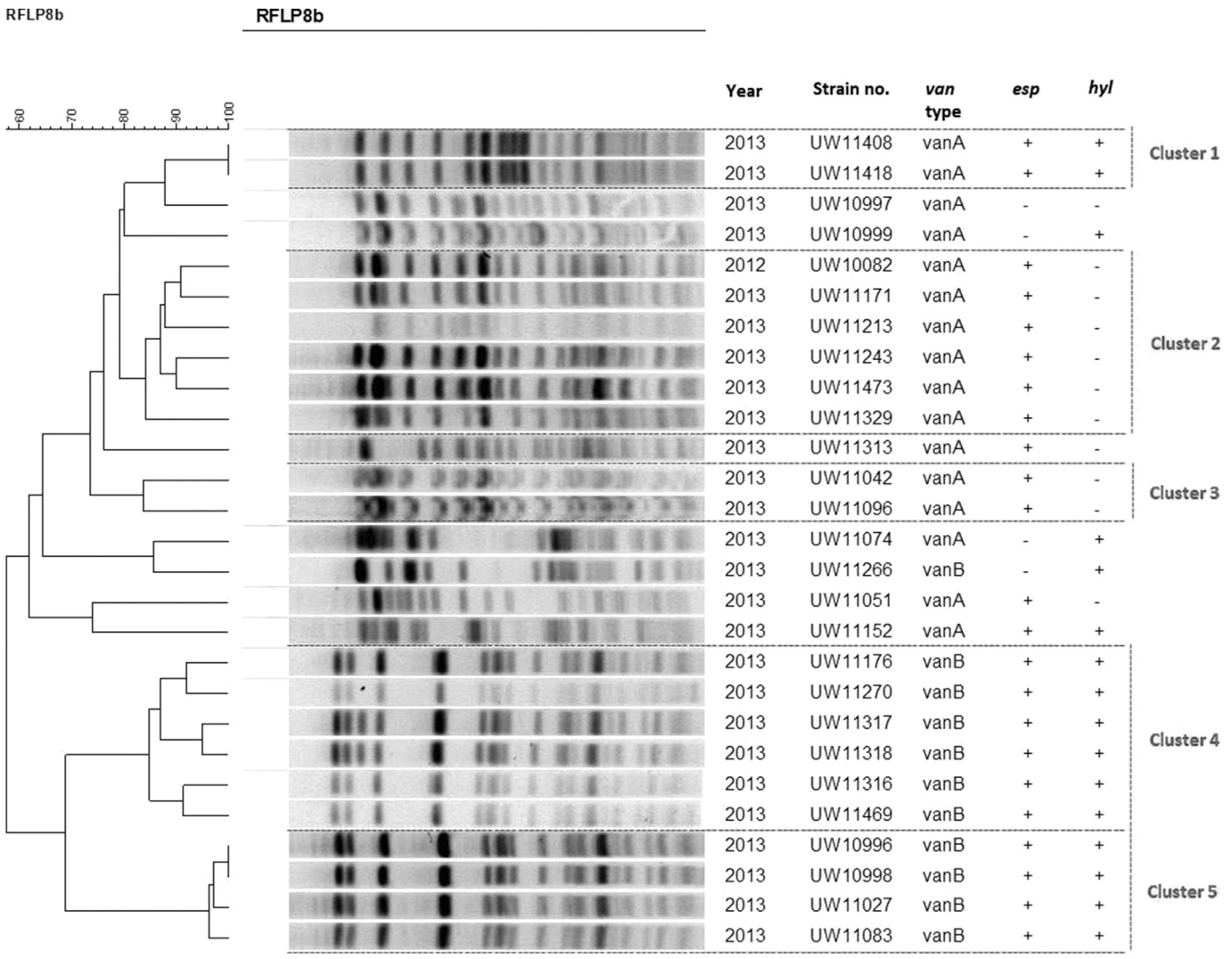

Figure 2. *Sma*I-macrorestriction analysis of 16 *vanA*- and 11 *vanB*-positive *Enterococcus faecium* isolates from the pre-intervention period.

control practitioner has to decide whether and what intervention would be adequate for their setting or epidemiological problem. This study shows how the problem of a steadily increasing prevalence of polyclonal VRE in an ICU could be reduced to a moderate level.

During the PRE-IP, all current infection prevention measures (including staff dedicated to VRE-positive, VRE-negative and VRE contact cases) were implemented and this was expected, based on successful reports from other groups, to lead to a reduction in nosocomial colonizations and infections [14]. Unfortunately, both nosocomial colonizations and nosocomial infections continued to rise.

Effect of the intervention on outcomes

In the POST-IP, the numbers of admitted and nosocomial VRE cases were reduced significantly. The reduction in the number of admitted cases was probably due, in part, to the reduction in the whole VRE burden within the ICU. In the PRE-IP, 11 VRE-positive patients were re-admitted and potentially considered as community-acquired cases; in the POST-IP, only one known VRE-positive patient was re-admitted. Fewer nosocomial VRE cases in the ICU led to fewer re-admitted VRE-positive cases and reduced incoming VRE burden. However, in the POST-IP, 33% of the patients with VRE detection on admission had a previous stay on the ICU, and may have acquired the VRE during their preceding stay. Colonizations with a low VRE burden might have been undetected due to the limited sensitivity of the screening method. Compared with stool culture, a single rectal swab culture may have a sensitivity of only 60%, but this can be increased by repeated swabs [15]. Molecular and phenotypic typing of selected VRE isolates showed transmission mostly in small clusters, and represented different circulating strains. For this epidemiological setting, antiseptic washing proved to be effective for reduction of VRE prevalence [16]. Additionally, contamination of healthcare workers' hands and medical devices may have been reduced, possibly resulting in the reduction of nosocomial VRE colonizations and infections [17,18].

Epidemiological analyses in VRE patient subgroups

To discover potential subgroups for VRE infection prevention, the VRE-positive patients were divided into five

subgroups. First, the study considered whether the number of nosocomial infections decreased. In the pre-intervention group, seven patients were infected, compared with one VRE infection in the post-intervention group ($P = 0.05$). Hence, the intervention seemed to be effective for reduction of nosocomial VRE infections. Second, the study considered if VRE colonization was predictive for an infection dependent on the intervention; this was not found to be significant (data not shown). Third, nosocomial colonizations were significantly reduced in the POST-IP. Climo *et al*. showed that chlorhexidine whole-body washing led to a reduction in VRE infections and no change in overall VRE prevalence; however, the present study showed a reduction in both [4]. The body washing technique (see below) or the antiseptic (octenidine) used may have been the reason for the effect in the present study. A study performed by Gastmeier *et al.*, also using octenidine, showed no reduction in VRE infections or colonizations, which was probably due to the low VRE prevalence during the study period [19].

Comparing the effects of antiseptic body washing in recent publications [4,9,10,19] with respect to a possible effect on BSI reduction, BSI was analysed retrospectively. Due to small numbers, the effect was not found to be significant in this study. However, Climo *et al*. [20] and Huang *et al*. [10] used large patient cohorts and found that antiseptic body washing reduced BSI. Interestingly, the effect was significant despite the fact that compliance with body washing was only approximately 60% in the study by Lowe *et al*. [21]. The present study estimated compliance of nearly 100%, as other washing products had been withdrawn from use. In addition, an infection control nurse provided four months of regular bedside education.

Octenidine has been shown to be more effective against some bacterial species than chlorhexidine [6]. To date, only one outbreak with a *B. cepacia* contaminated octenidine-containing mouth wash (octenidine 0.1%) has occurred [22], whereas antiseptic body washing with chlorhexidine or hexitidine has led to several outbreaks [10,23—25].

Time-series analyses for data containing few events are questionable. To obtain significance, time periods have to be prolonged or multi-centre studies have to be planned. To avoid an expensive study design, the permutation test was used in this study; this uses numerous random permutations of the data set. The hypothesis 'the data set may not be significantly different to all produced permutations' is then tested. Additionally, the permutation test controls for eventual seasonal changes in incidence data.

The results of this single-centre study may not justify generalization of the conclusions. Nonetheless, this study showed how to deal successfully with a high prevalence of VRE in a surgical ICU. Hand hygiene compliance observations and compliance with the intervention could not be performed. Hence, it is not possible to distinguish between the effects of hand hygiene compliance and antiseptic body washing in this study. However, the hand hygiene education of all medical staff was reinforced regularly, and in the same manner as during the PRE-IP.

In conclusion, in an ICU with high VRE prevalence and VRE transmissions in small clusters, whole-body washing with octenidine seemed to reduce nosocomial VRE colonizations and infections.

Acknowledgements

The authors wish to thank Dr Cori Diaz and Dr Anke Helmers who were responsible for microbiological routine diagnostics at MVZ Synlab Leverkusen. The authors also wish to thank Carola Fleige, Christine Guenther and Uta Geringer for excellent technical assistance at the NRC for Staphylococci and Enterococci. The authors wish to thank Schülke & Mayr GmbH for taking the costs for the statistical analysis. The results of this study were presented at IDWeek2014 in Philadelphia and at ECCMID 2014 in Barcelona.

Conflict of interest statement
None declared.

Funding sources
The cost of statistical analysis at University Dortmund was paid by Schülke & Mayr GmbH, 22851 Norderstedt, Germany. Schülke & Mayr had no influence on data analysis, intervention design, study enrolment, raw data management or manuscript preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2018.10.023.

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