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Prevention and Treatment of Methicillin-Resistant *Staphylococcus aureus* Colonization in the ICU: A Process of Care That Should Be Considered Mandatory*

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In this issue of *Critical Care Medicine*, Ziakis et al (1) present the results from a meta-analysis examining the prevalence and significance of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization at admission to the general ICU setting. Their study found that 6–8% of ICU patients are colonized at admission, with an upward trend in patient colonization observed between 1990 and 2010 for both the United States and Europe. Most importantly, the authors reported that MRSA-colonized patients had an eight-fold increased risk of developing an MRSA infection compared with patients without MRSA colonization. In other words, on average, 25% of MRSA-colonized patients will develop an MRSA infection. This report suffers from many of the limitations of meta-analyses including significant heterogeneity between studies reflecting the clinical variability of the patients studied and the methods used to determine colonization. The quality of studies included varied and some lacked complete patient-level data. Additionally, this analysis was limited by its inability to account for the influence of concurrent infection control programs on the rates of MRSA colonization, the lack of assessment of MRSA colonization occurring after ICU admission, and the influence of MRSA colonization on occurrence of specific infections (bacteremia, pneumonia, and wound). Despite these limitations, this report provides important rationale for considering the prevention and treatment of MRSA colonization in the ICU to be a mandatory process of care.

The prevention or treatment of MRSA colonization should be considered an essential element in every ICU's infection control program. According to the 2006/2007 annual data report from the National Healthcare Safety Network (NHSN), the surveillance branch of the Centers for Disease Control and Prevention (CDC), *S. aureus* was the second most common cause of healthcare-associated infections (HAIs) (2). Furthermore, it was the most common cause of surgical site infection (SSI) and ventilator-associated pneumonia (VAP). Therefore, the CDC has developed an MRSA toolkit to prevent infection in the healthcare setting (3). Core recommendations include hand hygiene, the implementation of contact precautions, cohorting colonized or infected patients, the recognition of previously colonized patients, rapid reporting of MRSA laboratory results, and education of healthcare professionals. The Centers for Medicare and Medicaid Services has updated the Inpatient Prospective Payment System fiscal rule for 2013 whereby hospitals will not receive the higher payment for cases when one of several selected conditions is acquired during hospitalization (i.e., was not present at admission) (4). Many of these conditions include MRSA infections that often appear in the ICU setting, including pressure ulcers, vascular catheter-associated infections, mediastinitis following coronary artery bypass graft, orthopedic SSIs (spine, neck, shoulder, and elbow), SSIs following bariatric surgery, and SSIs associated with cardiac implantable electronic devices. These governmental mandated recommendations and procedures highlight the importance that HAIs due to MRSA have attained, in the hope of encouraging practices aimed at reducing the morbidity and costs associated with their occurrence. A decade of emphasis on MRSA infections in the United Kingdom has resulted in significant reductions in healthcare-associated MRSA infections from a peak in 2003/2004 (5, 6). However, more than 12,000 cases per year of *S. aureus* bacteremia still occur there, highlighting the need for continued efforts (7, 8). In light of these data, and the need to minimize

*See also p. 433.

Key Words: colonization; infection; intensive care unit; methicillin-resistant *Staphylococcus aureus*

Dr. Kollef's effort was supported by the Barnes-Jewish Hospital Foundation. Dr. Boyer has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0b013e3182a84cb6

antibiotic utilization as part of hospital antimicrobial stewardship programs, specific measures for the prevention and treatment of MRSA colonization should be considered for routine implementation in the ICU.

Various types of MRSA infection prevention programs have been analyzed. Two of the most successful of these programs have focused on central catheter-associated bloodstream infections (CCABSIs) and postsurgical wound infections. Pronovost et al (9) employed an intervention comprising the CDC's evidence-based recommendations for the prevention of CCABSIs in 108 ICUs across Michigan. The median rate of CCABSIs per 1,000 catheter-days decreased from 2.7 infections at baseline to 0 infections at 3 months after implementation of the study intervention ($p \leq 0.002$). This effect was maintained throughout the 18-month study period. Comparable programs have been initiated in hospitals throughout the United States. According to the NHSN, although the prevalence of MRSA CCABSIs increased in all adult ICU types from 1997 to 2001, the prevalence subsequently decreased by 50% or greater from 2001 to 2007 (10). Notably, during the same period, MRSA accounted for an increasing proportion of all *Staphylococcal aureus* CCABSIs. Similarly, adherence to the Surgical Care Improvement Project infection prevention process of care measures (including optimal timing of antibiotic prophylaxis, blood sugar control, and urinary catheter removal) predicted a decrease in postoperative infection rates from 14.2 to 6.8 per 1,000 discharges (adjusted odds ratio, 0.85; 95% CI, 0.76–0.95) (11). However, controversy exists over how these measures should be implemented, with one study showing that the timing of antibiotic prophylaxis may not be so important as long as it is administered prior to surgical incision (12).

Universal surveillance for MRSA has been proposed as a strategy to prevent the transmission of MRSA and to reduce MRSA infection. However, the results of clinical trials have been mixed. Harbarth et al (13) found that a universal, rapid MRSA admission screening strategy did not reduce nosocomial MRSA infection in a surgical department with endemic MRSA prevalence but relatively low rates of MRSA infection. Two other analyses offered contrasting findings. Huang et al (14) retrospectively studied the effect of four infection control interventions on the occurrence and prevalence of MRSA bacteremia in a large hospital with eight ICUs. Routine surveillance of ICU patients and subsequent contact isolation precautions resulted in a hospital-wide 67% reduction in the prevalence density of MRSA bacteremia. Robicsek et al (15) examined the effect of expanded MRSA surveillance on MRSA disease prevalence in a large three-hospital healthcare organization. Three consecutive time periods were compared: no surveillance, surveillance of only ICU admissions, and universal surveillance of all hospital admissions. The aggregate hospital-associated MRSA disease prevalence density changed by –36.2% (CI, –65.4% to 9.8%; $p = 0.17$) from baseline to ICU surveillance and by –69.6% (CI, –89.2% to –19.6%; $p = 0.03$) from baseline to universal surveillance. Although decolonization during the universal surveillance period was recommended, adherence to this practice was not recorded. The cost and questionable impact of universal surveillance have caused many institutions to omit this practice despite the availability of polymerase chain reaction-based MRSA detection methods, which have facilitated the performance of MRSA surveillance.

Measures aimed at preventing the acquisition and spread of MRSA in the ICU have gained favor to include hand washing, gowning, gloving, wearing of short sleeve shirts, avoidance of white coats and ties, and patient cohorting (16–19). However, when these interventions are rigorously evaluated, their overall effectiveness is questionable. In a cluster randomized trial, Huskins et al (20) assessed the effect of surveillance for MRSA and vancomycin-resistant enterococci (VRE) colonization and the expanded use of barrier precautions as compared with existing practice on the prevalence of MRSA or VRE colonization or infection in adult ICUs. The intervention was not effective in reducing the transmission of MRSA or VRE although compliance among healthcare providers was less than required and the use of culture-based techniques to identify MRSA colonization could have prolonged turnaround times.

Decontamination with antiseptics represents the most aggressive approach for the prevention of MRSA infections. Labeau et al (21) performed a meta-analysis of trials employing oropharyngeal decontamination with either chlorhexidine or povidone-iodine for the prevention of VAP. Fourteen studies were included (2,481 patients), 12 investigating the effect of chlorhexidine (2,341 patients) and two povidone-iodine (140 patients). Overall, antiseptic use resulted in a significant risk reduction of VAP (risk ratio [RR], 0.67; 95% CI, 0.50–0.88; $p = 0.004$). Favorable effects were more pronounced in subgroup analyses for 2% chlorhexidine (RR, 0.53; 95% CI, 0.31–0.91) and in cardiosurgical studies (RR, 0.41; 95% CI, 0.17–0.98). Similarly, a recent meta-analysis examined the use of mupirocin nasal ointment in patients with identified *S. aureus* nasal carriage to reduce infection rates (22). The authors found a statistically significant reduction in the rate of *S. aureus* infections associated with intranasal mupirocin (RR, 0.55; 95% CI, 0.43–0.70). However, the infection rate caused by microorganisms other than *S. aureus* was significantly higher in patients treated with mupirocin compared with control patients (RR, 1.38; 95% CI, 1.118–1.72).

Two recent studies examined the role of whole-body decontamination using chlorhexidine baths. Climo et al (23) conducted a randomized, nonblinded, crossover trial involving eight ICUs and one bone marrow transplant unit comparing the role of chlorhexidine-impregnated washcloths with nonantimicrobial washcloths on the prevention of the acquisition of multidrug-resistant microorganisms and the reduction of hospital-acquired bloodstream infections (BSIs). Although the overall rate of MRSA or VRE acquisition was 23% lower during the intervention period (5.1 vs 6.6 cases per 1,000 patient-days, $p = 0.03$), the rate of MRSA acquisition was specifically decreased but not to a level of statistical significance. Additionally, although the overall rate of hospital-acquired BSIs was 28% lower during

the intervention period (4.78 vs 6.6 per 1,000 patient-day, $p = 0.007$), there was no difference in the rate of primary BSIs secondary to *S. aureus* (9 vs 8 BSIs, $p = 0.8$). The reduction in BSIs caused by fungal organisms or coagulase-negative staphylococci offered the greatest statistical impact. Another recent cluster randomized trial compared targeted versus universal decolonization for the prevention of BSIs (24). Adult ICUs among 43 hospitals were assigned to one of three MRSA prevention strategies, with all ICUs in a given hospital assigned to the same strategy. Group 1 implemented MRSA screening and isolation, the previous standard of care in all hospitals; group 2 used targeted decolonization with chlorhexidine baths and mupirocin nasal ointment (i.e., screening, isolation, and decolonization of MRSA carriers); and group 3 applied universal decolonization (i.e., no screening and decolonization of all patients). In pairwise comparisons, universal decolonization resulted in a significantly greater reduction in the hazard of infection (hazard ratio, 0.56; 95% CI, 0.49–0.65) than either screening and isolation (hazard ratio, 0.99; 95% CI, 0.84–1.16; $p < 0.001$) or targeted decolonization (hazard ratio, 0.78; 95% CI, 0.66–0.91; $p = 0.04$). However, similar to the analysis by Climo et al (23), the reduction in MRSA BSIs was not statistically different with universal decolonization compared with screening and isolation and targeted decolonization. The implication of these trials is that universal decolonization prevented infection, may obviate the need for surveillance testing, and could reduce the need for contact isolation. However, if universal decolonization becomes widely implemented, mupirocin and chlorhexidine resistance could emerge resulting in more difficult MRSA infections to treat (25).

The meta-analysis by Ziakis et al (1) adds to the growing impetus for all ICUs to prevent and treat MRSA colonization due to the risk of subsequent infection. Alternatively, the low risk of MRSA infection in noncolonized patients should not lead clinicians to forego empiric antimicrobials targeting MRSA due to the dire consequences of inappropriate antimicrobial coverage. At this time, it remains difficult to recommend specific MRSA prevention measures over others. The current evidence suggests that multifactorial approaches are most likely to succeed (26–28). Individual institutions and ICUs should have a mandatory MRSA prevention component to their infection prevention program. The type of MRSA prevention intervention(s) employed should be based on local expertise and resource availability. Nevertheless, to optimize success such programs should maintain ongoing management support for the program, engage frontline staff in the development and subsequent evaluation or updating of such programs, build the right multidisciplinary team to encourage compliance and adherence, and commit to data collection and feedback.

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Intermittent Positive-Pressure Ventilation, Chest Compression Synchronized Ventilation, Bilevel Ventilation, Continuous Chest Compression, Active Compression Decompression, and Impedance Threshold Device—The Complexity of Ventilation During Cardiopulmonary Resuscitation*

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As many as 300,000 out-of-hospital cardiac arrests may occur annually in the United States. Despite 50 years of research, survival rate remains low between 3% and 17% (1). To maximize the chances of survival of patients with cardiac arrest, it is necessary for the chain of survival to be as efficient as possible.

Chest compression method has not significantly changed since its first description by Kouwenhoven et al (2) in 1960. The two main additions for this mechanical part of the cardiopulmonary resuscitation (CPR) are the active compression decompression (ACD) CPR (3) and the mechanical CPR techniques (4). Even taking into account those changes, the basic idea remains the same: push hard and fast on the chest and do not stop.

***See also p. e89.**

Key Words: cardiopulmonary resuscitation; chest compression; gas exchange; hemodynamics; resuscitation; ventilation

The author has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/01.ccm.0000435688.85468.3a

For ventilation, the second part of CPR, things are much more complicated. There are several competing theories. The first one defended by Ewy et al (5) is in favor of performing continuous chest compressions only CPR, without ventilation, up to the first 15 minutes of CPR. The physiological explanation behind his theory is to limit interruptions of chest compressions by paramedics/firefighters. The second theory promoted by Lurie et al (3) favors the use of an impedance threshold device in combination with ACD CPR. The use of this combination, by decreasing negative intrathoracic and intracranial pressures, increases blood flow to the heart and the brain. This combination, in a prospective randomized trial, improves survival to hospital discharge with favorable neurological function 1 year after out-of-hospital cardiac arrest (6). A third theory is to optimize compression to ventilation ratios. The increase of this ratio caused a direct increase in cardiac output during CPR, related to the increased number of compressions delivered over a minute (30:2 vs 15:2 and vs 15:1) (7). Those three theories go in the same direction of limiting ventilation to control elevation of positive intrathoracic pressure and pauses during CPR, which are responsible for a decrease in venous return to the heart. The last theory promotes the use of mechanical ventilation with more "complicated" multipressure ventilation levels.

In this issue of *Critical Care Medicine*, Kill et al (8) have studied a novel mode of ventilation called "chest compression synchronized ventilation" (CCSV). In this ventilation mode, a

The Prevalence and Significance of Methicillin-Resistant *Staphylococcus aureus* Colonization at Admission in the General ICU Setting: A Meta-Analysis of Published Studies*

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Objective: To estimate the prevalence and significance of nasal methicillin-resistant *Staphylococcus aureus* colonization in the ICU and its predictive value for development of methicillin-resistant *S. aureus* infection.

Data Sources: MEDLINE and EMBASE and reference lists of all eligible articles.

Study Selection: Studies providing raw data on nasal methicillin-resistant *S. aureus* colonization at ICU admission, published up to February 2013. Analyses were restricted in the general ICU setting. Medical, surgical, and interdisciplinary ICUs were eligible. ICU studies referring solely on highly specialized ICUs populations and reports on methicillin-resistant *S. aureus* outbreaks were excluded.

Data Extraction: Two authors independently assessed study eligibility and extrapolated data in a blinded fashion. The two outcomes of interest were the prevalence estimate of methicillin-resistant *S. aureus* nasal colonization at admission in the ICU and the sensitivity/specificity of colonization in predicting methicillin-resistant *S. aureus*–associated infections.

Data Synthesis: Meta-analysis, using a random-effect model, and meta-regression were performed. Pooled data extracted from 63,740 evaluable ICU patients provided an estimated prevalence of methicillin-resistant *S. aureus* nasal colonization at admission of 7.0% (95% CI, 5.8–8.3). Prevalence was higher for North American studies (8.9%; 95% CI, 7.1–10.7) and for patients screened using polymerase chain reaction (14.0%; 95% CI, 9.6–19). A significant per year increase in methicillin-resistant *S. aureus* colonization was also noted. In 17,738 evaluable patients, methicillin-resistant *S. aureus* infections (4.1%; 95% CI, 2.0–6.8) developed in 589 patients. The relative risk for colonized patients was 8.33 (95% CI, 3.61–19.20). Methicillin-resistant *S. aureus* nasal carriage had a high specificity (0.96; 95% CI, 0.90–0.98) but low sensitivity (0.32; 95% CI, 0.20–0.48) to predict methicillin-resistant *S. aureus*–associated infections, with corresponding positive and negative predictive values at 0.25 (95% CI, 0.11–0.39) and 0.97 (95% CI, 0.83–1.00), respectively.

Conclusions: Among ICU patients, 5.8–8.3% of patients are colonized by methicillin-resistant *S. aureus* at admission, with a significant upward trend. Methicillin-resistant *S. aureus* colonization is associated with a more than eight-fold increase in the risk of associated infections during ICU stay, and methicillin-resistant *S. aureus* infection develops in one fourth of patients who are colonized with methicillin-resistant *S. aureus* at admission to the ICU. (*Crit Care Med* 2014; 42:433–444)

Key Words: colonization; infection; intensive care unit; meta-analysis; methicillin resistant; methicillin-resistant *Staphylococcus aureus*

***See also p. 477.**

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Dr. Ziakas did the study design, literature search, data collection, data extraction, statistical analysis and data interpretation, table and figure preparation, and manuscript writing. Dr. Anagnostou did the literature search, data collection, data extraction, and manuscript drafting. Dr. Mylonakis did the study design, data interpretation, manuscript writing, and project oversight.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by the Warren Alpert School of Brown University, the Department of Medicine and the Division of Infectious Diseases.

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e3182a66bb8

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been recognized as a major world-wide epidemic. In the United States only, it is estimated that more than 94,000 MRSA-associated infections occur annually leading to 18,650 MRSA-related deaths (1). Although MRSA colonization is considered a major risk factor of MRSA-associated infections (2), efforts to analyze MRSA prevalence are partially hampered by geographic inconsistencies

and methodological differences between studies of MRSA surveillance (3). ICUs are a major reservoir of MRSA, and multifaceted approaches are applied to control MRSA including surveillance cultures and prevention strategies of MRSA infection. However, controversy exists on efficacy and cost-effectiveness of surveillance strategies in adult ICUs, given the lack of high-quality data (4). The exact extent of the problem in the ICU and its impact on MRSA-associated morbidity is largely unknown. The aim of this review is to analyze the prevalence of MRSA colonization at ICU admission, identify time trends associated with rates of MRSA colonization, and determine the relationship between MRSA colonization and the risk of infection during ICU stay.

MATERIALS AND METHODS

Study Selection

MEDLINE and EMBASE were searched for clinical studies on MRSA nasal colonization at admission in the ICU. Broad search terms were applied and included "MRSA," "methicillin resistant *Staphylococcus aureus*," "colonization," and "carriage." The citations retrieved were initially accessed by title and abstract reading for relevance to the topic. All potentially relevant papers were assessed in full text to determine those eligible for data extraction. The references of eligible studies were also scrutinized to locate additional studies.

Studies that reported raw data on the prevalence of MRSA nasal colonization at admission in the ICU were eligible for data analysis. A language restriction was imposed for English literature. Eligibility was confined to studies reporting data in the general ICU setting, namely medical ICU (MICU), surgical ICU (SICU), interdisciplinary ICUs, and combined data from multiple ICUs in a single or multicenter setting. Studies confined only on highly specialized ICUs (such as pregnant, neonatal, pediatric, burn, neurocritical, and transplantation ICUs) were excluded. We did not include studies reporting data on highly specialized ICUs—because they represent outlying setting compared with a general MICU, SICU, or interdisciplinary ICU setting—thereby reducing potential selection bias due to extreme age (pediatric, neonatal ICUs), immunosuppression (transplantation), or extensive mucosal damage (burn ICUs). Additionally, all studies being identified as covering periods of MRSA "outbreaks" were also excluded from analysis. Data reported as abstracts, conference proceedings, and unpublished material were also excluded. The study conforms to the proposed Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations (5).

Outcomes of Interest

The first outcome of interest was prevalence of MRSA nasal colonization at admission in the ICU, defined as the number of patients colonized at admission, relative to the number "at-risk," that is, those that had the screening procedure at admission. The second outcome focused on the diagnostic value of admission screening to predict ensuing MRSA-associated infection in the ICU.

Data Extraction

After establishing the eligibility of a citation, two authors (P.D.Z., T.A.) independently assessed and extracted data in a blinded fashion. When the extraction was completed, the constructed charts were unfolded and discrepancies were discussed and resolved by consensus. For each study, apart from prevalence, we extracted data on the study design (prospective vs retrospective), the time frame the study was conducted, location and study population, ICU type(s), the screening method used (nasal swab only or nasal swab plus additional site), time from admission to screening, and method for MRSA detection (culture or polymerase chain reaction [PCR]-based assay). We stratified extrapolated information accordingly in discrete datasets, to estimate the weighted average and adjust for confounders. A study was considered having lower probability of bias if it reported extractable data on nasal MRSA colonization

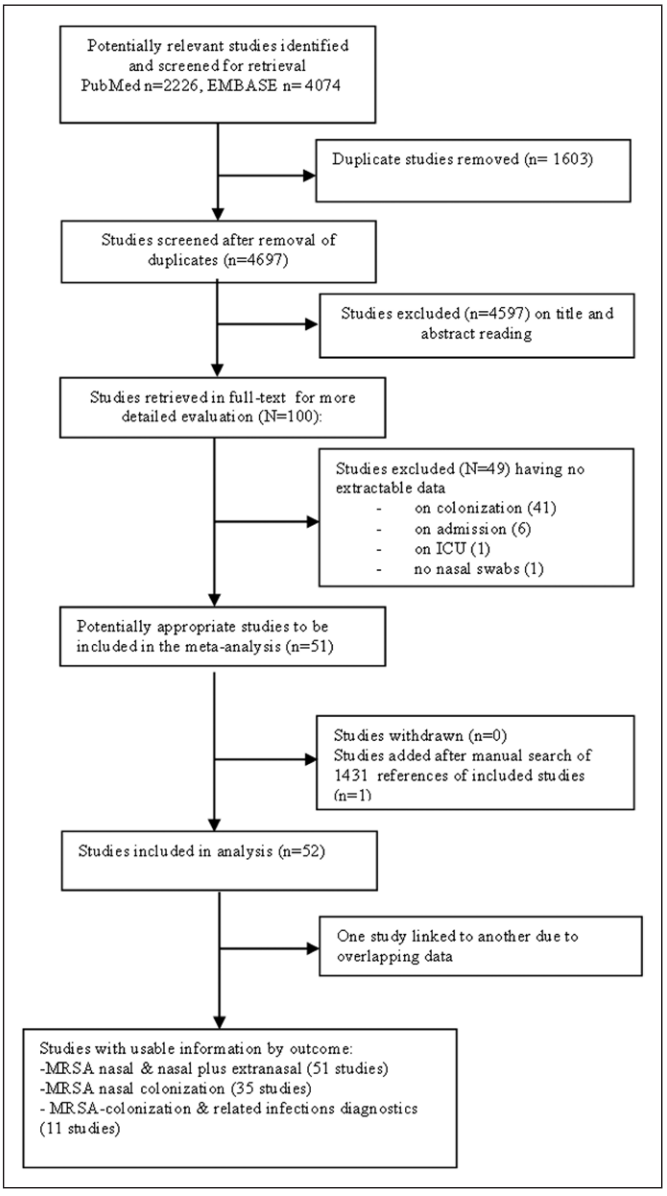

Figure 1. Flow diagram of meta-analysis. MRSA = methicillin-resistant *Staphylococcus aureus.*

TABLE 1. Characteristics of Eligible Studies

Study	Midyear	Location	Time	Screening	Method	*n*	% Methicillin-Resistant *Staphylococcus aureus* Colonized
Europe							
Pujol et al (71)	1991	Spain	NR	N	Culture	488	1.4
Girou et al (69)	1994	France	48–72 hr	N, A, P	Culture	1,390	2.7 (1.8)[a]
Corbella et al (70)	1994	Spain	NR	N	Culture	752	0.4
Talon et al (72)	NR	France	NR	N	Culture	157	8.3
Garrouste-Orgeas et al (67)	1996	France	< 48 hr	N	Culture	1,044	5.2
Lucet et al (64)	1997	France	< 24	N, S	Culture	2,347	6.3 (5.4)[a]
Lucet et al (59)	1998	France	< 24 hr	N	Culture	8,548	6.5
Troche et al (61)	1998	France	1 hr	N	Culture	1,843	3.8
Porter et al (66)	1999	United Kingdom	NR	N	Culture	565	2.8
Cepeda et al (57)	2000	United Kingdom	< 24 hr	N, G, T, W	Culture	866	19.4
Oztoprak et al (53)	2003	Turkey	< 48 hr	N	Culture	249	8.0
Thompson et al (41)	2003	United Kingdom	< 48 hr	N, G	Culture	5,785	8.1
Rymzhanova et al (40)	2004	France	< 48 hr	N	Culture	6,065	3.7
Harbarth et al (52)	2004	Switzerland	< 48 hr	N, P	PCR	1,053	6.7
Viale et al (26)	2005	Italy	NR	N	Culture	3,285	4.2
Harbarth et al (46)	2005	Switzerland	NR	N	Culture	150	8.0
Batra et al (42)	2005	United Kingdom	< 48 hr	S, A, P, T, R, W	Culture	1,470	4.3
Patel et al (43)	2005	United Kingdom	< 24 hr	N, E	Culture	416	6.5
Cunningham et al (44)	2005	United Kingdom	< 48 hr	N, T, A, G, W	Culture/PCR	1,403	7.0
Bloemendaal et al (36, 74)	2006	Europe	< 48 hr	N, P	Culture	629	7.8
Nseir et al (33)	2007	France	NR	N, R, E	NR	625	4.8 (3.5)[a]
Wilson et al (27)	2007	United Kingdom	NR	N, P	PCR	2,583	8.0
Stano et al (23)	NR	Italy	NR	N	PCR	376	6.9
North America							
Mest et al (73)	1992	United States	< 1 hr	N	Culture	484	3.9
Nijssen et al (60)	2000	United States	< 12 hr	N, E	Culture	158	5.7
Clancy et al (51)	2001	United States	< 72 hr	N	Culture	1,890	3.4
Furuno et al (58)	2002	United States	< 48 hr	N, R	Culture	2,440	7.2
Davis et al (62)	2002	United States	< 48 hr	N	Culture	758	3.4
Furuno et al (45)	2003	United States	< 48 hr	N	Culture	2,918	6.1
Jones et al (47)	2003	United States	NR	N	Culture	2,480	13.6
Ridenour et al (50)	2003	United States	NR	N, T, A, P, W	Culture	1,581	10.2
Ridenour et al (54)	2003	United States	NR	N	Culture	845	11.0
Warren et al (55)	2003	United States	< 48 hr	N	Culture	775	10.6
Honda et al (30)	2005	United States	< 48 hr	N	Culture	5,161	13.1
Climo et al (37)	2005	United States	< 48	N	Culture	5,320	11.1

(*Continued*)

TABLE 1. (*Continued*). Characteristics of Eligible Studies

Study	Midyear	Location	Time	Screening	Method	*n*	% Methicillin-Resistant *Staphylococcus aureus* Colonized
Niven et al (39)	2006	Canada	< 48 hr	N	Culture	1,308	3.8
Huskins et al (24)	2006	United States	< 48 hr	N	Culture	3,426	11.4
Nair et al (25)	2006	United States	< 72 hr	N	Culture	5,512	11.4
Blaine et al (28)	2006	United States	NR	N	PCR	840	18.1
Espinoza et al (29)	2006	United States	NR	N	PCR	1,187	12.6
Sarikonda et al (34)	2008	United States	< 48 hr	N	PCR	749	21.9
South America							
Korn et al (68)	1997	Brazil	NR	N, A	Culture	100	46.0
Moreira et al (49)	1997	Brazil	NR	N	Culture	451	16.0
Cavalcanti et al (56)	2003	Brazil	< 48 hr	N, S, A, P	Culture	231	13.0 (10.0)[a]
Asia							
Ho et al (63)	1999	Hong Kong	~ 12 hr	N, T, R	Culture	1,697	12.1
Lee et al (48)	2006	Korea	< 48 hr	N	Culture	218	14.7
Lauderdale et al (32)	2005	Taiwan	< 24 hr	N, T, A, P	Culture	650	10.0 (8.2)[a]
Kurup et al (31)	2008	Singapore	< 24 hr	N	Culture/PCR	647	13.1
Wang et al (35)	2009	Taiwan	< 24 hr	N, T, A, G	Culture	1,703	1.8
Australia							
Marshall et al (65)	2000	Australia	NR	N, T, A, G	Culture	1,185	6.8
Marshall et al (38)	2005	Australia	NR	N, T, A, G	Culture	1,118	6.7

Time = from admission to screening, NR = not reported, N = nose, A = axillae, P = perineum, S = skin, G = groins, T = throat, W = wound, R = rectal, E = endotracheal, PCR = polymerase chain reaction, *n* = evaluable sample.

[a]Data on nasal colonization in parenthesis.

Data stratified by location (Europe, North America, South America, Asia, and Australia) and midyear of each study.

(for consistency and accessibility purposes) and fulfilled at least one of the following: 1) reported data on a single ICU (or stratified data by ICU when multiple ICUs were involved), 2) reported year prevalence (or stratified data by year, when longer periods were covered), and 3) used the same methodology for MRSA detection (or stratified data by methodology used). Otherwise, the study was classified as having higher probability of bias and aggregated data were used. When the time frame of a study was extended to more than 1 year, we crudely adjusted for any time trends by using the midyear as index year of the study. Date of study publication was not used to model time trends, since it varies considerably from the time that each study was actually conducted.

Data Synthesis

We conducted a meta-analysis using a random effects model to estimate the pooled (combined) prevalence and 95% CIs, using the Freeman-Tukey arcsine methodology to deal with stabilizing variances (6). DerSimonian and Laird weights (7) are applied when heterogeneity is found. Between-study heterogeneity was explored using the Cochran's Q statistic and I^2, the latter describing (as proportion) the variation between studies attributed to heterogeneity rather than chance (8, 9). Small study effects were addressed with Egger's test for publication bias (10). We used the "trim and fill" method by Duval and Tweedie (11) to adjust for potentially missing studies. We incorporated a subgroup and meta-regression technique (12) to adjust for potential sources of heterogeneity. We a priori defined potential moderators of outcome, namely additional sites to nasal swabbing, population, index year, and method of MRSA isolation. Samples were classified based on geographic location as European, American, Asian, or Australian (provided that there are at least two eligible studies for each class). We used the index year as continuous variable to model time trends in meta-regression analysis. ICU types were classified as MICU, SICU, or interdisciplinary if the latter refer to data of a single ICU or combine data from multiple distinct disciplines ICUs. Finally, the potential role of methods for MRSA carriage documentation was explored by stratifying studies according to culture or PCR-based techniques. We also addressed the effect of studies with lower versus higher probability of bias.

TABLE 2. Combined (Pooled) Methicillin-Resistant *Staphylococcus aureus* Prevalence Estimates and Subgroup Analysis of Colonization Status at Admission in the ICU

Variable	Studies (Population)	% Prevalence (95% CI)	Heterogeneity	
			Q, *p*	I^2 (%)
All studies	51 (87,927)	8.1 (7.1–9.2)	2,270, < 0.001	96.3
Anatomic site				
Nasal colonization	35 (63,740)	7.0 (5.8–8.3)	1,680, < 0.001	97.2
Nasal colonization (lower bias only)	21 (23,498)	6.4 (4.8–8.3)	743, < 0.001	96.1
Nasal colonization (> 1,000 patients)	15 (51,881)	7.3 (5.5–9.2)	1,050, < 0.001	98.5
Nasal + colonization	21 (29,430)	9.3 (7.9–10.8)	680, < 0.001	94.8
Location[a]				
North America	15 (33,653)	8.9 (7.1–10.7)	616, < 0.001	96.8
South America	2 (682)	13.1 (7.9–19.5)	4.8, 0.03	Not applicable
North/Central Europe	9 (22,169)	4.4 (3.4–5.4)	129, 0.01	89.1
South Europe	5 (5,150)	3.5 (1.4–6.7)	76, < 0.001	94.8
Asia	3 (1,521)	12.0 (8.7–15.7)	12.6, 0.006	76.2
Screening method[a]				
Culture	29 (59,627)	6.3 (5.2–7.6)	1,411, < 0.001	97.0
Polymerase chain reaction	5 (3,488)	14.0 (9.6–19)	64, < 0.001	93.8
Time to screening (hr)[a]				
< 48 hr	13 (28,222)	8.0 (6.0–10.3)	760, < 0.001	97.8
< 24 hr	6 (14,525)	5.9 (4.7–7.3)	76, < 0.001	85.7
Type of ICU[a]				
Medical ICU	5 (3,920)	10.9 (3.6–21.7)	322, < 0.001	98.8
Surgical ICU	8 (12,021)	5.6 (3.5–8.3)	291, < 0.001	95.9

[a]Subgroup analysis is based on studies on nasal colonization only.

A diagnostic meta-analysis was then performed to assess the impact of MRSA nasal colonization on MRSA infection in the ICU (13, 14). We referred to the revised Quality Assessment of Diagnostic Accuracy Studies-2 for assessment of potential bias, which is regarded as suitable for studies when the reference outcome involves follow-up (15). The 2×2 contingency tables were constructed by patient-based data to calculate the sensitivity and specificity for each study. True-positive, false-positive, true-negative, and false-negative observations were the elements of the table based on nasal MRSA at admission and whether or not patients had MRSA-associated infection in the ICU at end of the reference follow-up time. To account for within- and between-study variability, we performed the diagnostic meta-analysis using a bivariate mixed-effects binomial regression model. Pooled (combined) sensitivity, specificity along with their 95% confidence contours, and diagnostic accuracy (area under the curve, AUC) were estimated (16, 17). The Q and I^2 statistics were used again to assess heterogeneity (8). Effects were visualized by plotting the summary receiver operating characteristic curve, with their corresponding 95% confidence contour (16, 18). This methodology is deemed more appropriate when variability beyond the threshold effect is documented (19, 20), suggesting that statistical heterogeneity is present.

We applied the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE, http://www.gradeworkinggroup.org/publications/JCE_series.htm) to assess the quality of evidence in our study regarding the outcome of interest, namely MRSA admission colonization and risk of infection.

The Stata version 11 software package (Stata Corporation, College Station, TX) and StatsDirect version 2.7.9 (StatsDirect, Altrincham, Cheshire, UK) were used for data analysis. The diagnostic meta-analysis was implemented by means of

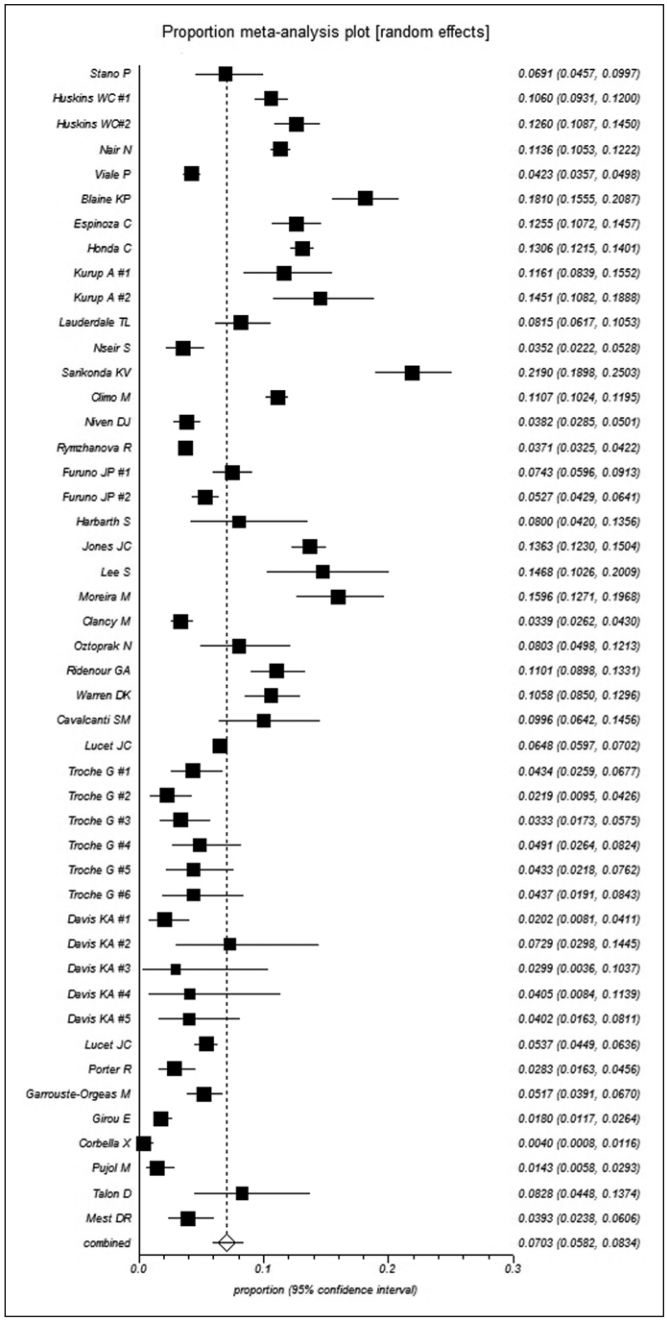

Figure 2. Forest plot with random-effects prevalence estimates (*boxes*) along with 95% CIs (*lines*) and combined (pooled) prevalence (*diamond*).

Meta-analytical Integration of Diagnostic Accuracy Studies set of commands (21, 22) in Stata. Significance threshold was set to 0.05. For heterogeneity testing, the cutoff was set to less than 0.1 due to the low power of the tests.

RESULTS

Our initial database search identified 4,697 nonduplicate citations to evaluate, and last access day was February 19, 2013. After title and abstract screening, 4,597 were excluded on the basis of relevance to the specified criteria, leaving 100 potentially eligible publications. Those were retrieved in full text and meticulously evaluated to gather extractable data on MRSA colonization at ICU admission, including a manual search of their references for additional studies. Forty-nine studies were further excluded mainly for not providing sufficient data to extrapolate. A total of 51 separate studies (coded from 52 published manuscripts) were in accordance with our criteria regarding MRSA colonization on ICU admission, providing admission data on 87,927 ICU patients (flow chart, **Fig. 1**).

Prevalence Estimates of MRSA Colonization Across Studies

The characteristics of the individual studies (23–74) are presented in **Table 1** (stratified data available in **online Appendix Tables S1** and **S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A745). The observed MRSA-colonization rates varied from 0·4% to 46% across studies. European and North American studies were the majority (23 and 18 studies, respectively) and outnumbered Asian (five studies), South American (three studies, all from Brazil), and Australian (two studies). Among the 18 North American studies, 17 were conducted in the United States. Thirty-five studies had extractable data on nasal swabbing only (Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/A745). Among the studies that reported minimal ICU stay, this was 12–72 hours (Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/A745). Data on MRSA colonization by swabbing of nares plus other sites could be extracted from 21 studies (Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/A745). The combined (pooled) estimate for MRSA nasal carriage was 7.0% (95% CI, 5.8–8.3), with significant heterogeneity across studies (**Table 2**; **Fig. 2**). There was evidence of small study effects (Egger's bias 3.75, $p = 0.02$). Estimates did not change with "trim and fill" adjustment. When we excluded studies with less than 1,000 patients, the combined estimate was 7.3% (95% CI, 5.5–9.2). For studies with lower probability of bias (Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/A745), the corresponding estimates were 6.4% (95% CI, 4.8–8.3). In subgroup analysis for screening practice (nasal swabs plus swabs at other sites compared with nasal swabs alone), the pooled prevalence estimates were higher ($p = 0.06$) (Table 2).

Interestingly, the pooled prevalence of MRSA was lower in studies conducted in Europe (4.4% and 3.5% point estimates for North/Central [10 studies] and South Europe [five studies], with difference being insignificant) compared with studies conducted in America (8.9% and 13.1% point estimates for North and South America, respectively) or Asia (12.0% point estimate) (Table 2). The point prevalence estimates for nasal screening within 24 and 48 hours after admission were 5.9% and 8.0%, respectively (Table 2).

Notably, the use of PCR assays was associated with a significantly higher prevalence rate (14.0%; 95% CI, 9.6–19) compared with culture methods (6.3%; 95% CI, 5.2–7.6; $p = 0.002$) (Table 2). Of note is that there was a trend indicating a higher prevalence of MRSA in MICU (10.9%; 95% CI, 3.6–21.7) compared with SICU (5.6%; 95% CI, 3.5–8.3; $p = 0.06$) (Table 2).

The study index year entered the meta-regression analysis to model time trends of colonization, and there was evidence

of significant association and increasing trends per year (**Table S3a**, Supplemental Digital Content 1, http://links.lww.com/CCM/A745). These trends are visualized in **Figure 3**, after adjustment for geographic location. The predicted prevalence estimates are significantly lower for studies reporting data from Europe, but the magnitude of this difference is small (year-adjusted mean difference, 0.3%) compared with U.S. studies. When PCR studies were excluded from meta-regression to remove their potentially confounding effect (**Table S3b**, Supplemental Digital Content 1, http://links.lww.com/CCM/A745), the differences in location (Europe vs United States) was similar (year-adjusted mean difference, 0.25%) and upward per year trend remained significant.

MRSA Nasal Colonization and MRSA Infections in the ICU

A total of 11 studies (23, 25–27, 30, 34, 57, 61, 62, 70, 73) reported extractable data on MRSA colonization at admission and MRSA-associated infections during ICU stay. Two studies included surveillance of other anatomic sites in addition to nasal screening and were excluded from the analysis (27, 57).

Study data and individual diagnostic estimates are summarized in **Table 3**. Additionally, the effect of PCR for MRSA rapid documentation was unknown (23, 34) and was considered a potential moderator of outcome.

The weighted risk across the remaining studies (17,738 evaluable patients at risk with 589 MRSA-associated infections) was 4.1% (95% CI, 2.0–6.8). The relative risk (RR) for colonized compared with noncolonized patients was estimated at 8.33 (95% CI, 3.61–19.20). The quality of evidence on this outcome was moderate based on the GRADE approach (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A745). The corresponding estimates were 0.32 (0.20–0.48) for sensitivity and 0.96 (0.90–0.98) for specificity, with an accuracy (AUC) of 0.74 (0.69–0.77) (**Table 4**; **Fig. 4**). After excluding PCR studies, the RR of MRSA infections did not change (8.73; 95% CI, 4.18–18.26). The estimates did not significantly alter for European versus U.S. studies or for year adjustment (data not shown).

The positive predictive value (PPV) and negative predictive value (NPV) of MRSA nasal colonization at admission were 0.25 (0.11–0.39) and 0.97 (0.83–1.00), assuming prior probabilities of MRSA-associated infection between 2.0% and 6.8%. These estimates suggest that on average of 25% of colonized patients at ICU admission will develop a MRSA-associated infection, compared with only 3% for noncolonized at admission screening.

There was high inconsistency ($I^2 = 98\%$) suggesting significant statistical heterogeneity. Studies with rapid PCR screening yielded an insignificant improvement in sensitivity (0.50; 0.15–0.86). There was also no significant difference between studies reporting data from United States compared with those reporting European data. More specifically U.S. studies had a combined sensitivity of 0.37 (0.19–0.55) and a combined specificity of 0.92 (0.85–0.99) versus 0.27 (0.08–0.45) and 0.98 (0.96–1.00), respectively, for European studies.

Of note is that the majority of studies analyzed in Tables 3 and 4 lack stratified data on the type of MRSA infection relative to colonization status at admission. Therefore, a combined analysis on type of MRSA infection is precluded. Nair et al (25) reported higher rates of bloodstream infection among MRSA colonized at admission compared with noncolonized (7.4% vs 1.3%, $p < 0.001$). In two other individual studies (62, 73), differences did not reach statistical significance. Notably, Sarikonda et al (34) addressed differences between MRSA bacteremia and pneumonia based on admission screening. The PPV of nasal swab was higher for pneumonia (0.18; 0.15–0.20) compared with bacteremia (0.11; 0.09–0.13), whereas the NPV was higher for bacteremia (0.90; 0.88–0.92) compared with pneumonia (0.84; 0.82–0.87) (34).

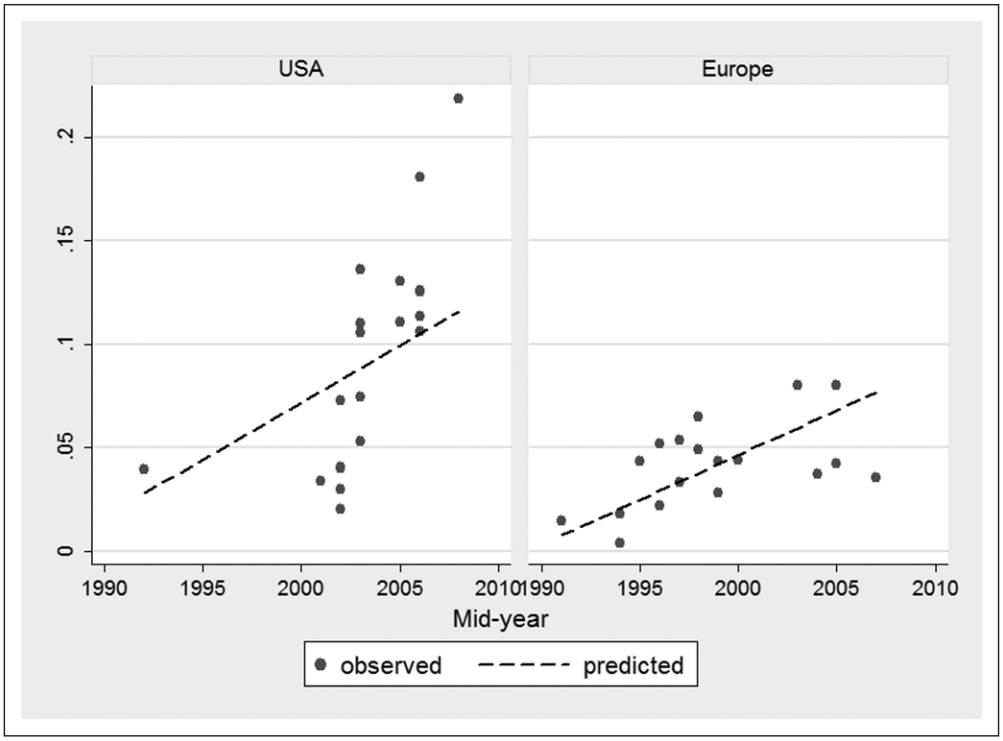

Figure 3. Observed (*closed circle*) and predicted (*dashed line*) prevalence estimates over time, stratified by study geography.

Other Outcomes of Interest

Stratified data on MRSA nasal colonization and mortality were reported in a small number (three of 35) of studies (25, 39, 66) and suggested a trend (RR, 1.31; 95% CI, 0.93–1.87; $p = 0.12$),

TABLE 3. Individual Study Data Included in the Diagnostic Meta-Analysis

Identification No.	Study	Year	Population	Screening	Method	Bias
1	Stano et al (23)	2012	Italy	Nasal	PCR	?
2	Nair et al (25)	2011	United States	Nasal	Culture	Low
3	Viale et al (26)	2011	Italy	Nasal	Culture	Low
4	Honda et al (30)	2010	United States	Nasal	Culture	Low
5	Sarikonda et al (34)	2010	United States	Nasal	PCR	?
6	Troche et al (61)	2005	France	Nasal	Culture	Low
7	Davis et al (62)	2004	United States	Nasal	Culture	Low
8	Corbella et al (70)	1997	Spain	Nasal	Culture	Low
9	Mest et al (73)	1994	United States	Nasal	Culture	Low

PCR = polymerase chain reaction, ? = unclear.

but the quality of evidence for this outcome (evaluated using the GRADE methodology) was low (Table S4, Supplemental Digital Content 1, http://links.lww.com/CCM/A745).

Studies reporting MRSA acquisition rates did not provide extractable data on subsequent MRSA infections (among those colonized during ICU stay and those remaining without colonization), with two exceptions: Corbella et al (70) reported a risk of MRSA infection at 50% among those acquiring MRSA colonization compared with null among those not colonized during ICU stay. Viale et al (26) found a risk of MRSA infection at 19% among those acquiring MRSA colonization compared with only 2.8% among those not colonized. We therefore had limited information to estimate this effect.

DISCUSSION

We conducted this analysis to assess the burden and significance of MRSA colonization in the ICU and its impact on MRSA-associated ICU infections. We have concluded that MRSA colonization at admission shows global variability, and 5.8–8.3% of patients are nasal carriers of MRSA at admission in the ICU. We adjusted this estimate for potential confounders and found that, in addition to geographic location, the MRSA screening method (PCR vs culture) is a significant moderator of outcome. Also, the addition of other anatomic sites to MRSA screening, as well as type of ICU (MICU compared with SICU), had a marginal effect in our estimates. Furthermore, we found a significant per year increase in our predicted prevalence estimates.

Overall, the PPV on the expected risk estimate of MRSA infection suggests that on average 25% of MRSA carriers at ICU admission will have an MRSA-associated infection compared with only 3% of noncarriers at ICU admission. This corresponds to a more than eight-fold risk of MRSA-associated infections, an effect that extends previous reports (75, 76). Furthermore, the high NPV of MRSA screening may be more important in clinical terms than its PPV, given that MRSA-associated infections are highly unlikely to develop in negative patients at admission screening. Therefore, it can be postulated that for this subset of patients, the need for empiric coverage with antistaphylococcal compounds may be obviated, unless strong clinical indication is present.

Acquisition of MRSA in the ICU remains an important variable of the problem and can persist even if strict infection control policies are implemented. In a recent randomized study of intervention (repeated MRSA screening, droplet isolation, decontamination with nasal mupirocin and chlorhexidine) compared with standard precautions, no difference was noted in MRSA infection acquisition (1.6% vs 1.6%) (77). This finding highlights the need for infection control measures and the need for optimal screening approach at admission. In our analysis, there was evidence to support that rapid PCR techniques for MRSA screening have led in documenting higher MRSA prevalence rates at ICU admission. This effect combined with the minimal turnaround time from admission to results reporting (78) will result in identifying more patients within a shorter time (79–82). This higher detection rate is achieved at the expense of more false-positive results, and this should be taken into account in future studies.

We limited our analysis only to studies with nasal swabbing for consistency and accessibility reasons, as investigators suggest that prevalence should be based to this approach and nares represent the major niche for *S. aureus* (3, 83, 84). Swabbing nares alone has a sensitivity that exceeds 80% and outperforms all other anatomic sites. In absolute numbers, the importance of swabbing nares is evident when a sole anatomic site is colonized; if nares are omitted, 25% of MRSA colonized patients will be lost, compared with only 5% for omission of throat culture (85, 86). An interesting finding from our data is that swabbing of additional sites will add a crude 2.3% to MRSA detection (Table 2). Practically, these patients would have been considered noncolonized with nasal swabs only and would be exempted for preventive measures of MRSA transmission.

We found that the epidemiology of MRSA infections shows considerable geographic variability. The phenomenon is attributed to the correlation of MRSA rates with antibiotic consumption policies and compliance with isolation policies, development of infection control and antibiotic stewardship

True Positive	False Positive	True Negative	False Negative	Sensitivity	Specificity
8	18	349	1	0.89 (0.52–1.00)	0.95 (0.92–0.97)
44	555	4,475	59	0.43 (0.33–0.53)	0.89 (0.88–0.90)
10	129	3,058	88	0.10 (0.05–0.18)	0.96 (0.95–0.97)
37	637	4,449	38	0.49 (0.38–0.61)	0.87 (0.87–0.88)
45	119	452	133	0.25 (0.19–0.32)	0.79 (0.76–0.82)
14	42	912	72	0.16 (0.09–0.26)	0.96 (0.94–0.97)
5	21	718	14	0.26 (0.09–0.51)	0.97 (0.96–0.98)
3	0	742	7	0.30 (0.07–0.65)	1.00
5	14	459	6	0.45 (0.17–0.77)	0.97 (0.95–0.98)

programs, and cultural characteristics that affect behavior among the healthcare personnel (87–89).

Prevalence of MRSA colonization can vary from 1% to 20% depending on the healthcare setting and screening policies, selection or not of high-risk patients, anatomic site of sampling, and time of sampling (3). It was interesting that we identified an increasing per year increase that contradicts to the relatively stable prevalence of MRSA nasal carriage among healthy subjects and the general hospital population (90). Although systemic limitations, including reporting bias, are a concern, it seems that the increasing rates in ICU colonization represent a valid trend, given that, as detailed in our analysis, the effect persists after excluding PCR studies (which provide an increased prevalence estimate) as well after adjustment for geographic variation.

Our analysis was limited by the quality of included studies, the majority of which do not provide stratified data on sex, age, prior comorbidities, community-acquired compared with healthcare-associated MRSA colonization, prior decontamination policies, or interventions during ICU stay. These limitations excluded adjusted analysis for our outcomes of interest. Also, the impact of admission colonization status on ensuing type of MRSA infection could not be addressed. Sarikonda et al (34) have suggested that diagnostic performance of MRSA screening may be different for MRSA bacteremia versus pneumonia, but generalization of this notion is questionable due to the relative lack of pertinent data.

All outcomes were characterized by significant statistical heterogeneity, which was only partially explained by the confounders we tested. This heterogeneity reflects the extended between and within studies clinical variability. Also it should be emphasized that screening and surveillance for MRSA constitute only a part of infection control programs with policies varying across countries and institutions, and their relative impact in overall control cannot be objectively estimated. Prevention strategies and decontamination policies are essential parts incorporated in control strategies (91), and adopted guidelines may result in significant reduction of MRSA-acquired infections in the ICU setting (92). Finally, global data may not apply to the specific situations of a center where local epidemiology, diverse population, and prevention strategies may affect outcomes of interest. Furthermore, our study obviously does not address the impact of methicillin-sensitive *Staphylococcus aureus* infections in ICU that is very important. Finally, it should be noted that English language restriction was imposed and that effects on highly specialized ICUs were not addressed.

CONCLUSION

As information on the magnitude of MRSA burden largely relies on swabs and clinical cultures taken at admission or during stay, the lack of a standardized prototype should be noted.

TABLE 4. Combined Effects (95% Confidence Contours) and Subgroup Analysis

Studies	Sensitivity (95% CI)	*p*	Specificity (95% CI)	*p*
All (nine studies)	0.32 (0.20–0.48)		0.96 (0.90 –0.98)	
Subgroup analysis				
Culture screening	0.29 (0.14–0.43)	0.25	0.97 (0.94–1.0)	0.24
Polymerase chain reaction screening	0.50 (0.15–0.86)		0.90 (0.73–1.0)	
U.S. studies	0.37 (0.19–0.55)	0.87	0.92 (0.85–0.99)	0.43
European studies	0.27 (0.08–0.45)		0.98 (0.96–1.00)	

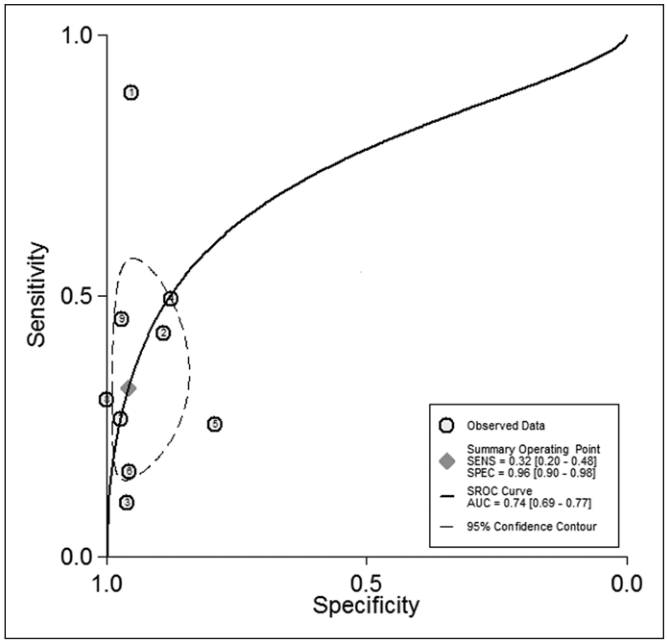

Figure 4. Summary receiver operating characteristics (SROC) curve for diagnostic performance of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal colonization on MRSA-associated infections (*circles* represent the observed estimates of individual studies, and numbers correspond to study Id number as seen in Table 3). AUC = area under the curve, SENS = sensitivity, SPEC = specificity.

Seeking of uniform policy is important and should include swabbing the anterior nares, as well as defining optimal time and method of screening that should probably include adaptation of molecular assays. Our analysis provided valuable data: it identified an upward trend of MRSA nasal colonization in ICU patients at admission, especially in the United States, and associated MRSA colonization with an eight-fold risk of MRSA-related infections. These findings provide support for the implementation of measures to prevent MRSA infections in critically ill patients.

ACKNOWLEDGMENT

We are indebted to Dr. Lori Scott-Sheldon for reviewing the statistical methodology and providing useful feedback.

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