MRSA Colonization and Risk of Infection in the Neonatal and Pediatric ICU: A Meta-analysis

BACKGROUND AND OBJECTIVE: Methicillin-resistant Staphylococcus aureus (MRSA) is a significant cause of morbidity and mortality in NICUs and PICUs. Our objective was to assess the burden of MRSA colonization on admission, study the time trends, and examine the significance of MRSA colonization in this population.

METHODS: PubMed and Embase databases were consulted. Studies that reported prevalence of MRSA colonization on ICU admission were selected. Two authors independently extracted data on MRSA colonization and infection.

RESULTS: We identified 18 suitable articles and found an overall prevalence of MRSA colonization of 1.9% (95% confidence interval [CI] 1.3%–2.6%) on admission to the NICU or PICU, with a stable trend over the past 12 years. Interestingly, 5.8% (95% CI 1.9%–11.4%) of outborn neonates were colonized with MRSA on admission to NICU, compared with just 0.2% (95% CI 0.0%–0.9%) of inborn neonates (P = .01). The pooled acquisition rate of MRSA colonization was 4.1% (95% CI 1.2%–8.6%) during the NICU and PICU stay and was as high as 6.1% (95% CI 2.8%–10.6%) when the NICU population was studied alone. There was a relative risk of 24.2 (95% CI 8.9–66.0) for colonized patients to develop a MRSA infection during hospitalization.

CONCLUSIONS: In the NICU and PICU, there are carriers of MRSA on admission, and MRSA colonization in the NICU is almost exclusively associated with outborn neonates. Importantly, despite infection control measures, the acquisition rate is high, and patients colonized with MRSA on admission are more likely to suffer a MRSA infection during hospitalization. Pediatrics 2014;133:e1015–e1023

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KEY WORDS
methicillin-resistant Staphylococcus aureus, MRSA, intensive care units, neonatal, pediatric, meta-analysis, infection, colonization

ABBREVIATIONS
CI—confidence interval
MRSA—methicillin-resistant Staphylococcus aureus
PCR—polymerase chain reaction

Drs Zervou and Zacharioudakis designed the study; performed the literature search; participated in data collection, extraction, and interpretation; prepared tables and figures; and drafted the manuscript; Dr Ziakas designed the study, performed the statistical analysis and data interpretation, prepared tables and figures, and reviewed and revised the manuscript; Dr Mylonakis conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the pediatric population range from skin and soft tissue to lower respiratory and bloodstream infections and are associated with significant morbidity and hospital costs. These infections are largely preceded by colonization with MRSA, and colonized children serve as a reservoir for the cross-transmission of 

A number of reports indicate that the trends in MRSA invasive infections in high-risk adult populations are decreasing. The epidemiology of MRSA invasive infections among critically ill neonates and children seems to follow a distinct course, with data on MRSA outbreaks in NICUs increasingly being published. In this systematic review and meta-analysis, we estimate the prevalence of MRSA colonization among patients upon admission to the NICU and PICU, review the time trends, and study the significance of MRSA colonization in this population.

**METHODS**

**Study Selection**

A literature search of the PubMed and Embase databases was conducted, and articles potentially relevant to our study were identified. The search was performed by 2 authors (FNZ, IMZ) independently, by using the following terms as keywords: (MRSA OR Methicillin AND resistant AND *Staphylococcus*) AND (Neonatal OR Pediatric). Among the citations extracted, abstracts were reviewed in an attempt to retrieve the clinical studies on MRSA colonization on admission to the NICU and PICU. Articles that were relevant, by title and abstract, were accessed in full text to determine those that provided sufficient information to be included in our meta-analysis. Finally, the references cited by each eligible study were scrutinized to identify additional articles. We performed our review and meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines.

**Inclusion and Exclusion Criteria**

Studies were included in our meta-analysis if they reported extractable data on the prevalence of MRSA colonization on admission to a NICU or PICU. A restriction for English literature was imposed.

**Outcomes of Interest**

The major outcome of interest was the prevalence of MRSA colonization on admission to the NICU or PICU. The prevalence was calculated by dividing the number of cases with positive MRSA surveillance cultures on admission by the total number of recruited individuals (ie, those who were screened for MRSA on admission to the NICU or PICU). We stratified the results for geographic location, type of ICU (NICU versus PICU), screening site(s) (nasal versus nasal and extranasal), and the MRSA isolation method (polymerase chain reaction [PCR] versus culture). As secondary outcomes of interest, we calculated the relative risk of ensuing MRSA infection among colonized on admission compared with noncolonized and the acquisition rate of colonization among noncolonized patients during their ICU stay. If the acquisition rate was not directly reported in the text, we approximated population at risk by subtracting patients colonized on admission from the population screened.

**Data Extraction**

Data from eligible studies were extracted independently by 2 reviewers (FNZ, IMZ) and summarized into a spreadsheet. Discrepancies were resolved by consensus. For each of the included studies, the following information was extracted: author names, year of publication, country of study conduct, study design (retrospective or prospective), type and number of ICUs (NICU or PICU), number of patients who were screened, time interval from admission to screening, number of MRSA-colonized patients, anatomic sites screened (nasal and extranasal sites), isolation method (culture or PCR) used, infection control policies applied to each ICU, MRSA infection rate among colonized and noncolonized patients, and acquisition rate of MRSA during hospitalization. Also, we extracted the information on whether the cases were inborn, outborn, or mixed. The population was considered outborn when neonates were transferred from outside nurseries and inborn when they were born in the obstetric unit of the same hospital. To depict the time trends of MRSA colonization on admission in the NICU and PICU, we used as an index year the year that the study was conducted and not the year of publication.

In cases of studies in which the screening process lasted >1 calendar year, the midyear was used as the index year.

**Quality Assessment**

The quality of eligible studies was assessed independently by 2 reviewers (FNZ, IMZ) using a set of prespecified criteria regarding the research design and the quality of data report, as previously described. In brief, quality points were given to studies with prospective design, multicenter trials, studies that stratified their results by year, and NICU or PICU setting as well as studies that provided some details on the method used to isolate the MRSA strain. High-quality studies were those with a quality score greater than the 75th percentile.

**Data Analysis**

A pooled random effects analysis was used to calculate the combined
prevalence and the 95% confidence intervals (CIs), by using the approach of DerSimonian and Laird.\textsuperscript{19} We used Freeman Tukey arcsine methodology to address stabilizing variances.\textsuperscript{20} The standard approach of inverse variance method to calculate pooled estimates and SEs does not perform well in meta-analysis of prevalence. For prevalence near 0 or 1 (ie, for studies with small or large prevalence), the inverse variance method adds disproportionately large weight, variance becomes small, and the calculated CI may lie outside of the 0 to 1 range. The double arcsine methodology corrects both variances instability and CIs.\textsuperscript{21} We assessed the heterogeneity of study results by the use of $I^2$ metric.\textsuperscript{19,22} Possible sources of heterogeneity were explored through a subgroup and meta-regression technique. The effect of small studies in publication bias was explored by the Egger’s test.\textsuperscript{23} For time trends, model coefficients were transformed to rates and plotted against the index year along with the observed prevalence rates.\textsuperscript{17} In a secondary analysis, restricted to studies providing data on MRSA infections, we calculated the relative risk of infection among colonized compared with noncolonized on admission patients. For our statistical analysis, we used the Stata v11 software package (Stata Corporation, College Station, TX) and MetaXL (EpiGear International Ltd, Queensland, Australia). The significance threshold was set at .05.

**RESULTS**

Our electronic database search yielded 2433 nonduplicate abstracts, and the date of our last search was October 10, 2013. Among these studies, 82 were initially considered eligible by title and abstract for our meta-analysis, and their full text was retrieved and assessed for study inclusion. Of these, 17 studies met our inclusion criteria and were subjected to the meta-analysis. Thirty of 82 studies were excluded because they did not include a screen for MRSA colonization on admission. Twelve studies were excluded because they provided non-stratified data for all hospitalized patients, including adults. Nine studies were not considered to have extractable data because, although they reported the number of MRSA carriers on admission, they did not report the number of patients screened. Finally, 14 studies performed screening both on admission and weekly thereafter without reporting the admission prevalence and were also considered nonextractable. Review of the reference lists of all the included articles yielded 1 additional eligible study. Among the 18 eligible studies, 2 had partially overlapping data,\textsuperscript{24,25} and the maximum relevant information was extracted (Fig 1). The 18 studies that fulfilled our eligibility criteria were published from 2006

![Flowchart of meta-analysis](image-url)
to 2013 and reported data from 1999 to 2011 (Table 1). The studies provided screening data on 19,722 neonatal and pediatric patients. More specifically, 11 studies reported data on 12,284 screened neonates in 12 NICUs, whereas 6 studies reported data on 7,107 children hospitalized in 6 PICUs. There was 1 study containing nonstratified data on 331 neonatal and pediatric patients. In studies that reported data stratified by year or ICU setting, data sets were split to discrete strata and considered separately. The majority of the included studies (11 of 18) were prospective, and the remaining 7 were retrospective.

The pooled prevalence of MRSA colonization on admission to the NICU and PICU was 1.9% (95% CI 1.3%–2.6%; Fig 2). Egger’s test for publication bias yielded insignificant effects (bias –3.92, P = .11), suggesting absence of small study effect. Also, quality score did not significantly affect colonization estimates (meta-regression coefficient –0.02, P = .26). Details of the quality assessment of all the eligible studies are provided in Supplemental Table 4.

Of the 18 studies, the most common place of origin was North America (11 studies; 61.1%), followed by studies from Asia (5 studies; 29.4%) and Europe (2 studies; 27.8%). No studies from South America, Africa, and Australia were identified. The pooled prevalence of MRSA colonization from the 11 studies that were conducted in the United States was 2.3% (95% CI, 1.6%–3.2%), compared with 1.3% (95% CI 0.3%–2.9%) from studies conducted in Asian countries; the observed difference was not statistically significant (P = .18). The summary prevalence estimates are presented in Table 2.

Among NICU patients, the prevalence of MRSA colonization on admission was 1.5% (95% CI 0.9%–2.2%), compared with 3.0% (95% CI 1.9%–4.5%) among patients hospitalized in the PICU. The observed difference was marginally significant (P = .05). Three of 18 eligible studies subgrouped their population into inborn and outborn and reported stratified data on 2,726 inborns and 990 outborns. Interestingly, the prevalence of MRSA colonization among outborn neonates was 5.8% (95% CI 1.9%–11.4%), compared with just 0.2% (95% CI 0.0%–0.9%) among inborn

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</table>

Time was from admission to screening. n was the evaluable sample. Data stratified by location (Europe, North America, Asia) and midyear of each study. A, axilla; C, culture; Coh, cohorting of colonized patients; CP, contact precautions to colonized patients; D, diaper area; Decol, decolonization policies (mupirocin and/or chlorhexidine bathing); E, ear; G, groin; N, nares; NR, not reported; OA, on admission; P, perineum; Pre-CP, preemptive contact precautions to patients admitted until their colonization status becomes known; R, rectum; T, throat; U, umbilicus.

a Decolonization with enteral vancomycin.
neonates, and the difference was statistically significant \((P = .01)\).

Among PICU patients, the nares were the only anatomic site screened in all but 1 study. Among studies that included NICU patients, the most common screening policy (in 6 of 11 studies) was sampling of extranasal sites such as umbilicus, axilla, groin, throat, rectum, and external acoustic meatus along with sampling of the nares, whereas in 1 study only extranasal sites were screened. In the NICU, sampling solely the nares yielded a prevalence of MRSA colonization of 1.7\% (95\% CI 0.9\%–2.7\%), which was not statistically different \((P = .72)\) from the colonization rates of other screening policies (1.4\%, 95\% CI 0.5\%–2.5\%).

Regarding the microbiological assays used in the studies included in our analysis, 12 studies exclusively used culture to isolate MRSA, 4 exclusively used PCR, and 2 used both culture and PCR. Of note is that PCR alone yielded a prevalence of 2.2\% (95\% CI 1.5\%–3.1\%), which was not significantly higher from the 1.9\% (95\% CI 1.2\%–2.8\%) of MRSA colonization detected by culture methods \((P = .80)\).

To model the course of MRSA colonization on admission to the NICU and PICU, we used the index year of the studies, as described in the Methods section, and we observed no significant time-trend \((P = .6; \text{Fig 3})\). Eight studies provided data on the acquisition of MRSA during the ICU stay. The acquisition rate was 4.1\% (95\% CI 1.2\%–8.6\%) among the neonatal and pediatric population, whereas among the neonatal population alone, 6.1\% (95\% CI 2.8\%–10.6\%) of patients acquired MRSA during the NICU stay. The pooled acquisition rate for the PICU population alone was not calculated because of insufficient data reporting (2 studies). The acquisition rate was lower in studies in which de-colonization measures were implemented (1.8\%; 95\% CI 0\%–6.7\%) compared with those that did not de-colonize patients (6.5\%; 95\% CI 2.0\%–13.2\%), but this difference failed to reach statistical significance \((P = .15)\).

Seven of 18 studies (4 that included NICU patients and 3 that included PICU patients) followed the patients until their discharge, transfer to another facility, or death and provided data on the development of MRSA infections. The data of each individual study are summarized in Table 3. Two studies were not analyzed because 1 did not have any patient colonized on admission, and 1 did not report any MRSA infection among both colonized and noncolonized patients. Across the 5 studies with analyzable data, we found that the relative risk for MRSA infections among patients who were colonized with MRSA on admission was 24.2 (95\% CI 8.9–66.0) compared with the patients who were not colonized (Fig 4). In clinical terms, this indicates that colonized neonates are 24.2 times more likely to develop a MRSA infection during their hospitalization compared with noncolonized neonates.

**DISCUSSION**

Recent multicenter studies have demonstrated a reduction in the rate of MRSA infection in various vulnerable populations. However, this does not appear to be the trend in the pediatric population. Because colonization is a major independent risk factor for infection, we conducted this meta-analysis to estimate the burden of MRSA colonization on admission to NICUs and PICUs, study its significance on MRSA-associated infections, and model its course over time.

Our results distinguish the epidemiology of MRSA colonization among the pediatric population compared with adults. The observed burden of MRSA colonization among pediatric patients admitted to the NICU and PICU is lower than that among adults admitted to the ICU. This is not surprising and is
associated with both the shorter exposure to the health care system and the smaller number of comorbidities in this population.\textsuperscript{30,43} Even though the estimated burden of MRSA on admission to NICUs is relatively low, it is interesting given the young age of NICU patients and the sterile in utero environment. Transmission of MRSA through breast milk,\textsuperscript{44,45} the birth canal,\textsuperscript{36,46} and contact with family members has been described.\textsuperscript{47,48} However, it appears that MRSA acquisition in this population is closely associated to contact with the health care setting.\textsuperscript{10,49}

A second finding that highlights the importance of contact with the health care setting in acquiring MRSA colonization in this population is the high

![Observed and fitted estimates.](image)

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A, axilla; C, culture; D, diaper area; G, groin; N, nares; R, rectum; T, throat; U, umbilicus.

ref, referent subgroup for comparison.

A second finding that highlights the importance of contact with the health care setting in acquiring MRSA colonization in this population is the high

![Observed and fitted estimates.](image)
acquisition rate during ICU stay. The observed rate is particularly worrisome if we consider that all included ICUs applied policies to prevent MRSA transmission (Table 1). Also, even though a higher rate of MRSA colonization can be observed during outbreaks,10,52 none of the included studies reported data during an outbreak. This observed breakthrough acquisition of MRSA could be explained by the 48-hour turn-around time of culture for MRSA isolation, which results in delays in implementation of infection control measures.53,54 Suboptimal application of such measures also remains a possibility. Of note is that because we did not have enough data to study the time trends of the acquisition rate, we cannot estimate the impact of such measures over time. Also, the time trend of MRSA colonization on admission to the NICU and PICU, which is shown to be stable, does not reflect possible changes in the implementation of cross-transmission policies during the last years because it is determined before the admission to the ICU.

Importantly, children and neonates who are carriers of MRSA on admission to the PICU or NICU are 24.2 times more likely to develop a MRSA-associated infection during their hospitalization (compared with noncolonized). Of note is that the corresponding figure among adult ICU patients was 8.3 (95% CI 3.6–19.2).42 These effects highlight the importance of previous colonization in development of MRSA infections in both populations. The intrinsic characteristics of newborn patients such as the immunologic immaturity, as well as the complexity of care needed in the majority of neonates hospitalized in NICUs,55–57 appear to render this population vulnerable to hospital-acquired infections and underscore the significance of the estimated colonization rate.

It should be noted again that a limitation of English literature was posed in our meta-analysis. Also, our analysis was limited by the quality of the included studies and by the fact that a number of studies that included screening on admission to their protocol did not report extractable data on the corresponding prevalence. Additionally, the acquisition rate could be extrapolated in less than half of eligible studies, and therefore pooled data may be underpowered to detect a significant effect of decolonization. The existing literature could not be used to depict the exact geographic distribution of MRSA colonization in NICU and PICU patients. Also, there were some methodologic differences between studies. As detailed earlier, among PICU patients, the nares were the only anatomic site screened in all but 1 study, whereas among studies that included NICU patients, the most common screening policy (in 6 of 11 studies) was sampling of extranasal sites. However, this difference did not affect our results, and MRSA colonization rate was not statistically different between studies that sampled only nares compared with studies that also sampled extranasal sites. This finding is not surprising and is in accordance with the recommendations of the Chicago Area Neonatal MRSA Working Group that nasal or nasopharyngeal sampling alone is considered sufficiently sensitive to detect MRSA carriage in neonates (recommendation IA—strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies).58

**CONCLUSIONS**

The acquisition rate of MRSA colonization during NICU and PICU stay is disproportionately high, and the 29-fold higher colonization rate of outborn compared with inborn neonates highlights the need of early detection of MRSA colonization among interhospital transfer. Also, the 24.2 relative risk of subsequent infection among MRSA carriers, compared with noncarriers, underscores the importance of reducing the acquisition rate in the NICU and PICU. The development and implementation of molecular diagnostic methods, strict compliance with infection control policies, and establishment of decolonization policies with favorable results among pediatric patients seem to be the necessary next steps in this effort.
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