

Association between nasal colonization of *Staphylococcus aureus* and surgical site infections in spinal surgery patients: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The study aimed at examining the relationship between nasal colonization of *Staphylococcus aureus* (SA) or methicillin-resistant *Staphylococcus aureus* (MRSA) and the risk of SSI after spinal surgeries

MATERIALS AND METHODS: PubMed, CENTRAL, Scopus, Web of Science, and Embase databases up to 24th September 2022 for articles on nasal colonization of SA/MRSA and spine surgeries.

RESULTS: Ten studies were included. Meta-analysis revealed that the incidence of SSI was not significantly different between SA-positive and SA-negative patients (RR: 0.75, 95% CI: 0.47, 1.18 $I^2=2%$ $p=0.21$). It was noted that when no decolonization was done, there was no statistically significant difference in the risk of SSI between MRSA positive and MRSA negative patients, but a tendency of higher SSI in MRSA carriers (RR: 2.40, 95% CI: 0.91, 6.32, $I^2=37%$ $p=0.08$). However, in the subgroup analysis with decolonization, the risk of SSI was significantly higher in the MRSA-positive group (RR: 2.99, 95% CI: 1.27, 7.03, $I^2=24%$ $p=0.01$). Specifically, the risk of MRSA-SSI was significantly higher in MRSA carriers with (RR: 6.05, 95% CI: 1.14, 31.99, $I^2=43%$ $p=0.03$) and without decolonization (RR: 7.54, 95% CI: 1.43, 39.85, $I^2=38%$ $p=0.02$).

CONCLUSIONS: Evidence from observational studies indicates that only MRSA nasal colonization increases the risk of SSIs in spinal surgery patients. Nasal decolonization was unable to reduce the risk of overall or MRSA-specific SSIs in MRSA carriers. Evidence was biased due to the extremely small number of MRSA-positive patients in the studies and the lack of adjustment of confounding factors.

Key Words:

Nasal decolonization, Infection, Prevention, Vertebrae, Spine surgery.

Introduction

Surgical site infections (SSIs) constitute some of the most dreaded complications after spinal surgery owing to its morbidity, mortality, and associated healthcare costs. Data indicate that SSIs account for 0.7-12% of all complications seen in such patients¹. Expenditure wise the direct and indirect costs due to spinal SSI in the USA alone were around 1 billion to 10 billion and corresponded to 8,000 deaths per year². Management of SSI is cumbersome requiring repeated admissions, wound debridement, implant removal, and extended intravenous and oral antibiotic regimens³. Therefore, there has been an emphasis on preventive measures to reduce the incidence of SSIs by managing patient comorbidities and modifying adverse environmental and surgical variables¹.

Staphylococcus aureus (SA) is one of the commonest commensal skin organisms which is responsible for a large proportion of SSIs⁴. Over time, antibiotic resistance has led to the development of two subgroups of SA, namely, methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA)⁵. Several studies^{5,6} on cardiothoracic, gastrointestinal, and orthopedic surgeries have noted a relationship between SA and MRSA colonization and the risk of SSIs. Compared to SA, MRSA poses a larger threat as infections are difficult to treat with higher mortality rates and healthcare costs⁷. Since up to 30% of humans can be asymptotically and permanently colonized with SA or MRSA, nasal screening and subsequent decolonization have become an efficient way of controlling SSIs in orthopedics surgery patients⁸. However, the data is not unambiguous.

Specific to spinal surgeries, some studies^{9,10} have shown that SA colonization increases the risk of SSI while others^{11,12} have demonstrated no such relationship. If the latter is true, the entire process of screening for nasal carriers before spinal surgery and subsequent decolonization methods only adds to the economic costs for the patient without any clinical benefits. In the past, several studies have attempted to assess the role of SA/MRSA colonization in the risk of SSI after spinal surgeries. But the limited sample size of individual studies and variable results have prevented strong conclusions. Recently, Ning et al¹³ conducted a systematic review on this topic but with only seven studies. With the publication of new studies^{11,12} in the recent past, we conducted an updated systematic review and meta-analysis to examine the relationship between SA/MRSA nasal colonization and the risk of SSI after spinal surgeries.

Materials and Methods

Search and Eligibility

The review protocol was registered on PROSPERO (CRD42022361357) and the PRISMA statement reporting guidelines were followed¹⁴. An exhaustive literature search was conducted in the PubMed, CENTRAL, Scopus, Web of Science, and Embase databases up to 24th September 2022 for articles on nasal colonization of SA/MRSA and spine surgeries. Only English language publications were considered but without any limitation on the date of publication.

We included all types of articles conducted on patients undergoing any type of spine surgery (population). The ‘exposure’ was nasal colonization of SA/MRSA before surgery. The ‘comparison’ variable was the absence of nasal colonization of SA/MRSA. The ‘outcomes’ to be assessed were overall SSI or MRSA-specific SSI. Studies fulfilling this PECO criterion were included in the review.

Exclusion criteria were: (1) Studies not reporting separate data on spinal surgeries. (2) Studies not reporting the number of patients who were SA/MRSA positive or negative at baseline. (3) Studies with duplicate data. (4) Studies not reporting data on any SSI. For articles with data from the same institute from the same period, the one with the maximum number of patients was included. Review articles, case reports, and editorials were not considered

for inclusion. We did not define SSI for the review and all definitions used by the studies were accepted.

A mix of free-text and MeSH search terms with Boolean operators (AND/OR) were used in the literature search. The search terms included “spine surgery”, “spinal surgery”, “lumbar fusion”, “thoracolumbar fusion”, “cervical fusion”, “staphylococcus”, “nasal”, “decolonization”, and “infection”. The PubMed search strategy is presented in detail in **Supplementary Table I**. Identical search strings were used for the remaining databases. The search results were deduplicated and scrutinized based on the eligibility criteria by two reviewers separately first at the title/abstract level and then at the full-text level. Articles completing all eligibility criteria were finally included. Any disagreements were solved by consensus. The references of included studies were also cross-checked for additional articles.

Data Management and Study Quality

Data on the authors, publication date, study location, study type, surgery type, sample size, age, male gender, the timing of nasal screening, SA/MRSA positive patients, decolonization, follow-up, and outcome data were extracted by two reviewers independent of each other. The review aimed at assessing rates of SSI and MRSA SSI in individuals with and without preoperative SA or MRSA colonization.

Two authors judged the study quality based on Newcastle Ottawa Scale (NOS)¹⁵. The NOS has three domains: representativeness of the study cohort, comparability, and measurement of outcomes. Points are given based on the preformatted questions. The final score of a study can range between 0 and 9.

Statistical Analysis

Statistical analysis was done using “Review Manager” (RevMan, version 5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Dichotomous data on SSI were combined to generate effect size as risk ratio (RR) with 95% confidence intervals (CI) in a random-effects model. Publication bias was examined using funnel plots when there were at least 10 studies in the meta-analysis. The I^2 statistic was the tool for examining inter-study heterogeneity. $I^2=25-50\%$ meant low, $50-75\%$ meant medium, and $>75\%$ meant substantial heterogeneity. Subgroup analysis was conducted based on any

decolonization performed for nasal carriers. A separate analysis was conducted for SA, MSSA, and MRSA. *p*-values of <0.05 were statistically significant.

Results

The flow diagram of the search results is shown in Figure 1. At first, 3,775 articles were obtained from all databases. 2,193 duplicates were removed. The remaining 1,582 studies were screened by the abstracts. 1,558 were not related to the study and were excluded. 24 full-text articles were examined and 14 were excluded for various reasons. The remaining 10 studies were then included in this review^{9-12,16-21}.

The data extracted from the studies is presented in Table I. Three^{9,17,21} of the studies were prospective, while the rest^{10-12,16,18-20} were retrospective. All studies had been published between 2014 and 2022. Most of them had been conducted in the USA, while there were two studies^{17,18} from Japan, one from India²¹ and France⁹ each. The sample size ranged between 132 and 4,573 patients. The mean age of the patients ranged from 13 to 63.2 years. The percentage of male patients ranged was 17-60%. The majority of

studies tested the patients for SA/MRSA colonization just before surgery. In five studies^{9-12,20}, the testing was done one week to 12 months before surgery. All studies used nasal swabs for testing. Five studies^{9,10,17,19,20} reported data on both SA and MRSA colonization while the remaining five^{11,12,16,18,21} provided data only on MRSA. Topical mupirocin was the most commonly used decolonization method. The follow-up of the studies ranged from one to 12 months. The NOS score was either 6 or 7.

Meta-Analysis

Four studies^{9,10,19,20} reported SSI between SA-positive and SA-negative patients. Meta-analysis revealed that the incidence of SSI was not significantly different between SA-positive and SA-negative patients (RR: 0.75, 95% CI: 0.47, 1.18, $I^2=2%$ $p=0.21$) (Figure 2). The same four studies^{9,10,19,20} also reported data on the incidence of SSI based on the presence of MSSA positivity. Meta-analysis showed no difference in SSI rates between MSSA positive and negative patients (RR: 0.67, 95% CI: 0.35, 1.27, $I^2=28%$ $p=0.22$) (Figure 3).

All 10 studies^{9-12,16-21} reported data on the incidence of SSI based on MRSA carrier status. However, some studies^{9,10,11,12,17,19} used decoloni-

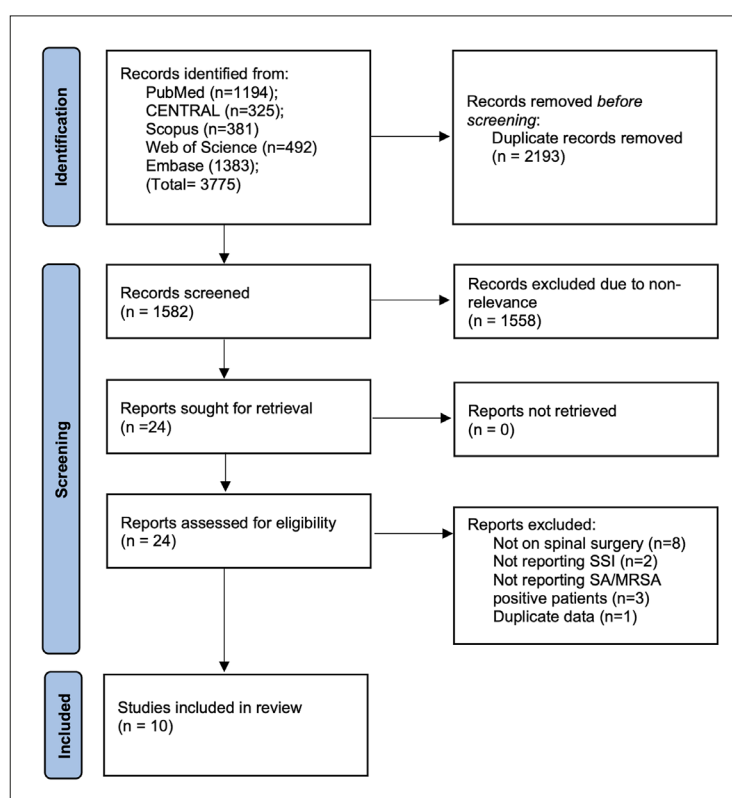


Figure 1. Study flowchart.

Table 1. Details of included studies.

Study	Location	Study type	Surgery type	Sample size	Mean age (years)	Male gender (%)	Timing of screening	Nasal SA positive (%)	Nasal MRSA positive (%)	Decolonization method	Follow-up (months)	NOS score
Thakkar et al ²⁰	USA	R	Arthrodesis and decompression	519	59	48	30 days before surgery	26	4.8	NR	12	6
Ramos et al ¹⁹	USA	R	Primary spinal fusion	3556	51	52	Before admission	18.8	2.7	Topical mupirocin and i.v. vancomycin	12	7
Luhmann and Smith ¹⁰	USA	R	All spine surgeries	339	13	NR	1-4 weeks before surgery	22.1	5.9	Topical mupirocin	12	6
Kobayashi et al ¹⁷	Japan	P	Instrumental spine surgery	132	45	50	Before admission	35.6	3.8	Topical mupirocin	12	6
Mallet et al ⁹	France	P	Adolescent idiopathic scoliosis surgery	331	16	17	Twice within 12 months before surgery	22.7	3	Topical mupirocin and i.v. vancomycin	11	7
Nielsen et al ¹⁶	USA	R	Posterior spinal fusion	1200	14	36	Before surgery	NR	2.8	NR	12	6
Kawabata et al ¹⁸	Japan	R	Elective spinal surgery	4573	61	60	Before surgery	NR	1.1	NR	12	7
Xiong et al ¹¹	USA	R	Primary lumbar fusion	755	63.2	39.9	Within 3 months before surgery	NR	1.7	Topical mupirocin	3	7
Pillai et al ²¹	India	P	All spine surgeries	248	47.5	50.8	Before surgery	NR	8	NR	1	6
Xiong et al ¹²	USA	R	Elective cervical spinal fusion	212	63.2	51.4	Within 3 months before surgery	NR	2.8	Topical mupirocin	3	7

R, retrospective; P, prospective; NR, not reported; NOS, Newcastle Ottawa scale.

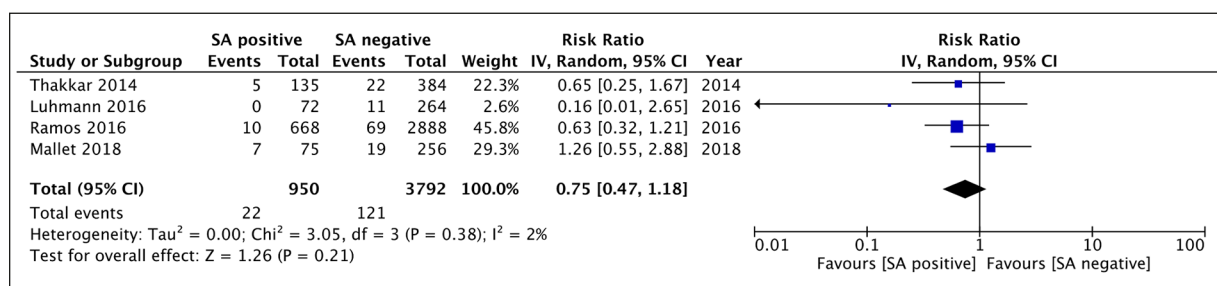


Figure 2. Meta-analysis of SSI between SA positive and negative patients.

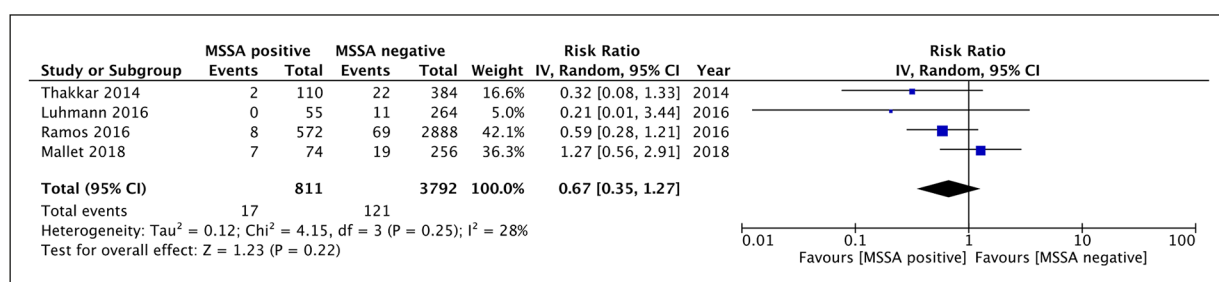


Figure 3. Meta-analysis of SSI between MSSA positive and negative patients.

zation before surgery while others did not^{16,18,20,21}. On subgroup analysis, it was noted that when no decolonization was done, there was no statistically significant difference in the risk of SSI between MRSA positive and MRSA negative patients, but a tendency of higher SSI in MRSA carriers (RR: 2.40, 95% CI: 0.91, 6.32, I²=37% p=0.08) (Figure

4). However, in the subgroup analysis with decolonization, the risk of SSI was significantly higher in the MRSA-positive group (RR: 2.99, 95% CI: 1.27, 7.03, I²=24% p=0.01) (Figure 4). There was no evidence of publication bias (Figure 5).

We also specifically assessed the risk of MRSA-SSI based on MRSA carrier status and de-

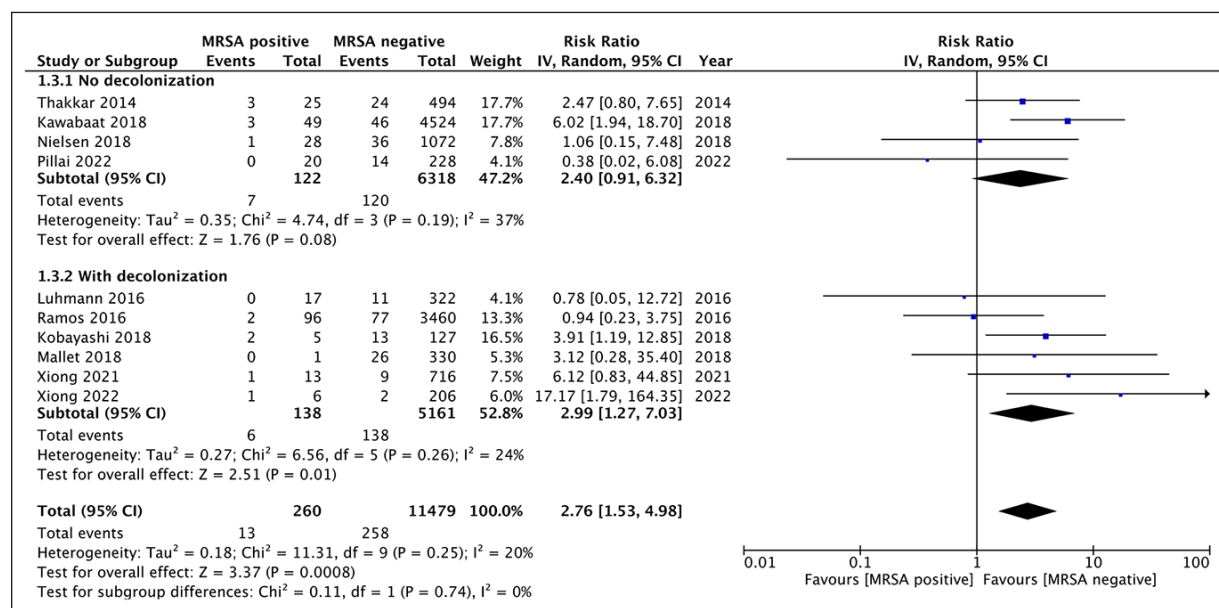


Figure 4. Meta-analysis of SSI between MRSA positive and negative patients with subgroup analysis based on decolonization.

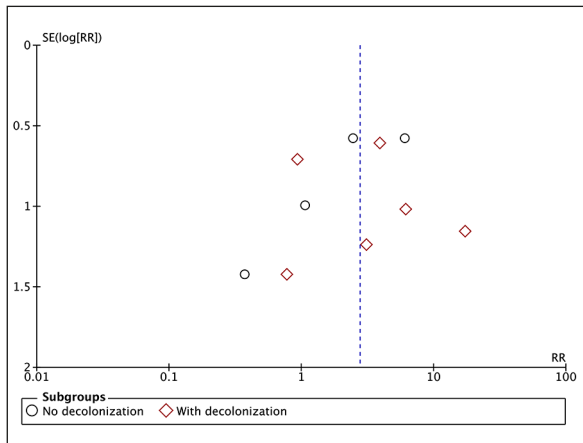


Figure 5. Funnel plot of meta-analysis of SSI between MRSA positive and negative patients.

colonization protocol. It was noted that the risk of MRSA-SSI was significantly higher in MRSA carriers with (RR: 6.05, 95% CI: 1.14, 31.99, $I^2=43%$ $p=0.03$) and without decolonization (RR: 7.54, 95% CI: 1.43, 39.85, $I^2=38%$ $p=0.02$) (Figure 6).

Discussion

The role of nasal carriage of SA/MRSA and subsequent nosocomial infections has been investigated by several studies. Ziakas et al²² examined the prevalence and significance of

nasal MRSA amongst general ICU patients. In a pooled analysis of 63,740 patients, they reported a nasal MRSA prevalence of 5.8-8.3% and a subsequent eight-times-increased risk of infections amongst positive patients. Pongbangli et al²³ have also shown that SA carriers have a higher risk of SSI in patients undergoing elective cardiac surgeries. Specific to orthopedic literature, in 2013, Levy et al²⁴ conducted a meta-analysis to show that nasal SA was a major risk factor for SSI in orthopedic surgery patients. Nevertheless, the authors cautioned in the generalized interpretation of the results owing to high heterogeneity in their meta-analysis. There were wide variations in the methodology of the included studies which prohibited strong conclusions. Furthermore, the review could not differentiate between SA and MRSA sub-groups. Questions on the link between SA carrier status and subsequent SSI have been raised in recent orthopedic studies as well. Nakamura et al²⁵ analyzed the nasal SA carrier state of 4,148 orthopedic surgical patients. 25% of them were SA carriers and 24 patients developed SSIs of which 12 were SA carriers and 12 were non-carriers. Furthermore, in only 7 cases SA was seen in preoperative nasal cultures and subsequent SSI. The results of our review also point in this direction. In the first part of our meta-analysis, we noted that SA or MSSA colonization did not increase the risk of SSI in spinal surgery patients. The SSI risk was 2.3% and 2.09% in SA and MSSA carriers,

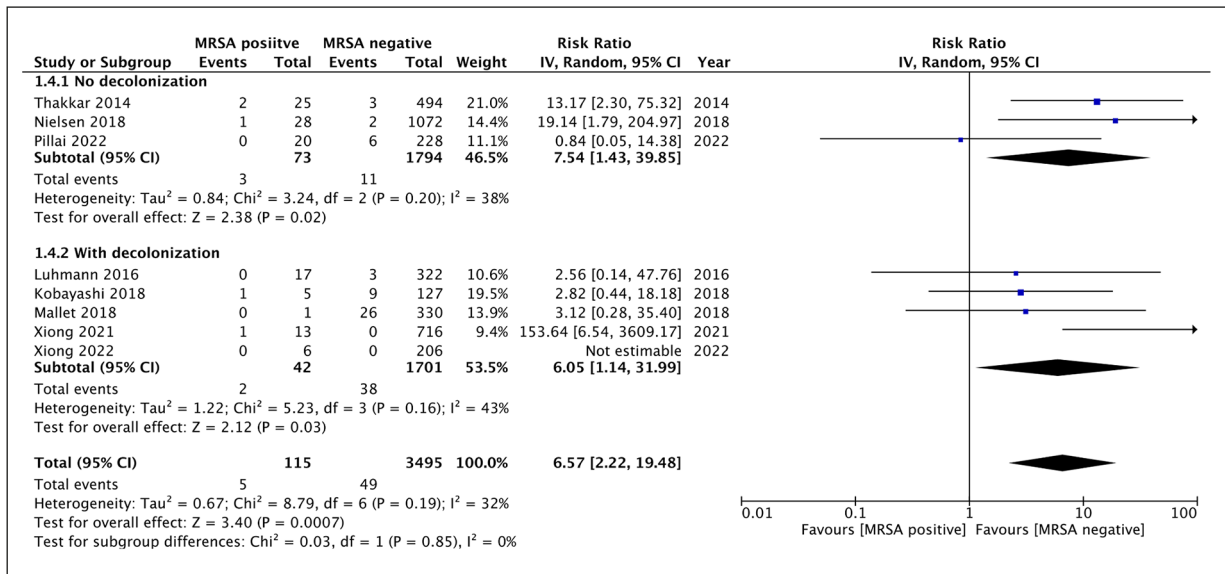


Figure 6. Meta-analysis of MRSA-SSI between MRSA-positive and negative patients with subgroup analysis based on decolonization.

respectively, while in the control group (i.e., in non-carriers) the risk was 3.19%. Similar results were obtained in the previous meta-analysis of Ning et al¹³. The lack of association of SA or MSSA carriage and subsequent SSI could be in part due to the aggressive antibiotic prophylaxis used in spinal surgery patients which could inhibit colonization of SA at the surgical site. Secondly, only four studies^{9,10,19,20} were available for this meta-analysis, thus it is plausible that the meta-analysis may not be powered to detect significant differences.

However, as compared to the previous review¹³, we included three^{11,12,21} new studies which changed the results of the second part of the analysis. Ning et al¹³ in their study assessing the risk of overall SSI amongst MRSA carriers noted that when decolonization was not applied, there was an increased risk of SSIs in MRSA-positive patients (RR: 3.04, 95% CI: 1.22, 7.62). However, while using decolonization, the risk became statistically non-significant (RR: 1.98, 95% CI: 0.78, 5.02). Contrastingly, our updated review discovered opposite results. It was noted that there was a tendency of increased risk of SSIs in MRSA-positive patients when no decolonization was applied, but the risk was statistically non-significant (RR: 2.40, 95% CI: 0.91, 6.32). Nevertheless, since the overall risk was 2.4 and the lower end of 95% CI was very close to 1, it can be considered that SSIs would be higher in MRSA carriers. In studies^{9,10,11,12,17,19} that used decolonization, the results still showed an increased risk of SSIs in MRSA carriers (RR: 2.99, 95% CI: 1.27, 7.03). For MRSA-SSI, Ning et al¹³ noted similar results wherein the risk was increased in MRSA carriers (RR: 15.02, 95% CI: 3.69, 61.19), but in the subgroup of studies using decolonization the risk was non-significant (RR: 2.85, 95% CI: 0.76, 10.66). We noted that the risk of MRSA-SSI was increased in studies not adopting decolonization (RR: 6.05, 95% CI: 1.14, 31.99), as well as in studies where decolonization was done (RR: 7.54, 95% CI: 1.43, 39.85).

Overall, it can be demonstrated by our analysis that there is a higher tendency of SSIs after spinal surgeries in MRSA carriers. In concurrence, Lin et al²⁶ have also shown a higher risk of SSIs in MRSA carriers in total joint arthroplasty patients. Thus, the evidence seems to suggest that specific preoperative screening for MRSA instead of SA or MSSA in spinal surgery patients may help predicting the risk of SSIs. However, the lack of

reduction in the risk of overall and MRSA-SSIs even after decolonization in our review raises important questions.

One reason for the lack of difference in SSI rates in studies using decolonization could be the low number of MRSA-positive patients in the analysis. On examination of the forest plot, it can be seen that in four studies^{9,11,12,17} the number of MRSA-positive patients was very low (total 1-13 patients). It was in these studies that no reduction in SSI rates was noted even with decolonization. Thus, the results may be biased due to such an imbalance in the total number of MRSA-positive and negative patients. A second reason could be the emergence of resistance to mupirocin amongst MRSA. Due to widespread and long-term use, resistance to mupirocin has been identified by many authors with results showing that high-level mupirocin-resistant MRSA can lead to decolonization failure²⁷. It has been suggested that bundle interventions should be used in MRSA carriers consisting of chlorhexidine bathing, topical mupirocin, and intra-operative vancomycin or cefazolin to reduce the concerns of mupirocin resistance.

It should be noted that SSIs in spinal surgery depend on numerous confounding variables. Patient's age, body mass index, baseline comorbidity status, nutritional status, type of surgery (instrumented vs. non-instrumented), use of minimally invasive surgery, duration of surgery, blood loss, antibiotic protocol, use of intra-wound vancomycin, etc. can all influence the risk of SSI in spinal surgery patients²⁸.

Limitations

In our meta-analysis, we could not pool adjusted data due to a lack of reporting by the included studies. Only unadjusted univariate data was analyzed which could have led to confounding bias in the overall results.

Amongst other limitations, one was the preponderance of studies from the USA with limited data from other countries. Surgical and antibiotic protocols differ worldwide and subsequently the risk of SSIs. Hence, currently, the review results cannot be generalized. Secondly, all studies in the review were observational, which is prone to selection bias. Also, there were methodological variations in the included studies for the included patient population, surgery type, and decolonization protocol which could have introduced variations in study results. Lastly, the efficacy of nasal decolonization in SA/MRSA carriers has to be

tested in stringent randomized controlled trials to produce optimal evidence. However, since there are ethical considerations, more stringent prospective studies with large sample sizes should be conducted.

Conclusions

Evidence from observational studies indicates that only MRSA but not SA or MSSA nasal colonization increases the risk of SSIs in spinal surgery patients. Nasal decolonization was unable to reduce the risk of overall or MRSA-specific SSIs in MRSA carriers. Evidence was biased due to the extremely small number of MRSA-positive patients in the studies and the lack of adjustment of confounding factors. There is a need for stringent prospective large-scale studies using similar decolonization protocols to further evaluate the efficacy of nasal decolonization of MRSA in spinal surgery patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

YL conceived and designed the study, LW and HT collected data and performed data analysis. YL and QJ wrote the draft of this manuscript. QJ edited the manuscript.

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