HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2019 May 02.

Published in final edited form as:

Clin Infect Dis. 2018 May 02; 66(10): 1535–1539. doi:10.1093/cid/cix1056.

Regional Epidemiology of Methicillin-Resistant *Staphylococcus aureus* Among Adult Intensive Care Unit Patients Following State-Mandated Active Surveillance

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Abstract

Background—In 2007, Illinois became the first state in the United States to mandate active surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA). The Illinois law applies to intensive care unit (ICU) patients; contact precautions are required for patients found to be MRSA colonized. However, the effectiveness of a legislated "search and isolate" approach to reduce MRSA burden among critically ill patients is uncertain. We evaluated whether the prevalence of MRSA colonization declined in the 5 years after the start of mandatory active surveillance.

Methods—All hospitals with an ICU having ≥10 beds in Chicago, Illinois, were eligible to participate in single-day serial point prevalence surveys. We assessed MRSA colonization among adult ICU patients present at time of survey using nasal and inguinal swab cultures. The primary outcome was region-wide MRSA colonization prevalence over time.

Results—All 25 eligible hospitals (51 ICUs) participated in serial point prevalence surveys over 8 survey periods (2008–2013). A total of 3909 adult ICU patients participated in the point prevalence surveys, with 432 (11.1%) found to be colonized with MRSA (95% confidence interval [CI], 10.1%–12.0%). The MRSA colonization prevalence among patients was unchanged during the study period; year-over-year relative risk for MRSA colonization was 0.97 (95% CI, .89–1.05; $P = .48$).

Conclusions—MRSA colonization prevalence among critically ill adult patients did not decline during the time period following legislatively mandated MRSA active surveillance. Our findings highlight the limits of legislated MRSA active surveillance as a strategy to reduce MRSA colonization burden among ICU patients.

Publisher's Disclaimer: ***Disclaimer*.** The funding source provided technical assistance in obtaining ethical review and suggestions for study design and analysis/interpretation of the data. Otherwise, the funding source had no role in the conduct of the study, collection or management of the data, preparation, review or approval of the manuscript, or the decision to submit the manuscript for publication. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of healthcare-onset infections in the intensive care unit (ICU) and is a target for reduction efforts because of its virulence and reduced antibiotic treatment options [1, 2]. Asymptomatic MRSA colonization is a precursor to invasive disease, and colonized patients can transmit MRSA via contaminated healthcare workers to other patients [3, 4].

An MRSA "search and isolate" strategy uses active surveillance to identify patients who are asymptomatically colonized with MRSA to place them in contact precautions. The "search and isolate" strategy has been used to control MRSA during outbreaks [5], but its role in controlling MRSA in the nonoutbreak (endemic) setting, which is the current status of most hospitals in the United States, is controversial [6].

In October 2007, Illinois became the first of several states in the United States to mandate hospitals to perform MRSA active surveillance [7, 8]. The Illinois law applies to all ICU patients; contact precautions are required for patients who test MRSA positive (MRSA Screening and Reporting Act) [9]. After the law went into effect, we performed a series of regional MRSA point prevalence surveys among adult ICU patients in Chicago, Illinois. We evaluated whether the prevalence of MRSA colonization would decline in the 5 years after the start of mandatory active surveillance.

METHODS

Subject Recruitment

In 2008, we invited all 25 hospitals in Chicago, Illinois, with ≥10 ICU beds to participate in regional point prevalence surveys for MRSA colonization. Over 5 years, we performed 8 regionwide point prevalence surveys, twice-yearly between June 2008 and July 2011, then yearly in 2012 and 2013. During each survey period, each hospital participated in a single-day survey on a rolling basis until all hospitals were surveyed. All patients in adult ICUs who were present at time of survey were eligible for participation. Written informed consent was waived. For patients with decisional capacity, we provided a scripted explanation of the project's rationale and asked for verbal agreement to participate.

Ethical Review

This surveillance project was reviewed at the Centers for Disease Control and Prevention by the National Center for Emerging and Zoonotic Diseases in accordance with institutional policy and was determined not to meet the regulatory definition of research (under 45 CFR §46.102[d]), and therefore it was not subject to institutional review board requirements. Furthermore, institutional review boards at participating hospitals (where applicable) reviewed the protocol and either determined that the survey was not human subjects research or approved the protocol with the requirement for written informed consent waived.

Culture and Data Collection

We provided facilities with standardized culturing supplies, data collection tools, and training. Local hospital staff (infection preventionists or ICU nurses) and 1 investigator (R. D. L.) collected specimens. Two body sites were cultured for MRSA: 1 swab was placed in a

nostril and rotated 3 times; a second swab was obtained from the inguinal/groin skin (10 cm × 10 cm).

At the time of specimen collection, the following patient characteristics were recorded: age, ICU length of stay (at the time of survey), sex, mechanical ventilation, contact precautions (for any reason), and the state-mandated hospital-reported MRSA screening result. If the hospital MRSA screening result was not available at the time of survey, the result was recorded as "pending" and hospitals reported the final MRSA result when available.

At each survey, hospitals reported facility-level infection control practice, including whether MRSA screening was culture based vs polymerase chain reaction (PCR) based, whether broth enrichment was used, and whether patients were placed in contact precautions while awaiting MRSA screening culture results. Hospitals also reported whether daily chlorhexidine gluconate bathing was used for ICU patients, and whether mupirocin was routinely used for de-colonization. Facility-level variables were time-varying in our analyses to account for changes in practices over time.

Laboratory Methods

We processed specimens in a central laboratory within 6 hours of collection. We cultured nasal and inguinal swab specimens in separate tubes of tryptic soy broth with 6.5% sodium chloride (Remel, San Diego, California). After overnight incubation, we inoculated the broth onto chromogenic MRSASelect agar (Bio- Rad, Hercules, California). After subculture, we confirmed *S. aureus* by colony morphology and standard biochemical methods. Oxacillin susceptibility was determined using the cefoxitin disk test [10]. We subtyped all MRSA isolates by pulsed-field gel electrophoresis [11] and classified MRSA isolates as community-associated (CA) MRSA or healthcare-associated MRSA by visual comparison of surveillance isolate pulsotypes with pulsotypes of well-characterized MRSA strains [12, 13]. We defined CA MRSA clonal subtypes as USA300/400/1000/1100. We determined mupirocin susceptibility using the E-test method (bioMerieux, Marcy-l'Etoile, France) with the following definitions: high-level resistance, minimum inhibitory concentration (MIC) ≥512 μg/mL; low-level resistance, MIC = 8–64 μg/mL; susceptible, MIC ≤4 μg/mL [14].

Statistical Analyses

This study was predicated on at least 80% power to detect a clinically meaningful change from 10% to 7% MRSA colonization prevalence among 2800 patients in adult ICUs over the surveillance period, with an α level of .05 in a 2-sided $\chi 2$ test of proportions. The actual obtained sample of 3909 subjects was sufficient to detect an absolute difference of 1.9% (eg, 10% vs 8.1%). We used SAS version 9.3 (SAS Institute, Cary, North Carolina) for all analyses except where noted. We calculated 95% confidence intervals (CIs) of proportions using exact binomial methods. For unadjusted trend analysis, we used the Cochran-Armitage test of trend. For primary outcome analysis, we constructed multilevel regression models with a binomial distribution to model prevalence trends, accounting for ICU level correlation across time (using the R lme4 package, R version 3.3.1; http://CRAN.R-project.org/).

RESULTS

In total, 25 of 25 eligible hospitals voluntarily participated in the point prevalence surveys, including 4 university and 21 nonuniversity institutions. There was a median of 1 ICU per hospital (range, 1–6). Fifty-one distinct ICUs participated, represented by the following unit types: 17 medical/surgical, 9 medical, 9 surgical, 6 coronary care, 5 neurology/neurosurgery, 2 cardiothoracic surgery, 2 burn, and 1 trauma.

The number of hospitals using routine daily chlorhexidine gluconate bathing in at least 1 ICU grew from 5 hospitals to 17 hospitals over the 5-year study period. The percentage of study patients who were in an ICU using chlorhexidine gluconate bathing grew from 28% to a peak of 59% by year 3 ($P < .001$ for trend). No hospital ICUs routinely used mupirocin for decolonization.

The overall participation rate in the point prevalence surveys among eligible adult ICU patients was high across the survey period (96% [3909/4091]). Patient demographics are listed in Table 1.

Hospital-Reported Surveillance for MRSA

All 25 hospitals reported that they complied with the 210 ILCS 83/ legislation by performing active surveillance testing for patients with no known history of MRSA colonization at the time of ICU admission. All hospitals reported admission MRSA screening using nares culture; none cultured extranasal sites, and none routinely screened at any time-point subsequent to patient admission. Thirteen hospitals reported using PCR-based MRSA testing at some point during the study; the proportion of study patients screened by PCR grew from 42% to 50% during the study period ($P = .003$ for trend). No hospital used broth enrichment of MRSA surveillance cultures. All hospitals placed known MRSA colonized patients in contact precautions; none did so preemptively while awaiting MRSA screening results.

We found high rates of compliance with the state law by hospitals across the study period, with 93% of patients in the study cohort receiving admission active surveillance testing for MRSA. The overall admission prevalence of MRSA colonization, as reported by hospitals, was 9.7% (95% CI, 8.8%–10.8%), which was unchanged over time ($P = .95$ for trend).

Point Prevalence Survey Results

Of 3909 adult ICU patients who participated in the point prevalence surveys, 432 (11.1%) were colonized with MRSA (95% CI, 10.1%–12.0%). The MRSA colonization prevalence among patients was unchanged during the study period (Figure 1; year-over-year relative risk for MRSA colonization was 0.97 (95% CI, .89–1.05; $P = .48$). The MRSA prevalence trend remained nonsignificant after adjusting for chlorhexidine gluconate and PCR use over time; furthermore, we did not detect any interactions, including time by chlorhexidine gluconate bathing status and time by PCR status.

CA MRSA Genotypes and Mupirocin Resistance

From point prevalence surveys, CA MRSA genotypes represented 39% (169/432) of all MRSA-positive patients. USA300 represented 97% (164/169) of CA MRSA genotypes.

During the study period, the proportion of prevalent MRSA isolates represented by CA MRSA genotypes did not change significantly.

Of 432 MRSA-positive patients, 17 (4%) carried MRSA with high-level mupirocin resistance, and an additional 17 (4%) carried MRSA with low-level mupirocin resistance. Low-level mupirocin resistance was stable over time, while the high-level mupirocin resistance increased, peaking at 9.5% by the final survey period ($P = .03$ for trend; Table 2). We did not find evidence of hospital clustering of high-level mupirocin-resistant MRSA isolates from the last 2 years of the study period when resistance rates were highest, as the 8 resistant isolates were recovered from 8 different hospitals.

Effectiveness of Routine ICU Admission Screening: Contact Precautions

Among patients identified as MRSA-positive by point prevalence surveys, 57% (247/431) were in contact precautions at the time of survey. We assessed possible explanations for the 184 MRSA positive patients who were not in contact precautions: 15 (8%) never received an admission MRSA screen; 16 (9%) had a positive admission MRSA screen known at the time of the point prevalence survey and were in a lag period between positive test result and initiation of contact precautions; 27 (15%) had a pending admission culture at the time of point prevalence survey that eventually became MRSA positive, reflecting test turnaround time; and 126 (69%) had a negative admission MRSA culture, thus representing either admission MRSA screen insensitivity or ICU acquisition.

Performance Characteristics of Testing Different Body Sites for MRSA Colonization

We assessed the performance characteristics of testing body sites individually for MRSA carriage (nose vs groin) using the reference standard of being MRSA positive in any combination of the 2 body sites during point prevalence testing. For patients who had MRSA culture results available for both nose and groin sites, nasal culturing alone identified 84% (327/388) MRSA positive patients; 61 patients (16%) were nasal culture negative and groin culture positive. Nasal MRSA screening had a negative predictive value of 98% (95% CI, 97.6%–98.5%).

DISCUSSION

We evaluated the burden of MRSA colonization among adult ICU patients in the city of Chicago during the 5 years following state-mandated active surveillance for MRSA. Through serial comprehensive regional point prevalence surveys, we found that 11% of ICU patients were colonized with MRSA, and that MRSA colonization did not change significantly from year 1 to year 5 of the postintervention period. Our findings highlight the limits of legislated MRSA active surveillance as a strategy to reduce MRSA colonization burden among ICU patients.

We designed this study to assess the total burden of MRSA carriage in our region, rather than rely on a surrogate such as MRSA infection. This is an important distinction because most MRSA carrying patients are asymptomatic, with a proportion of patients going on to develop symptomatic MRSA infection. Thus, studies that solely assess MRSA infection outcomes do not capture the entire burden of MRSA carriage, and MRSA infection trends

can be confounded by the incremental adoption of infection prevention activities that reduce infections caused by all pathogens, not limited to MRSA (eg, improved central line insertion bundles and reduced invasive device utilization) [15–17].

Our inability to find a decrease in MRSA burden following mandated active surveillance is consistent with the only randomized controlled trial of MRSA active surveillance (Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units [STAR*ICU]) [18], which showed that active surveillance for MRSA in ICUs was not associated with a significant decrease in MRSA colonization or infection. Other large-scale implementations of mandated MRSA active surveillance, such as that occurring in Veteran Affairs hospitals [19] and in England's National Health Service Trust hospitals [20], have included several other confounding infection control interventions such as hand hygiene campaigns. Mathematical modeling suggests that a MRSA "search and isolate" strategy has a negligible effect on colonization prevalence, simply because the majority of patients colonized with MRSA in the ICU are already colonized at the time of admission, and endemic ICU transmission rates of MRSA are low in acute care hospitals [21–23].

The intent of active surveillance is to identify all MRSA colonized patients and place such patients on contact precautions to reduce cross-transmission and, ultimately, MRSA infection. Despite excellent hospital compliance with active surveillance, approximately 4 in 10 MRSA-colonized ICU patients were not in contact precautions at the time of cross-sectional surveys. Most of the contact precautions deficit was explained by either MRSA admission screen insensitivity or ICU acquisition, but our study test method (which was more sensitive than routine hospital testing) did not allow us to measure the relative contribution of the 2 possibilities. Hospitals could improve routine MRSA testing sensitivity (eg, testing more body sites or performing serial testing) to incrementally increase the proportion of MRSA-colonized patients on contact precautions. However, it is unclear whether higher levels of contact precautions would lead to decreased transmission and infection for endemic MRSA [24–28].

Our study has limitations. First, MRSA active surveillance legislation was mandatory for all facilities in our region, precluding us from having a concurrent nonintervention control group to directly quantify the effect of the active surveillance legislation. Nevertheless, our city-wide data are similar to hospital-specific data from the preintervention period [22]. Second, we assessed MRSA colonization prevalence, not infection, because active surveillance's most direct impact is to reduce transmission and thus colonization prevalence. Although the rate of MRSA infection is generally thought to be proportional to rate of MRSA colonization prevalence, other nonlegislated infection control practices such as chlorhexidine gluconate bathing and catheter insertion prevention bundles could further reduce the risk of subsequent MRSA infection. Third, we assessed MRSA prevalence in a region where MRSA is widely endemic both in the community and within healthcare facilities. Our findings may not apply to regions with lower endemic rates of MRSA.

Since the passage of the MRSA active surveillance mandate in Illinois, new data from the Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA (REDUCE-MRSA) trial has suggested that a universal decolonization approach (nasal

mupirocin plus chlorhexidine gluconate bathing for all ICU patients, with discontinuation of MRSA active surveillance) is superior to MRSA active surveillance and contact precautions (i.e., Illinois legislative mandate) for reducing MRSA burden among ICU patients [29]. Alternatives to mupirocin for universal nasal MRSA de-colonization, such as nasal iodophor, may be needed for regions such as Chicago where sporadic mupirocin resistance without routine mupirocin use approaches 10% [30, 31]. Importantly, we note that the legislation in Illinois, as currently written, does not allow hospitals to stop active surveillance while adopting the more effective universal decolonization approach as tested in REDUCE-MRSA, highlighting a major drawback to legislating specific hospital infection control practices.

In summary, we did not observe a significant decline in MRSA colonization prevalence during the time period following implementation of legislatively mandated MRSA active surveillance for ICU patients. We also identified barriers that hampered prompt use of contact precautions for MRSA-colonized patients despite mandatory active surveillance. Our city-wide observational findings, together with results from recent clinical trials [18, 29], suggest that it is time for states to reconsider the practice of legislating MRSA active surveillance.

Acknowledgments.

The authors acknowledge and thank the following for their participation in the point prevalence surveys: patients; infection preventionists at all participating hospitals, including Rosemary Albright, Pat Alexander, Karlyn Ali, Therese Antony, Terry Arceo, Nina Balbarin, Christine Balintona, Laura Bardowski, Rochelle Bello, Cate Berends, Amanda Bonebrake, Judy Bova, Annie Braggs, Steve Brash, Stephanie Burtun, Mary Alice Byrnes, Nenita Caballes, Carol Cagle, Pam Camporese, Rose Chavis, Theresa Chou, Sue Cienkus, Cari Coomer, Delia DeGuzman, Onofre Donceras, Aurea Enriquez, Janet Franck, Mary Beth Fry, Sharon Fung, Sylvia Garcia-Houchins, Gerry Genovese, Marge Gentile, Maryann Gierloff, Gregg Gonzaga, Ed Goodwin, Patty Graves, Paula Green, Elsie Hernandez, Melinda Intoy, James Kerridge, Ather Khadijah, Jean Kirk, Robin Larson, Mary Alice Lavin, Susan Lee, Dee Leonore, Jan Lepinski, Thelma Lim, Anne Malloy, Rachel Marrs, Donna McMullin, Margaret McNally, Kristen Metzger, Anessa Mikolajczak, Anna O'Donnell, Toni Oats, Renee Partida-McClenic, Violetta Pasinos, Joann Patton, Cynthia Perez, Maria Perez, Stacy Pur, Debra Quaka, Linda Rakoski, Nympha Ramos, Sandra Reiner, Marlene Roma, Asif Saiyed, Mary Santine, Kimberly Schelling, Barbara Schmitt, Carol Schultz, Rose Marie Semar, Helen Sethuraman, Christina Silkaitis, Liz Stutler, Sylvia Suarez-Ponce, Sonia Terry, Dorothy Thompson, Kerensa Vinson, Flora White, Katherine Wickman, Robin Young); and hospital epidemiologists, including Maureen Bolon, Andrew Cha, Emily Landon, James Malow, Sunita Mohapatra, Monica Sikka, Sharon Welbel, and Teresa Zembower.

Financial support. This work was supported by the CDC's Prevention Epicenters Program (grant numbers 5U01CI000327 and 5U54CK000161 to R. A. W.).

Potential conflicts of interest. M. Y. L. has received research support in the form of contributed product from OpGen and Sage Products (now part of Stryker Corporation), and has received an investigator-initiated grant from CareFusion Foundation (now part of BD). M. K. H. has received research support in the form of contributed product from Clorox, Medline, Molnlycke, OpGen, and Sage Products, and has received an investigator-initiated grant from Clorox. R. A. W. has received research support in the form of contributed product from Clorox, Medline, Molnlycke, and Sage Products. W. E. T. has received an investigator-initiated grant from CareFusion Foundation. All other authors report no potential conflicts.

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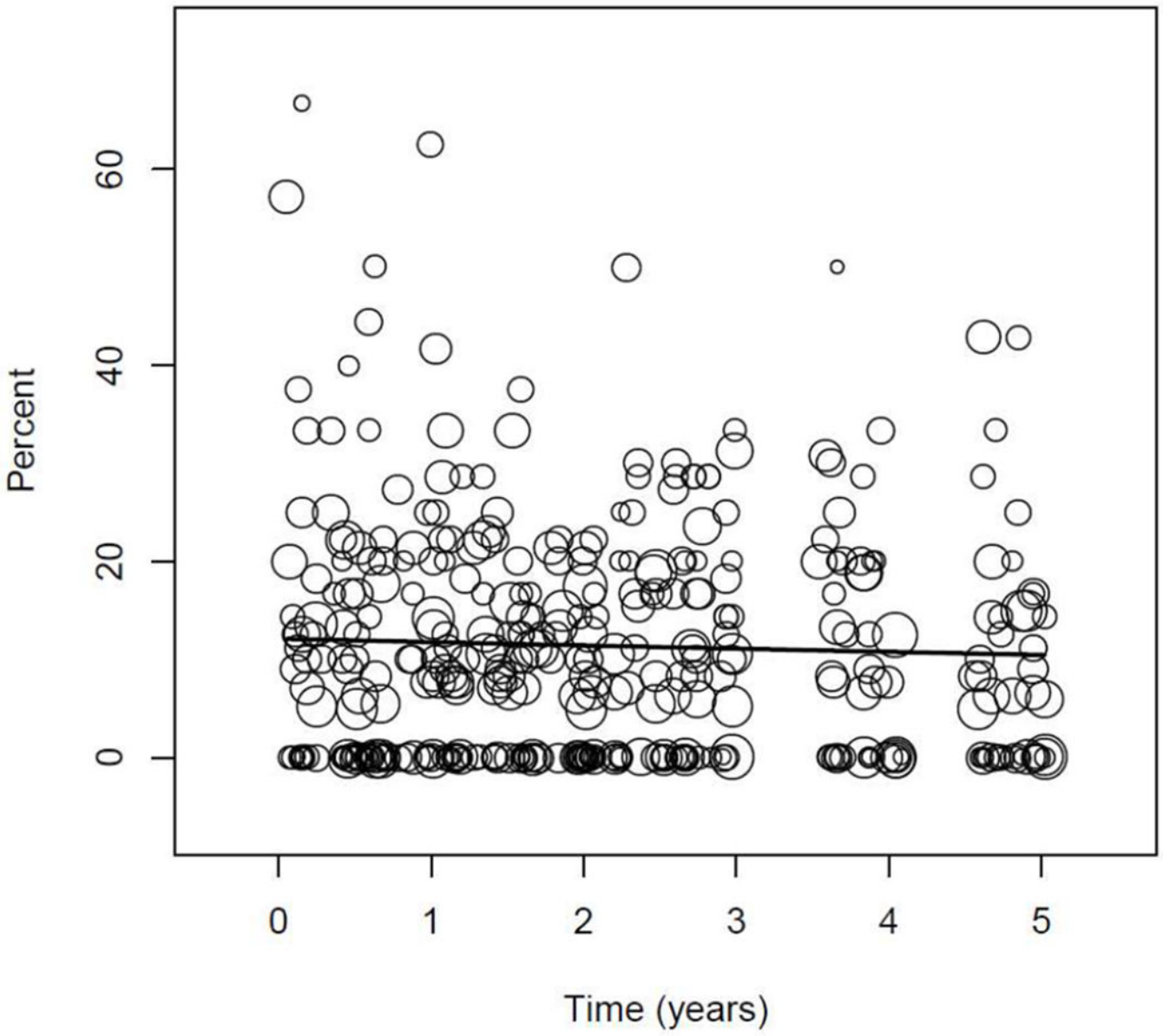

Figure 1.

Estimated methicillin-resistant *Staphylococcus aureus* (MRSA) colonization prevalence trend (solid line) for adult intensive care units during the 5-year study period; year-over-year relative risk for MRSA colonization was 0.97, 95% CI 0.89 to 1.05, *P*=0.48. Each circle represents a survey point at a single intensive care unit. Circle sizes are proportional to the number of patients contributing data at each survey point.

Table 1.

Patient characteristics of study cohort at the time of point prevalence survey

Covariate	Study cohort	
Length of stay[a], median day (IQR)	4	(2 – 9)
Male, n/N (%)	2142/3907	(55)
Age in years, median (IQR)	61	(49 – 73)
Ventilated, n/N (%)[a]	1393/3903	(36)
Contact isolation, n/N (%)[a]	995/3901	(26)

Note. IQR = Interquartile range.

[a]Intensive care unit length of stay, mechanical ventilation status, and contact isolation as measured at time of survey.

Table 2.

Prevalence of high level mupirocin resistance over time among patients colonized with methicillin resistant *Staphylococcus aureus*

	High level mupirocin resistance (n)	All MRSA+ patients (N)	High level mupirocin resistance, %
Year 1	3	125	2.4
Year 2	3	113	2.7
Year 3	3	103	2.9
Year 4	4	49	8.2
Year 5	4	42	9.5
Overall	**17**	**432**	**3.9**
Test of trend			P = 0.03