Comparison of the next-generation Xpert MRSA/SA BC assay and the GeneOhm StaphSR assay to routine culture for identification of Staphylococcus aureus and methicillin-resistant S. aureus in positive-blood-culture broths

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Comparison of the Next-Generation Xpert MRSA/SA BC Assay and the GeneOhm StaphSR Assay to Routine Culture for Identification of Staphylococcus aureus and Methicillin-Resistant S. aureus in Positive-Blood-Culture Broths


A bloodstream infection with Staphylococcus aureus, including methicillin-resistant S. aureus (MRSA), is a serious condition that carries a high mortality rate and is also associated with significant hospital costs. The rapid and accurate identification and differentiation of methicillin-susceptible S. aureus (MSSA) and MRSA directly from positive blood cultures has demonstrated benefits in both patient outcome and cost-of-care metrics. We compare the next-generation Xpert MRSA/SA BC (Xpert) assay to the GeneOhm StaphSR (GeneOhm) assay for the identification and detection of S. aureus and methicillin resistance in prospectively collected blood culture broths containing Gram-positive cocci. All results were compared to routine bacterial culture as the gold standard. Across 8 collection and test sites, the Xpert assay demonstrated a sensitivity of 99.6% (range, 96.4% to 100%) and a specificity of 99.5% (range, 98.0% to 100%) for identifying S. aureus, as well as a sensitivity of 98.1% (range, 87.5% to 100%) and a specificity of 99.6% (range, 98.3% to 100%) for identifying MRSA. In comparison, the GeneOhm assay demonstrated a sensitivity of 99.2% (range, 95.2% to 100%) and a specificity of 96.5% (range, 89.2% to 100%) for identifying S. aureus, as well as a sensitivity of 94.3% (range, 87.5% to 100%) and a specificity of 97.8% (range, 96.1% to 100%) for identifying MRSA. Five of six cultures falsely reported as negative for MRSA by the GeneOhm assay were correctly identified as positive by the Xpert assay, while one culture falsely reported as negative for MRSA by the Xpert assay was correctly reported as positive by the GeneOhm assay.

Bloodstream infection (BSI) is a serious condition, resulting in >500,000 hospitalizations per year in the United States, accounting for up to 11% of intensive care unit admissions (1, 2). Mortality associated with BSI can range from 25% to 80%, depending on underlying illnesses, and it is higher in nosocomial versus community-acquired infections (3–5). Bloodstream infections also carry a high monetary burden, ranging from $36,000 to $40,000 in additional expenses per patient as a result of prolonged hospitalization (4–6). The leading causes of community- and hospital-acquired BSI are Staphylococcus aureus, Staphylococcus epidermidis, and various other coagulase-negative Staphylococcus (CoNS) species (5, 7). Within this group of organisms, infection with methicillin-resistant S. aureus (MRSA) is most critical and has been associated with a mortality rate 1.70 to 1.93 times higher than that of methicillin-susceptible S. aureus (MSSA) strains (8, 9). The outcome of these infections can be positively impacted by early diagnosis and effective antimicrobial therapy (10–12). Rapid diagnostic methods, such as peptide nucleic acid fluorescence in situ hybridization (PNA FISH), matrix-assisted laser desorption ionization–time of mass spectrometry (MALDI-TOF MS), and nucleic acid amplification and detection have been successfully applied to directly analyze positive blood culture broths (13–17). These techniques reduce the time to the identification of pathogens, including Staphylococcus spp., by 18 to 48 h compared to that with conventional culture and biochemical identification methods. The differentiation of S. aureus from CoNS (commonly associated with culture contamination or inadequate skin preparation prior to specimen collection) in blood culture broths can result in a reduced length of hospital stay, vancomycin usage, and overall cost of care (13). Further benefits in patient outcome and cost of care can be achieved using nucleic acid amplification-based tests to detect and differentiate MRSA from MSSA and CoNS (10). This enables the optimization of antimicrobial therapy for MRSA versus MSSA infections (12).

The molecular tests for identification of Staphylococcus spp., including MRSA, directly from positive blood culture broths include the GeneOhm StaphSR assay (BD, Sparks, MD), Verigene BC-GP (Nanosphere, Northbrook, IL), FilmArray blood culture identification (BCID) (BioFire, Salt Lake City, UT), and the Xpert MRSA/SA BC assay (Cepheid, Sunnyvale, CA). Multiplexed assays, such as the Verigene BC-GP and FilmArray BCID, employ

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separate probes for detecting *S. aureus* and *mecA*, the gene that confers resistance to methicillin. This approach has proven to be sensitive for detecting MRSA; however, the independent detection of these markers can result in false-positive results when a culture contains both MSSA and a methicillin-resistant CoNS (MR-CoNS) (14, 18). In contrast, more traditional real-time PCR (RT-PCR)-based assays, including the GeneOhm StaphSR and Xpert MRSA/SA BC assays, target the junction of the staphylococcal cassette chromosome mec element (SCCmec) (a chromosomal cassette harboring *mecA*) and *orfX* in order to specifically identify MRSA. A benefit to this approach is the ability to discriminate MRSA from *S. aureus* and MR-CoNS in mixed cultures. The Xpert MRSA/SA BC assay contains additional primers and probes to ensure that *mecA* is present, reducing the chance of a false-positive result. Initial evaluations of the performance of the GeneOhm and Xpert MRSA/SA BC assays reported 98.3% to 100% sensitivity and 98.4% to 99.4% specificity for the identification of MRSA (17, 19). A drawback to the use of a surrogate marker (SCCmec-orfX) for identifying MRSA is the potential for genetic rearrangements or point mutations that affect either the SCCmec-orfX primer binding sites or the *mecA* gene itself, which can result in false-negative results. Recent studies using pure cultures of previously characterized isolates have reported sensitivities as low as 50% to 92% for identifying MRSA in simulated blood cultures, many of which contained the *mecC* determinant, or as a result of variant SCCmec types or genetic rearrangements/deletions within the SCCmec cassette (20–23).

We compared the performance of the next-generation Xpert MRSA/SA BC assay (Xpert) to that of the GeneOhm StaphSR assay for identifying and detecting *S. aureus* and methicillin resistance in prospectively collected blood broth cultures containing Gram-positive cocci. The new Xpert MRSA/SA BC assay cartridge contains all the reagents required to run the assay on-board, and the time to results is approximately 10 min longer due to changes in the automated sample processing. The two molecular tests were compared to routine culture and identification methods using latex agglutination and cefoxitin disk diffusion tests as the reference method.

**MATERIALS AND METHODS**

**Study enrollment.** Eight clinical centers representing different geographic locations within the United States participated in a prospective study to assess the clinical performance of the next-generation Xpert MRSA/SA BC assay. Each center enrolled blood cultures using BD Bactec Plus Aerobic/F (BD, Sparks, MD), VersaTREK REDOX 1 (Thermo Fisher), or bioMérieux BacT/Alert SA Standard Aerobic (bioMérieux, Hazelwood, MO) medium. The cultures that were identified as positive by an automated blood culture system were Gram stained to confirm the presence of bacteria. Cultures containing Gram-positive cocci as individual cells or in clusters were considered for enrollment in the study. The specimens were tested using the next-generation Xpert MRSA/SA BC assay and the GeneOhm assay, according to the product insert criteria for each test. Only one blood culture per patient was enrolled to avoid duplicate analysis of a single bacterial isolate. The study included blood cultures obtained from both adult and pediatric patients; however, pediatric patients were not the focus of the study and comprised <3% of the cultures enrolled in the study. To avoid bias, the results from the molecular assays were not known to the personnel conducting the reference culture method testing. This study protocol was independently approved by the institutional review board (IRB) at each clinical center.

**Xpert MRSA/SA BC assay.** For the Xpert MRSA/SA BC assay, blood cultures containing Gram-positive cocci were tested within 24 h of culture positivity if held at room temperature or within 72 h if held at 2 to 8°C. A 50-μl aliquot of the specimen was transferred to an elution reagent vial and vortexed for 10 s. The entire contents of the elution reagent vial were then transferred to an Xpert MRSA/SA BC test cartridge, which was sealed and inserted into the GeneXpert for analysis. The Xpert MRSA/SA BC assay targets *spa*, *mecA*, and the SCCmec-orfX junction using proprietary primer and probe sequences. The detection of all 3 targets was interpreted as positive for MRSA. If *spa* was detected alone or in conjunction with SCCmec but *mecA* was not detected, the result was interpreted as *S. aureus* (i.e., MSSA). If *spa* and *mecA* were detected in the absence of the SCCmec-orfX junction, the result was also interpreted as *S. aureus* (i.e., MSSA). If *spa* was not detected, the result was interpreted as negative for *S. aureus* regardless of SCCmec-orfX and/or *mecA* being detected.

**GeneOhm StaphSR assay.** The blood cultures were tested within 48 h of positivity using the GeneOhm assay. A 2-μl aliquot of culture medium was transferred to a sample buffer tube (provided) and vortexed for 10 s. Fifty microliters of the homogenized mixture was transferred to a second tube containing glass beads (provided), vortexed for 5 min to ensure lysis, and heated to 95°C for 2 min. Following reconstitution, 25 μl of reaction master mix and 3 μl of each lyzed heat-inactivated sample were added to individual SmartCycler PCR tubes. Real-time PCR was conducted in the Cepheid SmartCycler II. The results were interpreted as positive for MRSA, positive for *S. aureus*, or negative based upon the detection of amplicon corresponding to SCCmec-orfX and/or proprietary *S. aureus*-specific genetic targets. The specimens generating invalid results (i.e., a reading of “invalid,” “error,” “no result,” or “unresolved”) on either assay were repeated once. The specimens generating a second invalid result were excluded from statistical analysis.

**Reference culture method.** The blood culture broths were plated to agar medium containing 5% sheep blood and incubated for 18 to 48 h. Beta-hemolytic colonies were identified as *S. aureus* using Gram stain morphology, a positive catalase test, and positive *S. aureus* latex agglutination (BactiStaph; Remel, Lenexa, KS). All isolates identified as *S. aureus* were tested for oxacillin/methicillin resistance using the cefoxitin disk diffusion method in accordance with Clinical and Laboratory Standards Institute (CLSI) standards M02-A11 (24) and M100-S22 (25). In brief, a 0.5 McFarland suspension of the test strain was plated on Mueller-Hinton agar (MHA). A 30-μg cefoxitin disk was placed onto the plate, and the culture was incubated aerobically for 16 to 18 h at 35°C, at which point the zone of inhibition was measured and interpreted (≥21 mm, resistant; ≥22 mm, susceptible).

**Data analysis.** The results for each of the molecular assays were compared to those of the reference culture and antimicrobial susceptibility testing methods. The sensitivities and specificities were calculated using standard methods. The 95% confidence interval was determined using the binomial expansion method. The poolability of the data between sites was examined using Fisher’s exact test. If *P* values were <0.05, the difference between the groups was considered to be statistically significant. The statistical significance between the performance (sensitivity and specificity) of each assay was established using McNemar’s test (26).

**RESULTS**

**Study population.** A total of 795 blood culture broths (468 BD Bactec Plus Aerobic/F sites A, B, C, F, and H; 197 VersaTREK REDOX 1 sites D and G; and 130 BacT/Alert SA Standard Aerobic site E) meeting the study criteria were collected and tested at 8 clinical centers using the Xpert MRSA/SA BC assay. The prevalences based on culture-confirmed results were 29.7% (range, 20.8% to 38.6%) for *S. aureus* and 13.3% (range, 7.0% to 17.6%) for MRSA. The Xpert MRSA/SA BC assay successfully returned results for 764/795 broths (96.1%) following the initial test. This increased to 792/795 (99.6%) broths following a single retest of the specimens initially reported to be invalid, error, or no result. A
The identification of MRSA in blood culture broths showed greater variability between the two molecular tests (Table 2). The sensitivity of the Xpert assay was a combined 98.1% (103/105), while the sensitivity of the GeneOhm assay was 94.3% (99/105). The sensitivity of the Xpert assay ranged from 87.5% to 100% across the eight clinical centers but was a combined 100% (77/77) at six of the eight clinical centers. This intersite variability was not statistically significant (P > 0.05, Fisher’s exact test), nor was there a statistically significant difference in performance between the culture media. Across all test sites, the Xpert assay reported two blood cultures to be S. aureus that were confirmed to be MRSA by the cefoxitin disk diffusion test (i.e., false-negative Xpert assay results). Also, one of two blood cultures was negative for MRSA by the GeneOhm assay (Table 3, specimen G013), while the other was positive (Table 3, specimen G013). Of note, specimen G013 was reported to contain MRSA by reference culture, while specimen C039 was reported to contain both MRSA and MSSA. Across 5 test sites, GeneOhm assay reported 6 cultures to be negative for MRSA, for a combined sensitivity of 94.3% (range, 87.5% to 100%). All 6 false-negative reports were had a positive result for S. aureus by the GeneOhm assay only, but 5/6 tested positive for MRSA by the Xpert assay (Table 3).

The specificity of the Xpert assay for identifying MRSA was >99.6% (684/687), with 3 false-positive results across all 8 test sites (Table 2). Two of these results were obtained from blood cultures containing methicillin-susceptible S. aureus; however, one sample was negative for S. aureus by reference culture, indicating possible contamination or the presence of a nonviable organism. The specificity of the GeneOhm assay was 97.8% (662/677). Of the 15 false-positive results for MRSA, 7 blood cultures contained methicillin-susceptible S. aureus, and 9 were negative for S. aureus by reference culture.

### Table 1: Performances of Xpert MRSA/SA BC and GeneOhm StaphSR assays for detection of S. aureus compared to that of routine culture method

<table>
<thead>
<tr>
<th>Test</th>
<th>Site</th>
<th>Total no. of specimens tested</th>
<th>No. with result:</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TP</td>
<td>FP</td>
<td>TN</td>
</tr>
<tr>
<td>Xpert MRSA/SA BC</td>
<td>A</td>
<td>63</td>
<td>19</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>91</td>
<td>32</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>44</td>
<td>17</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>70</td>
<td>26</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>130</td>
<td>27</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>211</td>
<td>65</td>
<td>1</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>126</td>
<td>31</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>57</td>
<td>18</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>792</td>
<td>235</td>
<td>3</td>
<td>553</td>
</tr>
</tbody>
</table>

| GeneOhm StaphSR     | A    | 60                            | 18 | 0  | 42 | 0  | 100 (81.5—100) | 100 (91.6—100) |
|                     | B    | 91                            | 32 | 2  | 57 | 0  | 100 (89.1—100) | 96.6 (88.3—99.9) |
|                     | C    | 52                            | 20 | 1  | 30 | 1  | 95.2 (76.2—99.9) | 96.8 (73.2—95.8) |
|                     | D    | 63                            | 25 | 0  | 38 | 0  | 100 (86.3—100) | 100 (90.7—100) |
|                     | E    | 131                           | 28 | 4  | 99 | 0  | 100 (87.7—100) | 96.1 (90.4—98.9) |
|                     | F    | 202                           | 64 | 8  | 130| 0  | 100 (94.4—100) | 94.2 (88.9—97.5) |
|                     | G    | 127                           | 30 | 0  | 96 | 0  | 96.8 (83.3—99.9) | 100 (96.2—100) |
|                     | H    | 56                            | 17 | 4  | 30 | 0  | 100 (80.5—100) | 89.7 (75.8—97.1) |
|                     | Total| 782                           | 234| 19 | 527| 2  | 99.2 (97.0—99.9) | 96.5 (94.6—97.9) |

Notes:
- **TP**: true positive; **FP**: false positive; **TN**: true negative; **FN**: false negative.
- **CI**: confidence interval.
- **a**: Identified as MRSA and identified as S. aureus (MSSA) by the Xpert MRSA/SA BC assay.
- **b**: Identified as MSSA by culture.
- **c**: Identified as S. aureus (MSSA) by the Xpert MRSA/SA BC assay.
- **d**: Identified as MRSA by reference culture.
The next-generation Xpert MRSA/SA BC assay incorporates a modified sample preparation protocol to improve assay accuracy, although the specific changes to the assay are not publicly available. Though not statistically significant, the Xpert MRSA/SA BC assay demonstrated greater sensitivity than that of the GeneOhm StaphSR test for identifying MRSA. One of the two false-negative results reported by the Xpert assay contained both MSSA and S. aureus. This finding might suggest contamination of the reference culture with MRSA subsequent to molecular testing. The specificity of the Xpert MRSA/SA BC assay was >99.5% for both S. aureus and MRSA, which is equal to or greater than that of the GeneOhm assay. The three specimens with false-positive results for S. aureus by the Xpert assay were also settes” lacking a functional mecA gene (29, 30). Such strains may comprise up to 33% of the SCCmec types, including type IVa, which in some institutions comprise up to 33% of the SCCmec types (20, 22, 23, 28). Additionally, the specificities of these tests for identifying MRSA suffer for strains containing truncated SCCmec cassettes or “empty cassettes” lacking a functional mecA gene (29, 30). Such strains may account for up to 4.6% of the S. aureus strains carrying the cassette (28).

The next-generation Xpert MRSA/SA BC assay incorporates an on-demand sample-to-result molecular test for the identification of S. aureus and MRSA directly from positive blood culture broths. The detection and differentiation of S. aureus and MRSA are achieved by incorporating three nucleic acid targets, including the SCCmec-orfX junction, meca, and spa. The BD GeneOhm StaphSR test uses a two-target approach, relying on the detection of the SCCmec-orfX junction site and an S. aureus species-specific target for the identification of MRSA (17). The initial clinical evaluations of the original Xpert MRSA/SA BC assay and the GeneOhm StaphSR test demonstrated sensitivities of 93.7% to 100% for S. aureus and 98.3% to 100% for MRSA in positive blood culture broths (17, 19, 27). Subsequently, several published reports indicated sensitivities as low as 50% to 92% for detecting MRSA using the GeneOhm and Xpert MRSA/SA assays (20–23). These false-negative results were primarily attributable to mutations in the junction region of SCCmec-orfX, the target of the GeneOhm assay, or to variant SCCmec types, including type IVa, which in some institutions comprise up to 33% of the SCCmec types (20, 22, 23, 28). Additionally, the specificities of these tests for identifying MRSA suffer for strains containing truncated SCCmec cassettes or “empty cassettes” lacking a functional mecA gene (29, 30). Such strains may account for up to 4.6% of the S. aureus strains carrying the cassette (28).

<table>
<thead>
<tr>
<th>Specimen ID*</th>
<th>Zone diam (mm)b</th>
<th>Xpert MRSA/SA BC assay resultc</th>
<th>GeneOhm StaphSR assay result</th>
<th>Xpert MRSA/SA BC assay resultc</th>
<th>GeneOhm StaphSR assay result</th>
</tr>
</thead>
</table>
detected by the GeneOhm assay, suggesting that the reference culture results may have been falsely negative for these specimens.

Seven specimens generated false-negative results for MRSA on at least one of the molecular assays (Xpert MRSA/SA BC, n = 2; GeneOhm, n = 6). The possible causes for this include variant SCCmec cassettes, as previously discussed, the presence of the mecC resistance determinant, or high-level expression of penicillinases leading to borderline oxacillin resistance (31–34). All strains were confirmed to be phenotypically methicillin resistant, demonstrating zones of inhibition ranging from undetectable to 14 mm with the cefoxitin disk diffusion test. It is likely that the resistances in these strains were mediated by mecA as opposed the overexpression of a penicillinase, which typically results in cefoxitin zones of inhibition of ≥28 mm (35). MRSA harboring mecC will display high-level phenotypic resistance to cefoxitin, which is consistent with the MRSA strains not detected by the GeneOhm assay in this study. However, all but two of these strains were correctly identified as MRSA by the next-generation Xpert MRSA/SA BC assay, effectively ruling this out as an explanation for the false-negative results. Combined, this suggests that the false-negative MRSA results observed may have been due to variant SCCmec types not recognized by the GeneOhm assay.

A strength of this study is the participation of 8 clinical centers located in different geographic locations within the United States and the enrollment of a large number of clinical specimens (n = 795), which should account for regional and institutional strain variability. The clinical performance measures (sensitivity and specificity) of the next-generation Xpert MRSA/SA BC assay among all sites were statistically equivalent. This indicates the ability to accurately identify S. aureus and MRSA strains across different geographic locations, accounting for regional and institutional strain diversity. Additionally, these results demonstrate the ability of the next-generation Xpert MRSA/SA BC assay to generate equivalent results independent of laboratory variables, including different technologists, laboratory workflow practices, and blood culture media. Another strength of this study is the head-to-head comparison of the next-generation Xpert MRSA/SA BC assay with the GeneOhm StaphSR assay, a second commercially available FDA-cleared molecular test for the identification of S. aureus and MRSA in positive blood culture broths. Our data demonstrate statistically equivalent performances for these two tests; however, the workflow was simpler with the Xpert MRSA/SA BC assay, which required fewer preanalytic processing steps than the GeneOhm StaphSR and could be conducted on-demand using the random-access GeneXpert system.

A potential weakness of this study was the inclusion of specimens obtained from clinical centers located only within the United States. Several of the studies indicating poorer performances of the GeneOhm and Xpert assays were conducted in the European Union or Australia (20, 21, 23). Clinical evaluations of the redesigned Xpert MRSA/SA BC test in these locations will be necessary to confirm the improved performance demonstrated in the current study. Additionally, specimens that tested as false negative for MRSA were not fully characterized to establish the root cause of the false-negative result; however, only a single specimen tested as false negative on both molecular assays, suggesting that differences in the target and primer design between the tests accounted for the additional false-negative results observed with the GeneOhm assay. Finally, the specimens were not tested simultaneously on both molecular assays. Because the GeneOhm test lends to batch processing, these tests may have been initiated after the initiation of the Xpert test. It is possible that delayed testing negatively impacts results if the specimen contained nucleases that degrade target sequences or accumulated other inhibitory substances resulting from specimen degradation. Alternatively, delayed testing may increase sensitivity due to additional bacterial growth. These factors were not evaluated; however, both molecular tests were performed according to the specimen acceptability criteria set forth in the respective product insert.

The benefits of the rapid detection of S. aureus and MRSA directly from positive blood culture broths are well documented. Specifically, molecular testing for S. aureus and MRSA resulted in a 21% decrease in the number of patients receiving anti-MRSA therapy and a mean reduction of 12.2 h in the duration of therapy for patients with blood cultures containing Gram-positive cocci that tested negative for S. aureus (36). Likewise, the time to optimal antimicrobial therapy for the patients with cultures positive for MSSA was reduced by 38.4 to 44.6 h following the implementation of a molecular test (10, 36). These rapid results contributed to a mean reduction in the length of hospital stay of 6.2 days and a reduction of $21,387 in the total hospital cost per septic episode compared to those of patients diagnosed using routine culture and susceptibility testing methods (10). Importantly, these advantages are realized only when molecular testing can be performed on-demand and the results are actively reported to the clinician. The use of batched testing formats and passive reporting of results does not significantly reduce the time to optimal antimicrobial therapy despite definitive identification of S. aureus and MRSA ~13 h sooner than with culture methods (37). The Xpert and GeneOhm assays demonstrated statistically equivalent sensitivities and specificities for identifying S. aureus and MRSA in positive blood cultures compared to those with the culture method. A potential advantage of the Xpert MRSA/SA BC assay is the simplified sample-to-result workflow and on-demand capability, which gives it the potential to reduce the turnaround time for blood cultures containing S. aureus or MRSA.

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