Relationships Between the Importation, Transmission, and Nosocomial Infections of Methicillin-Resistant Staphylococcus aureus: An Observational Study of 112 Veterans Affairs Medical Centers

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Background. The study of hospital methicillin-resistant Staphylococcus aureus (MRSA) epidemiology is complicated by its transmissibility. Our objective was to understand how MRSA importation and transmission influence MRSA nosocomial infections in Veterans Affairs Medical Centers (VAMCs).

Methods. We performed hospital-level analyses of acute-care MRSA admission prevalence, acquisition rates, and incident nosocomial clinical culture (INCC) rates, each a surrogate measure of importation, transmission, and nosocomial infection, respectively. We studied 112 VAMCs from October 2007 through September 2010, after the start of a bundled intervention including active surveillance for MRSA. We analyzed data using generalized linear mixed models.

Results. A total of 2.9 million surveillance tests were collected from 1.4 million patient admissions. Overall MRSA admission prevalence was 11.4%, acquisition was 5.2 per 1000 patient-days at risk, and INCC was 1.8 per 1000 patient-days at risk. A 10% increase in a hospital’s average admission prevalence was associated with a 9.7% increase in its weekly acquisition rates (P < .001) and a 9.8% increase in its weekly INCC rates (P < .001). Significant decreases were observed in all 3 measures during the study period (P < .001). When INCC rates were stratified by nasal MRSA carriage at admission, a significant downward trend was observed only among those initially negative.

Conclusions. Measured associations between MRSA admission prevalence, acquisition rate, and INCC rate were consistent with the hypothesis that decreased acquisition led to decreased importation, which in turn further abated acquisition. The downward trend in INCC rate specifically among individuals with negative admission surveillance tests suggests that decreasing transmission contributed to lower rates of nosocomial MRSA infection.

Keywords. methicillin-resistant Staphylococcus aureus; transmission; healthcare-associated infection; prevalence; incidence.
acquisition or infection with vancomycin-resistant Enterococcus and MRSA were comparable between the intervention and control arms [9]. The quasi-experimental study that analyzed monthly data from all hospitals described a significant decrease in both MRSA acquisition and HAI following implementation of a MRSA bundle in Veterans Affairs Medical Centers (VAMCs) [10]. Several system and hospital factors may have contributed to the observed MRSA-HAI rates and could account for these seemingly discordant findings. MRSA importation into the hospital and transmission may explain some differences between MRSA-HAI rates in different settings [11]. One study suggested that MRSA-HAI decreases observed in the Veterans Affairs (VA) study may not be due to changes in transmission but other improvements in infection control [12].

The recent establishment of a coded national microbiology database in the VA system [13] provided an opportunity to investigate the role of MRSA importation and transmission on MRSA-HAI rates. Specifically, we tested the following hypotheses with surrogate markers of our targeted concepts: (1) MRSA importation was associated with transmission and vice versa; and (2) importation and transmission rates were associated with nosocomial MRSA infection.

METHODS

Setting and Data Source

By October 2007, all VAMCs had implemented the MRSA bundle [10]. This intervention mandated nasal surveillance tests on all inpatients upon admission, transfer, and discharge to all acute inpatient wards, except those of mental health.

We performed an analysis of hospitals by including data from all patients who contributed time during intensive and acute-care admissions (hereafter defined as “acute-care”) from 1 October 2007 through 30 September 2010. In regression models, we excluded the first year of outcomes (1 October 2007–30 September 2008) to reduce bias that would result as discharge surveillance improved [10]. Patients discharged under outpatient observation status were excluded. VAMC were included if they listed at least 10 operational, acute inpatient care beds during fiscal year 2007 (October through September). They were excluded if they had <20 weeks with at least 20 admissions per week. VAMCs were removed from regression models if surveillance test data were not found for >50% of admissions.

Clinical diagnostic culture and MRSA surveillance test results were extracted from microbiology reports and laboratory data as described elsewhere [13].

Conceptual Framework

To clarify terms and relationships, we used a model to map target concepts to surrogate measures. In Figure 1, patients who are already colonized or infected with MRSA at the time of hospital admission “import” MRSA into the hospital. When a patient without MRSA becomes colonized through contact with another patient, healthcare worker, or the environment, a “transmission” takes place. Colonization may “progress” to symptomatic infection through breaches in host defenses. An infection is considered “nosocomial” if progression to infection occurs after admission to the hospital [14].

Due to our inability to observe these processes directly, the following measures were used as surrogate indicators (Figure 1): admission prevalence (importation), acquisition rate (transmission), and incident nosocomial clinical culture (INCC) rate (nosocomial infection). Nasal swabs were used to infer colonization status. Clinical cultures were used to infer symptomatic, nosocomial MRSA infection.
Admission prevalence was defined as the proportion of positive tests among hospitalized patients screened for MRSA nasal carriage within 12 hours of admission. This cutoff was selected to minimize the misclassification of early acquisitions as prevalent admissions; approximately 25% of acquisitions occurred within 2 days after admission (unpublished data). An acquisition was defined as the first MRSA-positive surveillance test of an admission that followed an initial negative test during the same admission. An INCC was defined as a new MRSA-positive clinical culture that occurred ≥2 calendar days after admission in patients without prior MRSA-positive clinical cultures within the past year. To assess the reliability of this measure with respect to human assessment, we reviewed 169 MRSA clinical culture-positive admissions among fiscal years 2004 and 2008 at VA Salt Lake City Health Care System and found a Cohen’s κ of 0.50 (1.0 being ideal) between INCC and the infection preventionists’ assessment. For comparison, the κ between other human experts reviewing the same set was 0.29 (unpublished data). The further classification of INCC into “admission-carrier” and “new-carrier” categories referred to whether the INCC occurred after a positive or negative nasal test on admission, respectively. A new-carrier INCC reflected the occurrence of both transmission and progression during admission. An admission-carrier INCC reflected the occurrence of progression only. Rates were denominated by patient-days at risk when patients were eligible for the outcome of interest. Daily prevalence was defined as the proportion of MRSA nasal-positive patient-days among all patient-days from screened admissions, assuming that individuals with positive surveillance tests remained colonized until the end of their hospital stay.

Statistical models of surrogate measures were constructed to reflect the relationships of their underlying concepts. Mass action theory posits that the transmission rate (per susceptible individual) is proportional to the prevalence (or density) of infectious individuals in the population [15]. In hospital environments, this prevalence has been called “colonization pressure” [16]; daily prevalence is a surrogate measure of colonization pressure. Because admission prevalence affects daily prevalence, the mass action principle led to the prediction that admission prevalence influences acquisition (Figure 1). The effect is indirect because patients who acquire MRSA are not the same patients who import MRSA [17]. We also predicted that acquisition rate influences admission prevalence because patients who acquire MRSA may contribute to future admission prevalence when they are readmitted.

**Statistical Analyses**

Separate generalized linear mixed models were fit to admission prevalence, acquisition rate, INCC rate, and admission-carrier and new-carrier INCC rates (Supplementary Appendix A). Admission prevalence was used to predict acquisition rates and admission-carrier INCC rates. Acquisition rates were used to predict admission prevalence. Both admission prevalence and acquisition rates were used to predict INCC and new-carrier INCC rates. In each model, the dependent variable was aggregated weekly. Predictor variables were divided into 2 components, one to measure within-hospital variation and the other to measure between-hospital variation. The within-hospital component was calculated as a running average to reduce stochastic noise. An 8-week interval was used for smoothing all time-varying variables, except for the model predicting admission prevalence. In this case, a 20-week running average was used because 80% of readmitted patients were readmitted by this time.

Data were fit using the GLIMMIX procedure [18] from SAS to account for hospital-level clustering and autocorrelation. In each model, a log-link function and overdispersed Poisson distribution for the dependent variable were specified. A first-order autocorrelation structure empirically fit the data and therefore was used to account for correlation in outcomes over successive 1-week intervals. Outcomes were offset by patient-days at risk. Admission prevalence and acquisition were log-transformed as predictor variables, so that regression models related the relative change in the outcome variables to relative changes in predictor variables.

The following adjustment variables were included in models: academic affiliation [19]; rural hospital location based on postal zip code [20]; number of operational beds; fiscal year 2006 Medicare patient risk by diagnosis cost grouping (a measure of the relative expense that veterans at a hospital are expected to incur) [21]; and number of complex clinical programs (eg, neurosurgery, interventional cardiology) [22]. Mantel-Haenszel statistics were used for crude rate comparisons.

SQL Server 2008 (Microsoft, Redmond, Washington), Stata version 11 (StataCorp, College Station, Texas), and SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) were used in various stages of analysis. Data were stored and analyzed on the Veterans Informatics and Computing Infrastructure. This study was approved by the Research Review Committee of the VA Salt Lake City Health Care System and Institutional Review Board of the University of Utah.

**RESULTS**

**Description of the Population**

The Veterans Health Administration encompasses 152 acute-care hospitals. Forty hospitals were excluded from this study for the following reasons: incomplete electronic data (n = 24); insufficient number of weekly admissions (n = 14); and <10 acute-care beds (n = 2). Of the 112 included hospitals, 104 (92%) were academically affiliated (Table 1). Two additional hospitals were excluded from regression analyses because surveillance data were present for <50% of admissions.
A total of 2.9 million surveillance tests among 1.4 million admissions and 742,531 individuals were performed. Overall, 83.2% of included admissions had a surveillance test performed within 12 hours of hospital admission. The median time from admission to the collection of the first surveillance test was 1.95 hours (interquartile range [IQR], 0.50–5.45 hours). At least 1 other test was collected in 78.7% of admissions.

A total of 2.8 million inpatient clinical microbiology tests were obtained from 677,847 admissions and 403,533 unique individuals; 5.1% of admissions were positive for MRSA. MRSA was most frequently isolated from sputum (24.0%), followed by wounds (23.1%), blood (18.7%), and urine (13.0%).

**Admission Prevalence and Acquisition**

Overall median hospital admission prevalence was 11.1 per 100 admissions (IQR, 9.2–12.9 per 100 admissions). Mean admission prevalence was unchanged between the years starting October 2007 and October 2008 (0%, P = .45) but decreased by 10% the following year (P < .0001; Figure 2). Mean daily prevalence decreased from 16.9% in the first year to 15.1% in the last year (P < .0001). Overall median hospital acquisition was 4.8 per 1000 patient-days at risk (IQR, 3.9–6.1 per 1000 patient-days at risk). The mean acquisition rate decreased 10% between the first and second years (P < .0001) and 14% between the second and third years (P < .0001). In multivariable models, both admission prevalence and acquisition demonstrated significant downward secular trends (P < .001; Table 2).

The hospital acquisition rate on a given week was strongly associated with hospital average admission prevalence. To illustrate, in models predicting acquisition in Table 2, each 10% relative decrease in a hospital’s average admission prevalence was associated with a 9.7% decrease in its acquisition rate (P < .001). However, time-varying fluctuations around a hospital’s average admission prevalence were not significantly associated with acquisition rate. Altogether, 39% of between-hospital variance in acquisition was accounted for by between-hospital variation in admission prevalence.

Similarly, hospital admission prevalence on a given week was strongly associated with hospital average acquisition rate. In models predicting admission prevalence, each 10% decrease in a hospital’s average acquisition rate was associated with a 3.6% relative decrease in its admission prevalence (P < .001). Hospital admission prevalence on a given week was modestly predicted by smoothed acquisition rates over previous weeks.

**Incident Nosocomial Clinical Culture**

The overall incidence proportion for INCC was 0.59 per 100 admissions. The overall median hospital INCC rate was 1.7 per 1000 patient-days at risk (IQR, 1.4–2.0 per 1000 patient-days at risk).
risk). The mean INCC rate decreased 8% between the years starting October 2007 and October 2008 \( (P < .001) \) and also 16% between the years starting October 2008 and October 2009 \( (P < .0001) \); Figure 2). Overall 52.9% of INCC cases were MRSA admission-carrier INCC.

In models with INCC as the outcome, admission prevalence was a stronger predictor than acquisition. Each 10% decrease in a hospital’s average admission prevalence was associated with a 9.8% decrease in its INCC rate \( (P < .001) \); Table 2). Fluctuations in hospital admission prevalence over time were also associated with INCC rate; each 10% decrease in weekly admission prevalence was associated with a 3.2% decrease in INCC \( (P = .002) \). In contrast, hospital average acquisition was not significantly associated with INCC in the adjusted analyses. Smoothed acquisition rates during previous weeks were modestly associated with INCC. Each 10% decrease in hospital weekly acquisition was associated with a 1.2% decrease in INCC \( (P = .01) \). The INCC rate demonstrated a significant downward secular trend; the estimated relative decrease was 8.9% per year \( (P < .001) \).

Admission-carrier INCC rates did not decline significantly \( (P = .56) \). In contrast, new-carrier INCC rates decreased significantly; the relative reduction per year after adjustment for admission prevalence and acquisition rate was 12.2% \( (P = .002) \); Figure 3).

**DISCUSSION**

We examined surveillance and microbiology data from 112 VA hospitals to identify interrelationships between importation, transmission, and nosocomial infection. MRSA admission prevalence was predictive of MRSA acquisition rate and vice versa. Both admission prevalence and acquisition rate were significantly associated with the INCC rate and accounted for more than half of the variance in INCC rates.

MRSA transmission decreased and likely contributed to a decline in MRSA nosocomial infection rates. The finding that admission prevalence was a stronger predictor than acquisition rate for the outcome of INCC rate might suggest that transmission

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**Table 2. Model-Derived Estimates of Association Between Admission Prevalence, Acquisition, and Incident Nosocomial Clinical Culture**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>( \Delta \text{ in } \text{Outcome} )</th>
<th>95% CI</th>
<th>( P \text{ Value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Model Predicting Acquisition per Unit Change ( \Delta ) in the Predictor</td>
<td>( \Delta \text{ in Acquisition} )</td>
<td>95% CI</td>
<td>( P \text{ Value} )</td>
</tr>
<tr>
<td>1-y increase</td>
<td>(-14.0% )</td>
<td>((-16.7% \text{ to } -11.2%) )</td>
<td>(&lt;.001 )</td>
</tr>
<tr>
<td>hospital admission prevalence</td>
<td>• 10% ↓ in the average value (between hospitals)</td>
<td>(-9.7% )</td>
<td>((-12.3% \text{ to } -7.2%) )</td>
</tr>
<tr>
<td>• 10% ↓ in the time-varying value (within hospitals)</td>
<td>(-0.3% )</td>
<td>((-1.5% \text{ to } 1.0%) )</td>
<td>(.68 )</td>
</tr>
<tr>
<td>Between-hospital coefficient of variation is approximately 27% and 35% with and without adjustment for admission prevalence; 39% of between-hospital variance in acquisition accounted for by between-hospital variation in admission prevalence.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Model Predicting Admission Prevalence per Unit Change ( \Delta ) in the Predictor</td>
<td>( \Delta \text{ in Importation} )</td>
<td>95% CI</td>
<td>( P \text{ Value} )</td>
</tr>
<tr>
<td>1-y increase</td>
<td>(-7.1% )</td>
<td>((-8.3% \text{ to } -6.9%) )</td>
<td>(&lt;.001 )</td>
</tr>
<tr>
<td>hospital acquisition</td>
<td>• 10% ↓ in the average value (between hospitals)</td>
<td>(-3.6% )</td>
<td>((-4.5% \text{ to } -2.6%) )</td>
</tr>
<tr>
<td>• 10% ↓ in the time-varying value (within hospitals)</td>
<td>(-0.6% )</td>
<td>((-0.9% \text{ to } -0.3%) )</td>
<td>(&lt;.001 )</td>
</tr>
<tr>
<td>Between-hospital coefficient of variation is approximately 18% and 22% with and without adjustment for acquisition; 36% of between-hospital variance in admission prevalence accounted for by between-hospital variation in acquisition.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Model Predicting INCC per Unit Change ( \Delta ) in the Predictor</td>
<td>( \Delta \text{ in INCC} )</td>
<td>95% CI</td>
<td>( P \text{ Value} )</td>
</tr>
<tr>
<td>1-y increase</td>
<td>(-8.9% )</td>
<td>((-13.6% \text{ to } -3.9%) )</td>
<td>(&lt;.001 )</td>
</tr>
<tr>
<td>hospital admission prevalence</td>
<td>• 10% ↓ in the average value (between hospitals)</td>
<td>(-9.8% )</td>
<td>((-13.2% \text{ to } -6.4%) )</td>
</tr>
<tr>
<td>• 10% ↓ in the time-varying value (within hospitals)</td>
<td>(-3.2% )</td>
<td>((-5.3% \text{ to } -1.2%) )</td>
<td>(.002 )</td>
</tr>
<tr>
<td>in hospital acquisition</td>
<td>(-1.7% )</td>
<td>((-3.8% \text{ to } -0.4%) )</td>
<td>(.11 )</td>
</tr>
<tr>
<td>• 10% ↓ in the time-varying value (within hospitals)</td>
<td>(-1.2% )</td>
<td>((-2.0% \text{ to } -4%) )</td>
<td>(.01 )</td>
</tr>
<tr>
<td>Between-hospital coefficient of variation is approximately 25% and 37% with and without adjustment for acquisition and admission prevalence; 52% of between-hospital variance in clinical infection accounted for by between-hospital variation in acquisition and admission prevalence.</td>
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<td></td>
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</tbody>
</table>

Facility-level covariates were academic affiliation, rural location, number of hospital beds, patient risk, and number of complex programs.

Abbreviations: ↓, relative decrease; CI, confidence interval; INCC, incident nosocomial clinical culture.
played a minimal role in nosocomial infection; however, this observation may also be explained by importation’s influence on nosocomial infection directly through progression and indirectly through transmission and subsequent progression and readmission (Figure 1) [23, 24]. Importantly, the substantially steeper downward trend in new-carrier INCC (reflecting transmission and progression) compared to admission-carrier INCC (progression alone) provides evidence for transmission’s role in the decline of nosocomial infections.

There was evidence for a positive-feedback cycle between importation and transmission with declines in one leading to declines in the other. First, the overall decrease in MRSA acquisition rate began before the decrease in admission prevalence. Second, the mutual associations observed after appropriately accounting for temporality suggest that initial decreases in transmission rates contributed to subsequent decreases in importation, leading to further diminishment of transmission. Third, the disproportionate reduction in acquisition rate compared to admission prevalence is consistent with the interpretation that the risk of transmission, within a given level of exposure to MRSA, waned. Therefore it is likely that both declines in importation and in transmission helped to drive down nosocomial infection rates.

Our estimates of VA trends and MRSA burden are generally consistent with prior publications. However, different sources of data, definitions, and assessment modalities were used for this analysis than in previous studies of VA hospitals [10, 25], thus making superficial comparisons difficult. For example, the downward trend in INCC was less pronounced than that found in manually reported MRSA-HAI data in a similar cohort [10], but this may be due to differences between INCC and HAI measurement. Similarly, differences in admission prevalence definitions may explain differences in trends measured in this and similar VA cohorts [26]. More broadly, our observed temporal trends agree with those seen nationally [27, 28] and internationally [29].

In general, observed decreases in MRSA-HAI are likely due, in part, to infection control measures that reduce transmission and progression, such as contact precautions and vascular catheter bundles [30], respectively. A recent modeling study suggested that practices targeting progression may have been primarily responsible for decreased MRSA-HAI in VA [12]. That study assumed that importation was independent from transmission in VA. However, the feedback cycle between importation and transmission suggests that the ultimate effect of transmission control measures should be assessed with models that also include the impact of transmission on future importation.

The strengths of our analyses lie in the quality and quantity of data available, as well as in the efforts to address dependence between infectious MRSA outcomes. Individual-level data made it possible to implement rigorous definitions, such as for patient-days at risk. A high rate of adherence to screening protocols at both admission and discharge minimized measurement biases.

Our modeling approach advances the methods traditionally used in studies of transmission and nosocomial infection. When one individual acquires MRSA and transmits it to another individual, there is dependence between these outcomes that violates assumptions most statistical models make. To date relatively few studies have factored this into their analyses [31–35]. We were unable to find any other studies of importation, transmission, and nosocomial infection that considered the influence of each on the other to a similar extent and scale.

Our analysis was performed at a hospital level; therefore, it is appropriate to make inferences at the hospital rather than individual patient level [36]. Shared group exposures have a substantial influence on infectious outcomes because of non-independent events [37]. A large MRSA prevalence survey of
195 healthcare facilities found that hospital-level variables explained more variation between hospitals than did patient-level predictors [38].

Misclassification between our surrogate measures (Figure 1) may have diminished the interpretability of our statistical models. Obtaining MRSA surveillance tests from a single anatomic site [39] might have obscured relationships through underdetection of MRSA carriage. Another limitation of the analyses was lack of information about infection control practices, antibiotic use, healthcare worker contacts, and other factors that influence transmission [16]. We did not perform strain identification to better pinpoint who may have infected whom. Our use of clinical culture data instead of manual chart review to identify nosocomial infections was subject to error, and our use of INCC most likely included cases of colonization; however, manual methods would have been prohibitively time consuming, more difficult to reliably apply across hospitals, and susceptible to other forms of bias [40].

Time-varying admission prevalence was a much weaker predictor of acquisition rate and INCC rate than a hospital’s average admission prevalence. Because time-varying admission prevalence is estimated with far fewer cases than average admission prevalence, it fluctuates to a greater degree because of random variation. This tends to bias coefficient estimates toward the null. Moreover, average admission prevalence captures the bidirectional influence of transmission and importation on each other [33]. Effects that are relatively small over short periods of time may become magnified through positive feedback.

In conclusion, associations between MRSA admission prevalence, acquisition, and INCC were demonstrated that were consistent with theories of transmission dynamics. The findings suggest that decreased transmission led to decreased importation, which in turn further abated acquisition. Although we draw no conclusions about the effectiveness of the VA MRSA bundle, lower rates of nosocomial MRSA infection likely resulted from decreases in both transmission and importation. Further analyses fitting data to transmission models are a promising approach to improving our understanding of MRSA dynamics and control [31].

### Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

### Notes

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