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Review

Epidemiology and outcomes of vancomycin-resistant enterococcus infections: a systematic review and meta-analysis

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SUMMARY

Vancomycin-resistant enterococci (VRE) cause many infections in the healthcare context. Knowledge regarding the epidemiology and burden of VRE infections, however, remains fragmented. We aimed to summarize recent studies on VRE epidemiology and outcomes in hospitals, long-term-care facilities (LTCFs) and nursing homes worldwide based on current epidemiological reports. We searched MEDLINE/PubMed, the Cochrane Library, and Web of Science for observational studies, which reported on VRE *faecium* and *faecalis* infections in in-patients published between January 2014 and December 2020. Outcomes were incidence, infection rate, mortality, length of stay (LOS), and healthcare costs. We conducted a meta-analysis on mortality (PROSPERO registration number: CRD42020146389). Of 681 identified publications, 57 studies were included in the analysis. Overall quality of evidence was moderate to low. VRE incidence was rarely and heterogeneously reported. VRE infection rate differed highly (1–55%). The meta-analysis showed a higher mortality for VRE *faecium* bloodstream infections (BSIs) compared with VSE *faecium* BSIs (risk ratio, RR 1.46; 95% confidence interval (CI) 1.17–1.82). No difference was observed when comparing VRE *faecium* vs VRE *faecalis* BSI (RR 1.00, 95% CI 0.52–1.93). LOS was higher in BSIs caused by *E. faecium* vs *E. faecalis*. Only three studies reported healthcare costs. In

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contrast to previous findings, our meta-analysis of included studies indicates that vancomycin resistance independent of VRE species may be associated with a higher mortality. We identified a lack of standardization in reporting outcomes, information regarding healthcare costs, and state-of-the-art microbiological species identification methodology, which may inform the set-up and reporting of future studies.

Introduction

Vancomycin-resistant enterococci (VRE) are a global challenge as reported by the World Health Organization, the Centres for Disease Control and Prevention, and the European Centre for Disease Prevention and Control [1,2]. In the past decades, the epidemiology of VRE has changed markedly [3]. An increasing trend in vancomycin resistance in enterococci, in particular *Enterococcus faecium*, has been observed in many countries [4—6]. Furthermore, a shift of predominant strains and genotypes from the *vanA* genotype to the *vanB* genotype occurred in Germany in the past decade [3].

Enterococci generally display low levels of virulence and are mainly natural colonizers of the gastrointestinal tract [7]. The clinical significance of VRE or vancomycin-susceptible enterococci (VSE) isolated during diagnostic tests can be difficult to assess [4]. In urinary and respiratory tract infections, the relevance of enterococci has been questioned [8]. However, as an actual cause of infection, enterococci affect the most vulnerable patient groups, such as immunosuppressed patients [9]. Due to reduced therapeutic options, bacteraemia with VRE is associated with an increased morbidity and mortality compared with VSE bacteraemia [10].

Even though several studies, reviews and meta-analyses on the epidemiology of VRE have been published [11,12], these usually refer to the years before the increase in resistance rates in *E. faecium* was documented internationally. Additionally, as current VRE strains have replaced earlier variants, statements and surveys referring to these prior strains may not be transferable to the current strains and situation with possibly altered relevance regarding disease burden, transmissibility, and tenacity [3]. Furthermore, published data are usually restricted to limited settings, e.g., defined by an institution or region [13—15]. Therefore, this review aimed to summarize and stratify the most recent studies on VRE epidemiology in healthcare settings worldwide. Furthermore, the actual burden of VRE infections in terms of incidence, prevalence and mortality was analysed for patients in hospitals, long-term-care facilities (LTCFs) and nursing homes. The length of stay (LOS) and costs of VRE infections were evaluated to inform current clinical risk management from a (healthcare) providers' perspective.

Methods

Protocol and registration

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [16] and is being reported in accordance with the reporting guidance provided in the PRISMA statement from 2020 [17] (for PRISMA checklist, see Supplementary Table S1). The protocol has been registered within the PROSPERO database (registration number CRD42020146389).

Eligibility criteria

Human observational studies (case—control, cohort and cross-sectional) reporting results on VRE *faecium* and *faecalis* infections in hospital patients, patients in LTCFs and nursing homes were included. Studies on other *Enterococcus* species than VRE *faecium* or *faecalis*, as well as other study designs (randomized controlled trials, quasi-experimental studies, case reports, case series, animal studies, reviews) and ambulatory setting were excluded (see Supplementary Table S2).

Search strategy and information sources

We searched MEDLINE via PubMed, the Web of Science Core Collection (Clarivate Analytics), and the Cochrane Central Register of Controlled Trials (Wiley—Cochrane Library), for peer-reviewed articles published between 1st January 2014 and 31st December 2020, without language restrictions. Existing systematic reviews and meta-analyses were checked for additional references. Furthermore, manual searches and contact with authors were used where necessary. The search strategy comprised a combination of free-text words and index terms (including synonyms) as well as keywords (medical subject heading (MeSH) terms) associated with "VRE" and "burden of disease". This ensured that recent publications not yet categorized with MeSH were also captured. Furthermore, we performed a cross-reference check of relevant articles and reviews in order to refine and optimize the search strategy. A sample search strategy is provided in Supplementary Table S3 and was adapted for each database.

Selection process

Study selection was performed in two stages by two independent reviewers (C.B., H.G.). Discrepancies were resolved by consensus or consultation with a third researcher (V.M.E.). A first screening was performed by reviewing the title and abstract of each of the publications identified (C.B., H.G.). Then, selected full-text articles were included according to the eligibility criteria (C.B., H.G., V.M.E., N.T.M.). Inclusion and exclusion criteria are listed in Supplementary Table S2. Any discrepancies were discussed between the reviewers and a consensus was achieved in all cases.

Data collection process and data items

The results obtained from the three different databases were exported to a reference manager and duplicates were removed. Meta-analyses and systematic reviews were checked for any relevant primary articles and included, if necessary (i.e., not already included), but data extraction was not performed for these types of studies. Data was extracted using pre-defined data sheets and independently checked by at least two reviewers (C.B., H.G., C.S., V.M.E.). Data items were: author, year of publication, location/country, study population/design, study period, screened units, timing of screening (days after admission), number of VRE/VSE positive patients, number of patients screened, colonization rate (%), infection rate, source, species, mortality (%), odds ratio (OR) (95% confidence interval (CI)), LOS, median (interquartile range (IQR)), days, recurrent VRE infection (%), costs, median (IQR), US dollars (or converted to US dollar). Furthermore, documented vancomycin resistance rates and VRE prevalence per ward or healthcare facility were extracted separately. Whenever studies did not report the prevalence of VRE/VSE, this ratio was calculated by dividing the numbers of VRE isolates to the total numbers of tested enterococci isolates and multiplying by 100, if applicable. The colonization rate, if not reported, was calculated by dividing the numbers of VRE/VSE positive isolates by the total numbers of patients screened.

Data collection was differentiated by setting (hospitals, LTCFs and nursing homes), by level of care (ICUs vs non-ICUs), by patient population (paediatric vs adult patients), and partly by infection type (bloodstream infections (BSIs) and/or other invasive infections vs non-BSIs).

Risk of bias and quality of evidence assessment

At least two of the authors (V.M.E., K.L., H.G.) independently judged risk of bias according to the Newcastle–Ottawa Scale (NOS) [18]. The NOS covers three domains of potential bias at the study level, namely, selection, comparability and exposure. A total of 9 stars can be rewarded in the three domains. In general, within the NOS scoring, this leads to the following levels of evidence for individual studies (based on study design and methodological quality): high (i.e., high-quality RCTs), moderate (i.e., lower-quality RCTs, high-quality cohort/case–control studies, and cost-effectiveness studies), low (i.e., lower quality cohort/case-control studies and cost-effectiveness studies, cross-sectional studies with comparison, high-quality surveillance studies) and very low (i.e., low-quality surveillance or other observational studies, outbreak studies, cross-sectional studies without comparison). Unfortunately, there are currently no threshold scores available to align scores reached in the domains with the level of evidence.

Meta-analysis

We conducted a meta-analysis on the dichotomous outcome mortality. To account for possible heterogeneity, we performed separate analyses for the comparators VRE vs VSE and VRE *faecium* vs VRE *faecalis* using the metafor package [19] in R (Version 4.2.2). To display the results of individual studies, we created Forest plots for the aforementioned comparisons. We used a random effects model; effect sizes are indicated as risk ratios (RRs) with 95% confidence intervals (CIs).

Results

Study characteristics

A total of 681 publications were identified with the search strategy of which 10 were retrieved by the Cochrane Central Register of Controlled Trials, 478 by MEDLINE via PubMed, and 193 by the Web of Science Core Collection. After excluding 53 duplicates, an additional 403 articles were excluded based on title and abstract screening. Full-text screening was performed on 225 articles of which 165 publications did not meet the eligibility criteria. The remaining publications were subjected to full text analysis and data extraction (see study flow diagram, Figure 1). In total, 57 studies were included in the systematic review [20–76]. Crude data of the data collection process are displayed in a summary of findings table (Supplementary Table S4).

Risk of bias

All included studies were assessed for risk of bias according to NOS [18] (for results see Supplementary Table S5). Overall, the mean score across all studies was 6 stars. Risk of bias regarding 'comparability' was especially a concern in the cohort studies and the cross-sectional study. All studies had moderate to very low quality of evidence due to their set-up as observational studies.

Results of individual studies

Overall, 48 cohort studies, eight case–control studies and one cross-sectional study were included and analysed.

Epidemiology

VRE incidence, infection rate and prevalence. Four studies reported on the VRE incidence in highly heterogeneous patient populations and with differing outcome parameters (see Supplementary Table S4). While Elstrøm *et al*. reported an incidence of 7.09 per 100,000 person-years in the Norwegian population for infections/colonizations (2017) [33], Ho *et al*. reported an infection/colonization incidence for burn patients (2006–2007) of 33.3% before contact precautions were implemented and 42.9% for the period afterwards (2009–2010) [42]. In the study conducted by MacAllister and colleagues, the cumulative VRE bacteraemia infection incidence was found to be 2.910,000 patient days (95%CI: 2.0, 4.1) in hematopoietic stem cell transplant recipients [56]. Rosko *et al*. calculated a VRE BSI incidence of 0.12 per 1000 bed days [65].

VRE infection rate differed highly between settings and patient populations (see Supplementary Table S6). In paediatric patient populations, the VRE infection rate ranged between 3% and 22%. In patients with hematologic malignancies, this rate ranged between 1% and 55%. Transplant recipients had a VRE infection rate between 3.5% and 21.5% in the three included studies [32,51,73]. Rosko *et al*. report a VRE

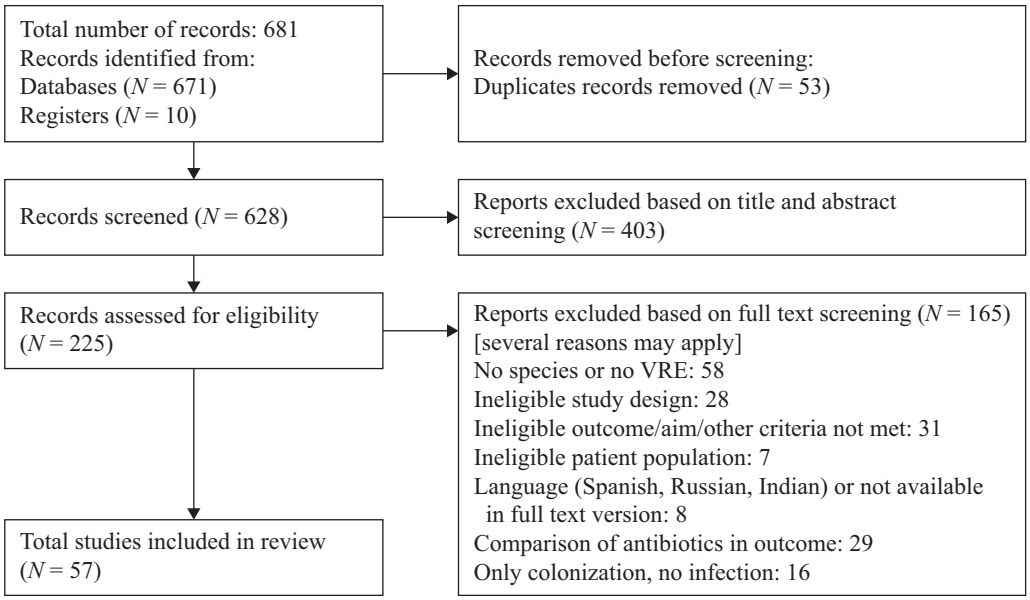

Figure 1. Study flow diagram according to PRISMA.

BSI infection rate between 0% and 3% over the analysed time period (1998–2011) [65].

VRE prevalence in terms of colonization rate was reported in 16 studies [20,23–25,34–37,42,44,52,56,58,59,69,74]. Colonization rates ranged from below 1% in solid organ transplant patients [23] and 61% in hematopoietic stem cell transplantation (HSCT) patients [37].

Burden of disease including mortality and LOS

Mortality. Forty-five studies reported on mortality outcomes in hospital settings. No studies retrieved by our search reported on mortality outcomes in LTCFs or nursing homes (see Supplementary Table S7).

Four studies reported on VRE invasive infections in hospitalized patients in general. Mortality for this type of infection ranged between 23% [70] and 60% [44] as well as 65% [68]. When differentiating between invasive VRE and VSE infections, Jiang and colleagues found a significant difference (31/48; 65% vs 56/142; 39%) [47]. Tripathi and colleagues reported a significant difference between infections caused by VRE *faecalis* (25/62; 40.3%) vs VRE *faecium* (6/24; 25%) [70].

Regarding BSI in hospitalized patients, 30-day mortality ranged for enterococcal BSI between 13% (VRE *faecium*) [24], 18% (both VRE *faecalis*/*faecium* and non-VRE *faecalis*/*faecium*) [48], 24% (non-VRE *faecium*/*faecalis*) [75] and 45% (both VRE *faecium* and non-VRE *faecium*) [50]. Pinholt and colleagues differentiated between BSI due to *E. faecium* and *E. faecalis* with 30-day mortality differing between these two: 35% vs 21%, respectively [62]. VRE BSI mortality ranged between 0% [43], 28% (attributable mortality) [55], 33.6% (30-day mortality) [41], 34.7% [63], 41% (30-day all-cause mortality) [66], 65.7% (30-day mortality) [64] and 70% [30]. When comparing VRE *faecalis* and VRE *faecium* in BSI, da Silva reported a mortality rate of VRE *faecalis* of 88.9% (8/9) vs VRE *faecium* of 68.4% (13/19) [30]. When comparing VRE BSI vs VSE BSI, López-Luis *et al.* found a 90-day crude mortality of 56% (59/106) vs 29% (24/83) [55]. In line with this, Lee *et al.* reported a 30-day mortality rate of 28% for VRE BSI vs 17% for VSE BSI [54]. Kramer *et al.* reported an in-hospital mortality of VRE *faecium* of 50.5% (52/103) vs VSE *faecium* of 39.6% (195/493) vs VSE faecalis of 24.4% (132/563) [53].

Four studies reported on a paediatric population, with an in-hospital mortality rate due to VRE infections ranging from 0% to 33% and 42% [20,59] in both endemic and outbreak settings.

Fourteen studies reported on patients with haematological malignancies (including acute leukaemia, febrile neutropenia and patients before and after allogeneic and/or autologous HSCT, with VRE-specific mortality ranging from no deaths [34], less than 1% [25], 38% [58] to 57% [52]. Specific mortality data on VRE BSI in this patient population ranged from 0% (three-month mortality) [35], 18% (seven-day mortality) [67], 31% (death at 30 days) [72] and 33% (60-day mortality) [37]. Ford reported a higher mortality in post-engraftment VRE BSI than pre-engraftment VRE BSI [35]. While Alatorre-Fernandez reported no significant difference between VRE *faecium* and VSE *faecalis* infections in haematological patients [21] and Macesic reported no difference in mortality between VRE and VSE in general [57], Gedik and colleagues found a higher mortality in VRE BSI compared with VSE BSI (50% [1/2] vs 33% [2/6]), although on a very limited number of patients [40]. Concordantly, Weber reported a higher overall survival 30 days post-BSI in VSE (90.7%) vs VRE (74.5%) in this specific patient population [71]. On a molecular level of analysis, Marchi reported that infections caused by VRE carrying *asa*1 gene resulted more frequently in death [58].

Specific mortality data in three surveillance cohort studies and on patients with solid organ transplantation (i.e., liver transplantation) are reported in Supplementary Table S7.

Meta-analysis of the raw mortality data of six studies, overall with moderate heterogeneity, revealed an RR of 1.46 in

the random effects model [95% CI 1.17–1.82] for VRE *faecium* bloodstream infections in comparison with VSE *faecium* bloodstream infections (Figure 2).

When analysing data of three studies, with high heterogeneity, regarding mortality of VRE *faecium* vs VRE *faecalis* BSI or invasive infections, no difference was observable (RR 1.00, CI 0.52–1.93) in the random effects model (see Figure 3). This non-significant finding persisted when only the two studies that included BSI [22,30] were included (RR 1.19, 95% CI 0.52–2.74).

LOS. Data on length of hospital stay were reported in 15 studies [20,22,26,30,32,35–37,47,49,53,56,63,69,72] with considerable heterogeneity regarding methodology and, if applicable, differences between reference groups that were used as comparators. Comparators included patients with VRE colonization (as opposed to infection), patients with VSE infection, patients with any enterococcal infection, and patients with *E. faecalis* infection (as opposed to *E. faecium*). Some studies descriptively reported LOS in patients with VRE bacteraemia. Da Silva *et al*. calculated a mean duration of hospitalization in patients with VRE bacteraemia of 35 ± 22.5 days [30]. MacAllister and colleagues reported that the LOS stay prior to HSCT was significantly associated with VRE bacteraemia in multivariable analysis (hazard ratio 1.06; 95% CI: 1.01, 1.11) [56].

Colonization vs infection

Akturk and colleagues reported in neonates a significantly longer LOS in patients with VRE infection than those with VRE colonization (81.8 ± 30.0 days vs 35.3 ± 2.3), albeit with an uneven group size between colonized (N=194) and infected (N=6) patients [20]. Similarly, but not reaching the level of significance, Sutcu and colleagues reported a longer total LOS between colonized patients vs infected patients (28.5 ± 3 days vs 68.1 ± 15 days) in a study population of >1000 patients admitted to the paediatric intensive care unit [69]. Again, groups were unbalanced with 97 colonized patients vs 11 infected patients.

Ford and colleagues reported a positive association between LOS and hospital-acquired gastrointestinal VRE colonization rates in patients with newly diagnosed acute leukaemia [37]. LOS in VRE BSI patients in this cohort was significantly higher than in non-VRE BSI patients (42 vs 29 days, P=0.0005). In patients before HSCT, VRE colonization did not influence hospital LOS [35]. VRE BSI in colonized patients was associated with a longer median LOS (24 vs 20.5 days, P=0.04) compared with colonized patients without BSI in a study conducted by Ford and colleagues [36]. Kaya *et al*. also reported a longer LOS in patients with VRE bacteraemia (50 days, 13 ± 125 days) vs patients with VRE colonization only (45 days, 8 ± 150 days) [49].

VRE vs VSE

In a study from Germany on patients undergoing liver transplantation, LOS was comparable between VRE BSI and VSE BSI (25.9 ± 8.5 vs 24.9 ± 7.7) [32]. In line with that, Kramer and colleagues did not find vancomycin resistance to additionally increase LOS when comparing VRE *faecium* and VSE *faecium* BSIs (54 days (36–85) vs 42 days (23–78)) [53]. Rao *et al*. also

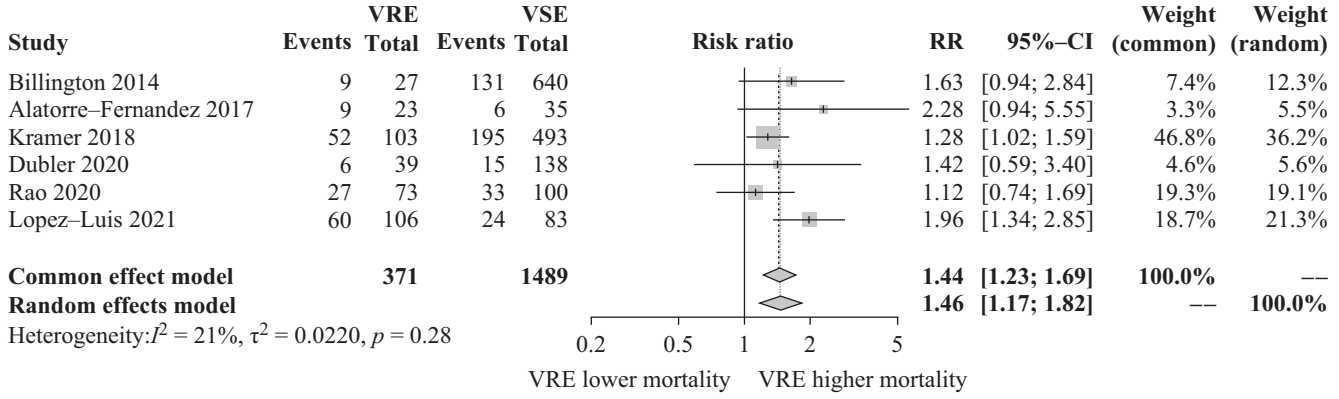

Figure 2. Meta-analysis of mortality data regarding vancomycin-resistant enterococci (VRE) *faecium* bloodstream infections in comparison with VSE *faecium* bloodstream infections. CI, confidence interval; RR, risk ratio.

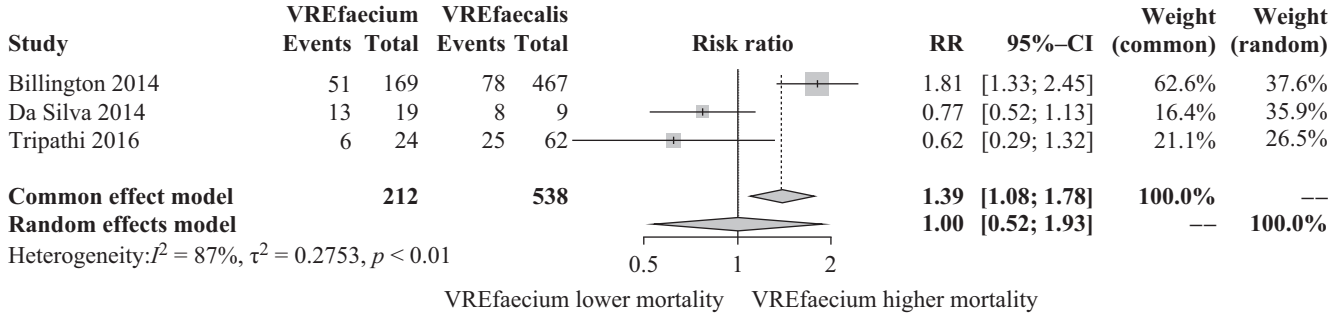

Figure 3. Meta-analysis of mortality data regarding vancomycin-resistant enterococci (VRE) *faecium* vs VRE *faecalis* bloodstream infections or invasive infections. CI, confidence interval; RR, risk ratio.

did not find a significantly different LOS between episodes of bacteraemia caused by VRE *faecium* vs VSE *faecium* (34.5 days vs 26.3 days, P=0.14) [63].

Da Silva and colleagues reported a mean duration of hospitalization of 36 ± 22.5 days (range 2–95 days). Overall, 50% of the 30 patients with VRE bacteraemia had a LOS in the hospital of up to 32 days [30]. Jiang and colleagues reported a significantly different LOS in patients with VRE invasive infections vs VSE invasive infections (55.4 ± 47.7 vs 38 ± 34 days, P=0.0009) [47]. Xie *et al*. reported descriptively a median total LOS of 38.5 days (range 2–138 days) in a cohort of haematology/oncology patients with VRE BSI. Medium LOS after VRE BSI was 18 days in this study [72].

VRE vs other enterococci

Chen and team reported in a study from Taiwan that LOS up until the timepoint of bacteraemia onset was similar between VRE BSI (median eight days, range 8–89 days) and any other enterococcal BSI (median 10 days, range 3–46 days) [26].

E. faecium vs E. faecalis

Billington *et al*. from Canada calculated in a population-based study a longer LOS for patients with BSI caused by *E. faecium* compared with *E. faecalis* (32.1 vs 17.8 days), while they did not distinguish between VRE or VSE [22]. Kramer and colleagues reported in a retrospective cohort study of over 1000 cases of BSI that the total LOS was significantly higher in BSIs caused by *E. faecium* vs *E. faecalis* (42 days, (23–78)) vs 32 days (16–61), P=0.000) [53].

Health-economic aspects

Attributable costs of infections. Cost-related outcomes were reported in three studies [35–37]. In a US-study on patients undergoing HSCT, a VRE BSI led to a per-patient increase of costs from $54,992 to $61,151 [36]. In another study by the same team on leukaemia patients, VRE BSI yielded almost twice the costs compared with no VRE BSI ($172,000 vs $86,000, P=0.0003), mainly driven by LOS [37]. A third study on patients undergoing HSCT showed that VRE BSI led to higher costs at both three months ($380,000 vs $180,000; P=0.0002) and 12 months ($520,000 vs $340,000; P=0.004) pertaining to post-engraftment bacteraemia compared with non-VRE BSI, while any bacteraemia was associated with higher costs than no bacteraemia [35]. However, the authors concede the limitation that blood culture contaminations with coagulase-negative staphylococci may have been counted towards the non-VRE BSI group, thereby leading to underestimation of costs related to 'true' non-VRE BSI. Of note, pre-engraftment bacteraemia caused by VRE was not associated with higher costs than non-VRE BSI.

Discussion

In this systematic review and meta-analysis, we showed a high disease burden of VRE, with infection rates ranging from 1% to 55%, depending on the setting and the patient cohort. In addition, mortality rates were as high as 70%, in particular among vulnerable patients, e.g., those with haematological/oncological diseases. Of note, our meta-analysis yielded a higher RR for mortality in infections caused by vancomycin-resistant *E. faecium* compared with vancomycin-susceptible *E. faecium*, while the pooled estimate of a limited number of heterogenous studies indicated no difference between vancomycin-resistant *E. faecium* and *E. faecalis*, respectively. Our data also indicate higher healthcare costs related to VRE, partly mediated by longer hospital stays of patients.

Our findings confirm contemporary reports of the increasing prevalence of VRE across different healthcare settings, and particularly the incidence rate among hospitalized and vulnerable patient cohorts [3]. The high mortality rates reported herein are also in line with previous meta-analyses [10,11]. However, these studies of VRE-related mortality had limitations, such as comparing VRE-infected patients with uninfected controls [11] or including largely older studies from before 2014 [10]. In contrast to the notion that the higher virulence and associated mortality in VRE is species-related (i.e., mediated by the fact that VRE are mostly *E. faecium*) [53], our findings indicate that the vancomycin resistance alone may be associated with a higher mortality, which contradicts some previous studies [32,53]. This is further substantiated by the lack of a significant difference between VRE *faecium* and *faecalis*, albeit the sample size was very small and studies were quite heterogeneous for this comparison. Of course, an additional reason for the differing results could be the selection of studies included in our systematic review and meta-analysis. Furthermore, species identification was largely based on biochemical methods or unclear methodology in these studies, such that inferred conclusions based on microbiological species differentiation are clearly compromised in terms of reliability.

LOS was higher in patients with VRE infections, compared with VRE colonization across different patient settings, although many studies were unbalanced in group size comparators. Studies on LOS in VRE vs VSE BSI or invasive infections were not analysed quantitatively in a meta-analysis in our study, due to the limited number of studies. However, based on the included studies, LOS did not seem to differ significantly, contradicting a recent meta-analysis [10]. Based on our systematic review, included studies showed *E. faecium* to cause longer LOS compared with *E. faecalis* infections, also when considering vancomycin resistance. Again, reasons for differing results of our systematic review compared with previous findings in the literature include study selection, enterococcal species identification methods and/or patient population selection. Additionally, LOS as outcome parameter in VRE infections is multi-faceted and influenced by many factors such as treatment recommendations, comorbidities, complications occurring during treatment (insufficient source control, recurrence, etc.) or consultation by an infectious disease physician [78], making it essential that LOS studies clearly define process indicators as well as make patient cohorts comparable based on propensity score matching. Healthcare costs were unanimously higher in patients with VRE infections in the three analysed studies, complementing similar results of a recent meta-analysis [11].

Strengths of the study are its scope as a comprehensive overview of the current evidence of the epidemiology and burden associated with VRE infections in patients in institutionalized healthcare. Furthermore, the in-depth data analysis of VRE *faecium* vs VRE *faecalis* and VRE vs VSE mortality data in a series of studies spanning over seven years is also a strength.

However, our study has limitations. Outcomes such as premature mortality (years of life lost), disability (years lived with disability) or both combined (disability-adjusted life years) were rarely reported, therefore we focused on incidence,

prevalence, mortality, LOS and healthcare costs. VRE surveillance was heterogeneous in the assessed studies and adapted to local epidemiological and regulatory situations. Similarly, our review was hampered by a lack of standardization in reporting outcomes and a lack of information especially in healthcare costs in many identified studies. In addition, study populations and reported outcome parameters were very heterogeneous and study designs of the included studies were limited to providing only moderate to very low quality of evidence. Included studies were designed for different purposes such that comparisons of outcome parameters were highly contextual. Comparisons on mortality outcomes were partly compromised by studies with insufficient species identification methodology making it difficult to infer valid conclusions regarding species-specific mortality. Adding to this, single-isolate-based species identification and susceptibility testing may not fully reflect within-patient genetic variability of enterococcus strains [77] and thus may limit results of the included studies. Furthermore, the meta-analysis on mortality outcomes in VRE vs VSE infections was hampered by a small overall number of included studies (N=6) which may explain why our findings contradict previous findings in the literature on VRE mortality [32,53]. Lastly, patients in LTCF and nursing homes were clearly under-represented in the studies identified in our review.

Despite the increasing and rapidly changing epidemiological and clinical significance of VRE-associated infections including current changes in pathogen-related factors such as burden, transmissibility and tenacity, there is a widespread lack of data on their incidence, prevalence, mortality, and economic outcomes. Our findings contribute to closing this knowledge gap and map current research needs in this field. The collected and analysed data in our study may serve as guidance for clinical risk management in VRE-colonized patients in the hospital setting in particular in the context of immunosuppression. We identified a lack of standardization in reporting outcomes, a lack of studies in LTCF and nursing home settings, and a lack of information especially in healthcare costs of VRE infections, which may provide guidance for future studies. Additionally, owing to the current changes in epidemiology and pathogen-related factors, future multi-centre screening studies across different countries need to shed light on the widely varying VRE incidence and colonization vs infection rates in clearly defined patient populations. Similarly, future studies need to apply a more rigorous, state-of-the-art microbiological species identification methodology (e.g., matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)), polymerase chain reaction (PCR)-based vancomycin resistance gene detection, and more granular VRE strain typing methods (e.g., whole-genome sequencing) in their study methods to ensure reliable discrimination not only between VRE *faecalis* and VRE *faecium* but also between VRE *faecium* vs non-VRE *faecium*.

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Author contributions

C.S., N.T.M., T.G. and V.M.E. wrote the initial protocol for the systematic review. C.S. and C.B. conducted the literature search. C.B., C.S., H.G., V.M.E. and N.T.M. conducted the full-text screening. H.G., C.S. and V.M.E. conducted the data extraction. K.L., H.G. and V.M.E. assessed the risk of bias and K.L. analysed the data according to the outcomes. C.P. performed the meta-analysis. All authors read and approved the final manuscript. N.T.M. is the guarantor of the review.

Conflict of interest statement

N.T.M. reports financial support for this study provided by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). M.M. reports a relationship with Tillotts Pharma GmbH that includes speaking and lecture fees. The remaining authors declare they have no competing interests.

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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.2023.09.008.

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