MRSA colonization status as a predictor of clinical infection: A systematic review and meta-analysis

Guillaume Butler-Laporte a,*, Samuel De L’Étoile-Morel b, Matthew P. Cheng a, Emily G. McDonald b, c, Todd C. Lee a, b, c, **

a Division of Infectious Diseases, Department of Medicine, McGill University Health Centre, Montréal, Canada
b Division of Internal Medicine, Department of Medicine, McGill University Health Centre, Montréal, Canada
 c Clinical Practice Assessment Unit, McGill University Health Centre, Montréal, Canada

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SUMMARY

Background: Vancomycin is often used as empiric therapy for methicillin-resistant Staphylococcus aureus (MRSA), but can be associated with clinically important adverse events including renal failure. MRSA colonization swabs are primarily used for infection control; their use as a diagnostic test to inform the decision to add empiric vancomycin therapy has not been well elucidated.

Methods: We performed a Medline and Embase systematic review for peer-reviewed studies reporting the diagnostic accuracy of using MRSA colonization status to predict MRSA infections. Meta-analysis was performed using Cochrane guidelines. Grey literature was excluded.

Findings: 29 studies were included involving 24225 patients. In cases where the pathogen is not known to be S. aureus, specificities were greater than 85% for bacteremia, lower respiratory tract infections, skin and soft tissue infections (SSTI), and all infections pooled together. Sensitivities ranged between 54.0% and 77.5%. In cases where the pathogen is known to be S. aureus, we found studies on bacteremia and SSTI and arrived at pooled estimates of specificities ranging between 56.6% and 56.9%, and of specificities greater than 90%. Most importantly, for most infections in settings where the prevalence of MRSA as a causative organism is below 15%, the negative predictive value of a negative MRSA colonization swab exceeds 90%.

Interpretations: In settings of low-moderate MRSA prevalence, negative MRSA screening swabs may prevent unnecessary vancomycin use. More research is needed to assess if this strategy can mitigate the cost of screening in areas with a low MRSA colonization rate.

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Introduction

Staphylococcus aureus is an important pathogen responsible for infectious syndromes including: skin and soft tissue, bone and joint, pneumonia, and bloodstream infections. Numerous studies have demonstrated a decreased risk of relapse and lower overall mortality associated with the use of targeted beta-lactam therapy over vancomycin, in the treatment of methicillin-susceptible S. aureus (MSSA) infections. The potential benefit of early beta-lactam therapy is often overshadowed by fear of omitting coverage for methicillin resistant S. aureus (MRSA). Such empiric treatment often leads to overuse of anti-MRSA agents, including vancomycin, even in the absence of a proven MRSA infection. For example, over a three-year period a Boston hospital recorded 2910 patients who received at least one dose of vancomycin during their hospital admission, while only 195 (6.7%) were diagnosed with an MRSA infection. Vancomycin can be associated with important adverse outcomes including: acute kidney injury that may occur in up to 29% when combined with piperacillin-tazobactam, increased monitoring costs, selection of vancomycin resistant enterococci, and delays in initiating targeted beta-lactam therapy.

Many healthcare institutions use screening swabs to detect MRSA colonization and institute infection prevention and control measures, including cohorting or isolation, to prevent cross-transmission between patients and healthcare workers. While the cost effectiveness of screening and isolation has been debated, there is data supporting the use of MRSA screening as a guide for empiric antibiotic therapy. Our group has previously published

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that in the absence of ongoing nosocomial transmission of MRSA, a patient’s known colonization status can help guide empiric MRSA therapy in cases of presumed Staphylococcus aureus bacteremia.\textsuperscript{13} Several other studies have evaluated the utility of a negative colonization status in predicting MRSA infection and have also suggested that, particularly in centres with lower prevalence, empiric MRSA therapy can be safely withheld. To better understand the potential role for MRSA colonization in determining the need for empiric coverage, we performed a systematic review of the literature and a meta-analysis of studies that have assessed the risk of MRSA infection as it relates to colonization status.

**Methods**

**Data sources and searches**

This article was prepared and reported according to PRISMA and MOOSE guidelines\textsuperscript{14,15} and followed the Cochrane recommendations for meta-analyses of diagnostic test accuracy.\textsuperscript{16} We performed two separate searches using the OvidSP search interface on the Medline and the Embase library databases from 1961 (the year MRSA was first reported\textsuperscript{17}). We included all original peer-reviewed studies that reported on the diagnostic properties of MRSA screening swabs to predict MRSA infections. The searches were limited to studies published in either English or French. Additional studies were identified by hand-searching references from relevant articles and other published communications.

We developed search strategies focusing on the following common clinical syndromes associated with S. aureus: bacteremia, skin and soft tissue infections (SSTI), surgical site infections (SSI), osteomyelitis, and lower respiratory tract infections (LRTI). Search terms combined MESH terms, text words, and exploded terms, including: methicillin resistant staphylococcus aureus, MRSA, methicillin resistance, carrier state, bacterial colonization, screening, bacteremia, bloodstream infection, pneumonia, surgical wound infection, surgical infection, osteomyelitis, cellulitis, sepsis, respiratory tract infections, pneumonia, and staphylococcal infection. For lower respiratory tract infections, we also analyzed individual studies included in a meta-analysis on the subject.\textsuperscript{15} The full search strategy is available in the supplement.

**Study selection**

To limit bias, only articles that reported sufficient data to allow for computation of two by two tables of MRSA carriage against MRSA infection were included. MRSA carriage status was determined using MRSA colonization screening swabs although methodology could differ between studies (discussed in results). MRSA infections were diagnosed using standard bacteriologic methods. We excluded studies if they were reviews or conference reports, and if they reported exclusively in vitro or non-human studies. Two independent reviewers (GBL and SDLM) screened the potentially relevant studies, first by title and abstract, and then assessed their eligibility and quality by full-text review.

**Data extraction and quality assessment**

Data extraction was performed with a standardized data-extraction form and a protocol was followed. Specifically, the number of true positives, false positives, true negatives, and false negatives were abstracted. Discrepancies were resolved at all stages by consensus. Basic epidemiological data including patient age and sex distributions, location, as well as the microbiological methods used for MRSA identification were abstracted to allow for comparison and patient inclusion and exclusion criteria were summarized. For two studies,\textsuperscript{5,19} the original authors were contacted to obtain itemized data. The Quadas-2 scale was used to assess study quality.\textsuperscript{20}

**Data synthesis and analysis**

Bivariate random effects models were used to generate pooled sensitivity and specificity for the MRSA screening swab in all infections. The meta-analysis was stratified by pathogens (MRSA vs. MSSA, or MRSA vs. any other pathogen), and subdivided by infectious syndromes (bacteremia, SSI, SSTI, LRTI, and all infections combined). For studies comparing MRSA to any other pathogen the inclusion criteria were, in general, broad and included either all patients with positive cultures or all patients with a given syndrome. However, some studies\textsuperscript{12,14} further restricted these groups to those in whom empiric vancomycin was used. The specific inclusion criteria for each study are included in the supplement.

Additionally, we investigated the negative and positive predictive values (NPV, PPV) of MRSA colonization swabs to rule out MRSA infection. We used pooled point estimates of sensitivities, specificities, and their variance–covariance matrices obtained from our meta-analyses to generate graphs of NPV and PPV and their confidence intervals as a function of MRSA disease prevalence by simulating random draws from their joint distribution. The graphs plotting NPV and PPV against MRSA infection prevalence can be found in the supplement. Here, we subjectively selected NPV and PPV levels to help readers understand the MRSA screening diagnostic properties, and we present the maximum prevalence of MRSA infection which could yield negative predictive values of 90% and 95%, respectively, and the minimal prevalence of MRSA infection yielding positive predictive values of 70% and 75%, respectively.

**Meta-analysis was performed and graphs were created with the R statistical software (version 3.2.0) using the meta (version 4.8-1) and the mada (version 0.5.4) packages.**

**Results**

**Included studies**

The original search was performed on February 24, 2017, and updated on May 13, 2018. Fig. 1 outlines the review process. After removing duplicates, 3521 titles were obtained: 746 from Medline, 2228 from Embase, 547 from both). After title and abstract review, 3476 records were excluded, and 48 articles were assessed for final eligibility. Of those, seven did not provide enough information about base infection rates to compute sensitivity and specificity, six did not provide information about MRSA screening practices, six group all S. aureus together without providing specific data on MRSA, four did not include enough data for our computations, and three articles were unrelated to our clinical question. Six articles were also added by screening references. Four papers\textsuperscript{21-24} were added by assessing references from Parente et al. meta-analysis\textsuperscript{18} on lower respiratory tract infections for inclusion. Of note, while their search strategy found four papers we had not found, our search had yielded two papers\textsuperscript{22,27} that were not included in theirs. A full description of reasons for exclusion of papers from Parente et al.\textsuperscript{16} can be found in the supplement. Nonetheless, with respect to pneumonia, the overall conclusions of our two analyses are essentially identical. This left 29 studies for our meta-analysis. Full study characteristics can be found in the supplement.

Although patient level characteristics were not reported precisely enough to perform meta-regression, the overall quality of included studies was satisfactory. The risk of bias from patient selection and microbiological testing was overall low though there were
some concerns over applicability (see Quadas-2 table in supplement). Multiple studies were performed on army veterans\textsuperscript{24–26,31,32} or on critical care patients\textsuperscript{24–26,31,32}, which may impact generalizability. Most studies had otherwise minimal requirements for patient inclusion though three studies required that patients received at least one dose of empiric vancomycin.\textsuperscript{4,21,22} There were variations in the way a patient’s colonization status was determined; some studies collected screening swabs prospectively upon enrolment in the study,\textsuperscript{21,28,31,33–40} while the remainder ascertained colonization before enrolment.\textsuperscript{4,13,19,22–27,29,30,41–47} Microbiological testing methods to determine MRSA colonization varied (see supplement), but were well described apart from two studies.\textsuperscript{20,31}

**Meta-analysis**

Sensitivities and specificities forest plots are shown in supplement 4 with their pooled estimates summarized in Table 1. Table 2 contains the prevalences at which MRSA colonization status would have a negative predictive value of 90% and 95% or positive predictive value of 50%, respectively. Finally, a two-dimensional representation of pooled estimates of the sensitivity as compared to the false-positive rate (1-specificity) is shown in Fig. 2.

**Pathogen unknown**

In cases where the organism responsible for a given infectious syndrome was either not known or included organisms other than *Staphylococcus aureus*,\textsuperscript{24–27,29–40,43,44,46,47} we were able to pool sensitivities and specificities for MRSA infection in the following five syndromes: bacteremia, LRTI, SSI, SSTI, and any infection type together. Specificity exceeded 85% in all cases except for SSI (73.0%, 95% CI: 41.4–91.2). Sensitivity was lower in cases of SSI (55.5%, 95% CI: 35.7, 73.7) and SSTI (54.0%, 95% CI: 37.7, 69.4). Consequently, bacteremia and LRTI had the best negative predictive values, though in the general case of MRSA infections a negative MRSA swab would have a 90% negative predictive value in settings with prevalence below 22.9%.
Table 1
Pooled results of the meta-analysis. Confidence intervals (CI) are based on the crosshair Cls. LRTI: lower respiratory tract infection, MRSA: methicillin resistant Staphylococcus aureus, SSTI: surgical site infection, SSI: skin and soft tissue infection.

<table>
<thead>
<tr>
<th>Including all organisms or when the organism is unknown, what does MRSA colonization say about</th>
<th>Number of patients</th>
<th>Range of outcomes % (min, max)</th>
<th>Pooled estimate % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The risk of MRSA infection</strong>[2,21,22,32,44,46]</td>
<td>Sensitivity 842</td>
<td>Specificity 14178</td>
<td>Sensitivity 55–74</td>
</tr>
<tr>
<td><strong>The risk of MRSA bacteremia</strong>[2,21,46]</td>
<td>Sensitivity 49</td>
<td>Specificity 1239</td>
<td>Sensitivity 71–74</td>
</tr>
<tr>
<td><strong>The risk of MRSA LRTI</strong>[2,22,27,30,32,43,46]</td>
<td>Sensitivity 117</td>
<td>Specificity 1611</td>
<td>Sensitivity 25–87</td>
</tr>
<tr>
<td><strong>The risk of MRSA SSTI</strong>[2,22,30,32,43,46]</td>
<td>Sensitivity 84</td>
<td>Specificity 673</td>
<td>Sensitivity 41–75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Knowing that S. aureus is the pathogen, what does MRSA colonization say about</th>
<th>Number of patients</th>
<th>Range of outcomes % (min, max)</th>
<th>Pooled estimate % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The risk of MRSA bacteremia</strong>[22,43,46]</td>
<td>Sensitivity 425</td>
<td>Specificity 1532</td>
<td>Sensitivity 40–79</td>
</tr>
<tr>
<td><strong>The risk of MRSA SSTI</strong>[22,30,32,43,46]</td>
<td>Sensitivity 466</td>
<td>Specificity 439</td>
<td>Sensitivity 31–94</td>
</tr>
</tbody>
</table>

Table 2
LRTI: lower respiratory tract infection, MRSA: methicillin resistant Staphylococcus aureus, SSTI: surgical site infection, SSI: skin and soft tissue infection. Graphs of post-test probability as a function of prevalence are included in the supplement.

<table>
<thead>
<tr>
<th>Including all organisms or when the organism is unknown, what does a MRSA colonization swab say about</th>
<th>Infectious syndrome</th>
<th>MRSA prevalence (%) above which the positive predictive value exceeds 50% (95% CI)</th>
<th>Median and range of MRSA prevalences in included studies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The risk of MRSA infection</strong>[2,21,22,32,44,46]</td>
<td>22.9 (19.8–26.8)</td>
<td>12.4 (10.5–14.8)</td>
<td>18.6 (12.2–24.4)</td>
</tr>
<tr>
<td><strong>The risk of MRSA bacteremia</strong>[2,21,46]</td>
<td>27.1 (21.2–36.8)</td>
<td>15.1 (13.3–21.6)</td>
<td>12.5 (6.4–19.6)</td>
</tr>
<tr>
<td><strong>The risk of MRSA LRTI</strong>[2,22,27,30,32,43,46]</td>
<td>31.3 (21.6–40.5)</td>
<td>17.8 (12.8–24.4)</td>
<td>11.3 (9.0–13.7)</td>
</tr>
<tr>
<td><strong>The risk of MRSA SSTI</strong>[2,22,30,32,43,46]</td>
<td>17.0 (7.0–28.9)</td>
<td>9.0 (3.5–16.2)</td>
<td>31.2 (9.9–61.6)</td>
</tr>
<tr>
<td><strong>The risk of MRSA SSTI</strong>[2,22,30,32,43,46]</td>
<td>18.7 (14.1–25.3)</td>
<td>9.8 (7.2–13.8)</td>
<td>11.9 (9.4–15.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Knowing that S. aureus is the pathogen, what does a MRSA colonization swab say about</th>
<th>Infectious syndrome</th>
<th>MRSA prevalence (%) above which the positive predictive value exceeds 50% (95% CI)</th>
<th>Range of MRSA prevalences in included studies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The risk of MRSA SSTI</strong>[2,22,30,32,46]</td>
<td>19.4 (10.9–35.7)</td>
<td>10.4 (5.5–20.8)</td>
<td>57.4 (45.3–77.1)</td>
</tr>
</tbody>
</table>

Fig. 2. Summary receiver operating characteristic curves. Each triangle represents an individual study’s diagnostic properties, the small circle is the pooled estimate, the lines are the pooled ROC curve, and the larger circle is the 95% confidence interval surrounding the resulting pooled ROC curve.

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Known *S. aureus*

In cases where the organism responsible for a given infectious syndrome was already known to be *S. aureus*, but methicillin resistance was still undetermined, we could meta-analyze MRSA screening swab sensitivities and specificities for MRSA infection for the following two syndromes: bacteremia and SSTI. Additional knowledge that the pathogen was *S. aureus* at the time of screening swab results increased specificity and decreased sensitivity of the MRSA swab in cases of bacteremia, but had little effect on predictive value in SSTI, perhaps reflecting the fact that *S. aureus* is a more common pathogen in cases of skin infections than other infectious syndromes we studied. Accordingly, when it is known that *S. aureus* is the causative pathogen in bacteremia, the MRSA swab NPV is less than that for an undifferentiated bacteremia, but the PPV is increased. Predictive values for SSTI were grossly unchanged in context of known *S. aureus* infection. Importantly, a negative screening swab has an excellent negative predictive value (>90%) in settings where MRSA is responsible for less than approximately 21% of the infectious syndromes we analyzed.

**Discussion**

For most infectious syndromes included in our study, a positive MRSA screening swab was very specific for MRSA as the causative infectious organism but had variable sensitivity depending on clinical context. For example, in cases of SSTI the specificity was high whether one considered all infections or those specifically due to *S. aureus*. However, the sensitivity was low in both cases meaning that absence of carriage in the sites screened may not adequately determine the presence of MRSA in purulent infected wounds where it may be more likely to be found. Correspondingly, the negative predictive value within this group was poor to exclude MRSA unless the prevalence in the population was very low. Notwithstanding this, in culture negative and non-purulent cellulitis, MRSA may remain an unlikely cause and the Infectious Diseases Society of America does not recommend empiric MRSA therapy for most of those patients. This illustrates the importance of contextualizing the MRSA screening result to the pretest probability based on the clinical scenario and known epidemiology.

In settings or conditions where the prevalence of MRSA disease is low, for bacteremia, LRTIs, SSTIs, and general undifferentiated infections, the screening swab result offers excellent negative predictive values. In the following common clinical scenarios, a negative MRSA colonization swab can help to rule out MRSA infection with greater than 90–95% accuracy: (1) healthcare associated infections, wherein the prevalence of *S. aureus* (MRSA and MSSA) in healthcare associated infections in the USA was 12% between the years 2011 and 2014; (2) bacteremia, wherein the prevalence of MRSA bacteremia (amongst all *S. aureus* bloodstream infections) is reported to be less than 25% (as it is in many European countries and Canada), and (3) MRSA community acquired pneumonia (which is an uncommon clinical entity in the USA). In these settings, for hemodynamically stable patients in the absence of epidemiological risk (local nosocomial outbreaks, known positive close contacts, a concomitant focus of purulent cellulitis), we suggest that clinicians may consider omitting empiric vancomycin. Such a practice could dramatically reduce vancomycin overuse (and other broad spectrum gram-positive coverage) and reduce the rate of vancomycin induced kidney injury, which may be as high as 15%.

Our study was limited by the heterogeneous timing of MRSA screening, by the variation in microbiological methods used, and by the differences in patient population. For example, MRSA screening was performed prospectively in some studies, while others included MRSA swabs that preceded the patient’s infectious presentation. However, we have previously demonstrated that accounting for a patient’s lifetime past MRSA colonization status increases sensitivity with some loss of specificity. Such an approach could further increase the negative predictive value. In some studies, MRSA colonization status was determined retrospectively, and there were considerable differences in the timing of included MRSA swabs in relation to the infectious presentation, and most studies did not specify their screening methodology. Specifically, screening frequency, patient population screened, and sites swabbed (whether systematically or on occasion) were not systematically reported. Although the exact improvement in sensitivity is unclear, more frequent screening and the inclusion of more than one body site leads to increased detection of MRSA colonization. Different practices could in part account for differences in sensitivity between studies.

Finally, significant differences were observed in the microbiological method used to determine MRSA colonization status between studies. Some used “in house” assays, whereas others used industry products. Whereas most studies used PCR or chromogenic based methods, others used a wide range of agars, and methicillin resistance confirmation tests. This may be significant as PCR methods have the greatest reported sensitivity although culture based methods can perform similarly well, if incubated for long enough. While both PCR and chromogenic agars are considered appropriate for MRSA detection, there are differences in performance between the different assays available on the market. Additionally, only three studies reported the use of an NaCl *S. aureus* enrichment broth, and only one reported its use in conjunction with an MRSA specific chromogenic agar. Enriched broths, especially if containing antibiotics such as cefoxitin or aztreonam, are known to significantly increase MRSA detection rates. Perhaps unsurprisingly, the latter study achieved one of the best sensitivities of all included articles.

While these factors increase heterogeneity between studies, their main effect is to reduce the overall sensitivity of MRSA screening swabs in predicting MRSA infections. In clinical settings where standardized microbiological methods are used and applied consistently as part of an MRSA colonization identification and infection control program, the sensitivity and thus negative predictive value of MRSA swabs would be increased compared to our results. We therefore believe our meta-analysis provides a conservative estimate.

Despite these limitations, our study has several strengths. We created a search strategy that allowed us to include good quality studies representative of clinical practice, and could answer an important clinical question relevant to physicians from diverse specialties. Additionally, we separated our results in terms of different infectious syndromes and identified the syndromes wherein MRSA screening swabs are most useful as predictive diagnostic tools. We have presented negative and positive predictive values based on the prevalence of infection to help clinicians utilize these analyses pragmatically.

Finally, this study also reinforces the need for further cost-effectiveness studies into the value of MRSA screening swabs. To date, published literature has addressed the cost effectiveness of MRSA screening to prevent spread of the pathogen, wherein the available evidence suggests that only targeted screening of high risk populations may be cost effective. It is not known if the avoidance of unnecessary empiric MRSA treatment (and associated adverse events) could balance out the financial loss incurred by broader screening programs in lower prevalence populations.

In conclusion, this meta-analysis suggests that a recent negative MRSA screening swab has clinically useful positive and negative predictive properties for MRSA as the causative agent in many infectious syndromes. In the absence of a randomized controlled trial, we propose that for appropriately selected patients, the re-
suits of the MRSA screening swab may be used to guide more appropriate use of empiric MRSA therapy, maximizing the early initiation of targeted beta-lactam therapy, and minimizing avoidable renal injury.

Conflict of interest
No author has any conflicts to declare.

Author contribution
All authors had access to the data and a role in writing the manuscript.

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Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2018.08.004.

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