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Multicenter Evaluation of the Xpert MRSA NxG Assay for Detection of Methicillin-Resistant *Staphylococcus aureus* in Nasal Swabs

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ABSTRACT Health care-associated methicillin-resistant *Staphylococcus aureus* (MRSA) infections are a burden on the health care system. Clinical laboratories play a key role in reducing this burden, as the timely identification of MRSA colonization or infection facilitates infection control practices that are effective at limiting invasive MRSA infections. The Xpert MRSA NxG assay recently received FDA clearance for the direct detection of MRSA from nasal swabs. This multicenter study evaluated the clinical performance characteristics of the Xpert MRSA NxG assay with prospectively collected rayon nasal swabs ($n = 1,103$) and flocked swab (ESwab) nasal specimens ($n = 846$). Culture-based identification methods and antimicrobial susceptibility testing were used as the reference standards for comparison. According to the reference method, the positivity rates for MRSA in the population evaluated were 11.1% (122/1,103) for rayon swabs and 11.6% (98/846) for flocked swabs. The overall sensitivity and specificity of the rayon swabs were 91.0% (95% confidence interval [CI], 84.6 to 94.9%) and 96.9% (95% CI, 95.7 to 97.8%), respectively, across eight testing sites. The flocked swab specimens were 92.9% sensitive (95% CI, 86.0 to 96.5%) and 97.6% specific (95% CI, 96.2 to 98.5%) for MRSA detection across six testing sites. The sensitivity and specificity of the combined flocked and rayon swab data were 91.8% (95% CI, 87.4 to 94.8%) and 97.2% (95% CI, 96.3 to 97.9%), respectively. The positive predictive value (PPV) for rayon swabs was 78.7%, versus 83.5% for ESwabs. The negative predictive values (NPVs) for rayon swabs and ESwab specimens were 98.9% and 99.1%, respectively. In conclusion, the Xpert MRSA NxG assay is a sensitive and specific assay for the direct detection of MRSA from nasal swab specimens.

Hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections are a major cause of morbidity and mortality worldwide (1–3). Recent data from the Centers for Disease Control and Prevention (CDC) estimated that the annual incidence of invasive hospital-acquired MRSA infections was over 55,000, resulting in over 7,700 deaths (4). The identification of carriers and those with active MRSA disease has the potential to reduce infections through infection control practices such as targeted decolonization protocols and patient isolation (5). Therefore, active surveillance of inpatients for MRSA is a strategy for preventing health care-acquired infections (HAIs) by MRSA.

Traditional methods for MRSA surveillance routinely consisted of culture-based screening programs in which nasal swabs were inoculated into medium that is selective and differential for *S. aureus* (6), with methicillin resistance being confirmed by using phenotypic methods. However, this process is burdensome and may take up to 3 days to produce results (7, 8). Chromogenic medium that is specific for MRSA may shorten the process by eliminating the need for susceptibility testing, but the requirement for overnight incubation and the relative lack of sensitivity are limiting compared to many molecular methods (9–13).

There are several FDA-cleared commercial assays available for the molecular detection of MRSA in nasal swabs (14); the Xpert MRSA NxG assay is a new FDA-cleared nucleic acid amplification test for the detection of MRSA from both rayon nasal swabs and ESwab specimens (15). Compared to the previous Xpert MRSA assay, the next-generation assay includes additional proprietary primers and probes that are inclusive of more staphylococcal cassette chromosome *mec* (SCC*mec*) types as well as both the *mecA* and *mecC* genes, which encode methicillin-oxacillin resistance. The sample-to-answer assay requires only a few minutes of hands-on time and takes about 1 h to produce results on a random-access platform. The objective of this study was to evaluate the clinical performance characteristics of the Xpert MRSA NxG assay for the detection of MRSA colonization.

MATERIALS AND METHODS

Specimens. Following institutional review board (IRB) approval at each site, anterior naris specimens were collected from individuals at risk for nasal colonization by MRSA during two separate prospective, multisite investigational studies. The study population consisted of subjects at risk for MRSA nasal colonization, such as patients who were previously isolated due to MRSA nasal colonization, patients with an extended stay in an acute-care or extended-stay facility, or an outpatient clinic population. For the first study, specimens were collected by using paired sterile rayon swabs (Cepheid, Sunnyvale, CA). One swab was used for the Xpert MRSA NxG assay, and the other was used for reference culture. Prior to testing, the swabs were gently brushed together with a twirling motion to ensure an equal distribution of the specimen on the swabs. Rayon swab specimens were collected and tested at 8 clinical trial sites representing different geographic locations both within and outside the United States. In the second study, nasal specimens were collected by using a Copan liquid Amies elution swab (ESwab; Copan Diagnostics, Murietta, CA). ESwab specimens were collected and tested at 6 clinical trial sites within the United States. One site participated in the collection of both rayon swab and ESwab specimens. At this site, either a rayon swab or an ESwab, but not both, was collected from each study participant.

Study sites. For the rayon swab study, specimens were tested at the Washington University School of Medicine (St. Louis, MO), The George Washington University Medical Center (Washington, DC), the Louis Stokes Cleveland DVA Medical Center (Cleveland, OH), the University of California—Davis (Sacramento, CA), TheraFirst (Fort Lauderdale, FL), and Geisinger Health (Danville, PA). Non-U.S. study sites included Changi General Hospital (Singapore) and the Institut für Medizinische Mikrobiologie, Universitätsklinikum Münster (Münster, Germany). ESwab specimens were tested in the United States at ProMedica Laboratories (Toledo, OH), Tampa General Hospital (Tampa, FL), TheraFirst (Fort Lauderdale, FL), the University of Chicago (Chicago, IL), the Harbor-UCLA Medical Center (Torrance, CA), and the University of Oklahoma Health Sciences Center (Oklahoma City, OK).

Xpert MRSA NxG assay. The Xpert MRSA NxG assay (Cepheid, Sunnyvale, CA) was performed according to the manufacturer's instructions (15). Briefly, one swab from the set of rayon swabs was inserted into the elution reagent vial and broken off at the score mark on the swab shaft. For the ESwab device, the specimen was vortexed for 5 s, and 300 μl of the specimen was added to the elution reagent vial. The vial was subjected to vortex mixing for 10 s, and the entire contents were transferred to the

TABLE 1 Demographics of study subjects

Subject parameter	No. (%) of specimens		
	Rayon swabs	ESwabs	All
Males	772 (70.0)	422 (49.9)	1,194 (61.3)
Females	331 (30.0)	424 (50.1)	755 (38.7)
Age range (yr)			
2–5	5 (0.5)	1 (0.1)	6 (0.3)
6–12	6 (0.5)	1 (0.1)	7 (0.4)
13–21	27 (2.4)	40 (4.7)	67 (3.4)
22–65	735 (66.6)	635 (75.1)	1,370 (70.3)
>65	330 (29.9)	169 (20.0)	499 (25.6)
Patient location			
Inpatient	669 (60.7)	302 (35.7)	971 (49.8)
Outpatient	309 (28.0)	272 (32.2)	581 (29.8)
Emergency department	125 (11.3)	272 (32.2)	397 (20.4)
Total	1,103	846	1,949

sample chamber of an Xpert MRSA NxG assay cartridge by using the provided transfer pipette. The cartridge was loaded into a GeneXpert instrument for testing. If the initial Xpert MRSA NxG assay result was indeterminate, the specimen was retested one additional time. On each day of testing, acceptable results from one positive control and one negative control were required prior to the testing of experimental specimens. Each Xpert MRSA NxG cartridge includes a sample processing control (SPC) and a probe check control (PCC). The SPC ensures adequate processing of the sample and monitors for the presence of inhibitors in the PCR mixture. The PCC verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability. Results of testing were considered invalid if either the SPC or PCC failed. All specimens were tested by using the Xpert MRSA NxG assay within 24 h of collection. Remnant ESwabs and the second rayon swab were shipped on wet ice to a reference laboratory (NorthShore University HealthSystem) for reference method testing.

Comparative reference method. The gold-standard method used for comparison consisted of inoculation into the FDA-cleared MRSA-selective chromogenic agar BBL CHROMagar MRSA II (Becton Dickinson, Franklin Lakes, NJ), incubation according to the manufacturer's instructions, and inoculation into Trypticase soy broth (TSB) containing 6.5% NaCl. After 18 to 24 h of incubation at 35°C, TSB was subcultured on a blood agar plate (BAP) containing 5% sheep's blood and BBL CHROMagar MRSA II selective agar. Isolates grown on selective agar were subcultured to a BAP for subsequent identification. Presumptive *S. aureus* colonies were confirmed by Gram staining and positive catalase and positive tube coagulase testing according to standard procedures. Susceptibility testing was performed on all confirmed *S. aureus* isolates by using cefoxitin (30 μg) disk diffusion as a surrogate for methicillin resistance. Susceptibility testing was performed and results were interpreted by using criteria reported in CLSI document M100-S24 (35). All specimens were tested by the reference method within 48 h of collection. The reference method result was considered positive for MRSA if the presence of MRSA was confirmed by either direct culture or enrichment culture.

Statistical analysis. For assessment of agreement with the reference method (culture and susceptibility), the sensitivity, specificity, PPV, and NPV were calculated by using standard methods. The 95% confidence intervals were calculated by using the Wilson score method. The poolabilities of results among different sites for the rayon swab and ESwab specimens were compared by using Fisher's exact test.

RESULTS

Study population. A total of 1,103 evaluable rayon swab specimens were tested by the Xpert MRSA NxG assay at 8 clinical sites. More than two-thirds of the subjects were male ($n = 772$; 70.0%), and the majority of the subjects were between 22 and 65 years of age ($n = 735$; 66.6%), with subjects >65 years of age ($n = 330$; 29.9%) representing the next most common population (Table 1). The overall positivity rate for MRSA based on the reference culture method was 11.1% (range, 0% to 43.3%). The majority of specimens were collected in an inpatient setting (60.7%). A total of 846 ESwab specimens were tested from 6 clinical sites. With ESwabs, the overall positivity rate for MRSA using culture-confirmed results was 11.6% (range, 0.0% to 31.0%). The gender distribution for the ESwab specimens was approximately equal (males, $n = 422$; 49.9%). The majority of subjects tested were between the ages of 22 and 65 years ($n = 635$; 75.1%), and 20.0% were >65 years of age ($n = 169$) (Table 1). The distributions of

TABLE 2 Clinical performance of the Xpert MRSA NxG assay using rayon nasal swabs[c]

Site	Total no. of specimens tested	No. of specimens with result				Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
		TP	FP	TN	FN				
A	90	34	5	46	5	87.2 (73.3–94.4)	90.2 (79.0–95.7)	87.2 (73.3–94.4)	90.2 (79.0–95.7)
B	78	3	0	75	0	100 (43.9–100)	100 (95.1–100)	100 (43.9–100)	100 (95.1–100)
C	228	23	6	199	0	100 (85.6–100)	97.1 (93.8–98.7)	79.3 (61.6–90.2)	100 (98.1–100)
D[a]	172	11	4	157	0	100 (74.1–100)	97.5 (93.8–99.0)	73.3 (48.1–89.1)	100 (97.6–100)
E	125	7	3	115	0	100 (64.6–100)	97.5 (92.8–99.1)	70.0 (39.7–89.2)	100 (96.8–100)
F[a]	5	0	0	5	0	NA	100 (56.7–100)	NA	100 (56.7–100)
G	125	5	3	116	1	83.3 (43.7–96.7)	97.5 (92.9–99.1)	62.5 (30.6–86.3)	99.1 (95.3–99.8)
H[b]	280	28	9	238	5	84.8 (69.1–93.4)	96.4 (93.2–98.1)	75.7 (59.9–86.6)	97.9 (95.3–99.1)
Total	1,103	111	30	951	11	91.0 (84.6–94.9)	96.9 (95.7–97.9)	78.7 (71.3–84.7)	98.9 (98.0–99.4)

[a]Non-U.S. site.
[b]Also participated in the evaluation of ESwab specimens.
[c]TP, true positive; FP, false positive; TN, true negative; FN, false negative; NA, not applicable.

ESwab specimens collected were nearly equivalent between inpatients (35.7%), outpatients (32.2%), and patients at the emergency department (32.2%).

Xpert MRSA NxG assay performance with rayon swab specimens. The Xpert MRSA NxG assay yielded 1,075 valid results in the initial round of testing of 1,106 rayon swab specimens, with 15 instrument error flags (1.4%), 9 invalid results (0.8%), and 7 specimens with no result (0.6%). Repeat testing of the 31 samples produced a valid result for 28 of these specimens. Of the 1,103 specimens tested with valid results, 12.8% ($n = 141$) were positive for MRSA by the Xpert MRSA NxG assay.

Testing of rayon swabs with the Xpert MRSA NxG assay demonstrated a combined sensitivity of 91.0%, with a range of 83.3% to 100%, across the 8 testing sites (Table 2). Repeat subculture from enrichment broth for the 11 false-negative results with the Xpert MRSA NxG assay confirmed MRSA positivity with the reference method. The overall specificity of the assay using rayon swabs was 96.9%, with a range of 90.2% to 100% (Table 2). After repeat subculture from enrichment broth, 30 of 30 rayon swab specimens with false-positive results by the Xpert MRSA NxG assay remained culture negative. For the population tested, the MRSA positive predictive value (PPV) was 78.7% (95% confidence interval [CI], 71.3 to 84.7%), and the negative predictive value (NPV) was 98.9% (95% CI, 98.0 to 99.4%) (Table 2).

Xpert MRSA NxG assay performance with ESwab specimens. The Xpert MRSA NxG assay yielded 846 valid results in the initial round of testing of 862 ESwab specimens, with 8 errors (0.9%) and 8 invalid results (0.9%). Repeat testing of ESwab specimens was not possible due to an insufficient volume remaining in the sample. Of the 846 specimens tested, 12.9% ($n = 109$) were positive for MRSA by the Xpert MRSA NxG assay.

For nasal specimens collected with ESwabs, the Xpert MRSA NxG assay had an overall sensitivity of 92.9%, with a sensitivity range of 75% to 100%, across the 6 testing sites (Table 3). Upon repeat subculture from enrichment broth, 6 of 7 specimens with false-negative results obtained by the Xpert MRSA NxG assay remained MRSA culture positive. The overall specificity of the assay using ESwabs was 97.6%, with a range of 80% to 100% (Table 3). Of 18 specimens with false-positive Xpert MRSA NxG test results, 17 remained culture negative after repeat subculture from enrichment broth. For the population tested, the MRSA PPV was 83.5%, and the NPV was 99.1% (Table 3).

Combined performance of the rayon and ESwab specimens. Analysis of the results from the rayon swab and ESwab specimens demonstrated that the data were poolable across collection devices ($P = 0.81$ for sensitivity and $P = 0.46$ for specificity). There were a total of 1,949 specimens tested, with 202 having a true-positive result, 48 having a false-positive result, 1,681 having a true-negative result, and 18 having a false-negative result. The sensitivity and specificity of the pooled data were 91.8% (95% CI, 87.4 to 94.8%) and 97.2% (95% CI, 96.3 to 97.9%), respectively. The PPV and NPV for

TABLE 3 Clinical performance of the Xpert MRSA NxG assay using ESwab nasal specimens[b]

Site	Total no. of specimens tested	No. of specimens with result				Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
		TP	FP	TN	FN				
H[a]	231	19	8	203	1	95 (76.4–99.1)	96.2 (92.7–98.1)	70.4 (51.5–84.1)	99.5 (97.3–99.9)
I	139	6	1	132	0	100 (61.0–100)	99.2 (95.9–99.9)	85.7 (48.7–97.4)	100 (97.2–100)
J	136	3	0	132	1	75.0 (30.1–95.4)	100 (97.2–100)	100 (43.9–100)	99.2 (95.9–99.9)
K	15	0	3	12	0	NA	80 (54.8–93.0)	NA	100 (75.8–100)
L	168	50	5	111	2	96.2 (87.0–98.9)	95.7 (90.3–98.1)	90.9 (80.4–96.1)	98.2 (93.8–99.5)
M	157	13	1	140	3	81.3 (57.0–93.4)	99.3 (96.1–99.9)	92.9 (68.5–98.7)	97.9 (94.0–99.3)
Total	846	91	18	730	7	92.9 (86.0–96.5)	97.6 (96.2–98.5)	83.5 (75.4–89.3)	99.1 (98.1–99.5)

[a]Also participated in the evaluation of rayon specimens.
[b]TP, true positive; FP, false positive; TN, true negative; FN, false negative; NA, not applicable.

the combined specimens were 80.8% (95% CI, 75.5 to 85.2%) and 98.9% (95% CI, 98.3 to 99.3%), respectively.

DISCUSSION

This is one of the first studies to evaluate the performance of the Xpert MRSA NxG assay, a rapid molecular test for the direct detection of MRSA from nasal swabs using primers and probes for the SCCmec insertion site and for the mecA and mecC genes (16). A recent review of the clinical performance of a previous generation of the Xpert MRSA assay described sensitivities and specificities ranging from 63 to 99% and 96 to 100%, respectively (14). False-negative results were partly attributed to variant SCCmec types that were not detected by the previous assay (17, 18).

The next-generation Xpert MRSA NxG assay has been updated to identify additional SCCmec subtypes, in addition to the detection of mecC, a recently discovered methicillin resistance determinant emerging in Europe (19). The lack of identification of new and emerging SCCmec variants has plagued other available molecular tests for the detection of MRSA in nasal swabs. Previous evaluations of the clinical performance of commercially available molecular tests for the detection of MRSA from nasal swabs have observed a wide variability in sensitivities, ranging from as low as 63% to >90% (14, 20, 21). One study that tested more than 25,000 specimens collected in a large health system in the United States found that the LightCycler MRSA Advanced test and a previous generation of the Xpert MRSA assay had sensitivities of 98.3% and 95.7%, respectively (22). The overall sensitivity of the Xpert MRSA NxG assay evaluated in this investigation was 91.8%. This sensitivity is higher than that determined in a recent retrospective study that evaluated the performance of ESwabs on the Xpert MRSA NxG assay for intensive care unit (ICU) and presurgical patients, which found that the assay was 77.8% sensitive compared to culture-based methods (16). In our study, there were 11 (1%) false-negative results with the rayon swab specimens and 7 (0.8%) false-negative results using ESwab specimens. All but one of these specimens was confirmed to be culture positive upon repeat testing, suggesting that MRSA was present but below the limit of detection of the molecular assay. Another possible explanation is the presence of yet another SCCmec subtype not targeted by the Xpert MRSA NxG assay. This is supported by the fact that 10 of the 11 false-negative results using rayon swabs occurred at just two testing sites, raising the possibility of a particular strain at these sites that is not detected by the Xpert MRSA NxG assay.

The overall PPV and NPV predicted from the results of our study are 80.8% and 98.9%, respectively. A high NPV is advantageous for a number of reasons. With a negative test result, a patient could be reliably removed from isolation precautions, increasing patient satisfaction and decreasing health care costs. A recent study demonstrated that rapid molecular MRSA screening resulted in a 44% reduction in the number of patient isolation days (23). One study estimated that the cost of contact precautions exceeds $100 per day (24). Thus, even one fewer day of patient isolation can reduce hospital costs, although the economic value of active surveillance for MRSA

in the hospital setting is an area of ongoing debate. Cost-benefit analyses have illustrated that MRSA screening is cost-effective in different settings with different MRSA prevalence rates (25, 26). Conversely, other studies have not demonstrated this cost benefit and have even advocated for universal decolonization rather than screening (27). Any potential cost savings could help justify the increased costs of molecular testing compared to those of culture, as the turnaround time (TAT) is greatly reduced with the Xpert MRSA NxG assay, which is completed in about 1 h, compared to the overnight incubation required for direct plating for agar-based culture systems or 48 h or more for culture systems that require broth enrichment prior to plating onto solid medium. In addition to its potential as a cost-effective measure for infection control programs, molecular testing for MRSA colonization may also improve patient outcomes, as was demonstrated by mathematical modeling that predicted that active surveillance testing with rapid diagnostic testing for MRSA would decrease the prevalence of nosocomial MRSA faster than culture (28). Both the prompt isolation of positive patients and decreased prevalences of MRSA-colonized patients are factors that contribute to lower rates of hospital-acquired MRSA infections (29, 30). To this end, the Xpert MRSA NxG assay can be performed on demand, with minimal setup time, facilitating the early identification of MRSA-positive patients to enable the rapid implementation of infection control measures and patient bed management.

False-positive detection of MRSA can lead to unnecessary isolation and increased costs. Previous evaluations of the specificity of commercial assays for the molecular detection of MRSA in nasal swabs indicate that most assays exhibit a specificity of ≥95% (22, 31, 32). The MRSA NxG assay evaluated in this study showed similar performance characteristics, with an overall specificity of 97.2%. Previous generations of MRSA molecular assays were prone to false-positive results when tested on strains containing an empty SCCmec cassette (i.e., mecA dropout strains), which are estimated to occur in about 7% of methicillin-susceptible S. aureus (MSSA) isolates in the United States (33). However, this problem was remedied in subsequent assays through the inclusion of primers and probes targeting both the junction of the SCCmec cassette with the orfx gene and the mecA gene. A few of the false-positive results generated in this study could have occurred for specimens containing a mixture of a methicillin-resistant coagulase-negative Staphylococcus strain and an empty-cassette-containing S. aureus strain. Given the regions targeted by the primers and probes in the Xpert MRSA NxG assay, this is theoretically possible but improbable. Another possibility is that the false-positive results were the result of the detection of residual nucleic acid from nonviable bacteria in patients who were recently treated with antimicrobial agents. In our study, potential subjects were excluded if they had systemic or nasal antibiotic use within the previous 7 days; however, antibiotic use prior to the previous 7 days was not a criterion for exclusion.

The strengths of this study include the large number (n = 1,949) of prospectively collected samples from multiple centers that encompassed a wide geographical area both within and outside the United States, which increased the likelihood that this study captured a diverse collection of MRSA strain types. Another strength of this study is the evaluation of multiple collection systems, including rayon swabs and ESwab specimens. We found that the sensitivities and specificities were similar between the two collection devices. This observation is supported by at least one study that found comparable performances of the two collection systems for the detection of MRSA using commercial molecular assays (34).

A potential limitation of this study is the fact that the ESwab specimens were collected only from clinical centers within the United States. Thus, the performance of the Xpert MRSA NxG assay with this collection device for MRSA strain variants that are more common in Europe and worldwide may not have been captured with this study. Additionally, only a minority of the rayon swab specimens were collected from females (30%), and a paucity of specimens of either type were collected from patients aged 21 years or younger (4.1%). Thus, further evaluation of specimens may be needed to determine the performance of this assay for these populations. Finally, there was no

second molecular testing method used for the arbitration of discrepant results between culture and the Xpert MRSA NxG assay, and isolates were not archived for additional analysis of false-negative molecular assay results.

In summary, the Xpert MRSA NxG assay exhibits a clinical performance that is superior or comparable to those of other commercially available tests for the direct detection of MRSA in nasal swabs. Advantages of this assay include its ability to detect more SCC*mec* types and *mecC*, which could result in increased assay sensitivity. In addition, the assay requires minimal hands-on time and is FDA cleared for both rayon swabs and ESwab specimens. Thus, it is adaptable for use by many clinical laboratories to provide beneficial information needed for infection prevention efforts.

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