Annual Surveillance Summary: Vancomycin-Resistant Enterococci (VRE) Infections in the Military Health System (MHS), 2016

NMCPHC-EDC-TR-370-2017

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14. ABSTRACT
The EpiData Center Department (EDC) conducts routine surveillance of vancomycin-resistant enterococci (VRE) incidence and prevalence among all beneficiaries seeking care within the Military Health System (MHS). This report describes demographics, clinical characteristics, prescription practices, and antibiotic resistance patterns observed for VRE in calendar year (CY) 2016. In 2016, VRE infection rates declined among MHS beneficiaries to 1.38 per 100,000 persons per year, following a three-year incline from 2013-2015. The United States (US) West and South regions had the highest rates, and healthcare-associated (HA) cases comprised the largest proportion of all infections identified (87%). While the majority of all prevalent infections were classified as hospital-onset (HO) (45%), a substantial proportion was also identified as community-onset (CO) (31%). Treatment for VRE infections among Department of Defense (DOD) beneficiaries primarily included daptomycin and linezolid, which remained effective throughout 2016. These findings warrant continued surveillance to understand the evolving impact of VRE within the MHS.

15. SUBJECT TERMS
Health Level 7 (HL7), microbiology, surveillance, vancomycin-resistant enterococci (VRE), Military Health System (MHS), multi-drug resistance (MDR), healthcare-associated infection (HAI), community-associated (CA) infection

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Abstract

The EpiData Center Department (EDC) conducts routine surveillance of vancomycin-resistant enterococci (VRE) incidence and prevalence among all beneficiaries seeking care within the Military Health System (MHS). This report describes demographics, clinical characteristics, prescription practices, and antibiotic resistance patterns observed for VRE in calendar year (CY) 2016.

Multiple data sources were linked to assess descriptive and clinical factors related to VRE. Health Level 7 (HL7)-formatted Composite Health Care System (CHCS) microbiology data identified *Enterococcus* species infections with vancomycin resistance. These infections were matched to HL7-formatted CHCS pharmacy data to assess prescription practices, the Standard Inpatient Data Record (SIDR) to determine healthcare-associated exposures, Defense Manpower Data Center (DMDC) rosters to determine burden among Department of Defense (DOD) active duty (AD) service members, and the DMDC Contingency Tracking System (CTS) to determine Department of the Navy (DON) deployment-related infections.

In 2016, VRE infection rates declined among MHS beneficiaries to 1.38 per 100,000 persons per year, following a three-year incline from 2013-2015. The United States (US) West and South regions had the highest rates, and healthcare-associated (HA) cases comprised the largest proportion of all infections identified (87%). While the majority of all prevalent infections were classified as hospital-onset (HO) (45%), a substantial proportion was also identified as community-onset (CO) (31%). Treatment for VRE infections among DOD beneficiaries primarily included daptomycin and linezolid, which remained effective throughout 2016. These findings warrant continued surveillance to understand the evolving impact of VRE within the MHS.

Contents

Background, Methods, and Limitations

The EpiData Center (EDC) at the Navy and Marine Corps Public Health Center (NMCPHC) prepares a retrospective report each calendar year (CY) that summarizes the demographics, clinical characteristics, prescription practices, and antibiotic susceptibility patterns for vancomycin-resistant enterococci (VRE) infections among Military Health System (MHS) beneficiaries.

Literature review did not provide any new developments or research for VRE infections. Additionally, no new methods or limitations were applied to this annual summary. As such, this report presents analytical results and discussion of CY 2016 data for VRE infections in the MHS. The background, methods, and limitations relevant to this analysis have been discussed in a previous report (CY 2015 annual report for VRE[1]).

The EDC also monitors other multidrug-resistant organisms (MDROs) of interest in the MHS.[2,3]

Results

Section A – Descriptive Epidemiology

Incidence of VRE

In 2016, the annual VRE incidence rate (IR) among MHS beneficiaries treated at a military treatment facility (MTF) was 1.38 per 100,000 persons per year. This reflects a 6.21% change below the weighted historic IR. Service-specific difference from the weighted historic IR also declined, where Air Force beneficiaries demonstrated the largest percent change below the weighted historic IR (by 21.51%) (Table 1).

Table 1. Incidence Rate (IR) for VRE Infections in the MHS, CY 2016

Population	2016 IR	Weighted Historic[a] IR 2013 - 2015	Two Standard Deviations: Weighted Historic[a] IR	2016	
				Direction	Percent Change[b]
MHS Beneficiaries	1.38	1.47	0.32	↓	6.21%
Air Force	1.05	1.34	0.56	↓	21.51%
Army	0.86	0.93	0.14	↓	6.76%
Marine Corps	--	--	--	--	--
Navy	1.28	1.55	0.61	↓	17.24%
DOD Active Duty	--	--	--	--	--

Rates are presented as the rate per 100,000 persons per year.
A green arrow indicates an increasing percent change and a blue arrow indicates a decreasing percent change.
[a] Historic IR reflects the weighted average of the three years prior to the analysis year.
[b] This reflects the percent change from the weighted historic IR to the IR of the current analysis year.
Rates are not provided when the incidence count is less than or equal to 10.
Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 June 2017.

Demographic Distribution of VRE

In 2016, there were 130 incident VRE infections identified among all MHS beneficiaries treated at an MTF. Incidence rates among males (1.52 per 100,000 persons per year) slightly exceeded females (1.24 per 100,000 persons per year). Beneficiaries aged 65+ (3.83 per 100,000 persons per year) and 45-64 (1.36 per 100,000 persons per year) demonstrated the highest rates, as well as retirees (1.69 per 100,000 persons per year) (Table 2). Individuals with an 'other' beneficiary type (n=36) include persons who are not classified as active duty, retired, or family members; the majority were either 45-64 years old (n=9) or 65+ years old (n=25), or had a service category of 'other' (n=34) (data not shown).

Table 2. Demographic Characteristics of VRE Infections in the MHS, CY 2016

	N = 130	
	Count	Rate
Gender		
Female	57	1.24
Male	73	1.52
Age Group (in Years)		
0-17	3	--
18-24	2	--
25-34	7	--
35-44	5	--
45-64	28	1.36
65+	85	3.83
Beneficiary Type		
Active Duty	6	--
Family Members	51	0.93
Retired	37	1.69
Other[a]	36	--

[a] Rate is not reported due to variation in population denominator.
Rates are presented as the rate per 100,000 persons per year.
Rates are not provided when the incidence count is less than or equal to 10.
Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS M2 database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 June 2017.

Seasonality

Throughout 2016, VRE monthly incidence rates were variable, trending above and below two standard deviations of the MHS weighted historic IR; however, these highly variable trends may be explained by the overall low frequency of infections identified during the year (n=130), thus translating to even lower monthly frequencies (range: n=6 to 19 incident infections per month; median: n=11 incident infections in 2016). The highest monthly IR occurred in February (n=19; 0.20 per 100,000 persons per year) and the lowest monthly IR occurred in September (n=6; 0.06 per 100,000 persons per year). The median monthly incident rate for 2016 was 0.12 per 100,000 persons per year. The monthly incidence rate for VRE infections did not exceed 0.20 per 100,000 throughout the entire year (data not shown).

VRE Clinical Characteristics

There were 138 prevalent VRE infections identified among all MHS beneficiaries treated at an MTF during 2016. A larger percentage of these infections were identified in the inpatient setting (63.0%) than the outpatient setting (37.0%), and the majority were classified as non-invasive (77.5%). By collection site, urine accounted for the largest proportion of infections (54.3%), and respiratory sites accounted for only 0.7%. Approximately half of prevalent infections were identified as *E. faecium* (54.3%), followed by unidentified *Enterococcus* species (31.9%); *E. faecalis* (13.8%) accounted for the lowest proportion of prevalent infections (Table 3).

Table 3. Clinical Characteristics of VRE Prevalent Infections in the MHS, CY 2016

	N = 138	
	Count	Percentage
Specimen Collection Location		
Inpatient	87	63.0
Outpatient	51	37.0
Infection Type		
Invasive	31	22.5
Non-Invasive	107	77.5
Body Collection Site		
Blood	25	18.1
Respiratory	1	0.7
SSTI/Wound	19	13.8
Urine	75	54.3
Other	18	13.0
Organism Species		
Enterococcus faecalis	19	13.8
Enterococcus faecium	75	54.3
Enterococcus species	44	31.9

Data Source: NMCPHC HL7-formatted CHCS microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 June 2017.

Exposure Burden Metrics

Table 4 presents two different metrics defining MDRO infection rates for healthcare-associated exposures. In 2016, there were 239,946 direct care inpatient admissions across all MHS MTFs. The overall MDRO prevalence rate for VRE infections was 0.58 per 1,000 inpatient admissions; this measures the amount of exposure of infection at any point during the admission or one year prior. The US West (0.75 per 1,000 inpatient admissions) and US South (0.74 per 1,000 inpatient admissions) regions had the highest overall MDRO prevalence rates. The admission MDRO prevalence rates were lower than the overall MDRO prevalence rates, at 0.37 per 1,000 inpatient admissions; this measures the magnitude of importation of VRE infection at the time of admission (importation of MDRO into the healthcare system) or one year prior. As with overall MDRO prevalence, the US West region (0.56 per 1,000 inpatient admissions) and the US South region (0.35 per 1,000 inpatient admissions) demonstrated the highest admission MDRO prevalence rates. Comparison of these two metrics suggests that VRE infections are imported into the hospital setting from the community, as the admission MDRO prevalence rate accounts for over half of the overall MDRO prevalence rate. Five or fewer laboratory results met the overall or admission MDRO prevalence definitions and were identified in the OCONUS, US Midwest, and US Northeast regions, thus rates were either suppressed or equal to zero (Table 4).

Table 4. MDRO Healthcare-Associated Exposure Burden Metrics among VRE in the MHS, CY 2016

	Overall MDRO Prevalence[a]		Admission MDRO Prevalence[b]	
	Count	Rate[c]	Count	Rate[c]
Region				
OCONUS	2	--	2	--
US Midwest	5	--	5	--
US Northeast	0	--	0	--
US South	42	0.74	20	0.35
US South Atlantic	35	0.44	20	0.25
US West	56	0.75	42	0.56
Total	140	0.58	89	0.37

[a] Overall MDRO prevalence included all individuals with an MDRO infection identified from a sample collected at any point during the admission, as well as samples that tested positive for infection in the prior calendar year.
[b] Admission MDRO prevalence included all individuals with an MDRO infection identified from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year.
[c] Rates are presented as the rate per 1,000 inpatient admissions per year. Rates are not provided when the prevalence count is less than or equal to 10.
Data Source: NMCPHC HL7-formatted CHCS microbiology and SIDR databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 June 2017.

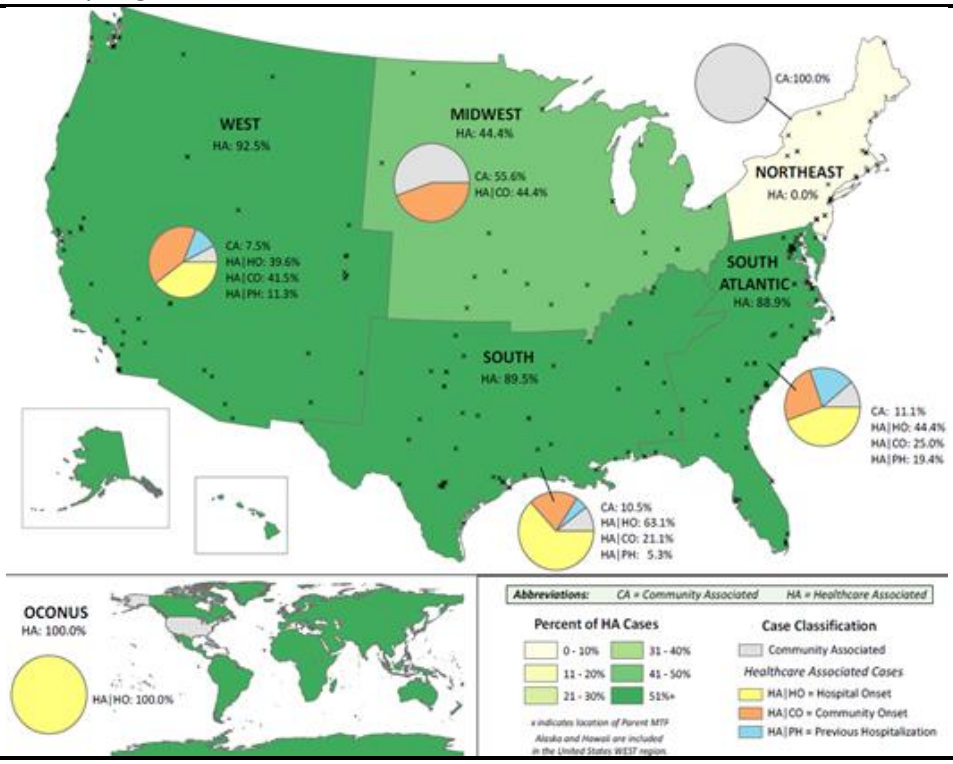
Regional Epidemiologic Infection Classifications

Among all prevalent VRE infections identified in the MHS in 2016, 87% were healthcare-associated (HA) cases and 13% were community-associated (CA) cases. With the exception of the US Northeast and US Midwest, each region demonstrated a substantially larger proportion of HA cases than CA cases, with the US West region experiencing 92.5% of cases as HA. In the US Midwest, the percentages of CA cases (55.6%) and HA cases (44.4%) were more evenly distributed. In the US Northeast, only one prevalent VRE infection was identified in 2016 and it was classified as a CA case (Figure 1).

HA cases were further categorized into hospital-onset (HO), community-onset (CO), or previous hospitalization (PH) groupings. Among all prevalent VRE infections, the greatest proportion were classified as HO (44.9%), indicating the specimen was collected after the third day of admission and therefore likely a result of the current hospitalization. The second largest proportion of prevalent infections were CO (31.2%), demonstrating that the infection was most likely acquired in the community (i.e., specimens were collected within the first three days of hospital admission). Small percentages (10.9%) of all prevalent infections were PH, indicating the specimens were not associated with a current admission but the patient had a prior hospitalization in the previous 12 months (data not shown).

The distribution of HA case classifications varied by region. Of all regions, the US South Atlantic demonstrated the most distribution between PH cases (19.4%), HO cases (44.4%), and CO cases (25.0%). While the US South demonstrated the largest difference between HO cases in relation to CO cases (63.2% vs. 21.1%), the percentages of HO cases and CO cases were more evenly distributed in the US West (39.6% vs. 41.5%). All HA cases in the US Midwest (n=4) were classified as CO. Only one HA case was identified OCONUS, classified as HO (Figure 1).

Figure 1. Proportion of Healthcare- and Community-Associated Cases among VRE Infection in the MHS by Region, CY 2016



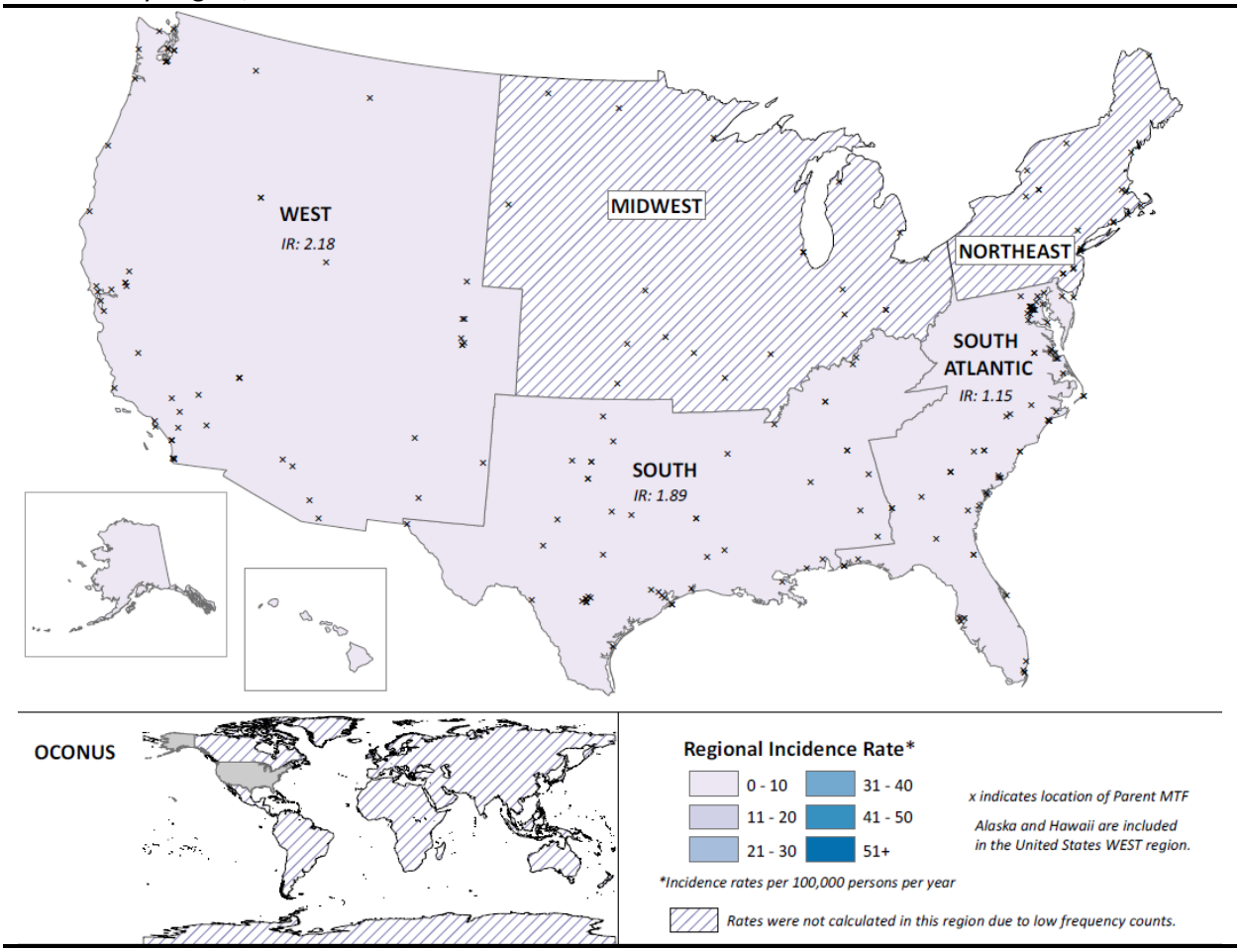
Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 June 2017.

Section B – Antimicrobial Resistance and Use

Regional Multidrug Resistance

The 2016 annual VRE IR among all MHS beneficiaries was 1.38 per 100,000 persons per year. Regionally, the highest IRs occurred in the US West (2.18 per 100,000 persons) and US South (1.89 per 100,000 persons) regions. Low frequency of infections occurred in the US Midwest (n=8), US Northeast (n=1), and OCONUS regions (n=1); rates were not calculated for these regions (Figure 2).

Figure 2. Annual Incidence Rate (IR) and Percentage of Multidrug Resistance among VRE Infections in the MHS by Region, CY 2016



Rates are presented as the rate per 100,000 persons per year.
Regional rates are not provided when the incidence count is less than or equal to 10.
Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 June 2017.

Antibiogram

Table 5 displays an antibiogram of VRE incident infections for all MHS beneficiaries from 2011 through 2016. In 2016, VRE infections were most susceptible to daptomycin (97.2%), linezolid (91.7%), and gentamicin high level (81.3%). A statistically significant trend in susceptibility was observed only for gentamicin high level, which displayed an increase from 61.8% in 2011 to 81.3% in 2016. Ciprofloxacin (13.0%), levofloxacin (19.0%), ampicillin (20.6%), penicillin (20.7%), and tetracycline (20.9%) demonstrated the lowest efficacies in 2016 (Table 5).

Table 5. Antibiogram of VRE Infections Identified in the MHS, CY 2011-2016

Antibiotics	2011	2012	2013	2014	2015	2016	Susceptibility Trend	Comment[a]
Ampicillin	13.1	18.3	24.7	29.3	21.2	20.6	30 10	
Ciprofloxacin	7.3	2.0	13.6	8.3	15.8	13.0	20 0	
Daptomycin	--	--	--	92.7	98.0	97.2		
Doxycycline	--	--	--	--	--	--		
Erythromycin	--	--	--	--	--	--		
Gentamicin High Level	61.8	73.0	84.5	82.5	86.6	81.3	90 60	↑
Levofloxacin	10.8	--	25.0	8.3	20.0	19.0		
Linezolid	87.2	92.9	97.4	87.5	95.2	91.7	100 80	
Nitrofurantoin	32.7	35.2	50.9	50.0	36.8	45.9	60 30	
Penicillin	12.2	9.2	28.8	24.0	16.7	20.7	30 0	
Quinupristin/ Dalfopristin	--	86.7	--	--	--	--		
Rifampin	--	--	--	--	--	--		
Streptomycin High Level	66.7	69.5	77.8	69.4	68.2	69.6	80 60	
Tetracycline	27.4	14.1	16.0	18.3	8.2	20.9	40 0	

'--' indicates that fewer than 30 isolates were tested.

[a] Arrow indicates the antibiotics with a significant change in direction of trend for significant two-tailed Cochrane-Armitage tests for trend established for a single antibiotic over time. A significant increase in susceptibility is denoted by a green upward arrow and a significant decrease in susceptibility is denoted by a blue downward arrow.

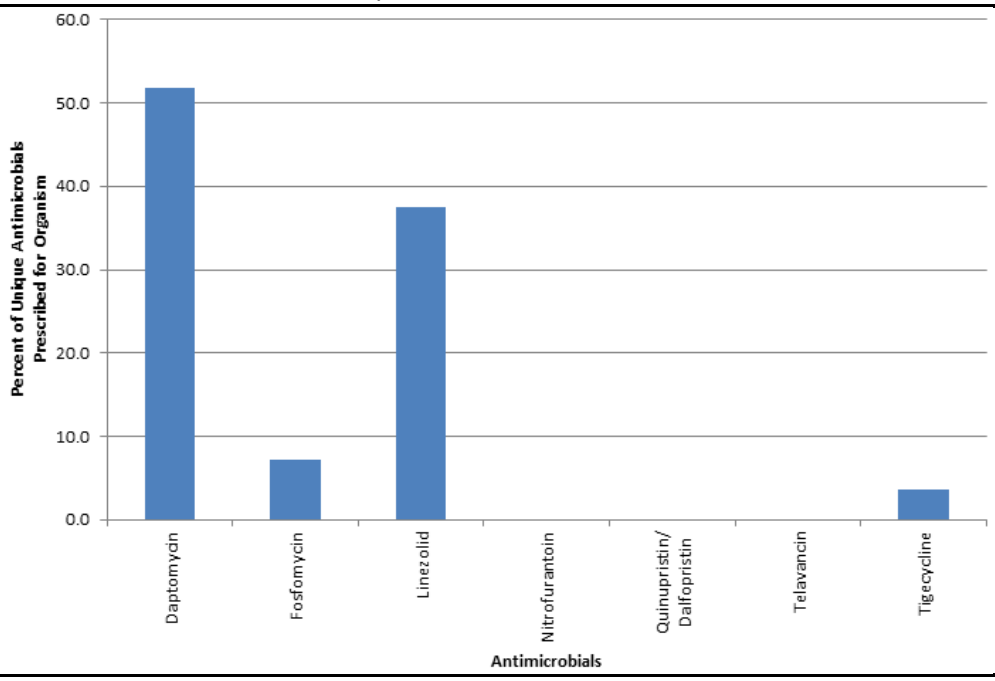
Data Source: NMCPHC HL7-formatted CHCS microbiology database.

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 June 2017.

Antimicrobial Consumption/Prescription Practices

Figure 3 displays the percentage of unique antimicrobials associated with prevalent VRE infections during 2016, including seven antibiotic classes recommended for VRE treatment according to the Johns Hopkins Antibiotic Guide.[4] Among all MHS beneficiaries, the most commonly prescribed antibiotics associated with VRE infections in 2016 were daptomycin (51.8%) and linezolid (37.5%). Fosfomycin (7.1%) and tigecycline (3.6%) were less commonly prescribed. No prescriptions for telavancin, quinupristin/dalfopristin, or nitrofurantoin were identified (Figure 3).

Figure 3. VRE Infection and Prescription Practices in the MHS, CY 2016



Only the first occurrence of a unique antibiotic was counted per person per infection, regardless of administration route.
Data Source: NMCPHC HL7-formatted CHCS microbiology and pharmacy databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 June 2017.

Section C – Special Populations

Of the 138 prevalent VRE infections in the MHS in 2016, only one occurred among Department of the Navy (DON) AD deployed personnel. This deployment-related VRE infection was identified in a male between the ages of 25-34 years.

Discussion

This analysis found a decrease in VRE infection rates, though minimal, from the weighted historic IR of 1.47 infections per 100,000 persons to 1.38 infections per 100,000 persons in 2016. This marks the first decline in VRE infection rates over the past three years, which had continually increased from 1.16 infections per 100,000 persons in 2013 to 1.60 infections per 100,000 persons in 2015. A recent meta-analysis of VRE incidence in the US between 2000 and 2015 suggests that while pooled national rates have remained stable, localized surveillance studies from cities such as Atlanta and Detroit demonstrated increasing VRE infection rates during this time.[5] The results from this assessment indicate changes in national VRE infection rates among MHS beneficiaries are also driven by regional trends. From 2015 to 2016, the largest decline in VRE infection rates occurred in the US West (from 2.57 infections per 100,000 persons to 2.18 infections per 100,000 persons) and US South (from 2.15 infections per 100,000 persons to 1.89 infections per 100,000 persons).[1]

Geographic analyses indicated that the regions with the highest overall VRE rates, including US West, US South, and US South Atlantic, also demonstrated large proportions of HA cases. In the US, VRE surveillance primarily originates within hospital settings, and little research suggests that transmission among healthy adults occurs at a significant extent in the community.[6] However, as colonized patients leave the hospital environment, the possibility for transmission into the community cannot be disregarded. Research demonstrates that patients can remain colonized for weeks to months and are often still colonized at the time of readmission to the hospital.[7] In this report, healthcare-associated exposure burden metrics implicate importation of VRE from the community to healthcare settings within the MHS. The admissions prevalence rate during 2016 (0.37 per 1,000 inpatient admissions) accounted for approximately two-thirds of the overall prevalence metric (0.58 per 1,000 inpatient admissions), demonstrating that the majority of VRE burden was identified within the first three days of an inpatient admission and thus more likely imported from the community rather than pre-existing in the hospital setting. These results underscore the need for drug-resistance surveillance outside of hospital settings due to continued potential for community transmission.

Demographic analyses from this study found the highest VRE rates among males, people aged 65 years and older, and retirees. In 2015, elevated rates in male MHS beneficiaries were observed (1.96 infections per 100,000 males vs. 1.23 infections per 100,000 females), a departure from results reported during 2014 that demonstrated equal rates stratified by gender.[1,8] This gender disparity is not as apparent during 2016 (1.52 infections per 100,000 males vs. 1.24 infections per 100,000 females); however, these results are still notable, given the majority of infections originated from urine specimens and females are typically more prone to urinary tract infections (UTIs) than males.[9] Almost half of all women will experience a UTI in their lifetime, and nearly one in three will have experienced at least one UTI episode requiring antimicrobial therapy by the age of 24 years.[10] The elevated rates observed among males may be attributed to higher rates of VRE in this report among elderly populations (those aged 65+), as the elderly represent a subpopulation at greater risk for UTIs. In genitourinary infections affecting elderly populations, asymptomatic bacteriuria is believed to affect up to 50% of geriatric women and 30% of geriatric men.[10]

Treatment for VRE infections, particularly *E. faecium*, may pose serious challenges due to resistance against multiple antibiotics; however, VRE infections still maintain susceptibility to some antibiotics.[4,6] Daptomycin and linezolid were the most commonly prescribed antimicrobials for VRE infections in the MHS during 2016, which is consistent with current treatment recommendations and MHS microbiology results confirming susceptibilities above 90% for these two antibiotics.[4] Daptomycin remains the only antibiotic with in-vitro bactericidal activity against VRE that is approved by the US Food and Drug Administration (FDA). Researchers caution clinicians to be aware of the potential emergence of daptomycin non-susceptible enterococci strains, particularly with the treatment of bloodstream infections, as data for this susceptibility remains limited.[4,11] The Johns Hopkins Antibiotic Guide recommends evaluating the susceptibility of isolates to monitor minimum inhibitory concentrations of sequential isolates recovered during daptomycin treatment.[4] Close monitoring of daptomycin through antibiotic stewardship programs in MHS populations is warranted to ensure efficacy remains high and system practices do not encourage adaptations to resistance patterns.

In summary, this report documents a decline in VRE infection rates among MHS beneficiaries during 2016, following a three-year incline from 2013-2015. The US West and US South regions accounted for the highest incidence rates during 2016, and cases were primarily characterized as HA. Almost one-third of all prevalent infections were classified as CO, and the elevated admission prevalence for healthcare-associated exposure burden metrics indicate a higher magnitude of VRE is imported into the healthcare system rather than preexisting as a reservoir. The antibiogram analysis indicates viable treatment options are still available for VRE infections and that prescribing practices are supported by susceptibility testing patterns in the MHS. Continued surveillance for VRE is warranted to monitor any changes in burden, susceptibility, and treatment options and to guide targeted prevention efforts.

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Appendix A: Acronym and Abbreviation List

Acronym/Abbreviation	Definition
AD	active duty
CA	community-associated
CHCS	Composite Health Care System
CO	community-onset
CTS	Contingency Tracking System
CY	calendar year
DMDC	Defense Manpower Data Center
DOD	Department of Defense
DON	Department of the Navy
EDC	EpiData Center Department
HA	healthcare-associated
HL7	Health Level 7 format
HO	hospital-onset
IR	incidence rate
M2	MHS Data Mart
MDRO	multidrug-resistant organism
MHS	Military Health System
MTF	military treatment facility
NMCPHC	Navy and Marine Corps Public Health Center
OCONUS	outside the continental United States
PH	previous hospitalization
SIDR	Standard Inpatient Data Record
US	United States
UTI	urinary tract infection
VRE	vancomycin-resistant enterococci