ORIGINAL ARTICLE

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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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.

OBJECTIVE. To systematically review the incidence of VRE infection in the United States and the clinical and economic outcomes.

METHODS. We searched various databases for US studies published from January 1, 2000, through June 8, 2015, that evaluated incidence, mortality, length of stay, discharge to a long-term care facility, 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 postinfection length of stay, 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 length of stay (3-4.6 days longer or 1.4 times longer), increased risk of discharge to a long-term care facility (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.

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Vancomycin-resistant enterococci (VRE) infections are endemic in hospitals across the United States.[1] VRE are the second most common antimicrobial-resistant pathogens causing healthcare-associated infections in the United States.[2,3] According to the National Healthcare Safety Network data in 2009-2010, 38.6% of enterococci isolated from device-associated healthcare-associated infections and 23.1% of those isolated from surgical site infections 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 United States, we conducted a systematic literature review of studies that were conducted in the United States, were published during or

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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 United States, (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). We excluded studies that (1) used the *International Classification of Diseases, Ninth 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 postinfection (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 postinfection 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

One author (H.-Y.C.) reviewed the titles and abstracts of all articles to determine whether they met the inclusion criteria. For each included study, 2 of 4 reviewers (H.-Y.C., R.N., E.N.P., M.L.S.) 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 on 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 (adjusted ORs) from the literature or raw data when adjusted ORs 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 National Healthcare Safety Network 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 (ie, 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 ($P = .001$). 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 Detroit Medical Center system, the incidence of VR *Enterococcus faecalis* infections increased from 0.72 per 1,000 patient-days in 2003 to 1.68 per 1,000 patient-days in 2009 ($P < .001$), and the incidence of VR *Enterococcus 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 the southeast Michigan area (71% vs 29%).[14]

Among patients admitted to all Veterans Affairs (VA) hospitals, the incidence of VRE decreased between 2007 and

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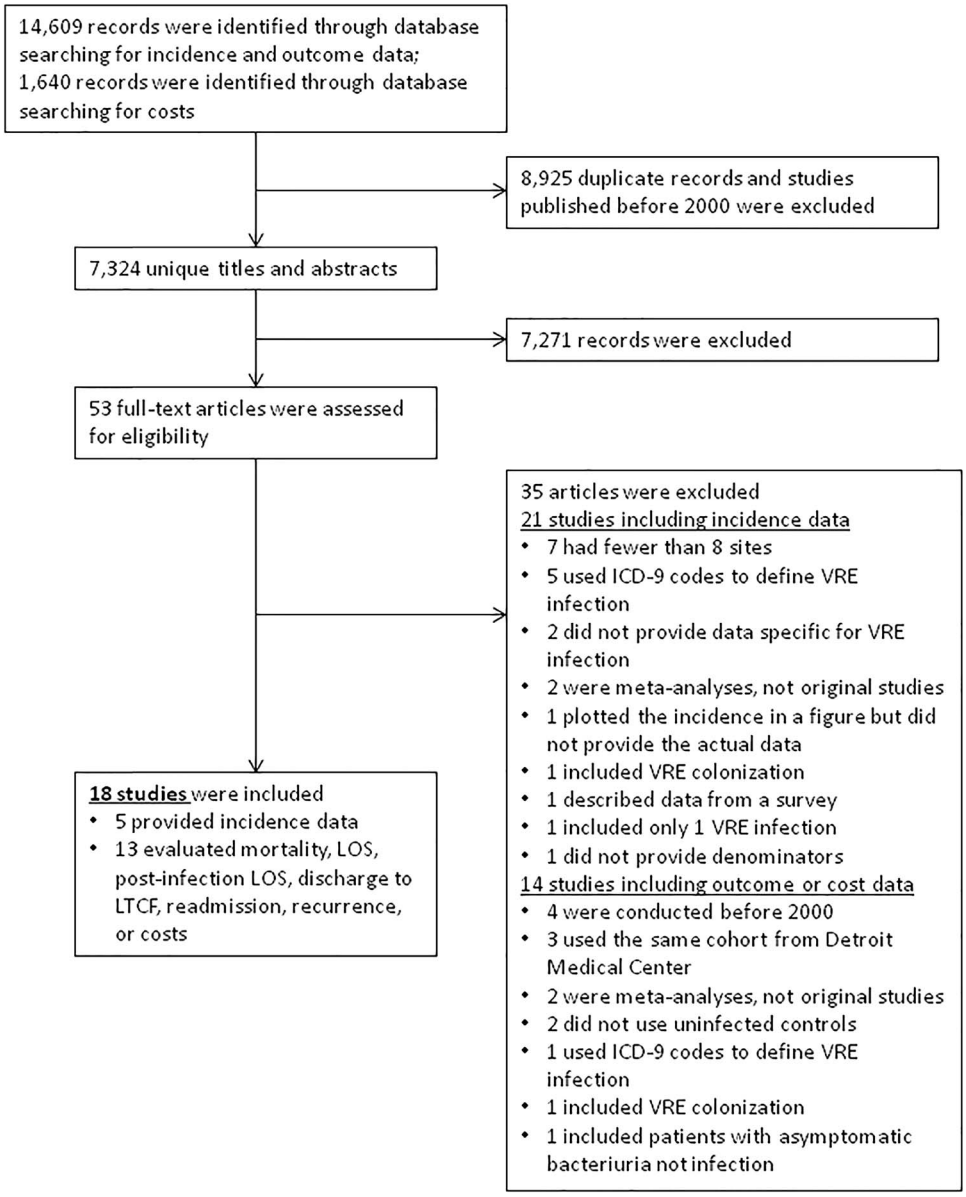

FIGURE 1. Flow diagram of search strategy. ICD-9, *International Classification of Diseases, Ninth Revision*; LOS, length of stay; LTCF, long-term care facility; VRE, vancomycin-resistant enterococci.

2010 from 1.51 to 0 per 1,000 patient-days for patients admitted to intensive care units (ICUs) ($P < .001$) and decreased from 0.33 to 0.09 per 1,000 patient-days for patients admitted to non-ICU units ($P < .001$).[15] Between 2005 and 2011, the incidence of VRE infections did not change significantly among Medicare patients who had 1 of the 4 conditions (ie, acute myocardial infarction, congestive heart failure, pneumonia, or conditions requiring surgery).[16]

The National Healthcare Safety Network reported that the pooled incidence of VR *E. faecium* central line–associated bloodstream infections (BSIs) 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 Detroit Medical Center used different subgroups of patients: BSIs caused by VR *E. faecalis* or VR *E.*

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TABLE 1. Risk of Bias Assessment Using Newcastle-Ottawa Tool[11]

	Selection				Comparability	Outcome		
First author (year)	Representativeness of infected cases	Selection of the noninfected 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)[25c]	*	*	*	*	**	*	*	-
Scheetz (2010)[26]	*	No uninfected controls	*	*	No uninfected controls	*	*	*
Santayana (2012)[27]	*	No uninfected controls	*	*	No uninfected controls	*	*	*
Vydra (2012)[28]	*	*	*	*	*	*	*	*
Ford (2015)[29]	*	*	*	*	**	*	*	*

NOTE. 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 VRE 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 $P = .001$ ■ 1997–1998: 0.77 ■ 1998–1999: 1.01 ■ 1999–2000: 1.60 African American ■ All years: 2.59; increasing trend $P < .001$ ■ 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
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 $P < .001$ ■ 2003: 0.72 ■ 2004: 0.61 ■ 2005: 0.72 ■ 2006: 0.77 ■ 2007: 1.09 ■ 2008: 1.38 ■ 2009: 1.68 Per 1,000 patient-days VR *E. faecium* ■ 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

TABLE 2. *Continued*

First author (year)	Study population	Study period	VRE infection type	Number of VRE infections	Incidence rate
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 ICUs ■ All years: Decreasing trend $P < .001$ ■ 2007: 1.51 ■ 2010: 0.00 Non-ICUs ■ All years: Decreasing trend $P < .001$ ■ 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 Acute MI ■ All years: 0; did not increase significantly ■ 2005–2006: 0 ■ 2007 & 2009: 0 ■ 2010–2011: 0 CHF ■ All years: 0.26; did not increase significantly ■ 2005–2006 : 0 ■ 2007 & 2009: 0.37 ■ 2010–2011: 0.32 Per 1,000 hospitalizations Pneumonia ■ All years: 0.66; did not increase significantly ■ 2005–2006: 0 ■ 2007 & 2009: 0.41 ■ 2010–2011: 0.96 Conditions requiring surgery ■ All years: 0.76; did not decrease significantly ■ 2005–2006: 1.04 ■ 2007 & 2009: 0.62 ■ 2010–2011: 0.66

NOTE. 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; CSF, cerebrospinal fluid; ICU, intensive care unit; MI, myocardial infarction; NHSN, National Healthcare Safety Network; VR, vancomycin-resistant; VRE, vancomycin-resistant enterococci.

TABLE 3. Studies That Evaluated Outcomes Attributable to VRE Infections

First author (year)	Study population	Study period	No. of patients	Mortality (%), OR (95% CI)	LOS, median (IQR), d	Discharge to a LTCF after being admitted from home (%), OR (95% CI)	Readmission[a] OR (95% CI)	Recurrent VRE infection (%)	Costs, median (IQR), US$
Multicenter Studies									
Hayakawa (2012)[17]	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); $P < .001$ ■ 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); $P < .001$ ■ 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)	-	-
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); $P < .001$ ■ 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%	-
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%; $P < .001$ ■ 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

TABLE 3. *Continued*

First author (year)	Study population	Study period	No. of patients	Mortality (%), OR (95% CI)	LOS, median (IQR), d	Discharge to a LTCF after being admitted from home (%), OR (95% CI)	Readmission[a] OR (95% CI)	Recurrent VRE infection (%)	Costs, median (IQR), US$
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%	-
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, nonsurgical 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); $P < .001$ 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)
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	-	-	-	-

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)	-	-	-	-	-

NOTE. APR-DRG, All Patient Refined-Diagnosis Related Group; BSI, bloodstream infection; DMC, Detroit Medical Center; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; 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 (ie, 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 *International Classification of Diseases, Ninth Revision* (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 on the basis of their propensity to develop VRE BSI (propensity scores matching).

[k]Non-relapse mortality is defined as deaths that 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.

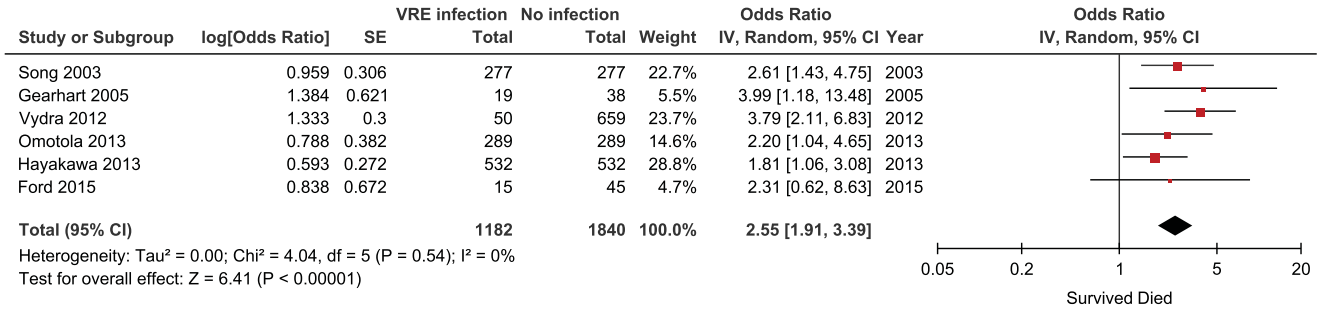

FIGURE 2. Forest plot of 6 studies providing mortality data.[18,19,21,24,28,29] IV, inverse variance; VRE, vancomycin-resistant enterococci.

faecium in 2008–2010,[17] all VR *E faecalis* infections in 2008–2009,[18] and all community-onset 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] nonsurgical patients,[25] or patients with leukemia.[29] Five studies evaluated only VRE BSIs,[17,21,25,28,29] 1 study evaluated community-onset 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, 2.55 [95% CI, 1.91–3.39]). The heterogeneity among studies was negligible ($P = .54$ 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 (pooled OR, 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.

Postinfection LOS and LOS Attributable to VRE

Five studies that did not include uninfected control patients found postinfection LOS ranging from 9 to 22 days. The median postinfection 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 postinfection LOS for patients infected with linezolid-resistant or linezolid-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

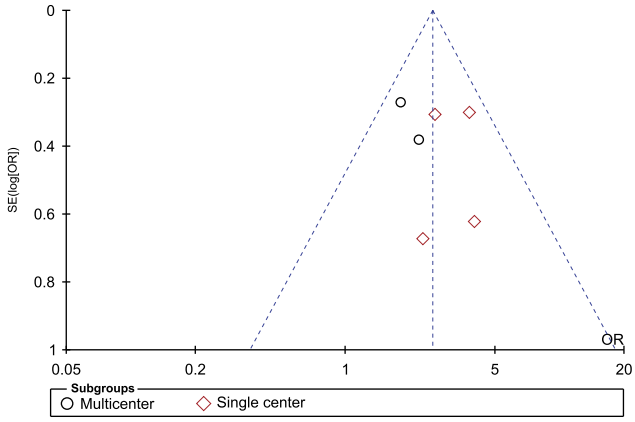

FIGURE 3. Funnel plot of 6 studies providing mortality data.[18,19,21,24,28,29] OR, odds ratio.

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 an LTCF

Two multicenter studies evaluated the likelihood that patients admitted to Detroit Medical Center 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 community-onset VR *E. faecalis* infections had a 6.5-fold increased risk (4.7% vs 26.3%).[19]

Readmission

Only 1 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

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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[21] 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. Butler et al[25] found that the costs for nonsurgical patients with VRE BSIs were $9,949 USD more than the costs for uninfected patients.

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 who 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 healthcare-associated infections.[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 the United States 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.[37,38] As of May 2015, 8 of 14 vancomycin-resistant *S. aureus* infections in the United States occurred in southeastern Michigan, where the incidence of VR *E. faecalis* is higher than in other regions.[18,37] Thus, monitoring the regional incidence of VRE could help public health officials assess the potential for emergence and spread of vancomycin-resistant *S. aureus*.

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 (pooled OR, 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 who 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 (pooled OR, 1.80 [95% CI, 1.38–2.35]). Our meta-analysis evaluated studies published during the same 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[8] previously found that the effect of clinical outcomes associated with MRSA surgical site infections was 2- to 3-fold greater when uninfected patients were used as controls than when patients with methicillin-susceptible *S. aureus* surgical site infections were used, 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.

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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[40] performed a systematic review to estimate the magnitude of time-dependent bias. They compared the conventional method of calculating excess LOS attributable to healthcare-associated infections 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.

In conclusion, VRE infections still increase mortality, hospital LOS, and costs in the United States 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 United States and identifies gaps that should be addressed by future studies, so that we can estimate accurately the incidence and outcomes attributable to VRE infections.

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SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2016.254

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