Title: Incidence and Outcomes Associated with Infections Caused by Vancomycin-Resistant Enterococci in the United States: Systematic Literature Review and Meta-Analysis

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Main Points

The incidence of vancomycin-resistant enterococci infections increased in Atlanta and Detroit but did not increase in national samples. VRE infection is associated with large attributable burdens, including excess mortality, prolonged in-hospital length of stay, and increased treatment costs.

Abstract

Background: Information about the health and economic impact of infections caused by vancomycin-resistant enterococci (VRE) can inform investments in infection prevention and development of novel therapeutics. Our objective was to systematically review the incidence of VRE infection in the US and the clinical and economic outcomes of these infections.

Methods: We searched various databases for US studies published between 1/1/2000 and 6/8/2015 that evaluated incidence, mortality, length of stay (LOS), discharge to a long-term care facility (LTCF), readmission, recurrence, or costs attributable to VRE infections. We included multicenter studies that evaluated incidence and single center and multicenter studies that evaluated outcomes. We kept studies that did not have a denominator or uninfected controls only if they assessed post-infection LOS, costs, or recurrence. We performed meta-analysis to pool the mortality data.

Results: Five studies provided incidence data and 13 studies evaluated outcomes or costs. The incidence of VRE infections increased in Atlanta and Detroit but did not increase in national samples. Compared with uninfected controls, VRE infection was associated with increased mortality (pooled odds ratio 2.55), longer LOS (3 - 4.6 days longer or 1.4 times longer), increased risk of discharge to a LTCF (2.8 to 6.5-fold) or readmission (2.9-fold), and higher costs ($9,949 higher or 1.6-fold more).

Conclusions: VRE infection is associated with large attributable burdens, including excess mortality, prolonged in-hospital stay, and increased treatment costs. Multicenter studies that use suitable controls and adjust for time at risk or confounders are needed to estimate the burden of VRE infections accurately.

Abbreviations

HAI, healthcare-associated infections; LOS, length of stay; LTCF, long-term care facility; VRE, vancomycin-resistant enterococci.

Introduction

Vancomycin-resistant enterococci (VRE) infections are endemic in hospitals across the US [1]. VRE are the second most common antimicrobial resistant pathogens causing healthcare-associated infections (HAIs) in the US [2, 3]. According to the National Healthcare Safety Network (NHSN) data in 2009 – 2010, 38.6% of enterococci isolated from device-associated HAIs and 23.1% of those isolated from surgical site infections (SSIs) were vancomycin resistant [3].

Multiple epidemiological investigations of VRE infections have been published; however most prior studies were performed before newer antibiotics such as quinupristin-dalfopristin, linezolid, or daptomycin were used widely [4]. Most studies that reported the incidence of VRE infections were completed at single centers and evaluated small patient populations. Additionally, some studies claiming to report the incidence of VRE infections did not report a denominator-based incidence rate but instead reported the proportion of enterococcal isolates from infections that were vancomycin resistant [5, 6]. Furthermore, only a few studies evaluated outcomes, and some of these studies either included both colonized patients and infected patients or included patients infected with vancomycin-susceptible enterococci (VSE) as the comparator and did not include an uninfected control group [4 ,7]. Studies that use patients with VSE infections as the comparator can assess only the impact of antimicrobial resistance, but not the effect of antimicrobial resistance in addition to the infection itself [8].

To address gaps in our understanding about the current burden associated with VRE infections in the US, we conducted a systematic literature review of studies that were conducted in the US, were published during or after 2000, and reported the incidence of VRE infections or outcomes related to these infections. Our goals were to describe the recent incidence of VRE infections, and to evaluate the clinical and economic outcomes attributable to VRE infections.

Methods

Search Strategy

We conducted a systematic review according to the Meta-analysis of Observational Studies in Epidemiology [9] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [10] guidelines. See supplementary document for a detailed description of the search strategy. We reviewed reference lists from each article we retrieved to identify additional studies.

Inclusion and Exclusion Criteria

Studies were included if they: 1) were conducted in the US, 2) reported data from any year from 2000 through 2015, and 3) evaluated the incidence of VRE infections or outcomes attributable to VRE infections, including mortality, length of stay (LOS), discharge to a long-term care facility (LTCF), readmission, recurrence, or costs. We included multicenter studies that had at least 8 sites when we assessed the incidence of VRE infections. For studies presenting outcome data, we included single center studies because most multicenter studies that assessed outcomes evaluated the same patient population (Detroit Medical Center, DMC). We excluded studies that: 1) used the *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* diagnosis codes to define VRE infections, 2) combined patients with VRE colonization with those who had infections, 3) did not report original data, 4) did not have a denominator or an uninfected control group, or 5) were published in a language other than English. We included studies that did not have an uninfected control group if they assessed the post-infection (after the first positive culture of VRE) outcomes of LOS, costs, or recurrence. For LOS or costs, we excluded studies if they did not measure post-infection LOS or costs, or did not match cases with controls on either the time at risk (time from admission to infection for cases, time from admission to discharge for uninfected controls), or on propensity scores. The current study did not require Institutional Review Board approval.

Data Extraction and Quality Assessment

Dr. Chiang reviewed the titles and abstracts of all articles to determine if they met the inclusion criteria. For each included study, 2 of 4 reviewers (Drs. Chiang, Nair, Perencevich, Schweizer) independently abstracted data on: study design, population, setting, location, definition of VRE infection, incidence data, and clinical and economic outcomes. Reviewers resolved disagreements by consensus. We assessed the risk of bias using the Newcastle-Ottawa tool [11] for all studies and the Consensus Health Economic Criteria [12] for studies evaluating costs.

Meta-Analysis of Mortality

We performed a meta-analysis of the studies that provided mortality data. We abstracted adjusted odds ratios (aORs) from the literature or raw data when aORs were not available. We pooled data using both random-effects and fixed-effects models with inverse variance weighting, and we used the Cochran Q statistic and the I^2 statistic to assess heterogeneity. Publication bias was determined by visually evaluating the funnel plot.

Results

We screened 7,324 unique studies for eligibility (Figure 1). Eighteen studies were eligible for inclusion including: 5 multicenter studies reporting the incidence of VRE infections [2, 13-16] and 13 studies (4 multicenter and 9 single center) evaluating relevant outcomes [17-29].

Five studies used the NHSN definition of hospital-acquired VRE infections [2, 15, 21-23], 8 studies included patients with VRE recovered from sterile sites [13, 16, 17, 20, 25, 27-29], 4 studies included patients with VRE recovered from sterile sites or urine [14, 18, 19, 26], and 1 study did not define VRE infection [24]. Overall, the risk of bias among all studies evaluated was low (Table 1).

Incidence of VRE infections

The incidence varied by study location, population, and the denominator used (i.e., person-years, patient-days, device-days, or number of hospitalizations) (Table 2). Thus, we could not calculate a summary incidence estimate. The incidence of VRE infections in Atlanta increased from 0.77 per 100,000 person-years in 1997 to 1.60 per 100,000 person-years in 2000 (P = 0.001). The increasing trend was significant in the African Americans but not in the White residents, and the overall incidence was significantly higher in the African Americans than in the White populations (2.59 vs 0.70 per 100,000 person-years) [13]. Among patients admitted to the 8-hospital DMC system, the incidence of VR *E. faecalis* infections increased from 0.72 per 1,000 patient-days in 2003 to 1.68 per 1,000 patient-days in 2009 (P < 0.001), and the incidence of VR *E. faecium* increased from 1.97 to 2.67 per 1,000 patient-days (not statistically significant) [14]. Consistent with previous literature, VR *E. faecium* caused a higher proportion of the infections than did VR *E. faecalis* in Atlanta (83% vs 6%) [13] and in southeast Michigan area (71% vs 29%) [14].

Among patients admitted to all Veterans Affairs (VA) hospitals, the incidence of VRE decreased between 2007 and 2010 from 1.51 to 0 per 1,000 patient-days for patients admitted to ICUs ($P < 0.001$) and decreased from 0.33 to 0.09 per 1,000 patient-days for patients admitted to non-ICU units ($P < 0.001$) [15]. Between 2005 and 2011, the incidence of VRE infections did not change significantly among Medicare patients with 1 of the 4 conditions (i.e., acute myocardial infarction, congestive heart failure, pneumonia, or conditions requiring surgery) [16].

NHSN reported that the pooled incidence of VR *E. faecium* central-line associated bloodstream (BSIs) infections during 2006 and 2007 was 0.18 (range: 0.06 to 0.37) per 1,000 device-days in ICUs and 0.14 (range: 0.13 to 0.15) per 1,000 device-days in non-ICUs. The pooled incidence of VR *E. faecium* catheter-associated urinary tract infections was 0.14 (range: 0.05 to 0.18) per 1,000 device-days in ICUs and 0.25 (range: 0.12 to 0.45) per 1,000 device-days in non-ICUs [2].

Outcomes attributable to VRE infections

Table 3 summarizes the results of 13 studies that reported outcomes or costs attributable to VRE infections. The 3 multicenter studies from DMC used different subgroups of patients: BSIs caused by VR *E. faecalis* or VR *E. faecium* in 2008 – 2010 [17], all VR. *E faecalis* infections in 2008 – 2009 [18], and all community-onset (CO) VR *E. faecalis* in 2008 – 2009 [19]. The study populations of the single center studies included all hospitalized patients [21], patients with liver transplants or stem cell transplants [24, 28], non-surgical patients [25], or patients with leukemia [29]. Five studies evaluated only VRE BSIs [17, 21, 25, 28, 29], 1 study evaluated CO VRE infections [19], and 2 studies evaluated all VRE infections [18, 24].

Mortality

Figure 2 summarizes the ORs from 6 studies that reported mortality data. These studies included a total of 1,182 VRE-infected patients and 1,840 uninfected controls. Compared with uninfected controls, patients who had VRE infections had a 2.5-fold higher risk of death (random-effects model; pooled OR [pOR] = 2.55; 95% CI [1.91, 3.39]). The heterogeneity among studies was negligible (P = 0.54 for Q statistic test and I^2 = 0%). The funnel plot (Figure 3) was not consistent with publication bias. The pooled mortality estimate from the 4 single center studies [21, 24, 28, 29] was higher (pOR = 3.15; 95% CI [2.15, 4.60]) than the estimates from the 2 multicenter studies (OR = 1.81; 95% CI [1.06, 3.08] and OR = 2.20; 95% CI [1.04, 4.65]) [18, 19], which was not surprising because small single center studies often overestimate true effects.

Post-infection LOS and LOS attributable to VRE

Five studies that did not include uninfected control patients found post-infection LOS ranging from 9 to 22 days. The median post-infection LOS for patients with VRE BSI ranged from 9.1 to 13 days in 2 multicenter studies [17, 20] and was 17 days in a single center study [23]. In 2 other single center studies, the post-infection LOS for patients infected with linezolid-resistant or -intermediate VRE was 3 to 4 days longer than that for patients infected with linezolid-susceptible VRE (median 13 vs 9 days [26]; mean 22 vs 19 days [27]).

Four studies assessed LOS attributable to VRE infections by either matching infected patients and uninfected patients on time at risk or by matching on propensity scores. These studies found that LOS for patients with VRE infections was 3 to 4.6 days (median difference) longer [18, 19, 25] or 1.4 times (multiplicative increase) longer [21], than for uninfected patients.

Discharge to a LTCF

Two multicenter studies evaluated the likelihood that patients admitted to DMC from home would be discharged to LTCFs. Compared with uninfected patients, patients with VR *E. faecalis* infections had a 2.8-fold increased risk (11.4% vs 33.9%) [18] of being discharged to a LTCF and patients with CO VR *E. faecalis* infections had a 6.5-fold increased risk (4.7% vs 26.3%) [19].

Readmission

Only one multicenter study evaluated readmissions associated with VRE infections. The authors found that patients with VR *E. faecalis* infections were 2.9-fold more likely to be readmitted within 6 months (after the first culture positive for VRE for infected cases and after admission for uninfected controls), compared with matched controls (74.5% vs 50.8%) [18].

Recurrence

Two studies evaluated recurrence rates. Of patients treated for VRE BSI in VA centers, 23.6% had recurrences within 60 days after completing treatment [20]. Fifteen percent of patients treated for VR *E. faecium* at a cancer center had recurrences within 30 days [22].

Costs

Two single center studies evaluated costs associated with VRE infections and matched on either time at risk [21] or propensity score [25]. Song et al. found that the costs of a hospital admission were $124,257 for patients with VRE BSIs and $46,699 for uninfected controls. The adjusted analysis showed that the costs for patients with VRE BSIs were 1.6-fold higher than the costs for uninfected controls [21]. Butler et al. found that the costs for non-surgical patients with VRE BSIs were $9,949 USD more than the costs for uninfected patients [25].

Discussion

Our systematic literature review found that the incidence of VRE infections varied by study. Patients with VRE infections were more likely to die in the hospital, to have longer hospital stays, to be discharged to LTCFs after being admitted from home, to be readmitted within 6 months, and to have higher hospital costs compared with uninfected patients.

Incidence

Two studies assessing the incidence of VRE infections in individual metropolitan areas found that the incidence increased during their study periods [13, 14]. In addition, the VRE infection incidence was significantly higher among African Americans than among White residents in Atlanta. The investigators postulated that African Americans had a higher rate of chronic conditions, which increased their need for healthcare and, thereby, increased their risk for staphylococcal infections and vancomycin exposure [13].

A study among a subset of Medicare patients that had few VRE infections found stable VRE infection rates during 2005 – 2011 [16]. The findings of this study may indicate that the incidence of VRE infections among low risk populations has not changed significantly since 2000. In contrast, a study of all VA patients found that the incidence of VRE infections and methicillin-resistant *Staphylococcus aureus* (MRSA) infections decreased during 2007 – 2010, after VA hospitals implemented a bundle to decrease MRSA HAIs [15]. The decline in VRE infections may have been related to the decline in MRSA infections and less frequent use of vancomycin or to improved overall infection prevention practices associated with the MRSA intervention.

To avoid misclassification bias, we did not include studies that used ICD-9-CM diagnosis codes (V09.80, V09.81, 041.04) to define VRE infection [30-34]. Administrative coding was designed for billing not

research. Prior studies have shown that codes for acute conditions such as infections often overestimate the incidence of these conditions [35, 36]. To our knowledge, no published study has validated the ICD-9-CM codes for either VRE or enterococcal infection with lab-confirmed VRE infection. Until they have been validated, these codes should not be used to estimate the burden of VRE infections.

Most VRE infections in US are caused by enterococcal isolates that have the *VanA* plasmid, which carries the vancomycin-resistant gene. This plasmid occurs more commonly in VR *E. faecalis* than in other species of *Enterococcus* and may be transferred to *S. aureus*, causing the isolates to become vancomycin resistant (VRSA) [37, 38]. As of May 2015, 8 of 14 VRSA infections in the US occurred in southeastern Michigan, where the incidence of VR *E. faecalis* is higher than other regions [18, 37]. Thus, monitoring the regional incidence of VRE could help public health officials assess the potential for emergence and spread of VRSA.

Mortality

Our study, which compared the risk of mortality among VRE infected patients with uninfected patients, found that VRE infection was significantly associated with mortality (pOR = 2.55). Three prior meta-analyses also evaluated mortality among VRE infected patients but used patients with VSE infections as their comparison groups. Two of these meta-analyses only included studies that were conducted before 2003, when newer antimicrobial agents such as daptomycin, linezolid, and quinupristin-dalfopristin were not widely available. The first meta-analysis of 13 studies found that patients with VRE BSI had a 2-fold higher risk of mortality compared with patients that had VSE BSI [4]. The second meta-analysis, which assessed 9 studies and adjusted for severity of illness, found that patients with VRE BSI were 2.5 times more likely to die than patients with VSE BSI [38]. The third meta-analysis only included studies that were published after the approval of new antimicrobial agents effective against VRE [39]. That meta-analysis compared patients with VRE infections with those who had VSE infections and found a

smaller unadjusted association between VRE infection and mortality (pOR = 1.80; 95% CI [1.38, 2.35]).Our meta-analysis evaluated studies published during the same time period as the third meta-analysis. However, we assessed studies that used uninfected controls, which likely explains the stronger association we found between mortality and VRE infection. In addition, VSE and VRE have relatively low virulence. Kaye et al. previously found that the effect of clinical outcomes associated with MRSA SSIs was 2 to 3-fold greater when uninfected patients were used as controls than when patients with MSSA SSIs were used [8]. Whereas, clinical outcomes of VRE wound infections were similar when controls were uninfected or when they were infected with VSE. They postulated that the magnitude of the effect was related to the virulence of the pathogen being studied.

Other Outcomes

We found that the attributable hospital LOS was 3 – 4.6 days or 1.4 times longer and the attributable cost was $10,000 USD or 1.6-fold more for patients with VRE infections than those for uninfected controls. Our estimates are likely to be less biased than those of prior studies because we included studies that used uninfected controls that matched on the time at risk [18, 19, 21] or on a propensity score [25]. Studies that do not account for the time from admission to infection overestimate the LOS attributable to the infection because of time-dependent bias. Nelson et al. performed a systematic review to estimate the magnitude of time-dependent bias [40]. They compared the conventional method of calculating excess LOS attributable to HAIs with that calculated after matching patients on time at risk. They found that estimates of the LOS calculated by conventional methods were on average 12.6 days longer or 139% greater than those generated when controls were matched on time to infection. Similarly, studies that do not account for patient characteristics in the analyses or do not match on propensity scores may overestimate the LOS or cost attributable to VRE because patients

infected with resistant organisms often have severe underlying diseases, which are independently predictive of adverse outcomes and increased costs.

Limitations

Our study has several potential limitations. First, the definition of VRE was not consistent across studies. Second, we could not pool incidence data because denominators and study populations varied by study. Third, the Newcastle-Ottawa risk of bias tool was not useful because the questions about comparability and outcome assessment were not applicable to the incidence studies and the questions about selection of non-infected controls and comparability were not applicable to studies including only VRE infected patients. However, we do not think these limitations would cause us to underestimate or overestimate the burden of VRE infections.

Conclusion

VRE infections still increase mortality, hospital LOS, and costs in the US despite the current treatment options and infection prevention measures. Most published studies evaluating outcomes attributable to VRE infections had small sample sizes or did not consider the time at risk or confounders. In addition, many studies assessed outcomes attributable to vancomycin-resistance instead of those attributable to VRE infections. However, our study, which evaluated studies that used uninfected patients as controls, found that VRE infection was associated with poor outcomes. Our study provides valuable information about the current burden of VRE infections in the US and identified gaps that should be addressed by future studies, so that we can estimate accurately the incidence and outcomes attributable by VRE infections.

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Potential conflicts of interest. None.

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Figure Titles and Footnotes (see attachments for figures)

Figure 1. Flow diagram of search strategy

ICD-9, International Classification of Diseases, 9th Revision; LOS, length of stay; LTCF, long-term care facility; VRE, vancomycin-resistant enterococci.

Figure 2. Forest plot of six studies providing mortality data [18, 19, 21, 24, 28, 29]

Figure 3. Funnel plot of six studies providing mortality data [18, 19, 21, 24, 28, 29]

Table 1. Risk of bias assessment using Newcastle-Ottawa tool [11].

	Selection				Comparability	Outcome		
Author (Year)	**Representativeness of infected cases**	**Selection of the non-infected controls**	**Ascertainment of infection**	**Outcome was not present at the beginning of study**	**Case and controls comparability**	**Assessment of outcome**	**Follow-up long enough for outcome to occur**	**Adequacy of follow up of cohort**
Studies that assessed incidence[a]								
Camins (2007) [13]	*	*	*	NA	NA	NA	NA	NA
Hidron (2008) [2]	*	*	*	NA	NA	NA	NA	NA
Hayakawa (2011) [14]	*	*	*	NA	NA	NA	NA	NA
Jain (2011) [15]	*	*	*	NA	NA	NA	NA	NA
Wang (2014) [16]	*	*	*	NA	NA	NA	NA	NA
Studies that assessed outcome[b]								
Hayakawa (2012) [17]	*	No uninfected controls	*	*	No uninfected controls	*	*	-
Hayakawa (2013) [18]	*	*	*	*	*	*	*	-
Omotola (2013) [19]	*	*	*	*	*	*	*	-
Britt (2015) [20]	*	No uninfected controls	*	*	No uninfected controls	*	*	*
Song (2003) [21][c]	*	*	*	*	**	*	*	*
Raad (2004) [22]	*	No uninfected controls	*	*	No uninfected controls	*	*	-
DiazGranados (2005) [23]	*	No uninfected controls	*	*	No uninfected controls	*	*	*
Gearhart (2005) [24]	*	*	*	*	**	*	*	-
Butler (2010) [25][c]	*	*	*	*	**	*	*	-
Scheetz (2010) [26]	*	No uninfected controls	*	*	No uninfected controls	*	*	*
Santayana (2012) [27]	*	No uninfected controls	*	*	No uninfected controls	*	*	*
Vydra (2012) [28]	*	*	*	*	*	*	*	*
Ford (2015) [29]	*	*	*	*	**	*	*	*

A star (*) indicates the study had a low risk of bias and high quality in that category. A maximum of 2 stars can be given for comparability category. NA = Not applicable because the study did not assess outcome.

a. The 5 studies reporting incidence each had a low risk of bias in the selection of the study populations.
b. The outcome studies had some risk of bias because 6 studies did not provide information about patients who were lost to follow up [17-19, 22, 24, 25].
c. The 2 studies reporting costs had low risk of bias because 1 study [25] met 14 of the 19 Consensus Health Economic Criteria [12] and another study met 17 criteria [21].

Table 2. Multicenter studies that evaluated incidence data on vancomycin-resistant enterococcal infections.

First Author (Year)	Study Population	Study Period	VRE Infection Type	Number of VRE Infections	Incidence Rate
Camins (2007) [13]	Atlanta population	07/1997 – 06/2000	▪ Invasive VRE infections ▪ Defined as VRE recovered from the blood, CSF, pleural fluid, pericardial fluid, synovial fluid, and sterile surgical sites	192 ▪ 12 (6%) VR *E. faecalis* ▪ 161 (83%) VR *E. faecium* ▪ 74% Hospital-acquired (defined as VRE recovered >48 hours after admission) ▪ 84% BSI	Per 100,000 person-years All cohort ▪ All years: 1.29; increasing trend P = 0.001 ▪ 1997 – 1998: 0.77 ▪ 1998 – 1999: 1.01 ▪ 1999 – 2000: 1.60 African American ▪ All years: 2.59; increasing trend P < 0.001 ▪ 1997 – 1998: 1.85 ▪ 1998 – 1999: 2.10 ▪ 1999 – 2000: 3.61 White ▪ All years: 0.70; increase was not significant ▪ 1997 – 1998: 0.53 ▪ 1998 – 1999: 0.77 ▪ 1999 – 2000: 0.81
First Author (Year)	**Study Population**	**Study Period**	**VRE Infection Type**	**Number of VRE Infections**	**Incidence Rate**
Hidron (2008) [2]	Patients with catheters or central lines; data from National Healthcare Safety Network	01/2006 – 10/2007	▪ Hospital-acquired CLABSI and CAUTI caused by VR *E. faecium* ▪ Defined by CDC NHSN criteria	▪ CLABSI: 384 VR *E. faecium* ▪ CAUTI: 244 VR *E. faecium*	VR *E. faecium*, per 1,000 device-days CLABSI ▪ ICUs: pooled 0.18 (range 0.06 – 0.37) ▪ Non-ICUs: pooled 0.14 (range 0.13 – 0.15) CAUTI ▪ ICUs: pooled 0.14 (range 0.05 – 0.18) ▪ Non-ICUs: pooled 0.25 (range 0.12 – 0.45)
Hayakawa (2011) [14]	Patients in Detroit Medical Center, southeast Michigan	01/2003 – 12/2009	▪ VRE infections ▪ Defined as VRE recovered from clinical specimens	8,048 ▪ 2,322 (28.9%) VR *E. faecalis* ▪ 5,726 (71.1%) VR *E. faecium*	Per 1,000 patient-days VR *E. faecalis* ▪ All years: 0.99; increasing trend P < 0.001 ▪ 2003: 0.72 ▪ 2004: 0.61 ▪ 2005: 0.72 ▪ 2006: 0.77 ▪ 2007: 1.09 ▪ 2008: 1.38 ▪ 2009: 1.68

Table 2. Continued.

First Author (Year)	Study Population	Study Period	VRE Infection Type	Number of VRE Infections	Incidence Rate
Hayakawa (2011) - Continued					Per 1,000 patient-days <u>VR *E. faecium*</u> ▪ All years: 2.43; did not increase significantly ▪ 2003: 1.97 ▪ 2004: 2.14 ▪ 2005: 2.72 ▪ 2006: 2.75 ▪ 2007: 2.36 ▪ 2008: 2.47 ▪ 2009: 2.67
Jain (2011) [15]	Patients in Veterans Affairs hospitals	10/2007 – 06/2010	▪ Hospital-acquired VRE infections ▪ Defined as VRE recovered > 48 hours after admission ▪ Defined by CDC NHSN criteria	Not provided	Per 1,000 patient-days <u>ICUs</u> ▪ All years: Decreasing trend P < 0.001 ▪ 2007: 1.51 ▪ 2010: 0.00 <u>Non-ICUs</u> ▪ All years: Decreasing trend P < 0.001 ▪ 2007: 0.33 ▪ 2010: 0.09
Wang (2014) [16]	Medicare patients ≥ 65 years of age, with acute MI, CHF, pneumonia, or conditions requiring surgery; data from Medicare Patient Safety Monitoring System	01/2005 – 12/2007, 01/2009 – 12/2011	▪ Hospital-acquired VRE infections ▪ Defined as VRE recovered from sterile sites (blood, joint aspirates, pleural fluid, or peritoneal fluid) > 48 hours after admission	29	Per 1,000 hospitalizations <u>Acute MI</u> ▪ All years: 0; did not increase significantly ▪ 2005 – 2006: 0 ▪ 2007 & 2009: 0 ▪ 2010 – 2011: 0 <u>CHF</u> ▪ All years: 0.26; did not increase significantly ▪ 2005 – 2006 : 0 ▪ 2007 & 2009: 0.37 ▪ 2010 – 2011: 0.32

Table 2. Continued.

First Author (Year)	Study Population	Study Period	VRE Infection Type	Number of VRE Infections	Incidence Rate
Wang (2014) - Continued					Per 1,000 hospitalizations <u>Pneumonia</u> ▪ All years: 0.66; did not increase significantly ▪ 2005 – 2006: 0 ▪ 2007 & 2009: 0.41 ▪ 2010 – 2011: 0.96 <u>Conditions requiring surgery</u> ▪ All years: 0.76; did not decrease significantly ▪ 2005 – 2006: 1.04 ▪ 2007 & 2009: 0.62 ▪ 2010 – 2011: 0.66

BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; CDC, Centers for Disease Control and Prevention; CHF, congestive heart failure; CLABSI, central-line associated bloodstream infection; ICU, intensive care unit; MI, myocardial infarction; NHSN, National Healthcare Safety Network; VRE, vancomycin-resistant enterococci.

Table 3. Studies that evaluated outcomes attributable to vancomycin-resistant enterococcal (VRE) infections.

First Author (Year)	Study Population	Study Period	Number of Patients	Mortality (%), OR (95% CI)	Length of stay (LOS), median (IQR), days	Discharge to a LTCF after being admitted from home (%), OR (95% CI)	Readmission[a], OR (95% CI)	Recurrent VRE infection (%)	Costs, median (IQR), US dollars
Multicenter Studies									
	Patients with VR *E. faecalis* bacteremia, DMC	01/2008 – 10/2010	105 patients with bacteremia	-	Overall ▪ Post-infection: 11.5 (7.0 – 21.6) ▪ ICU post-infection LOS: 0.8 (0.0 – 11.8) Subgroup of patients who survived during hospitalization: ▪ Post-infection: 10.9 (7.2 – 21.8)	-	-	-	-
	Patients with VR *E. faecium* bacteremia, DMC	01/2008 – 10/2010	197 patients with bacteremia	-	Overall ▪ Post-infection: 8.5 (4.2 – 18.4) ▪ ICU post-infection LOS: 0.9 (0.0 – 6.1) Subgroup of patients who survived during hospitalization: ▪ Post-infection: 9.1 (5.2 – 20.1)	-	-	-	-
Hayakawa (2013) [18]	Patients with VR *E. faecalis* vs uninfected patients, DMC	01/2008 – 12/2009	532 patients with VR *E. faecalis* (defined as VRE recovered from clinical specimens) were matched to 532 uninfected patients[b]	Overall ▪ In-hospital: 9.8% vs 6.6%; OR, 1.81 (1.06 – 3.08) ▪ 90-day[c]: 18.3% vs 10.1%; OR, 2.58 (1.64 – 4.05)	Overall ▪ 11.4 (2.6 – 21.4) vs 4.2 (1.1 – 11.9); P < 0.001 ▪ 7.2 days attributable to VRE infections Subgroup of patients who survived during hospitalization: ▪ 6.6 (1.4 – 17.6) vs 2.0 (0.9 – 7.8); P < 0.001 ▪ 4.6 days attributable to VRE infections	Overall ▪ 33.9% vs 11.4% OR, 2.76 (1.68 – 4.55)	Overall ▪ 74.5% vs 50.8% OR, 2.86 (2.12 – 3.87)	-	-

Table 3. Continued.

First Author (Year)	Study Population	Study Period	Number of Patients	Mortality (%), OR (95% CI)	Length of stay (LOS), median (IQR), days	Discharge to a LTCF after being admitted from home (%), OR (95% CI)	Readmission[a], OR (95% CI)	Recurrent VRE infection (%)	Costs, median (IQR), US dollars
Omotola (2013) [19]	Patients with community-acquired VR *E. faecalis* infections vs uninfected patients, DMC	01/2008 – 12/2009	289 patients with community-acquired VR *E. faecalis* (defined as VRE recovered <48 hours after admission) were matched to 289 uninfected patients[b]	Overall ▪ In-hospital: 9.1% vs 4.8%; OR, 2.20 (1.04 – 4.65) ▪ 90-day[c]: 19.9% vs 6.8%; OR, 5.00 (2.44 – 10.23)	Overall ▪ 5 (1 – 10) vs 2 (2 – 3); P < 0.001 ▪ 3 days attributable to VRE infections	Overall ▪ 26.3% vs 4.7%; OR, 6.50 (2.27 – 18.60)	-	-	-
Britt (2015) [20]	Adult patients with VRE BSI who were treated with linezolid or daptomycin, Veterans Affairs hospitals	1/2004 – 1/2013	644 patients with BSI: 319 linezolid-treated; 325 daptomycin-treated	-	Overall ▪ Post-infection, after antibiotic treatment began: 13 (6 – 25) Subgroup ▪ Linezolid-treated: 14 (7 – 25) ▪ Daptomycin-treated: 12 (6 – 25)	-	-	Overall ▪ 60-day recurrence after antibiotic treatment began: 23.6% Subgroup of linezolid-treated patients: ▪ 60-day recurrence: 25.1% Subgroup of daptomycin-treated patients: ▪ 60-day recurrence: 22.2%	-

Table 3. Continued.

First Author (Year)	Study Population	Study Period	Number of Patients	Mortality (%), OR (95% CI)	Length of stay (LOS), median (IQR), days	Discharge to a LTCF after being admitted from home (%), OR (95% CI)	Readmission[a], OR (95% CI)	Recurrent VRE infection (%)	Costs, median (IQR), US dollars
Single Center Studies									
Song (2003) [21]	Patients with VRE bacteremia vs uninfected patients, Johns Hopkins Hospital	01/1993 – 12/2000	277 patients with hospital-acquired VRE bacteremia were matched to 277 uninfected patients[d]	Overall ▪ 50.2% vs 19.9%; P < 0.001 ▪ Adjusted OR[e]: 2.61 (1.43 – 4.75) Subgroup of 159 pairs who had identical APR-DRG complexity level: ▪ 50.3% vs 27.7% ▪ Adjusted OR[f], 3.04 (1.66 – 5.53)	Overall ▪ Total LOS: 42 vs 22 ▪ ICU LOS: 13 vs 1 ▪ Adjusted multiplicative increase (95% CI)[g] for total LOS: 1.44 (1.24 – 1.7) Subgroup of 159 pairs who had identical APR-DRG complexity level: ▪ Total LOS, 53 vs 28; ▪ ICU LOS, 24 vs 7	-	-	-	Overall ▪ Unadjusted: $124,257 vs $46,699 ▪ Adjusted multiplicative increase (95% CI)[h]: 1.55 (1.32 – 1.84) Subgroup of 159 pairs who had identical APR-DRG complexity level: ▪ Difference, $81,208
Raad (2004) [22]	Adult patients with cancer who were treated with linezolid or quinupristin-dalfopristin for VR *E. faecium* infection, University of Texas M.D. Anderson Cancer Center	08/1998 – 12/2001	40 patients with hospital-acquired VR *E. faecium* (defined by CDC NHSN): 19 linezolid-treated; 21 quinupristin-dalfopristin-treated	-	-	-	-	Overall ▪ 30-day recurrence after antibiotic treatment completed: 15% Subgroup of linezolid-treated patients: ▪ 30-day recurrence: 21.1% Subgroup of Quinupristin-dalfopristin - treated patients: ▪ 30-day recurrence: 9.5%	-

Table 3. Continued.

First Author (Year)	Study Population	Study Period	Number of Patients	Mortality (%), OR (95% CI)	Length of stay (LOS), median (IQR), days	Discharge to a LTCF after being admitted from home (%), OR (95% CI)	Readmission[a], OR (95% CI)	Recurrent VRE infection (%)	Costs, median (IQR), US dollars
DiazGranados (2005) [23]	Patients with VRE BSI and neutropenia, Emory University Hospital in Atlanta	11/1994 – 01/2001	22 patients with hospital-acquired BSI (defined as VRE recovered > 72 hours after admission)	-	Overall ▪ Post-infection: 17 (range 0 – 52)	-	-	-	-
Gearhart (2005) [24]	Patients with VRE infections vs uninfected patients (all patients had liver transplants), University of Cincinnati	1995 – 2002	19 infected patients, 38 uninfected patients[i]	Overall ▪ 47.4% vs 18.4% ▪ OR, 3.99 (1.18, 13.47)	-	-	-	-	-
Butler (2010) [25]	Patients with VRE BSI vs uninfected patients, non-surgical patients, Barnes-Jewish Hospital	01/2002 – 12/2003	▪ 94 infected patients, 20,150 uninfected patients ▪ 88 infected patients were matched to 88 uninfected patients[j]	-	Overall ▪ Unadjusted: 14.6 (7.3 – 28.3) vs 4.0 (2.9 – 6.2); P < 0.001 Subgroup of 88 pairs: ▪ Difference (95% CI): 3.5 (2.1 – 7.3)	-	-	-	Overall ▪ Unadjusted: $42,106 ($16,310 – $93,870) vs $8,192 ($5,615 – $13,495) Subgroup of 88 pairs: ▪ Difference (95% CI): $9,949 ($1,579 – $24,693)

Table 3. Continued.

First Author (Year)	Study Population	Study Period	Number of Patients	Mortality (%), OR (95% CI)	Length of stay (LOS), median (IQR), days	Discharge to a LTCF after being admitted from home (%), OR (95% CI)	Readmission[a], OR (95% CI)	Recurrent VRE infection (%)	Costs, median (IQR), US dollars
Single Center Studies									
Scheetz (2010) [26]	Adult patients with VR *E. faecium* infections, Northwestern Memorial Hospital, Chicago	2002 - 2007	72 infected patients (defined as VR *E. faecium* recovered from clinical specimens): 18 isolates were linezolid-resistant or –intermediate and 54 isolates were linezolid-susceptible	-	Subgroup of patients with linezolid-resistant or –intermediate VRE: ▪ Post-infection LOS 13 (3 – 21) Subgroup of patients with linezolid-susceptible VRE: ▪ Post-infection LOS 9 (3 – 16)	-	-	-	-
Santayana (2012) [27]	Adult patients with VRE infections, University of Chicago Medical Center	01/2000 – 09/2008	144 infected patients (defined as VRE recovered from sterile sites): 48 isolates were linezolid-resistant or –intermediate and 96 isolates were linezolid-susceptible	-	Subgroup of patients with linezolid-resistant or –intermediate VRE: ▪ Post-infection LOS, mean 22 Subgroup of patients with linezolid-susceptible VRE: ▪ Post-infection LOS, mean 19	-	-	-	-

Table 3. Continued.

First Author (Year)	Study Population	Study Period	No. of Patients	Mortality (%), OR (95% CI)	Length of stay (LOS), median (IQR), days	Discharge to a LTCF after being admitted from home (%), OR (95% CI)	Readmission[a], OR (95% CI)	Recurrent VRE infection (%)	Costs, median (IQR), US dollars
Single Center Studies									
Vydra (2012) [28]	Patients with VRE bacteremia vs uninfected patients, recipients of allogeneic hematopoietic stem cell transplantation, University of Minnesota	01/2004 – 12/2008	50 patients with VRE bacteremia, 659 uninfected patients	Overall ▪ 1-year non-relapse mortality[k]: 48% vs 19.6% ▪ Adjusted HR[l]: 4.2 (3.1 – 6.9) Subgroup of adult patients: ▪ 53% vs 22% ▪ OR, 3.90 (2.01 – 7.55) Subgroup of pediatric patients: ▪ 30% vs 15% ▪ OR, 2.46 (0.61 – 9.97)	-	-	-	-	-
Ford (2015) [29]	Adult patients with VRE BSI vs uninfected patients, with newly diagnosed acute myelogenous or acute lymphoblastic leukemia, LDS Hospital, Salt Lake City, Utah	10/2006 – 12/2012	15 infected patients were matched to 45 uninfected patients[m]	Overall ▪ 60-day mortality: 33% vs 18% ▪ HR, 1.9 (0.87 – 5.1)	-	-	-	-	-

APR-DRG, All Patient Refined-Diagnosis Related Group; BSI, bloodstream infection; CI, confidence interval; DMC, Detroit Medical Center; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; LTCF, long-term care facility; OR, odds ratio; VRE, vancomycin-resistant enterococci.

a. Readmissions within 6 months following VRE isolation for infected patients or within 6 months after admission for uninfected patients.
b. VRE infected patients and uninfected patients were matched by hospital or outpatient facility, unit or clinic, calendar year, and time at risk (i.e., time from admission to culture for infected patients, time from admission to discharge for uninfected patients).

c. Deaths within 90 days after VRE isolation for infected patients or within 90 days after admission for uninfected patients.
d. Patients with VRE BSI and uninfected patients were matched on time at risk and at least 3 of the following criteria: age (± 10 years), calendar year (± 2 years), principal ICD-9 diagnosis code at admission, primary ICD-9 procedure code during hospitalization, or APR-DRGs.
e. Adjusted for severe illness (APR-DRG complexity level 4), being transferred from another healthcare facility, and staying in an ICU.
f. Adjusted for being transferred from another healthcare facility.
g. Adjusted for severe illness (APR-DRG complexity level 4).
h. Adjusted for severe illness (APR-DRG complexity level 4) and staying in an ICU.
i. VRE infected patients and uninfected patients were matched (1:2) by age, gender, underlying disease, United Network for Organ Sharing status, primary or re-transplant, transplant date.
j. Patients with VRE BSI and uninfected patients were matched based on their propensity to develop VRE BSI (propensity scores matching).
k. Non-relapse mortality is defined as deaths which could not be attributed to disease relapse or progression.
l. Adjusted for acute graft-vs-host disease (GVHD), chronic GVHD, engrafted by day 42, age, sex, diagnosis, cytomegalovirus, donor type, and Karnofsky performance score.
m. VRE infected patients and uninfected patients were matched (1:3) by leukemia type, age, admitting Karnofsky performance status, and initial treatment regimen.