Semi-Automated Visualization and ANalysis of Trends: A “SAVANT” for Facilitating Antimicrobial Stewardship Using Antistaphylococcal Resistance and Consumption as a Prototype

Robert J. Clifford, Uzo Chukwuma, Michael E. Sparks, Douglas Richesson, Charlotte V. Neumann, Paige E. Waterman, Jacob Moran-Gilad, Michael D. Julius, Mary K. Hinkle, and Emil P. Lesho

Background. Governments and health care regulators now require hospitals and nursing homes to establish programs to monitor and report antimicrobial consumption and resistance. However, additional resources were not provided. We sought to develop an approach for monitoring antimicrobial resistance and consumption that health care systems can implement with minimal added costs or modifications to existing diagnostic and informatics infrastructure.

Methods. Using (1) the electronic laboratory information system of a nationwide managed care network, (2) the 3 most widely used commercial microbiology diagnostic platforms, and (3) Staphylococcus aureus, one of the most common causes of infections worldwide, as a prototype, we validated the approach dubbed “SAVANT” for Semi-Automated Visualization and ANalysis of Trends. SAVANT leverages 3 analytical methods (time series analysis, the autoregressive integrated moving average, and generalized linear regression) on either commercial or open source software to report trends in antistaphylococcal use and resistance.

Results. All laboratory results from January 2010 through December 2015 from an annual average of 9.2 million health care beneficiaries were queried. Inpatient and outpatient prescription rates were calculated for 8 key antistaphylococcal compounds. Trends and relationships of antistaphylococcal consumption and resistance among 81,840 unique S. aureus isolates from >6.5 million cultures were revealed.

Conclusions. Using existing or freely available resources, SAVANT was successfully implemented across a complex and geographically dispersed 280-hospital network, bridging a critical gap between medical informatics, large-scale data analytics, and mandatory reporting of health care quality metrics.

Keywords. antibiotic consumption and resistance; antimicrobial stewardship; informatics; Staphylococcus aureus.

Antimicrobial resistance (AMR) poses one of the greatest threats to global public health [1, 2]. To help address the ongoing crisis of escalating AMR, governments and health care regulators recently required hospitals and nursing homes to establish programs to monitor and report antimicrobial consumption and resistance, but they did not provide additional funds or resources to facilitate compliance [3, 4]. Lack of funding is a major barrier to compliance, and participation in such stewardship programs is also linked to reimbursement by the Centers for Medicare-Medicaid Services (CMS) and a new Joint Commission (JC) standard [3–6]. The ability of large and geographically dispersed health care systems to trend antibiotic use and resistance with a minimum of additional resources would facilitate regulatory compliance and inform preventive strategies. Although many conventional and novel strategies are being employed to fight the escalating problem of antimicrobial resistance, reports using configurations and combinations of existing medical informatics, software, and diagnostic platforms are scarce.

We aimed to develop an approach for monitoring antibiotic resistance and antibiotic consumption that health systems can implement with minimal cost or modification to existing electronic health care information and bacterial diagnostic systems. Our method used resources already existing at or freely available to most health care systems: (1) an electronic health record and/or laboratory information system linked to an automated diagnostic platform (ie, Seimens MicroScan, BD Phoenix, or bioMérieux Vitek II), (2) open source software, (3) a microbiologist, and (4) an epidemiologist or statistician.

To demonstrate the utility of the approach, we then sought to see if it could be applied to a large, geographically dispersed national health care network (the Department of Defense...
[DoD]) to analyze trends in antibiotic prescriptions and resistance. We chose *Staphylococcus aureus* as the prototype because it is a leading cause of serious health care–associated infections in the United States, and it is the most common cause of soft tissue infections and infective endocarditis worldwide [7–10]. Furthermore, we studied the incidence of a specific subtype of *S. aureus* we termed “problematic vancomycin-susceptible *S. aureus*” (PVSSA) and the usage of major antistaphylococcal agents in the DoD. We chose the term PVSSA for the following rationale.

First, it would be one of the most challenging and problematic antibiotic-microbe (“drug-bug”) combinations for such an approach. Although manual broth dilution is the reference standard for determining vancomycin minimum inhibitory concentration (MIC), it is laborious and infeasible in busy hospital laboratories, especially for testing thousands of isolates. Therefore, hospitals unavoidably rely on commercial automated antibiotic susceptibility testing (AST) platforms. The 3 most popular platforms are the Phoenix, Vitek, and MicroScan, and larger health systems may use more than 1 platform. In fact, the DoD has 288 fixed location treatment facilities and uses all 3 platforms. Furthermore, the reported MIC for *S. aureus* can vary according to the type of AST platform used, especially in the upper ranges of susceptible–intermediate [11]. Therefore this “drug-bug” combination would be one of the least amenable to and most “problematic” for automated electronic data mining and reporting across large health networks that use more than 1 type of AST platform and process large volumes of isolates. Second, a vancomycin MIC between 1.5 and 2.0 µg/mL, although in the sensitive range, had previously been associated with adverse outcomes and mortality in *S. aureus* bacteremia. Therapeutic failure had occurred even for methicillin-susceptible *S. aureus* (MSSA) strains [12–15].

Our main goal was to illustrate an alternative approach, using freely available software, for analyzing and reporting of large volumes of drug consumption and antibiotic resistance data support of stewardship efforts. A byproduct of having successfully met that goal would be the ability to use it to investigate correlations between usage of a drug (in this case, antistaphylococcal agents) and increases in mean MICs of a key therapeutic (in this example, vancomycin) among *S. aureus*.

Only 2 basic types of data are needed for SAVANT analyses: (1) the number of isolates per month meeting a prespecified drug susceptibility, either a categorical variable (S, I, or R) or a numeric value of minimum inhibitory concentrations; and (2) some unit of drug consumption per month, either milligrams, grams, prescriptions, day of therapy, or defined daily doses. Examples of the required data format and code are provided in the Supplementary Appendix (sample_input_data).

**METHODS**

**Vancomycin-Susceptible *S. aureus* Isolates and Susceptibility Data**

The DoD’s health system, its beneficiaries, and detailed methods for mining its electronic health records (EHRs) have been described previously [16, 17]. Briefly, there are 280 fixed location treatment facilities. Most are ambulatory clinics and medium-sized community hospitals (150-bed average). Eleven of those are larger tertiary referral centers located in the states of California, Hawaii, Maryland, North Carolina, Ohio, Texas, Virginia, Washington, and Germany. All hospitals are accredited by the Joint Commission. Health care beneficiaries include all races and ages including neonates and elderly residents of long-term skilled nursing facilities (not just young active duty soldiers and sailors). The EHRs of all beneficiaries (approximately 9.2 million annually) were queried for all cultures that grew vancomycin-susceptible *S. aureus* (VSSA). All isolates are from infections or suspected infections because polymerase chain reaction–based platforms are used for surveillance screening of nares for colonization. As such, no surveillance isolates are produced and available for further analysis. Data were deduplicated based on 1 isolate per patient per month using a “30-day interval from initial isolate” scheme [18]. Monthly counts of both community-acquired and hospital-acquired VSSA isolates, defined as those with vancomycin MICs of ≤2 µg/mL, were tabulated from January 2010 through December 2015. MICs were determined by automated methods with the bioMérieux Vitek II, Siemens MicroScan Walkaway, or BD Phoenix testing platforms, depending on the hospital, and were interpreted according to Clinical and Laboratory Standards Institute guidelines. Due to the known diminished reliability of automated vancomycin MIC measurements >2 µg/mL and because our focus was on susceptible isolates, we only considered isolates with MICs no greater than 2 µg/mL. Similarly, we did not include those having uninterpretable values (eg, a reported MIC of “≤2 µg/mL” rather than 0.25, 1.0, etc.) in our definition of PVSSA. *S. aureus* (SA) isolates were also stratified on the basis of methicillin susceptibility.

We determined both proportion- and rate-based measures of PVSSA incidence [18, 19]. The proportion was defined as the number of PVSSA (1.5 µg/mL < MIC ≤ 2 µg/mL) samples per 100 VSSA (MIC ≤ 2 µg/mL) isolates, and the rate was defined as the number of PVSSA isolates per 1000 patient encounters.

**Antistaphylococcal Drug Use**

Inpatient and outpatient prescription rates (ie, prescriptions per 1000 encounters) from January 2010–December 2015 were calculated for 8 key antistaphylococcal compounds: vancomycin, daptomycin, linezolid, doxycycline, trimethoprim-sulfamethoxazole, cefazolin, cephalexin, and nafcillin. We evaluated associations with various prescription rates both within the current time period (ie, rate of prescription in the same month as the rate of PVSSA) and lagged 1 month (ie, rate of prescription in the previous month compared with the rate of PVSSA in the current month).

**Trends in Staphylococcal Resistance and Antistaphylococcal Use**

Our goal was to develop a method for semi-automated trending and predicting incidences of PVSSA across large health...
care networks using an EHR network. To demonstrate the usefulness of this approach, we sought to (1) determine trends in PVSSA incidence rates and proportions over a 6-year observation period, (2) test whether PVSSA incidence differed geospatially or by facility type (referral or community hospital), and (3) determine consumption trends for relevant therapeutics. To ensure that this approach wasn’t limited to a single drug-bug combination, we performed the same analyses with a different antistaphylococcal drug. We examined whether the proportions of MRSA and MSSA isolates that were also PVSSA were significantly different using the chi-square test. Comparisons of VSSA and PVSSA incidences were performed using the 2-sample proportion test.

In addition, we used 2 methods to analyze and report trends in antistaphylococcal use and resistance, time series analysis and the autoregressive integrated moving average (ARIMA). We then used generalized linear regression to see if results from all methods were concordant, and to see if any associations existed between drug use and resistance. Time series analysis can reveal trends in historical observations of a variable of interest and forecast that variable’s behavior in the future [20–23]. Seasonal trend decomposition using Loess (STL) is a mathematical procedure to divide time series data into 3 components: seasonal variation, a trend, and random noise. ARIMA uses an autoregressive moving average to trend values of a variable of interest based on its past observed values. PVSSA incidence levels were predicted with the seasonal ARIMA models using the adjusted Akaike information criterion as an objective function. The optimal model was then fitted to in-sample data and used to generate forecasts about the data series’ behavior 24 months into the future (January 2016 through December 2017).

Trends in prescription rates were extracted using STL decomposition, and their significance was assessed using basic Mann-Kendall tests. Pearson’s correlation coefficient was calculated to assess the robustness of results under differing comparative measures.

Composite time series were disaggregated into seasonal, trend, and residual components using a local regression-based, Loess decomposition technique (STL) [24]. Seasonal and basic Mann-Kendall tests assessed the significance of trends in aggregate series and extracted trend components, respectively [25].

All time series–related analyses were performed using the R forecast package [26]. Other statistics were performed on R, version 3, and SAS, version 9 [27].

Generalized linear models were calculated using the PROC GLM statement in SAS. Each variable was assessed at the univariate level. Model building was accomplished in reverse stepwise fashion to arrive at the most parsimonious model. PVSSA rate and PVSSA percentage as outcome variables were modeled separately.

**RESULTS**

**Quality Control of Input Data, and Regional and Service-Specific Variation of PVSSA Incidences**

Six and a half million bacterial cultures were obtained from 230 million patient encounters during the 2010–2015 study period, yielding 81 840 unique (1 isolate per patient per month) VSSA isolates. The testing platform could not be confirmed for 8.0% of VSSA isolates, so these data were excluded from further analysis (Figure 1). Antibiotic susceptibilities of the remaining VSSA isolates were assayed on 3 platforms; 58.2% of these were tested on Vitek, 19.8% on MicroScan, and 14.0% on Phoenix. Initial trend analysis using combined data collected on all 3 platforms suggested that the incidence of VSSA was increasing at a biologically implausible rate, inconsistent with trends reported in other US populations or in previous reports of the DoD population [16, 28–30]. Therefore, for the final analysis, we excluded results collected on MicroScan from further analysis because this platform reports erroneously high vancomycin MICs, upwardly skewing the apparent number of PVSSA isolates [11]. This platform-driven erroneous effect and trend are illustrated in Supplementary Figure 1 and explained in more detail in the “Discussion” section.

Reliable vancomycin susceptibility data from the Phoenix or Vitek instruments were therefore available for 58 558 unique clinical isolates.
VSSA rates and PVSSA proportions significantly differed between geographic regions and military branch. The highest rates of VSSA were at Navy and Army facilities in the eastern United States, and the highest proportions of PVSSA occurred at naval facilities in the northwest and southeast.

Overall, VSSA and PVSSA incidences were significantly higher in the South, and proportions of VSSA were significantly lower in the North. See incidence_by_region.xlsx in the Supplementary Data files. The rates and proportions of PVSSA were significantly different between Navy/Army and Navy/Air Force, but not between Army/Air Force (See incidence_by_service.xlsx in the Supplementary Data files).

**Trends in PVSSA Incidences and Antistaphylococcal Use**

The incidence rates of VSSA and PVSSA decreased over the study period (Figure 2, top and middle panels). Furthermore, the proportion of VSSA isolates that were PVSSA also decreased from 2010 to 2015 (Figure 2, bottom panel).

These downward trends were observed throughout the DoD and did not vary by military branch or facility type (community or referral) (data not shown). Rate-based PVSSA incidence had a strong seasonal component, peaking in roughly late summer, the nadir being during the late fall/early winter (data not shown). Seasonal variation was much less pronounced for proportion-based PVSSA incidence. All usage trends of the 8 antistaphylococcal antibiotics were downward or flat (Figure 3).

It was difficult to infer contributory relationships between antibiotic use and PVSSA incident proportions as the trends in both fluctuated in the same directions. Therefore, we compared their relative rates of change, that is, the number of prescriptions per month, with the monthly incident proportion of PVSSA (Figure 4). The red lines indicate the overall trend. A positive slope indicates that the denominator (PVSSA incidence) was decreasing faster than the numerator (number of prescriptions) was decreasing.

**SAVANT and Other Combinations**

We performed the same analyses with a different antistaphylococcal drug as an extra control or validation. We chose trimethoprim-sulfamethoxazole because it is one of the most frequently prescribed agents, it is primarily used for *Staphylococcus* infections, (unlike doxycycline, which is heavily used for malaria prophylaxis in this population), and because there are prior studies of resistance trends that we could use as frames of reference [31, 32]. Trends of incidence rates and proportions of trimethoprim-sulfamethoxazole-resistant *S. aureus* over the same period are not shown.

**Linear Regression**

As a second type of validation, we then compared how STL- and ARIMA-based results compared with those obtained by a more commonly used analysis, linear regression. Generalized linear regression analyses revealed trends in PVSSA incidence and antistaphylococcal compound usage that agreed with trends determined by the STL and ARIMA methods (Table 1).

Using either rate or proportion of PVSSA as the outcome variable, we found that both were also decreasing over time (Table 1, black bolding). Looking at pathogen-drug associations, PVSSA rate was positively associated with trimethoprim-sulfamethoxazole and vancomycin use (Table 1, green bolding) and negatively associated with cephalexin (Table 1, red bolding). PVSSA percentage was positively associated with cefazolin and trimethoprim-sulfamethoxazole (Table 1, purple bolding) and negatively associated with nafcillin (Table 1, orange bolding). Results of lagged prescription rates were similar to the current prescription rates (data available from the corresponding author).

**DISCUSSION**

As the JC and government agencies mandate new ASP standards and conditions of participation for reimbursement in acute and long-term care facilities [3, 4, 33], semi- or fully automated analysis of antibiotic use-resistance relationships would facilitate regulatory and reporting compliance. Here, we demonstrate an approach that clinical laboratories and integrated health care networks can use to monitor such relationships with minimal additional investment in their existing electronic health record or laboratory information system infrastructure. Furthermore, SAVANT can monitor trends for antimicrobial-pathogen combinations other than vancomycin and *S. aureus*. Three elements are required: the free program R, an electronic health record system, and an epidemiologist or biostatistician. In this case, both the pathogen of interest (PVSSA) and the usage of antistaphylococcal antibiotics decreased over the observation period, but PVSSA decreased significantly faster than antibiotic use. Five of the 8 antistaphylococcal drugs studied associated (either positively or negatively) with PVSSA proportions or rates. We also examined whether there might be a delay between antibiotic exposure and observed changes in PVSSA frequency by stratifying the results via a 1-month and 6-month time-lagged approach. This did not change the overall results, nor did stratification by methicillin susceptibility.

Use-resistance relationships have been reported previously, and our results in this study were congruent with those studies [17, 32]. Similar to previous reports, we found that incidences and trends of *S. aureus* varied by season and geographic region [28, 30, 34]. Infection prevention and surveillance are not fully standardized or uniformly applied across all 3 services. Certain locations may have more intense activity due to research studies or performance improvement initiatives [35–37]. This could account for the differences between the 3 military branches. However, other investigators do not believe that differential application of infection prevention strategies accounted for the regional differences they observed [30]. They posit that bio-ecologic or molecular/clonal differences might be a major reason.
Military training populations are at risk for skin and soft tissue infections caused by *S. aureus*, especially those in close living conditions [35–37]. In this observation, regions that had Army bases with the largest numbers of basic trainees and/or Naval bases that supported submarines (northwest and southeast) had higher incidences of *S. aureus*. Based on time series analysis and generalized linear regression, the Air Force had the lowest incidences of *S. aureus* while the Army and Navy had higher amounts. In the Air Force, living conditions are generally more advanced (access to showers) during deployments, and basic training is less physical or trauma-prone, resulting in fewer wounds and less skin irritation. As most of the isolates in this study were from wounds or skin and soft tissue infections, the timing was similar to other studies with peaks in the hotter,
The seasonal variation we observed was more pronounced in incidence rates than incidence proportions, so perhaps there were more patients with skin diseases or injuries during those times.

Our results are notable for several reasons. First, they were derived from one of the largest microbiological data sets and a large, geographically dispersed managed care network in the United States. Epidemiologists can apply a “plug and play” approach by analogizing the branches of the military to their local/regional integrated health or hospital networks (i.e., replace Army with Ascension, Navy with Kaiser Permanente, and Air Force with Hospital Corporation of America); all DoD hospitals are required to maintain JC accreditation standards and are increasingly mandated to participate in national reporting and stewardship requirements such as the National Health Safety Network.

Second, clinical practitioners are generally more concerned with proportions as a means to guide empirical therapy, while epidemiologists and/or public policy makers are often more interested in the burden of resistance in a population at a given point in time, which is arguably better captured using rates [19]. Therefore, to accommodate the interests of both groups, we used 2 measures of PVSSA incidence: (1) the proportion of PVSSA relative to 100 vancomycin-susceptible S. aureus isolates tested and (2) the rate of PVSSA isolates per inpatient per 1000 days.

Third, the MicroScan has been implicated in potentially overcalling true vancomycin MICs of 1 µg/mL for S. aureus [11], and our findings were consistent with this (Supplementary Figure 1).

Figure 3. Antistaphylococcal antibiotic usage trends. Time series analysis using the autoregressive integrated moving average procedure of prescriptions per 1000 patients for the 8 most commonly prescribed antistaphylococcal drugs. Dark blue and light blue shading indicate the 95% and 80% confidence intervals, respectively.
The true incidence of PVSSA in our study was less than 2%, but when we initially included the MicroScan data, we obtained an erroneous incidence of almost 50%. Reportedly, newer panels that have been released since these data were acquired and MicroScan-derived data for vancomycin-

Staphylococcus should be included in future approaches. Furthermore, that MicroScan limitation would not apply to other drug-bug combinations such as carbapenem-

Enterobacteriaceae.

An important limitation of this study is the that fact that we used the number of prescriptions for outpatients and the number of physician orders for inpatients as proxies for actual amounts of antibiotics consumed instead of days of therapy or defined daily dose. This was unavoidable in the case of outpatient use. The number and dispersion of facilities in the health care system made it nearly impossible to get precise patient-days or patient-years of inpatient antibiotic usage for the entire system. However,

Figure 4. Trends in antibiotic usage relative to Staphylococcus aureus incidence. Each panel, with a red trend line, show plots of prescriptions per patient vs percentage of problematic vancomycin-susceptible Staphylococcus aureus (PVSSA) among vancomycin-susceptible S. aureus (VSSA). Each dot is the ratio of the number of prescriptions to the percent vancomycin-susceptible Staphylococcus aureus that were PVSSA. A positive trend indicates the denominator (proportion of PVSSA) is decreasing more rapidly than the numerator (antibiotic usage). Trend lines were derived using seasonal trend decomposition using Loess time series analysis.
Table 1. Trends in PVSSA Incidence and Antistaphylococcal Compound Usage

| Variable             | Estimate Unadjusted | PValue Unadjusted | Estimate Adjusted | PValue Adjusted |
|----------------------|---------------------|------------------|-------------------|-----------------|
|                      |                     |                  |                   |                 |
| Date                 | –0.00003            | <.0001           | –0.0001           | .01             |
| Quarter              |                     |                  |                   |                 |
| First                | Ref.                | .40              |                   |                 |
| Second               | –0.002              | .60              |                   |                 |
| Third                | 0.003               | .10              |                   |                 |
| Last                 | –0.001              | .60              |                   |                 |
| Various Prescription Rates |               |                  |                   |                 |
| CFZ rate             | 0.001               | .001             |                   |                 |
| LEX rate             | 0.003               | .004             | –0.004            | .0007           |
| DOX rate             | 0.0002              | .55              |                   |                 |
| DAP rate             | 0.051               | .12              |                   |                 |
| NAF rate             | –0.017              | .69              |                   |                 |
| LZD rate             | 0.037               | .03              |                   |                 |
| TMP rate             | 0.007               | <0.001           | 0.007             | <.001           |
| VAN rate             | 0.005               | .002             | 0.008             | <.001           |

Black bolding: both rate and proportion of PVSSA were decreasing over time. Green bolding: PVSSA rate was positively associated with trimethoprim-sulfamethoxazole and vancomycin use. Red bolding: PVSSA rate was negatively associated with cephalexin. Purple bolding: PVSSA percentage was positively associated with cefazolin and trimethoprim-sulfamethoxazole. Orange bolding: PVSSA percentage was negatively associated with nafcillin.

Abbreviations: CFZ, cefazolin; DAP, daptomycin; DOX, doxycycline; LEX, cephalexin; LZD, linezolid; NAF, nafcillin; TMP, trimethoprim; VAN, vancomycin.

to make querying the full DoD electronic health records system for such drug usage data feasible, this potential tradeoff in accuracy was required. Furthermore, unlike the DoD, an increasing number of hospitals and managed care systems do have ready access to days of therapy and defined daily doses, which would permit more robust assessment of use-resistance relationships. However, our goal was not to provide a standardized defined daily dose metric for comparison with other networks or countries. Nor did we seek to definitively determine whether usage of antistaphylococcal agents correlated with increases in mean minimum inhibitory concentrations of a key therapeutic (vancomycin) among S. aureus.

To be clear, although the cost to implement SAVANT is negligible, some expertise is required, but most larger hospitals and nearly all multicenter health networks already have that expertise in the form of a microbiologist and an epidemiologist or data analyst. Another limitation of SAVANT is that most commercially available electronic health care systems do not provide ready access to advanced types of antibiotic usage data such as defined daily doses or days of therapy. Therefore, some level of algorithm development or purchase of the software package is required. However, basic tallies of number of prescriptions and numbers of targeted isolates meeting a certain predetermined characteristic can be readily queried by the pharmacy and microbiology laboratory. Additionally, many of the major vendors have on-site support staff for developing electronic best practice alerts and automated user-defined queries. For example, our regional health system in Rochester, New York, like many others, uses EPIC CareConnect, which provides “physician and clinical builders.” They are a vendor-certified team whose responsibility is to participate in the design, development, and implementation of tools to perform the clinical activities of the electronic medical record. They have participated in automating monthly “days of antibiotic therapy” reports for the stewardship program.

Despite these limitations, this study shows how SAVANT is a low-cost, useful approach for enhancing antimicrobial stewardship efforts. Hospital and health care networks can utilize this technique on electronic medical information systems regardless of the microbiology identification and susceptibility testing platform or bacteria-antibiotic combination.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Disclaimer. The material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or the US Government.

Financial support. This work was supported by US Army Medical Command grant MedCom 15-042 and Global Emerging Infections Surveillance grant 20160280023 to E.L. The funding source had no role in the study design, collection, analysis and interpretation of data, writing of the manuscript, or in the decision to submit the paper for publication.
Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References
1. President’s Council on Advisors on Science and Technology. National action plan for combating antibiotic-resistant bacteria. Available at: https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf. Accessed 5 September 2017.
2. World Health Organization. Antimicrobial resistance: global report on surveillance 2014. Available at: http://apps.who.int/iris/bitstr eam/10665/112642/1/9789241564748_eng.pdf?ua=1. Accessed 5 September 2017.
3. Joint Commission on Hospital Accreditation. APPROVED: new antimicrobial stewardship standard. Jt Comm Pract 2016; 36;1, 3–4, 8.
4. Centers for Medicare and Medicaid Services. CMS issues proposed rule that prohibits discrimination, reduces hospital acquired conditions, and promotes anti-biotic stewardship in hospitals. Available at: https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-06-13.html. Accessed 5 September 2017.
5. Stenehjem E, Hynn DY, Septimus E, et al. Antibiotic stewardship in small hospitals: barriers and potential solutions. Clin Infect Dis 2017; 65:691–6.
6. Sexton DJ, Moehring RW. Implementation of antimicrobial stewardship programs in small community hospitals: recognizing the barriers and meeting the challenge. Clin Infect Dis 2017; 65:697–8.
7. Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999-2005. Emerg Infect Dis 2007; 13:1840–6.
8. Nienaber JJ, Sharma Kuinkel BK, Clarke-Pearson M, et al. International Collaboration on Endocarditis-Microbiology Investigators. Methicillin-susceptible Staphylococcus aureus endocarditis isolates are associated with clonal complex 30 genotype and a distinct repertoire of enterotoxins and adhesins. J Infect Dis 2011; 204:704–13.
9. Bowler VG Jr, Miro JM, Hoen B, et al. ICE Investigators. Staphylococcus aureus endocarditis: a consequence of medical progress. JAMA 2005; 293:3012–21.
10. Daum RS. Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. N Engl J Med 2007; 357:380–90.
11. Rybak MJ, Vidaillac C, Sader HS, et al. Evaluation of vancomycin susceptibility testing for methicillin-resistant Staphylococcus aureus: comparison of Etest and three automated testing methods. J Clin Microbiol 2013; 51:2077–81.
12. Holmes NE, Turnidge JD, Munchho WJ, et al. Antibiotic choice may not explain poorer outcomes in patients with Staphylococcus aureus bacteremia and high vancomycin minimum inhibitory concentrations. J Infect Dis 2011; 204:340–7.
13. van Hall SJ, Bowler VG Jr. Is it time to replace vancomycin in the treatment of methicillin-resistant Staphylococcus aureus infections? Clin Infect Dis 2013; 56:1779–88.
14. Dhand A, Sakoulas G. Reduced vancomycin susceptibility among clinical Staphylococcus aureus isolates (‘the MIC Creep’): implications for therapy. F1000 Med Rep 2012; 4:4.
15. Haver sp, Bouchillon SK, Hoban DJ, et al. Rising incidence of Staphylococcus aureus with reduced susceptibility to vancomycin and susceptibility to antibiotics: a global analysis 2004–2009. Int J Antimicrob Agents 2011; 37:219–24.
16. Landrurn ML, Neumann C, Cook C, et al. Epidemiology of Staphylococcus aureus blood and skin and soft tissue infections in the US military health system. 2005–2010. JAMA 2012; 308:50–9.
17. Lesho EP, Clifford RJ, Chukwuma U, et al. Carbapenem-resistant Enterobacteriaceae and the correlation between carbapenem and fluoroquinolone usage and resistance in the US military health system. Diagn Microbiol Infect Dis 2015; 81:119–25.
18. Hinder JE, Stelling J. Analysis and presentation of cumulative antibiograms: a new consensus guideline from the Clinical and Laboratory Standards Institute. Clin Infect Dis 2007; 44:867–73.
19. Schwaber MJ, De-Medina T, Carmeli Y. Epidemiological interpretation of anti-biotic resistance studies—what are we missing? Nat Rev Microbiol 2004; 2:979–83.
20. Crabbtree BF, Ray SC, Schmidt PM, et al. The individual over time: time series applications in health care research. J Clin Epidemiol 1990; 43:241–60.
21. Gharbi M, Moore LS, Gilchrist M, et al. Forecasting carbapenem resistance from antimicrobial consumption surveillance: lessons learnt from an OXA-48-producing Klebsiella pneumoniae outbreak in a West London renal unit. Int J Antimicrob Agents 2015; 46:150–6.
22. Willmann M, Marschal M, Holzl F, et al. Time series analysis as a tool to predict the impact of antimicrobial restriction in antibiotic stewardship programs using the example of multidrug-resistant Pseudomonas aeruginosa. Antimicrob Agents Chemother 2013; 57:1797–803.
23. Polgreen PM, Yang M, Kunzt JL, et al. Using oral vancomycin prescriptions as a proxy measure for Clostridium difficile infections: a spatial and time series analysis. Infect Control Hosp Epidemiol 2011; 32:723–6.
24. Cleveland RB, Cleveland WS, McRae JE, Terpenning I. STL: a seasonal-trend decomposition procedure based on Loess. J Offic Stat 1990; 6:3–73.
25. Mann HB. Nonparametric tests against trend. Econometrika 1945; 13:245–59.
26. Hyndman RJ, Khandakar Y. Automatic time series forecasting: the forecast package for R. J Stat Softw 2008; 27:22.
27. R Core Team. R: A Language and Environment for Statistical Computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing. 2015.
28. Sutter DE, Milburn E, Chukwuma U, et al. Changing susceptibility of Staphylococcus aureus in a US pediatric population. Pediatrics 2016; 137:e20153099.
29. Ray GT, Suaya JA, Baxter R. Microbiology of skin and soft tissue infections in the age of community-acquired methicillin-resistant Staphylococcus aureus. Diagn Microbiol Infect Dis 2013; 76:24–30.
30. David MZ, Daum RS, Bayer AS, et al. Staphylococcus aureus bacteremia at 5 US academic medical centers, 2008–2011: significant geographic variation in community-onset infections. Clin Infect Dis 2014; 59:798–807.
31. Nuryadi D, Schäfer J, Friedrich-Janicek B, et al. Predominance of difG as determinant of trimethoprim resistance in imported Staphylococcus aureus. Clin Microbiol Infect 2015; 21:1095.e5–9.
32. Wang A, Daneman N, Tan C, et al. Evaluating the relationship between hospital antibiotic use and antibiotic resistance in common nosocomial pathogens. Infect Control Hosp Epidemiol 2017; 38:457–63.
33. Society for Healthcare Epidemiology of America. Infectious Diseases Society of America, Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS), Infect Control Hosp Epidemiol 2012; 33:322–7.
34. Leekha S, Diekema DJ, Perencevich EN. Seasonality of staphylococcal infections. Clin Microbiol Infect 2012; 18:927–33.
35. Morrison SM, Blesing CR, Millar EV, et al. Evaluation of methicillin-resistant Staphylococcus aureus skin and soft-tissue infection prevention strategies at a military training center. Infect Control Hosp Epidemiol 2013; 34:841–3.
36. Ellis MW, Griffith ME, Dookey DP, et al. Targeted intranasal mupirocin to pre-vent colonization and infection by community-associated methicillin-resistant Staphylococcus aureus strains in soldiers: a cluster randomized controlled trial. Antimicrob Agents Chemother 2007; 51:359I–8.
37. Whitman TJ, Herlihy RK, Schlett CD, et al. Chlorhexidine-impregnated cloths to prevent skin and soft-tissue infection in Marine recruits: a cluster-randomized, double-blind, controlled effectiveness trial. Infect Control Hosp Epidemiol 2010; 31:1207–15.