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Regional Epidemiology of Methicillin-Resistant *Staphylococcus aureus* Among Critically Ill Children in a State With Mandated Active Surveillance

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Abstract

Background.—In theory, active surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) reduces MRSA spread by identifying all MRSA-colonized patients and placing them under contact precautions. In October 2007, Illinois mandated active MRSA surveillance in all intensive care units, including neonatal intensive care units (NICUs) and pediatric intensive care units (PICUs). We evaluated MRSA trends in a large metropolitan region in the wake of this law.

Methods.—Chicago hospitals with a NICU or PICU were recruited for 8 single-day point prevalence surveys that occurred twice-yearly between June 2008 and July 2011 and then yearly in 2012 to 2013. Samples from all patients were cultured for MRSA (nose and umbilicus for neonates, nose and groin for pediatric patients). Hospital-reported admission MRSA-screening results also were obtained. Point prevalence cultures were screened for MRSA by using broth enrichment, chromogenic agar, and standard confirmatory methods.

Results.—All eligible hospitals (N = 10) participated (10 NICUs, 6 PICUs). Hospital-reported adherence to state-mandated MRSA screening at admission was high (95% for NICUs, 94% for PICUs). From serial point prevalence surveys, overall MRSA prevalences in the NICUs and PICUs were 4.2% (89 of 2101) and 5.7% (36 of 632), respectively. MRSA colonization

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prevalences were unchanged in the NICUs (year-over-year risk ratio [RR], 0.93 [95% confidence interval (CI), 0.78–1.12]; $P = .45$) and trended toward an increase in the PICUs (RR, 1.25 [95% CI, 0.72–2.12]; $P = .053$). We estimated that 81% and 40% of MRSA-positive patients in the NICUs and PICUs, respectively, had newly acquired MRSA.

Conclusions.—In a region with mandated active MRSA surveillance, we found ongoing unchanged rates of MRSA colonization and acquisition among NICU and PICU patients.

Keywords

active surveillance; colonization; epidemiology; intensive care unit; methicillin-resistant *Staphylococcus aureus*

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important healthcare-associated pathogen among critically ill children in neonatal and pediatric intensive care units (NICUs and PICUs, respectively). Asymptomatic MRSA colonization is a precursor to invasive disease such as sepsis, which leads to significant cost and morbidity [1, 2]. In theory, active MRSA surveillance aims to reduce bacterial transmission by identifying all MRSA-colonized patients (including asymptomatic carriers) and placing them under contact precautions [3, 4]. However, the use of active MRSA surveillance in nonoutbreak (endemic) settings is controversial [5–9].

The epidemiology of MRSA among critically ill children is incompletely understood. Previous epidemiologic studies of MRSA colonization in NICUs and PICUs were primarily performed at single centers, some during MRSA outbreak periods, which limits their generalizability [10]. Furthermore, since 2000, the epidemiology of MRSA among hospitalized children in the United States has evolved in many geographic regions as a result of an epidemic of community-associated (CA)-MRSA colonization and infection [11, 12].

In October 2007, Illinois became the first US state to mandate active surveillance of MRSA for all patients in intensive care units (ICUs); isolation precautions were required for MRSA-positive patients (MRSA Screening and Reporting Act) [13]. After the start of the law, we performed a series of regional point prevalence surveys to assess the epidemiology of MRSA colonization among NICU and PICU patients across all hospitals in a large metropolitan city (Chicago, IL). We evaluated whether the prevalence of MRSA colonization would decline in the 5 years after the active surveillance mandate.

METHODS

Subject Recruitment

In 2008, we invited all hospitals in Chicago with a NICU or PICU to participate in regional point prevalence surveys for MRSA colonization. Over 5 years, 8 region-wide point prevalence surveys were performed twice-yearly between June 2008 and July 2011 and then yearly in 2012 and 2013. All patients in these NICUs and PICUs who were present at the time of the surveillance visit were eligible. Written informed consent was waived. For

parents at bed-side and for minors able to verbalize understanding, we provided a scripted explanation of the project's rationale and asked for verbal assent.

Ethical Review

This project underwent ethical review at the Centers for Disease Control and Prevention and was determined to be a public health assessment (not human subjects research). In addition, institutional review boards at the participating hospitals (where applicable) reviewed the protocol and either determined that the survey did not constitute human subjects research or approved the protocol with the requirement for informed consent waived.

Culture and Data Collection

For each survey, facilities were provided standardized culturing supplies, data collection tools, and training. Local hospital staff (infection preventionists or ICU nurses) and 1 investigator (R.D.L.) collected the specimens.

Samples from 2 body sites of each patient were obtained using sterile dry rayon swabs (CultureSwab Liquid Stuart, BD) and cultured for MRSA. For both neonatal and pediatric patients, 1 swab was placed in a nostril and rotated 3 times. A second swab was obtained from the umbilical region of neonates (3 × 3 cm) or the inguinal/groin region (10 × 10 cm) of pediatric patients.

At the time of specimen collection, the following patient characteristics were recorded: age, ICU length of stay, sex, mechanical ventilation status, contact precautions status, and hospital-reported admission MRSA-screening result. At each survey, the hospitals reported the timing of their routine surveillance testing (on ICU admission and at additional time points thereafter) and use of polymerase chain reaction (PCR) versus culture-based MRSA detection; these variables were allowed to be time-varying in our analyses to account for changes in practice over time.

Laboratory Methods

Specimens were transported to a central laboratory and processed within 6 hours of collection. Nasal, inguinal, and umbilical swab specimens each were cultured in separate tubes of tryptic soy broth with 6.5% sodium chloride (Remel). After overnight incubation, the broth was inoculated onto chromogenic MRSASelect agar (Bio-Rad). After subculture, *S aureus* was confirmed by colonial morphology and standard biochemical techniques. Susceptibility to oxacillin was determined by using the cefoxitin disk-diffusion method [14]. All MRSA isolates were subtyped by pulsed-field gel electrophoresis [15]. CA-MRSA clonal types were defined as USA300/400/1000/1100 [16]. Mupirocin susceptibility was determined by using the E-test method (high-level resistance, minimum inhibitory concentration [MIC] ≥ 512 μg/mL; low-level resistance, MIC = 8–64 μg/mL; susceptibility, MIC ≤ 4 μg/mL) [17].

Statistical Analyses

This study was predicated on at least an 80% power to detect a change from 5% to 2.5% MRSA colonization prevalence among 1924 patients in a NICU over the surveillance period,

with an α level of .05 in a 2-sided χ^2 test of proportions. The actual obtained sample of 2101 subjects was sufficient to detect a difference of 1.5% (eg, 5% vs 3.5%). For bivariable comparisons, we used Fisher's exact test or the Wilcoxon-Mann-Whitney test, as appropriate. Exact binomial methods were used to calculate 95% confidence intervals (CIs) of proportions. We constructed multilevel regression models with a binomial distribution to model prevalence and incidence trends, accounting for ICU-level correlation across time (using the R lme4 package). We used SAS version 9.2 (SAS Institute, Cary, NC) or R version 3.1.1 (http://CRAN.R-project.org).

RESULTS

In total, 10 of 10 eligible hospitals (10 NICUs and 6 PICUs) voluntarily participated in the point prevalence surveys. The median NICU size was 38.5 beds (range, 10–88 beds), and the median PICU size was 12 beds (range, 7–42 beds). Five hospitals were university based (5 of 10 NICUs, 4 of 6 PICUs). One hospital (1 NICU, 1 PICU) was an independent children's hospital; the rest were combined pediatric/adult hospitals. Each NICU was pod based during the survey period with the exception of one that changed its configuration to individual rooms for the last survey period. Routine chlorhexidine bathing was not performed in any NICU or PICU during the survey periods. All hospitals placed known MRSA-colonized patients under contact precautions; none did so empirically while awaiting MRSA-screening results.

Across the study period, the overall patient participation rates were high for the NICUs (99.6% [2101 of 2110]) and PICUs (92.3% [632 of 685]). Patient demographics are shown in Table 1.

Hospital-Reported Surveillance for MRSA

All 10 hospitals reported that they complied with the Illinois legislation by performing active surveillance testing for MRSA colonization. Nine NICUs performed admission MRSA screening using nares cultures; 1 NICU performed the admission culture on a defined day of the week by using a combined nares/axilla/groin culture with a single swab. PCR-based MRSA testing was used in 4 of the 10 NICUs; the remaining NICUs used culture-based detection methods, and 1 hospital used broth enrichment. In addition to admission screening, 7 of 10 NICUs reported using periodic screening strategies at some point during the 5-year study. Weekly surveillance was the most common periodic surveillance strategy (affecting 47% [985 of 2101] of patients in all the NICUs during the study) followed by a twice-per-month strategy (5%) and 10 days after admission (4%); the remaining 45% of the patients had no additional surveillance beyond admission.

In comparison, PICU MRSA-screening practices were relatively consistent. Of the 6 PICUs, all performed active surveillance for MRSA at the time of admission using nasal sampling. One of the 6 PICUs used PCR-based MRSA testing. Screening at time points after admission was not routinely performed in any of the PICUs.

We found high rates of compliance with the state law by hospitals across the study period, with 95% of patients in the NICUs and 94% of patients in the PICUs receiving active surveillance testing for MRSA.

The overall admission prevalences of MRSA colonization as reported by the hospitals were 1.5% (95% CI, 1.0%–2.2%) in the NICUs and 5.9% (95% CI, 4.0%–7.8%) in the PICUs. The admission prevalences did not change significantly across the 8 survey periods for either the NICUs or the PICUs.

Point Prevalence Survey Results (Primary Outcome)

Of 2101 patients in the NICUs who participated in the surveys, 89 (4.2%) were colonized with MRSA (95% CI, 3.4%–5.1%). The MRSA colonization prevalences among patients in the NICUs were unchanged during the study period (Figure 1A; year-over-year relative risk for MRSA colonization, 0.93 [95% CI, 0.78–1.12]; $P = .45$).

Of 632 patients in the PICUs who participated in the surveys, 36 (5.7%) were colonized with MRSA (95% CI, 4.0%–7.8%). The prevalence of MRSA colonization among patients in the PICUs trended toward an increase over time (Figure 1B; year-over-year relative risk for MRSA colonization, 1.25 [95% CI, 0.72–2.12]; $P = .053$).

Estimated Incidence Rates

We estimated rates of ICU MRSA acquisition by considering each patient with a negative nasal hospital admission culture result (as reported by the hospital) and a subsequent positive nasal culture result during a point prevalence survey (on ICU day 3 or beyond) to have acquired MRSA in the ICU. In the NICU, we estimated that 81% (54 of 67) of MRSA colonization prevalence events identified by our surveys were ICU acquired (ie, incident cases) versus 40% (10 of 25) of those in the PICU (difference, $P < .001$). We analyzed trends in incident cases per 100 susceptible patients over the 5-year surveillance period (Table 2). Neither the NICU nor the PICU had a statistically significant change in the MRSA-acquisition rates during the survey period.

CA-MRSA Genotypes and Mupirocin Resistance

From the point prevalence surveys, CA-MRSA genotypes were represented in 46% (41 of 89) of MRSA isolates from the NICUs and 36% (13 of 36) of MRSA isolates from the PICUs. During the study period, the proportions of MRSA isolates that had a CA-MRSA genotype did not change significantly for either the NICUs or the PICUs. The proportions of incident cases that involved CA-MRSA were 48% (26 of 54) in the NICUs and 30% (3 of 10) in the PICUs.

High-level mupirocin resistance was detected in 3% (3 of 89) of the NICU MRSA isolates tested; none of the isolates demonstrated low-level resistance. Among the 36 PICU MRSA isolates tested, 8% (n = 3) demonstrated high-level resistance; 3% (n = 1) demonstrated low-level resistance.

Epidemiologic Differences in Endemic MRSA Colonization Between NICUs and PICUs

The epidemiology of MRSA colonization differed in terms of ICU-day distribution between the NICU and PICU settings (Figure 2). In the NICUs, MRSA colonization was detected in neonates only on ICU day 3 or beyond; of the 192 neonates (9% of total sample) surveyed within the first 2 ICU days, none were MRSA colonized. In contrast, MRSA-colonized patients in the PICUs were found throughout the entire range of ICU days. The median ICU day for detecting MRSA colonization in patients in the NICUs was 29 versus the median of 9 for patients in the PICUs ($P < .001$).

Contact Precautions in the Setting of Active Surveillance

Among patients identified as MRSA positive by the point prevalence surveys, 56% (50 of 89) in the NICUs and 33% (12 of 36) in the PICUs ($P = .03$ for difference) were not under contact precautions at the time of the point prevalence survey. Lack of contact precautions was particularly common for neonates identified by the point prevalence survey as being MRSA colonized during the first 14 days of their NICU stay (84% [21 of 25] of the MRSA-colonized neonates during the first 14 days were not under contact precautions versus 45% [29 of 64] on days 14 and beyond; $P < .001$ for difference; Figure 2).

We explored possible explanations for the lack of contact precautions among MRSA-colonized patients in our study cohort. To account for the additional sensitivity of testing 2 body sites (study protocol) versus 1 body site (routine hospital testing), we repeated our analysis using data only from the patients whose nasal cultures were positive for MRSA; the results were unchanged (54% and 33% of MRSA-colonized patients not under contact precautions in the NICUs and PICUs, respectively). Furthermore, we noted that none of the MRSA-positive patients detected by our point prevalence surveys and lacking contact precautions had tested positive for MRSA by the hospital at the time of admission, thus making either a lag time to the admission test result or a lag time to implementing contact precautions after a positive test result an unlikely explanation for the lack of isolation.

Effect of Hospitals Choosing Periodic Screening in NICUs

We compared the MRSA epidemiology between the 2 dominant strategies for MRSA screening among the NICUs: weekly surveillance (47% of patients) versus admission-only screening (45%). There was no significant difference in MRSA colonization prevalences during NICU time periods in which a weekly surveillance strategy was used and during those with no periodic screening (3.7% vs 5.1%, respectively; $P = .12$) and no difference in the estimated incidence (3.6 vs 3.9 incident cases per 100 patient-days, respectively; $P = .78$). Furthermore, we found that the proportions of MRSA-colonized patients who lacked contact precautions were similar during NICU periods in which weekly surveillance was performed and during those with no periodic screening (58% vs 54%; $P = .82$).

Effect of Hospitals Choosing PCR Versus Culture-Based Testing

We found no difference in MRSA colonization rates between hospitals that routinely used PCR versus culture-based MRSA-detection methods (NICUs, 4.2% vs 4.3% [$P = .99$]; PICUs, 5.8% vs 5.7% [$P = .99$]). Among patients found by the point prevalence surveys to be MRSA positive, a hospital's use of PCR testing did not significantly affect the likelihood

of a patient being under contact precautions (PCR vs culture, 59% vs 44% [$P = .14$], NICUs/PICUs in aggregate).

Performance Characteristics of Testing Different Body Sites for MRSA Colonization

We assessed the performance characteristics of testing body sites individually for MRSA carriage (nose or umbilicus for patients in the NICUs, nose or groin for patients in the PICUs) by using the reference standard of being MRSA positive in any combination of the 2 body sites during point prevalence testing. For patients in the NICUs who had MRSA culture results from both the nose and umbilicus sites available, nasal culturing alone identified 87% (62 of 71) of MRSA-positive neonates; 9 neonates (13%) were nasal culture negative and umbilical culture positive (Table 3). For patients in the PICUs, nasal culturing alone identified 85% (23 of 27) of MRSA-positive patients; 4 patients (15%) were nasal culture negative and groin culture positive. For all the patients in the NICUs and PICUs, a negative nasal surveillance culture result had >99% negative predictive value.

DISCUSSION

We studied the epidemiology of MRSA colonization among patients in NICUs and PICUs across a spectrum of community and academic hospitals in Chicago during the 5 years after state-mandated active surveillance for MRSA. Using serial point prevalence surveys, we identified MRSA colonization in approximately 1 in 25 patients in NICUs and 1 in 20 patients in PICUs, and there was evidence of ongoing ICU acquisition in both unit types. We did not find a decrease in MRSA colonization during the 5 years of surveillance; rather, NICU colonization rates were unchanged, and PICU colonization rates trended toward an increase over time.

Previous single-center studies among patients in a NICU, performed over prolonged time periods, found MRSA colonization rates that ranged from 1.3% to 2.0% [4, 18, 19]. Higher MRSA colonization rates of 6.7% to 40% were reported among other single centers during possible or confirmed epidemic periods [2, 20–24]. Sparse data are available for patients in PICUs; single-center endemic MRSA colonization rates of 3.2% to 6.3% have been reported [25–28]. Our multicenter study found MRSA colonization prevalence rates that were comparable with those in previous single-center studies, which expands our understanding of endemic MRSA epidemiology to a diverse group of hospitals.

The goal of active MRSA surveillance is to identify all MRSA-colonized patients, to appropriately apply infection-control precautions, and to prevent patient-to-patient transmission. We found high rates of compliance with active surveillance across all the NICUs and PICUs in our study. Yet, we found that among MRSA-colonized patients identified through the point prevalence surveys, more than half of those in the NICUs and one third of those in the PICUs were not under contact precautions at the time of survey.

We explored potential explanations for the deficits in contact precautions. On the basis of sensitivity analysis, it is unlikely that differences in study versus routine testing methods, lag times in obtaining hospital admission test results, or lag times in instituting contact precautions explain the majority of the contact-precaution deficits. Rather, our findings

suggest that ongoing MRSA acquisition in the ICU (or possibly, for patients in the PICUs, the emergence of un-detected endogenous carriage) was the dominant reason for the deficit in contact precautions.

Whether improving the proportion of MRSA-colonized patients under contact precautions would decrease MRSA-transmission rates remains uncertain. A study of universal glove and gown use carried out among only adult patients (effectively placing all MRSA-colonized patients under contact precautions) did not result in a reduction in the primary end point, which was the composite rate of MRSA and vancomycin-resistant *Enterococcus* transmission, but it did demonstrate a decrease in the MRSA-specific transmission rate in a secondary outcome analysis [29].

We assessed MRSA epidemiology during a time period when CA-MRSA strain types had already become prevalent in many urban centers in the United States [4, 10, 26, 27]. We found CA-MRSA strains in a substantial proportion of the patients in the NICUs and the PICUs, and we also found that CA-MRSA strains contributed to ICU acquisition proportional to prevalence rates in the respective unit types. Because the majority of MRSA colonizations in the NICU are hospital acquired, future epidemiologic investigation through whole-genome sequencing is likely needed to better understand potential sources of in-hospital CA-MRSA transmission [30].

Our study provides insight into some important knowledge gaps regarding active MRSA surveillance in the pediatric population [31]. Consistent with previous studies [19, 32], we found MRSA to be uncommon among patients in the NICUs within 2 days of admission; therefore, if facilities choose to perform active MRSA surveillance among patients in the NICU, they should consider performing surveillance at at least 1 additional time point beyond the first 2 ICU days.

Our findings also suggest that screening the anterior nares alone is sufficient to detect MRSA colonization. For both the NICU and the PICU populations, nares screening alone had a negative predictive value of 99%. Other studies have supported the nares as the single best site for screening MRSA colonization among patients in the NICU [21,33].It should be noted that we did not screen the pharynx among patients in the PICUs; testing samples from this site was reported in 1 study to result in higher sensitivity than testing samples from the nares for MRSA surveillance [34].

Our study had limitations. Hospital acquisition rates were potentially biased toward higher values across all surveys, even when we compared the same body sites, because the MRSA surveillance testing used in the point prevalence surveys included broth enrichment, which makes point prevalence testing slightly more sensitive than the routine admission testing performed by hospitals [35]. However, the primary outcome of MRSA colonization prevalence, which relied only on serial point prevalence survey testing using an identical method, was unbiased. Second, intermittent point prevalence surveys may have missed clustered MRSA outbreaks. However, the length of observation (5 years) enabled us to be confident that we were measuring a true secular trend of endemic MRSA prevalence. Third, our assessment of the effect of mandated active surveillance on MRSA prevalence

was restricted to hospitals that were performing active surveillance, and we did not have a non-surveillance control group as a comparator, which limits our ability to assess the full impact of mandated active surveillance. However, in the NICUs, we found that mandated active surveillance failed to result in half of the MRSA-colonized patients being placed under contact precautions, and more intensive surveillance (eg, weekly) was not associated with improvement. Ongoing MRSA transmission and infection despite aggressive active surveillance efforts were detailed previously in a single-institution study [4]. Our finding of a lack of dose response among a large group of hospitals to increased active surveillance raises questions about the effectiveness of legislated active surveillance in controlling MRSA in regions where it is already endemic, emphasizes the need for alternative control strategies [36, 37], and supports calls for eliminating the mandate [38].

In summary, in a region with mandated active MRSA surveillance, we found ongoing MRSA colonization and acquisition in a substantial proportion of patients in NICUs and PICUs in a large metropolitan city. Our findings highlight the shortcomings of using a mandatory active surveillance strategy to reduce MRSA burden among critically ill children. We also found significant differences in the epidemiology of endemic MRSA carriage between patients in the NICUs and PICUs, particularly with respect to admission prevalence and timing of acquisition, which may inform future prevention interventions.

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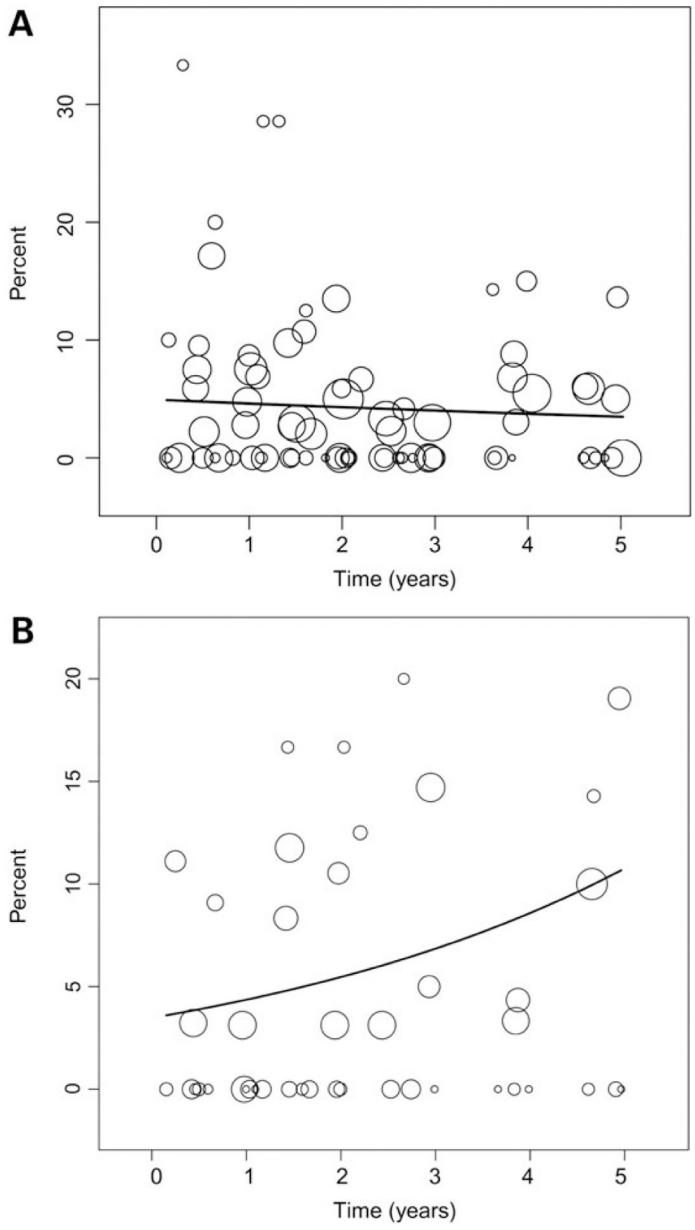

Figure 1.

Estimated methicillin-resistant *Staphylococcus aureus* colonization prevalence trends for neonatal (A) and pediatric (B) intensive care units during the 5-year study period. 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.

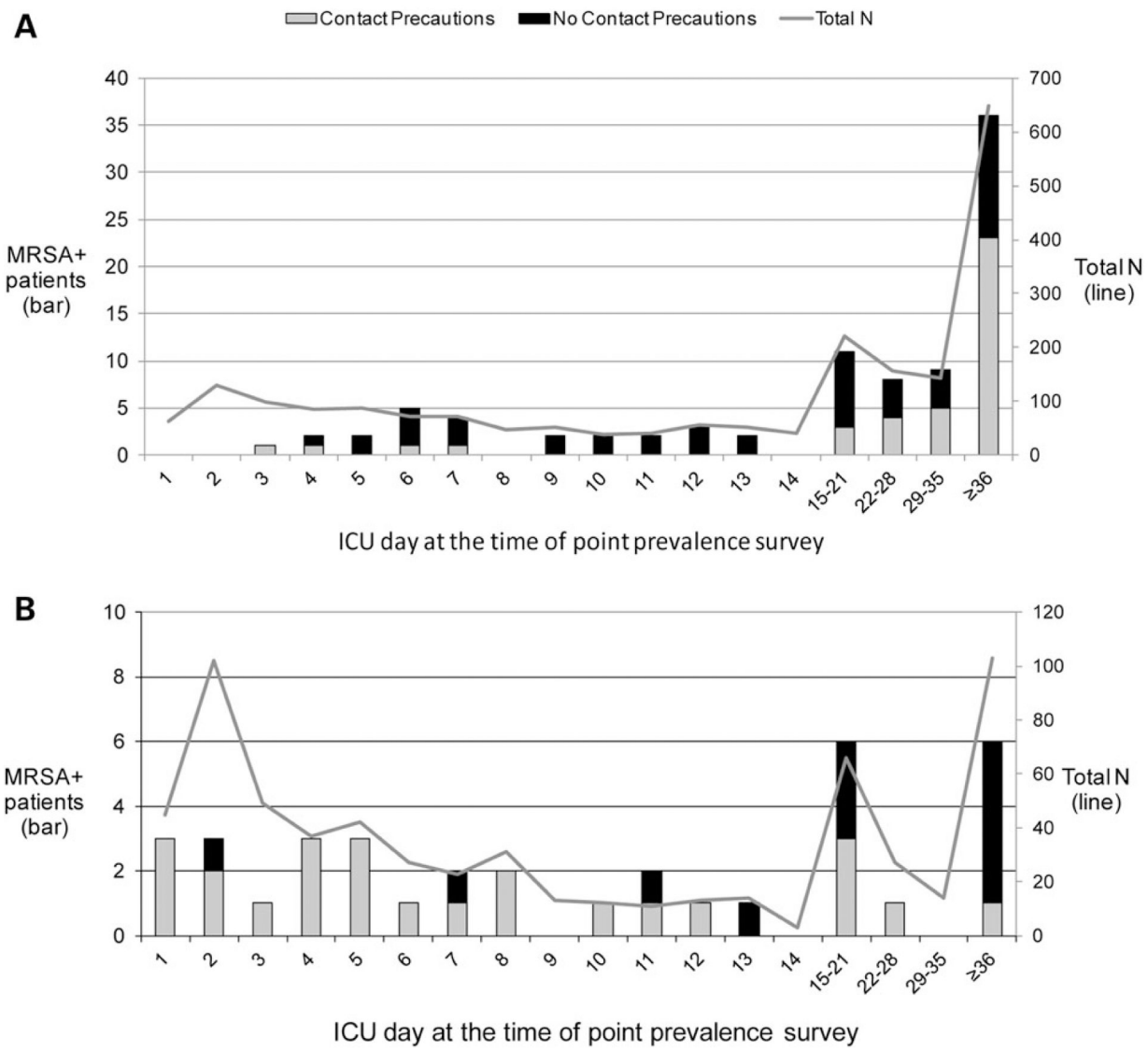

Figure 2.

Distribution of methicillin-resistant *Staphylococcus aureus*–colonized (MRSA+) patients across intensive care unit (ICU) days of surveillance for neonatal (A) and pediatric (B) ICUs.

Table 1.

Patient Characteristics of the Study Cohort at the Time of the Point Prevalence Survey

Characteristic	NICU Patients (n = 2101)	PICU Patients (n = 632)	*P*
Length of stay[a] (median [IQR]) (days)	18 (6–43)	7 (3–20)	<.001[b]
Male (n [%])	1141 (55)	350 (55)	.79[c]
Age (median [IQR])	19 d (7–42)	1.8 y (0.4–10)	<.001[b]
Ventilated (n [%])	422 (20)	182 (29)	<.001[c]
Contact isolation (n [%])	114 (5)	266 (42)	<.001[c]

Abbreviations: IQR, interquartile range; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

[a]Intensive care unit length of stay, as measured at time of the survey.

[b]Wilcoxon-Mann-Whitney test.

[c]Fisher's exact test.

Table 2.

Estimated MRSA-Acquisition Rates Over the 5-Year Survey Period

	NICU		PICU	
Survey Period	**n/N[a]**	**Acquisition Rate per 100 Patients**	**n/N[a]**	**Acquisition Rate per 100 Patients**
Year 1	17/351	4.8	2/111	1.8
Year 2	18/400	4.5	2/111	1.8
Year 3	4/338	1.2	4/83	4.8
Year 4	10/179	5.6	1/39	2.6
Year 5	5/190	2.6	1/51	2.0
Overall	54/1458	3.7	10/395	2.5
Test of trend (*P*)		.57		.89

Abbreviations: MRSA, methicillin resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

[a]N represents patients eligible to acquire MRSA (ie, nares negative for MRSA colonization, as determined by the hospital's surveillance culture at admission).

Table 3.

Performance Characteristics of Individual Body-Site Testing for MRSA Colonization[a]

Sample Type	Sensitivity (% [95% CI])	Negative Predictive Value (% [95% CI])
NICU		
Nose only	87 (77–94)	99.4 (99–100)
Umbilicus only	55 (43–67)	98 (97–99)
Nose and umbilicus (reference)	—	—
PICU		
Nose only	85 (66–96)	99 (98–100)
Groin only	41 (22–61)	97 (95–98)
Nose and groin (reference)	—	—

Abbreviations: CI, confidence interval; MRSA, methicillin resistant. *Staphylococcus aureus*; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

[a]Because a positive culture result for MRSA was always considered true positive, the specificities and positive predictive values were 100% for every body site.