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Impact of Routine Intensive Care Unit Surveillance Cultures and Resultant Barrier Precautions on Hospital-Wide Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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Background. Serial interventions are often used to reduce the risk of health care–associated methicillin-resistant *Staphylococcus aureus* (MRSA) infections. To our knowledge, the relative impact of these interventions has not previously been ascertained.

Methods. We conducted a retrospective study of 4 major infection control interventions using an interrupted time series design to evaluate their impact on MRSA bacteremia in an 800-bed hospital with 8 intensive care units (ICUs). Interventions were introduced 1 at a time during a 9-year period and involved the promotion of compliance with maximal sterile barrier precautions during central venous catheter placement, the institution of alcohol-based hand rubs for hand disinfection, the introduction of a hand hygiene campaign, and the institution of routine nares surveillance cultures for MRSA in all ICUs for patients on ICU admission and weekly thereafter while in the ICU. Positive cultures resulted in the initiation of contact isolation precautions.
Using segmented regression analyses, we evaluated changes in monthly incidence and prevalence of MRSA bacteremia from their predicted values. Methicillin-susceptible *Staphylococcus aureus* bacteremia was monitored as a control.

Results. Routine surveillance cultures and subsequent contact isolation precautions resulted in substantial reductions in MRSA bacteremia in both ICUs and non-ICUs. In 16 months, the incidence density of MRSA bacteremia decreased by 75% in ICUs ($P = .007$) and by 40% in non-ICUs ($P = .008$), leading to a 67% hospital-wide reduction in the incidence density of MRSA bacteremia ($P = .002$). Methicillin-susceptible *S. aureus* bacteremia rates remained stable during this time. The other interventions were not associated with a statistically significant change in MRSA bacteremia.

Conclusions. Routine surveillance for MRSA in ICUs allowed earlier initiation of contact isolation precautions and was associated with large and statistically significant reductions in the incidence of MRSA bacteremia in the ICUs and hospital wide. In contrast, no similar decrease was attributable to the other infection control interventions.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the leading cause of health care–associated infections among clinically relevant, antibiotic-resistant pathogens [1]. By 2003, methicillin resistance among health care–associated infections due to *S. aureus* reached 60% among intensive care unit (ICU) patients and 50% among patients hospitalized in units other than the ICU (hereafter, referred to as non-ICU) [1–3].

MRSA acquisition is highly associated with subsequent infection. We previously found that 29% of newly detected MRSA carriers developed invasive disease within 18 months [4]. Nearly one-third of these infections involved bacteremia.

Several infection control practices have emerged over the years to prevent health care–associated transmission of and infection with pathogens, such as MRSA. Much of the seminal research has been highlighted in guidelines by the Healthcare Infection Control Practices Ad-

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visory Committee [5–7], the Infectious Diseases Society of America [5, 7], and the Society for Healthcare Epidemiology of America [5, 7–9]. Practice guidelines have included contact isolation precautions for patients harboring antibiotic-resistant organisms [6, 9], sterile barrier precautions during central venous catheter placement [7, 8], alcohol-based hand rubs for hand hygiene [5], and routine surveillance for MRSA and vancomycin-resistant enterococcus in areas where high-risk patients are hospitalized [8].

Hospitals commonly apply these infection control practices together. We conducted a 9-year retrospective study of the impact of the sequential implementation of 4 infection control interventions on MRSA bacteremia.

METHODS

Data collection. We used an interrupted time series design to evaluate the impact of 4 infection control prevention measures on MRSA bacteremia among adult patients admitted to Brigham and Women's Hospital (BWH; Boston, MA) from 1 January 1996 through 31 December 2004. These measures included a campaign to increase sterile barrier precautions during central venous catheter placement, the hospital-wide institution of alcohol-based hand rubs for hand disinfection, the introduction of a hand hygiene campaign, and the institution of routine nares surveillance for MRSA in all ICU patients on ICU admission and weekly thereafter while hospitalized in the ICU. These interventions were introduced one by one, which allowed for the opportunity to evaluate their individual and cumulative impacts. Aside from surveillance cultures, there were no new infection control interventions implemented that might have influenced MRSA transmission or bacteremia during the study period. All interventions continued through the end of the study period. This study was approved by the institutional review board at BWH.

We identified intervention start dates, including phase-in periods and dates by which interventions were stably in place. For hand hygiene promotion and routine MRSA surveillance cultures, we collected compliance data.

We evaluated changes in MRSA bacteremia using several epidemiologic measures common to infection control and hospital epidemiology. In particular, we evaluated incidence and prevalence using 2 denominators—one of hospitalized patients, which were used as the denominators for calculating incidence and prevalence, and the other of hospitalized patient-days, which were used as the denominators for calculating incidence density and prevalence density—because both are widely used and they provide different metrics of the frequency of events. In general, prevalence measures the percentage of all patients with an event, and incidence measures the percentage of patients without a prior event who experience an event for the first time.

Specifically, these measures were defined as follows. We calculated monthly prevalence as the number of patients with any MRSA bacteremic event in a given month, divided by the number of patients hospitalized that month (no. of case patients per 1000 monthly patients). Monthly prevalence density used the same numerator but used a denominator of patient-days (prevalent cases per 1000 monthly patient-days). Patients who experienced multiple bacteremic events were counted once each month. Monthly hospital-associated incidence was calculated as the number of patients with first-ever institutional MRSA bacteremia occurring >2 days after hospital admission, divided by the number of patients who had never had MRSA bacteremia (no. of first-ever case patients with health care–associated MRSA per 1000 monthly patients at risk). Monthly hospital-associated incidence density used the same numerator but used a denominator of patient-days (number of first-ever case patients with health care–associated MRSA per 1000 monthly patient-days).

Hospital-associated incidence generally excludes cases that are detected within 2 days of hospitalization to prevent community-acquired cases from being attributed to hospital acquisition. However, because patients acquiring MRSA in hospitals may not develop infection until after discharge [4] and can present during a subsequent admission with MRSA bacteremia, we also calculated overall monthly incidence and overall monthly incidence density, whereby incident case patients with first-time institutional MRSA bacteremia also included cases that occurred within 2 days of hospital admission. These late-occurring bacteremic events should be accounted for, because they also can be reduced by interventions that interrupt MRSA transmission. To support the inclusion of these cases, we reviewed medical records to assess the proportion of patients for whom first-time institutional MRSA bacteremia occurred within 2 days of admission who had been hospitalized at BWH during the previous year.

We collected automated microbiological data on all blood cultures positive for MRSA, including culture date and unit location. Monthly total patient-days were obtained from hospital census records and aggregated into monthly ICU, monthly non-ICU, and monthly total hospital patient-days for prevalence density and incidence density measures. Patient-level denominators for calculating prevalence and incidence of MRSA bacteremia were only available at the hospital level. We similarly collected data on methicillin-susceptible *S. aureus* (MSSA) as a control for surveillance cultures that targeted MRSA but not MSSA.

Analysis. We used an interrupted time series design, which is particularly suited to addressing secular trends and evaluating multiple interventions [10–13]. Segmented regression models [10–13] were used to assess changes in ICU, non-ICU, and total hospital incidence density, hospital-associated incidence

Table 1. Dates of infection control interventions.

Intervention	Phase-in period	Date of full implementation
Campaign for sterile CVC placement	1 Nov 1999–31 Aug 2000	1 Sep 2000
Institution of alcohol-based hand rubs	1 Aug 2001–31 Aug 2001	1 Sep 2001
Hand hygiene campaign	None	1 Jul 2002
Routine ICU surveillance for MRSA	1 Sep 2002–31 Aug 2003	1 Sep 2003

NOTE. The study period began on 1 January 1996 and ended on 31 December 2004. CVC, central venous catheter; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

density, and prevalence density of MRSA bacteremia attributable to the 4 infection control interventions. We additionally modeled total hospital incidence and prevalence (denominator data not available at the ICU and non-ICU levels).

Monthly epidemiologic measures of MRSA bacteremia were entered into separate models that were segmented by infection control interventions. Interventions were separated by at least 10 months. All models included a term wherein changes in MRSA bacteremia rates prior to any intervention were evaluated as a measure of underlying secular trend. Data from intervention phase-in periods did not inform models unless there was an overlap between one intervention and the phase-in period of another; in such an instance, data from the phase-in period were attributed to the preceding intervention.

Times series analyses provided results as changes in level (abrupt changes in outcome immediately after an intervention begins) and trend (changes between an outcome's preintervention slope and its slope across the entire intervention) of outcome measures while controlling for secular trend and previous interventions. Intervention impact was also expressed as the absolute difference between the outcome at the end of the intervention and its counterfactual value extrapolated by levels and trends of MRSA bacteremia prior to the intervention. Finally, we adjusted for serial autocorrelation using the Durbin-Watson statistic [14], because adjacent outcome measurements can be correlated when evaluating the outcome of an infectious agent. As a control, MSSA bacteremia was similarly analyzed. All analyses were 2-tailed and were conducted using SAS Proc Autoreg, version 9.1 (SAS Institute).

Because conducting routine MRSA surveillance cultures in the ICU enabled us to systematically assess MRSA transmission, we calculated the hospital-associated incidence of MRSA carriers hospitalized in all adult ICUs using a combination of clinical and surveillance cultures. MRSA carriers were defined as patients harboring MRSA in a symptomatic or asymptomatic state. To assess a reduction in ICU transmission due to surveillance, we compared the mean monthly hospital-associated incidence of MRSA carriage in ICUs in the first half of the MRSA surveillance intervention period with the last half using 2-tailed *t* tests. To account for changes in MRSA imported into ICUs as a cause of changing transmission, we similarly assessed monthly ICU admission prevalence, defined as the number of patients ever known to harbor MRSA before or within 2 calendar days of ICU admission divided by the total number of patients hospitalized in ICUs each month.

RESULTS

At the time of the study, BWH housed nearly 800 adult beds, including 80 beds in 8 ICUs. Approximately 43,000 adult patients were admitted annually, with >6000 annual ICU admissions. The average length of stay was 5 days hospital-wide and 4.3 days in the ICU.

Dates of the 4 hospital interventions are provided in table 1. The campaign to promote maximal sterile barrier precautions during central venous catheter placement involved annual hands-on training of medical and surgical interns, bundling of all necessary protective gear and sterile barriers, and use of a checklist to confirm sterile technique. This intervention was associated with a substantial decrease in all-cause catheter-associated bacteremia in ICUs (data not shown).

Hospital-wide institution of alcohol-based hand rubs involved the dissemination of educational materials describing the change to alcohol-based hand rubs as the primary means of hand disinfection, as well as placement of hand rub dispensers in each patient room and in readily accessible areas outside each room. Compliance was assessed by infection control personnel who observed 30 opportunities for hand hygiene per ICU (and selected non-ICU areas) each week and provided feedback on a weekly basis. The hand hygiene campaign included additional focused education on proper hand hygiene application and technique during routinely scheduled medical and surgical housestaff conferences. It also involved widely publicized competitions and periodic rewards for high-level compliance among medical and surgical housestaff. Overall hand hygiene compliance increased from 40% to 80% in the first campaign year, but decreased to 60% thereafter.

Routine MRSA surveillance involved nares cultures for all ICU patients at admission and weekly (while in the ICU), on a predetermined weekday. Contact isolation precautions were

initiated for patients who had a culture positive for MRSA, which generally occurred 48 h after the culture was performed. Compliance was assessed using detailed ICU census logs and by calculating the proportion of patients from whom microbiological specimens were obtained at admission and on a weekly basis. Compliance during the phase-in year of this program was 40%, but it abruptly increased to 88% after institution of daily (7 days a week) physician orders for admission and weekly nares cultures beginning 1 September 2003.

Results of time series models evaluating the impact of the 4 infection control interventions on the incidence density of health care–associated MRSA bacteremia are shown in figure 1. Before any intervention was implemented, there was a substantial secular trend of increasing incidence density of MRSA bacteremia. Among the interventions, only routine ICU MRSA surveillance was associated with a significant decrease in the incidence density of MRSA bacteremia. This decrease was seen in both ICUs and non-ICUs.

Similar decreases were observed in incidence, prevalence, and prevalence density, which collectively demonstrated a significantly increasing secular trend in the occurrence of MRSA bacteremia prior to any intervention, as well as a decrease in the occurrence of ICU, non-ICU, and hospital-wide MRSA bacteremia associated with routine ICU surveillance (table 2). All decreases in the occurrence of MRSA bacteremia were attributable to changes in trend rather than level, as previously defined in the Methods section. In addition, because the hand hygiene campaign substantially overlapped with the phase-in period of routine MRSA surveillance, models were repeated, with the exclusion of overlapping data. There was no difference in the results when these data were excluded.

Table 3 provides the overall impact of routine MRSA surveillance in the ICU. After 16 months, routine screening was associated with a 75% decrease in hospital-associated incidence density in ICUs, a 40% decrease in non-ICUs, and a 67% decrease hospital wide, compared with expected values accounting for secular trend. Similar reductions were seen in all epidemiologic measures. As a conservative estimate, discounting secular trend, routine screening was associated with a 67% decrease in hospital-associated incidence density in ICUs (−1.5 cases per 1000 patient-days), a 39% decrease in non-ICUs (−0.2 cases per 1000 patient-days), and a 53% decrease hospital wide (−0.3 cases per 1000 patient-days) across the 16-month period. All findings were statistically significant; *P* values as reported for the time series models are presented in table 2.

We assessed the impact of routine surveillance on MRSA transmission and found a statistically significant reduction in MRSA acquisition in ICUs (43 cases per 1000 patients at risk vs. 23 cases per 1000 patients at risk; $P < .001$) when comparing the first and last halves of the intervention period exclusive of the phase-in period. This occurred despite a stable MRSA importation rate into ICUs (mean monthly prevalence at admission, 12% [first half] vs. 11% [last half]). Comparable preintervention estimates were not possible, because weekly surveillance cultures

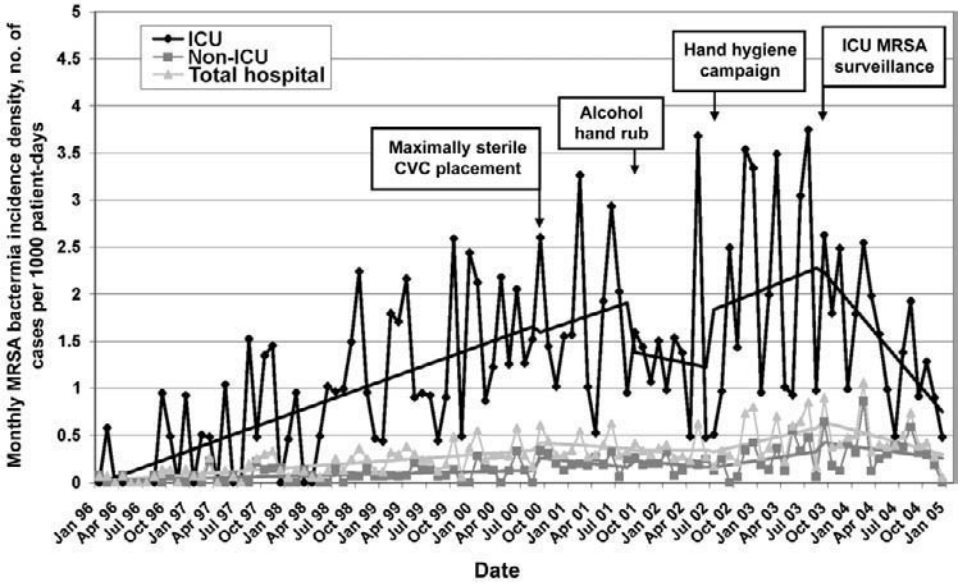

Figure 1. Risk of health care–associated methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. The graph shows the monthly incidence density of bacteremia in intensive care units (ICUs), areas other than the ICU (non-ICUs), and hospital wide. The plotted lines are derived from time series models of the impact of various infection control interventions. A statistically significant increasing secular trend is seen prior to any intervention in ICUs ($P < .001$) and hospital wide ($P = .001$), with a trend toward statistical significance in non-ICUs ($P = .08$). Only routine surveillance cultures were significantly associated with a decrease in health care–associated MRSA bacteremia in ICUs ($P = .007$), non-ICUs ($P = .008$), and hospital wide ($P = .002$). CVC, central venous catheter.

Table 2. Time series analysis showing preintervention trend and impact of infection control interventions on methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.

Epidemiologic measure, location	Annual trend prior to any intervention	*P*	Change following routine MRSA surveillance	*P*
ICU				
Prevalence density	0.6	**<.001**	−2.2[a]	**.02**
Incidence density	0.4	**<.001**	−1.2	.08
Hospital-associated incidence density	0.4	**<.001**	−1.6	**.007**
Non-ICU				
Prevalence density	0.09	**<.001**	−0.6	**.002**
Incidence density	0.05	**.02**	−0.4	**.01**
Hospital-associated incidence density	0.02	.08	−0.3	**.008**
Hospital wide				
Prevalence density	0.1	**<.001**	−0.7	**<.001**
Incidence density	0.1	**<.001**	−0.6	**.004**
Hospital-associated incidence density	0.07	**.001**	−0.5	**.002**
Prevalence	0.7	**<.001**	−3.9	**<.001**
Incidence	0.5	**<.001**	−3.0	**.004**
Hospital-associated incidence	0.4	**.002**	−2.6	**.002**

NOTE. Only model variables significantly associated with the outcome are shown. All other interventions were included in final models, but were not significantly associated with MRSA bacteremia. *P* values in boldface type are statistically significant. ICU, intensive care unit.

[a] Interpreted as a continuing decrease in prevalence density of ICU MRSA bacteremia of 2.2 cases per 1000 patient-days for each sequential year after the initiation of routine admission surveillance and weekly surveillance.

enhanced the detection of incident cases, and admission surveillance cultures enabled the distinction between imported versus truly incident cases.

When assessing total incidence density versus hospital-associated incidence density, we included an additional 341 cases of first-ever institutional MRSA bacteremia occurring within 2 days of hospital admission. Among these 341 cases, 283 (83%) had been hospitalized at BWH during the previous year.

Figure 2 shows the impact of the 4 infection control interventions on hospital-associated incidence density of MSSA bacteremia, as a control. We found no statistically significant secular trend and no impact of any infection control interventions on rates of MSSA bacteremia.

DISCUSSION

We conclude that routine screening for MRSA in ICUs, adopted after other recommended control measures were in place, prevented the majority of cases of MRSA bacteremia, both in ICUs and non-ICUs. Two observations support this conclusion. One was the concomitant reduction in MRSA transmission within ICUs. MRSA screening allowed for early identification and isolation of MRSA carriers and decreased ICU-associated transmission by 47%. This finding of a reduction in MRSA acquisition is consistent with an ultimate reduction in MRSA bacteremia, because patients who newly acquire MRSA are at high risk for subsequent bacteremia [4]. This is particularly true in ICUs where >35% of MRSA carriers develop bacteremia during the same ICU stay [15, 16]. The other supporting observation was the absence of any decrease in MSSA bacteremia, which served as a marker for nonselective changes in care. Since the conclusion of this study, we have noticed a sustained decrease in hospital-wide and ICU MRSA bacteremia in the absence of further intervention.

Notably, we found that surveillance limited to ICUs also reduced the incidence of MRSA bacteremia in non-ICU settings. This finding of a benefit in units where interventions were not implemented has not been previously reported, to our knowledge, and may be a reflection of 2 phenomena. One is the known delay in the development of MRSA sequelae following ICU acquisition [17]. We previously reported that one-third of bacteremic sequelae following MRSA acquisition are detected on readmission [4]. A second potential explanation is the reduction in opportunities for MRSA transmission in non-ICU areas, because fewer MRSA carriers are being discharged from ICUs. Other studies have shown reductions in bacteremia [18, 19] or health care–associated infection [20–22] following institution of MRSA surveillance of selected patients or in selected patient care areas. However, none evaluated a control organism to assess whether results were caused by surveillance, rather than changes in patient population or medical practice.

Table 3. Times series analysis that shows a decrease in methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia attributable to 16 months of routine surveillance.

Epidemiologic measure, location	Dec 2004 model projection of MRSA bacteremia in absence of surveillance[a]	Dec 2004 actual value of MRSA bacteremia	Total decrease in bacteremia[b]
ICU			
Prevalence density	4.1	1.6	−2.5 (61)
Incidence density	2.5	1.0	−1.5 (60)
Hospital-associated incidence density	2.8	0.7	−2.1 (75)
Non-ICU			
Prevalence density	1.2	0.6	−0.6 (48)
Incidence density	0.9	0.5	−0.4 (46)
Hospital-associated incidence density	0.5	0.3	−0.2 (40)
Hospital wide			
Prevalence density	1.4	0.6	−0.8 (54)
Incidence density	1.1	0.5	−0.6 (52)
Hospital-associated incidence density	0.9	0.3	−0.6 (67)
Prevalence	7.1	3.2	−3.9 (55)
Incidence	5.6	2.6	−3.0 (54)
Hospital-associated incidence	4.6	1.5	−3.1 (67)

NOTE. The 16-month time period covered in this analysis is 1 September 2003–31 December 2004. ICU, intensive care unit.

[a] Time series model projection of the value of MRSA bacteremia in December 2004 in the absence of MRSA surveillance based on secular trends prior to the institution of routine surveillance.

[b] Total decrease in MRSA bacteremia at the end of the intervention period for routine surveillance. Value is calculated as the difference (and percent decrease) between the time series model's projected value in the absence of routine surveillance minus the actual value in December 2004.

Additionally, none described benefits in patient areas where interventions were not carried out.

Furthermore, we found that overall incidence of bacteremia, including cases that do not satisfy the current definition of health care–associated infection, may be a more comprehensive measure of the impact of routine MRSA surveillance. Because MRSA carriers are at risk for infection for many months following acquisition [4], bacteremia during the first few days of a subsequent hospitalization would also be prevented by an intervention that prevented acquisition. Similar to other studies [23, 24], we found that 83% of patients presenting with MRSA bacteremia on admission had been hospitalized at BWH during the previous year. These bacteremic events should be included when evaluating outcomes for which post-discharge sequelae exist.

Interestingly, the other infection control initiatives studied did not significantly impact epidemiologic measures of MRSA bacteremia. Although we previously found that maximizing sterile barrier precautions during central venous catheter placement produced dramatic decreases in catheter-associated bacteremia in ICUs at BWH (data not shown), only a small percentage of MRSA bacteremia cases were catheter associated; as such, this intervention did not have a separately observable effect on overall MRSA bacteremia. This is in keeping with other studies showing that most of invasive MRSA sequelae following acquisition are not line related, but nevertheless result in a high risk for developing bacteremia [4, 25]. The lack of effect following institution of alcohol hand rubs suggests that effective hand disinfection is an inadequate measure for the reduction of MRSA transmission in the absence of prompt and effective isolation precautions. It is possible, however, that use of hand rubs contributed to the effectiveness of the contact precautions resulting from surveillance cultures.

Limitations of this study include potential changes in our hospital's patient population during the 9-year study period. If the overall severity of patient illness decreased in later years and they became less prone to MRSA bacteremia, then our findings would overestimate the benefit of MRSA surveillance. However, BWH case mix data suggest that the overall severity of illness in our patient population increased over time. In addition, we would have expected such changes in our hospital population or level of care to similarly impact MSSA, but this was not observed. Furthermore, time series analyses limit confounding to those factors changing at or around the same time

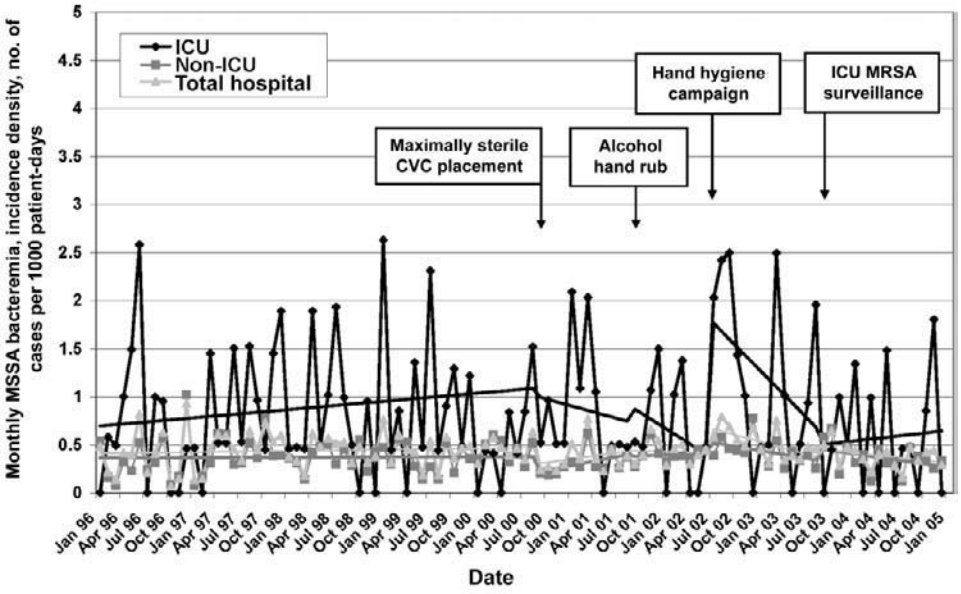

Figure 2. Risk of health care–associated methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia as a control measure. The graph shows the monthly incidence density of bacteremia in intensive care units (ICUs), areas other than ICUs (non-ICUs), and hospital wide. The plotted lines are derived from time series models of the impact of various infection control interventions. There was neither a statistically significant secular trend nor a statistically significant impact on MSSA bacteremia rates with any infection control intervention. CVC, central venous catheter.

as the intervention and are related to the outcome. Unless our hospital population changed at the time routine surveillance was instituted, changes are unlikely to confound these results.

Another alternative explanation for our results could be that prophylactic vancomycin use increased in response to positive MRSA cultures arising from surveillance. Although we cannot exclude this possibility, hospital-wide vancomycin use was stable when surveillance was instituted and remained stable throughout the study period.

We did not preemptively isolate patients on ICU admission while MRSA screening cultures were pending. Thus, contact isolation was instituted when cultures were known to be positive—generally, 48 h after the culture was performed. Preemptive isolation or use of rapid diagnostic tests, such as PCR, could result in even more dramatic findings, but our results suggest that culture-based surveillance can have a substantial impact on transmission and infection, even with a delay of 2 days. This is likely to be true, because ICU patients generally have a hospital length of stay that substantially exceeds 2 days, which is further prolonged by MRSA carriage if MRSA infection ensues.

Although not a limitation, per se, routine surveillance depends on the ability to implement contact precautions in a sufficiently rigorous manner to contain transmission. Therefore, the surveillance initiative actually measured the composite impact of surveillance and effective adherence to precautions. Although overall adherence to contact precautions is extremely difficult to assess, the profound reduction in MRSA bacteremia provides evidence that compliance was sufficiently high in these ICUs to make an important difference. The hand hygiene interventions may have contributed to the success of contact precautions, both through their direct effect and also by generally raising staff awareness of precaution policies.

Finally, the generalizability of this study depends on importation and incidence rates of MRSA carriage and bacteremia. It is possible that a threshold exists for endemic carriage below which routine MRSA screening confers no sustained and measurable benefit.

In conclusion, we found that routine MRSA surveillance, limited to ICUs at admission and on a weekly basis, resulted in marked ICU, non-ICU, and hospital-wide reductions in MRSA bacteremia during prolonged observations in a nonoutbreak setting. For the outcome of reducing MRSA bacteremia, this intervention performed better than the introduction of alcohol hand rub as the primary means of hand disinfection and other nationally recommended infection control practices. Targeted surveillance for MRSA in high-risk units, combined with effective contact isolation procedures, may prevent large numbers of MRSA infection across an entire institution.

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