The burden of vancomycin-resistant enterococcal infections in
US hospitals, 2003 to 2004∗

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Abstract

Despite significant concern in the health care community regarding vancomycin-resistant enterococci (VRE), there are no estimates of the total number of VRE infections that occur each year in US hospitals. Using data from a national survey of hospital discharges and a national antimicrobial resistance surveillance system, we estimated the annual number of US hospitalization with VRE bloodstream, urinary tract, and wound or intra-abdominal infections. Because of the inexact nature of hospital discharge diagnosis coding, we made both a conservative and liberal estimate of hospitalization with VRE infection by using a variety of data sources. For the years 2003 and 2004, we conservatively estimated that there were 20 777 and 20 931 VRE infections, respectively; for those same years, the liberal estimates were 78 330 and 85 586, respectively. Because there are such a large number of hospital discharges for which an infection is coded without an organism code, it is likely that the conservative estimate is an underestimate of the true burden. These estimates highlight the importance of controlling VRE and the need to develop improved methods for tracking the burden of such infections.

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Keywords: Vancomycin; Resistance; Enterococcus; Burden

1. Introduction

Vancomycin-resistant enterococci (VRE) were 1st isolated from patients in Europe in 1988 (Leclercq et al., 1988; Uttley et al., 1989) and in the United States in 1989 (Centers for Disease Control and Prevention, 1993). Since then, VRE have spread rapidly throughout the United States and the world and have become a significant infection control problem for many hospitals (Huang et al., 2007). In 1994, the Centers for Disease Control and Prevention Hospital Infection Control Practices Advisory Committee (HICPAC) issued guidelines for preventing the spread of VRE (Centers for Disease Control and Prevention, 1995). The guidelines focused primarily on reducing the unnecessary use of vancomycin to reduce the selective pressure that supports the spread of VRE in health care facilities. Although adherence to the HICPAC guidelines may have slowed the increase in vancomycin resistance, the upward trend of resistance has persisted. As of October 2004, the National Nosocomial Infections Surveillance system reported that more than one-quarter of health care-associated enterococcal infections were associated with organisms resistant to vancomycin (Centers for Disease Control and Prevention, 2004).

VRE infections adversely affect clinical outcomes. They more than double the risk of death when compared with uninfected patients, cause serious complications, and require longer hospital stay (Carmeli et al., 2002; Edmond et al., 1996). VRE infections can be very difficult to treat because they are often resistant to multiple antimicrobial drugs (Murray, 2000) and require the use of linezolid, quinupristin–dalfopristin, or other more costly drugs (Cosgrove and Carmeli, 2003; Eliopoulos, 2003). Unfortunately, VRE infections that are resistant to linezolid already have been reported (Dobbs et al., 2006; Seedat et al., 2006).

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Despite significant concern in the health care community regarding VRE, there are very little data available on the total number of VRE infections that occur annually in US hospitals. Although several surveillance systems are in place to track the proportion of enterococcal infections that are resistant to vancomycin (Centers for Disease Control and Prevention, 2004; Deshpande et al., 2007; Jones et al., 2004), these studies have never been paired with quantitative data to formulate the national incidence of resistant enterococcal infections. The primary goal of this study was to estimate the overall rate of VRE infections in the United States using data from the National Hospital Discharge Survey (NHDS) and The Surveillance Network® (TSN; Focus Bio-Innova, Herndon, VA). This approach was used recently by Kuehnert et al. (2005) and Klein et al. (2007) to estimate the number of methicillin-resistant Staphylococcus aureus hospitalization in the United States.

2. Methods

The annual incidence of enterococcal infections was estimated from the number of hospital discharge records citing enterococcal-related diagnoses in the NHDS, a national surveillance database. Public use data from the 2003 and 2004 NHDS were used to calculate the number of hospital discharges with at least 1 enterococcal-related discharge diagnosis (Kozak et al., 2004). All acute care hospitalization was included with the exception of newborns.

For this study, 2 different estimates were made: 1 using more conservative inclusion criteria, the other using more liberal inclusion criteria. Both estimates used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code specific for enterococcal infection, 041.04 (enterococcal infection in condition classified elsewhere or of unspecified site), to identify enterococcal infection-related discharges (American Medical Association, 1995).

Included in the conservative estimate, along with those records coded for enterococcal infection (i.e., ICD-9-CM 041.04), were cases with ICD-9-CM code 038.0 (streptococcal septicemia). Because the diagnosis of streptococcal septicemia likely includes cases due to both group D (defined as enterococcal) and non-group D Streptococcus (defined as nonenterococcal), only a portion of these records were included. Based on a survey of blood culture isolates by Karlowsky et al. (2004), it was estimated that 73% of streptococcal septicemias were likely caused by enterococci. Therefore, the weighted analysis of any record that included streptococcal septicemia but did not specify an organism code was determined to be 0.73.

In addition to cases identified using more conservative criteria, the liberal estimate included a fraction of wound or intra-abdominal infections (WND/IAIs), urinary tract infections (UTIs), and bloodstream infections (BSIs) for which no organism code was listed. Because only 7 ICD-9-CM codes are included in each discharge record of the NHDS as opposed to hospital information systems, which often have 15 to 20 diagnosis codes (Ollendorf et al., 2002), some of these records likely correspond to enterococcal infections in which the organism code was omitted for lack of space. Based on previously published surveys of bacteremia, UTIs, and WND/IAIs, it was concluded that 13.8% of BSIs, 12.8% of UTIs, and 24.9% of WND/IAIs are likely caused by enterococci (Biedenbach et al., 2004; Goldstein and Snydman, 2004; Gordon and Jones, 2003; Jones et al., 2003; Jones et al., 1997; Karlowsky et al., 2004; Wisplinghoff et al., 2004). Records indicating these types of infections (but no organism code) were, therefore, weighted accordingly.

The infection site was identified by using the ICD-9-CM codes for specific infection sites. An infection was categorized as a BSI if the diagnosis included a code for septicemia, bacteremia, or endocarditis. An infection was categorized as a UTI if the diagnosis included a code for acute pyelonephritis, cystitis, or UTI. An infection was categorized as a WND/IAI if the record included a focal code for infection in an area between the chest and legs (except those related to a pregnancy). Where multiple infection sites were included in the diagnosis, BSIs were preferentially included, followed by UTIs, and lastly, WND/IAIs. In all cases, a single discharge record was counted only once, regardless of the number of enterococcal-related diagnoses.

Hospitalization coded for enterococcal infection (i.e., ICD-9-CM 041.04) but without discharge diagnoses indicating BSI, UTI, or WND/IAI was defined as “unknown” with regard to infection site.

The percentage of enterococcal isolates resistant to vancomycin was determined from the antimicrobial susceptibility testing results of a large sample of enterococcal isolates obtained from blood, wound, and urine cultures from patients in US hospitals. This study used 2003 and 2004 data from TSN Database—USA. TSN is an electronic database of isolate-specific, qualitative and quantitative, antimicrobial susceptibility test data reported by clinical laboratories in North America that has been used extensively in the past to evaluate various trends regarding antimicrobial susceptibility (Jones et al., 2004; Karlowsky et al., 2004; Sahm et al., 2003). Isolates were classified as VRE if the vancomycin susceptibility result was resistant according to CLSI standards (i.e., intermediate resistance was not included) (CLSI, 2006).

To obtain the estimates of annual VRE-associated hospitalization from NHDS data, we stratified both the liberal and conservative estimates of enterococcal infections by infection site and multiplied it by the stratum-specific percentage of vancomycin resistance among inpatients. The variance of the annual estimated number of hospitalization associated with enterococci was calculated using the formulas provided in the NHDS documentation (National Center for Health Statistics [U.S.], 2005). The variance of the vancomycin-resistant proportions was calculated under the assumption that the TSN data consisted of a random sample.
of all enterococcal isolates in the United States during 2003 and 2004. The 2 years were compared by calculating the incidence ratio and its associated 95% confidence interval.

3. Results

Using conservative criteria, the estimated number of hospital discharges associated with enterococcal infections in the United States was 130,922 in 2003 and 125,134 in 2004 (Table 1). Using a more liberal case definition, the estimated number of hospital discharges associated with enterococcal infections was 516,387 in 2003 and 521,285 in 2004. As a proportion of all infections, the liberal estimate included a greater proportion of UTIs and smaller proportion of BSIs than the conservative estimate, but otherwise, the distributions of infection sites in the 2 estimates were similar (data shown in Table 2). Most of the records that included codes for streptococcal septicemia, BSI, UTI, and WND/IAI did not include a specific organism code.

The TSN data set included susceptibility test results for more than 130,000 enterococcal isolates. The proportion of enterococcal isolates that were vancomycin resistant was higher among blood and wound isolates than among urine isolates. Approximately 70% of Enterococcus faecium isolates were vancomycin resistant compared with approximately 3% of Enterococcus faecalis isolates. The proportion of vancomycin-resistant isolates was higher in the Northeast and Midwest and lower in the South and West regions as defined by the US Census Bureau (2001).

Using the conservative case definition, there were an estimated 20,777 hospitalization associated with VRE infections in 2003 and 20,931 in 2004 (Table 2). Using the more liberal case definition, the 2003 and 2004 estimates increase to 78,330 and 85,586 VRE infections, respectively. The estimates produced by this study show a slight (nonsignificant) increase in the annual incidence of hospitalization associated with VRE.

Finally, the estimated incidence of VRE hospitalization was highest in the Northeast and Midwest and lowest in the South and West (Table 3). Again, the incidence varied substantially depending on whether the conservative or liberal criteria were used—the estimated rates per 10,000 hospital discharges ranged from 4.38 (South) to 9.19

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coded for enterococcal infection</td>
<td>100,918</td>
<td>96,893</td>
</tr>
<tr>
<td>Streptococcal septicemias with no organism code</td>
<td>411,016</td>
<td>386,869</td>
</tr>
<tr>
<td>Estimated attributable (73.1%)</td>
<td>30,004</td>
<td>28,241</td>
</tr>
<tr>
<td>Total conservative estimate</td>
<td>130,922</td>
<td>125,134</td>
</tr>
<tr>
<td>Coded for enterococcal infections</td>
<td>100,918</td>
<td>96,893</td>
</tr>
<tr>
<td>BSIs with no organism code</td>
<td>440,498</td>
<td>487,111</td>
</tr>
<tr>
<td>Estimated attributable (13.8%)</td>
<td>51,979</td>
<td>57,479</td>
</tr>
<tr>
<td>UTIs with no organism code</td>
<td>157,763</td>
<td>165,251</td>
</tr>
<tr>
<td>Estimated attributable (12.8%)</td>
<td>20,193</td>
<td>21,152</td>
</tr>
<tr>
<td>WND/IAIs with no organism code</td>
<td>648,809</td>
<td>624,059</td>
</tr>
<tr>
<td>Estimated attributable (24.9%)</td>
<td>161,553</td>
<td>155,391</td>
</tr>
<tr>
<td>Total liberal estimate</td>
<td>516,387</td>
<td>521,285</td>
</tr>
</tbody>
</table>

Table 2: Conservative and liberal estimates of US hospitalization with enterococcal and VRE infection based upon the NHDS and data from The Surveillance Network™, 2003 to 2004

<table>
<thead>
<tr>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSI</td>
<td>38,466</td>
</tr>
<tr>
<td>UTI</td>
<td>63,247</td>
</tr>
<tr>
<td>WND/IAI</td>
<td>9,872</td>
</tr>
<tr>
<td>Unknown</td>
<td>19,337</td>
</tr>
<tr>
<td>Annual estimate (95% CI)</td>
<td>20,777 (12,567–28,987)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSI</td>
<td>60,441</td>
</tr>
<tr>
<td>UTI</td>
<td>265,184</td>
</tr>
<tr>
<td>WND/IAI</td>
<td>17,142</td>
</tr>
<tr>
<td>Unknown</td>
<td>19,337</td>
</tr>
<tr>
<td>Annual estimate (95% CI)</td>
<td>78,330 (51,142–105,518)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

a Number of hospitalization with enterococcal infection.
b Proportion of Enterococcus isolates with resistance to vancomycin.
c Number of hospitalization with VRE infection.
(Northeast) when the conservative criteria were used and from 17.78 (West) to 32.54 (Northeast) when the liberal criteria were used. Regardless of the criteria used, the Northeast and Midwest had significantly higher rates than the South and the West, although the relative ranks of regions varied slightly between the 2 estimates.

4. Discussion

This study provides the 1st national estimates of VRE infection in the United States. The estimates show that the national burden of VRE is substantial; Although there was no significant increase between 2003 and 2004, it was still large enough to have serious patient care and financial implications for the health care community.

The liberal estimate is more than triple the conservative estimate. This reflects the large number of hospitalization records that contain codes indicating an infection of the BSI, UTI, or a WND/IAI but does not contain an organism code. Given the substantial number of records lacking organism codes, it seems likely that the conservative estimate is an underestimate of the true burden of VRE infection. The most prominent difference between the 2 estimates is in the relative proportion of infections of the bloodstream and urinary tract. However, the pattern of regional variation was consistent regardless of the criteria used. Future studies that use administrative claims data to estimate the burden of infections and antimicrobial resistance should consider this important factor and identify methods to account for records with no organism code.

The vancomycin-resistant proportion of enterococcal isolates, based upon TSN data, was significantly greater among isolates from the Northeast and Midwest. The cause of this variation is unknown, but this study confirms that the difference is significant and is associated with higher incidence of VRE-associated hospitalization. Whether this regional difference is due to variation in prevalent strains, hospital practices, or other factors is an open question, though the pattern is similar to studies of other organisms such as methicillin-resistant S. aureus (Kuehnert et al., 2005) and Clostridium difficile-associated disease (McDonald et al., 2006).

This study is subject to a number of limitations. First, enterococcal infections may not have been accurately identified by ICD-9-CM codes. Some episodes of colonization may have been falsely recorded as enterococcal infections, and true enterococcal infections may have gone unidentified if the diagnosis was not laboratory confirmed by a laboratory. There have been no validation studies of coded enterococcal diagnoses reported to date, and such validation would be important for further refining these estimates. Furthermore, because only 7 principle diagnoses are included in each NHDS record, true cases of enterococcal infection may not have been identified because of lack of space on the survey instrument. This type of misclassification would particularly affect the conservative estimate. In an attempt to correct for underuse of organism-specific ICD-9-CM codes, a proportion of infections for which no organism code was provided were included in the liberal estimate. The proportion of each infection type was based on previously published literature describing broad surveys recording the microbial etiology of infection (Goldstein and Snydman, 2004; Jones et al., 2003, 2004; Jones et al., 1997; Karlowsky et al., 2004). In applying these estimates in this study, it was assumed that the use of an organism-specific ICD-9-CM code was independent of the organism’s identity. Finally, because key data elements came from different databases, the results may be skewed because both were not fully stratified random samples. Strengths of this study include the large sample size of the TSN data set. This study is the 1st to use a national sample to estimate the incidence of VRE-associated hospitalization. Our estimates of such a large number of VRE infections suggest that the prevention and control of vancomycin resistance remains an important public health problem.

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References


