Title: Rapid PCR Tests for MRSA in Hospitalized Patients: Diagnostic Accuracy, Clinical and Cost-Effectiveness

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Context and Policy Issues:
Staphylococcus aureus (SA), a gram positive bacterium, is found in the nostrils and on the skin of 30% of the general population \(^1\-^3\) and this increases to 50% for healthcare workers and hospital inpatients.\(^2,^3\) SA can cause a range of illnesses from minor skin, soft-tissue and wound infections to systemic life-threatening infections such as bacteraemia, pneumonia, and endocarditis.\(^1\-^3\) Methicillin resistant staphylococcus aureus (MRSA) refers to SA strains that have acquired the mecA gene making them resistant to all beta-lactam antibiotics, including the penicillins (e.g. methicillin) and cephalosporins.\(^2,^3\) MRSA infections are associated with increased morbidity and mortality, prolonged hospitalization, and increased costs.\(^4\) The Canadian Nosocomial Infection Surveillance Program has documented a rise in reported MRSA colonisation (presence of organism without signs or symptoms of infection) and infection in sentinel hospitals geographically dispersed across Canada. Specifically, between 1995 and 2003, MRSA colonisation and infection rates rose from 0.46 to 5.10 cases per 1,000 admissions and MRSA infection rates rose from 0.25 to 1.61 cases per 1,000 admissions.\(^4,^5\) Using MRSA surveillance, treatment and management cost data from a tertiary care, university-affiliated teaching hospital in Toronto, Canada, Canadian Nosocomial Infection Surveillance Program MRSA rate data, and Statistics Canada’s hospital discharge data, Kim et al.\(^6\) conservatively estimated the economic burden of MRSA for Canadian hospitals during the late 1990s. The mean cost to treat an MRSA infection was $14,360 per patient; the mean cost for isolation and management of colonised patients was $1,363 per admission; the annual cost for MRSA screening was $109,813; and the cost associated with MRSA in Canadian hospitals was estimated to be $42 to $59 million annually.
In hospitals, the main mode of MRSA transmission is from MRSA colonised or infected patients to other patients via the transiently colonised hands of healthcare workers, although airborne and environmental transmission also occurs.\(^2\) A major component of controlling the spread of MRSA is screening to identify those colonised or infected and then implementing procedures to minimize the spread to other patients. Screening involves taking swabs from one or more body sites and performing laboratory tests on the samples. Swabs are taken from the site of primary infection, if present, or sites where carriage is most common (e.g. anterior nares, throat, or groin). The conventional laboratory method for detecting MRSA involves culture followed by antibiotic susceptibility testing; a process usually requiring several days. Alternative methods, such as polymerase chain reaction (PCR), a technique for amplifying genetic material so that it is more easily detected, can be completed within 2 hours of taking the swab allowing quicker implementation of control and treatment strategies.\(^1\) Nonetheless, high costs, specimen processing workload, and the lack of trained laboratory technicians have been reported as limitations to routine PCR-based MRSA screening.\(^10\)

Institutional screening policies span the spectrum from no screening, to targeted screening, to screening of all patients and staff (e.g. Netherlands and Scandinavian countries).\(^11\) Targeted screening involves assessing patients with respect to their risk of MRSA carriage or infection and their susceptibility to MRSA infection and subsequently screening the high-risk/susceptible patients. Examples of high-risk patients include transfers from other hospitals or a history of MRSA colonisation/infection, and examples of susceptible patients include those admitted to intensive care, burns, orthopaedic, or trauma units. Actions taken while awaiting screening results would be dictated by the risk/vulnerability assessment and resources available.\(^1\)

MRSA is a growing costly problem in Canadian hospitals and confusion exits regarding the best diagnostic test and screening policy for minimizing its adverse consequences in a cost-effective sustainable manner. To assist in evidence-based decision making, this HTIS report examines the empirical evidence regarding the diagnostic accuracy, clinical- and cost-effectiveness of rapid PCR tests compared to culture for identifying MRSA in hospitalized patients. Finally, although some research has been published which examines the accuracy, clinical- and cost-effectiveness of PCR tests after overnight broth enrichment of samples\(^12\)\(^-\)\(^14\) this report focuses on “rapid” PCR testing conducted directly from swab samples.

**Research Questions:**

1) How does the diagnostic accuracy of rapid PCR testing compare with culture-based testing for identifying MRSA in hospitalized patients?

2) What is the clinical- and cost-effectiveness of rapid PCR testing relative to culture-based testing for identifying MRSA in hospitalized patients?

3) What Canadian and international guidelines exist regarding routine MRSA testing in hospitalized patients?

**Methods:**

A literature search was conducted on key health technology assessment resources, including Medline, Embase, Biosis, CINAHL, The Cochrane Library (Issue 2, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI’s HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include English language publications from 2002 to date. Links to online full-text are provided when available.
Summary of Findings:

Health Technology Assessments
One recent health technology assessment, completed for the Scottish National Health Service, was identified. It reviewed the clinical- and cost-effectiveness evidence of MRSA screening programmes. The assessment involved critical appraisal of evidence identified through a review of literature, experts, and patient interest groups; economic modelling; focus groups to ascertain the views of staff and public regarding the management of MRSA in hospitals; a survey questionnaire to assess current MRSA screening in Scottish hospitals; and peer review and public consultation. Although a large body of literature regarding the clinical-effectiveness of MRSA screening was identified, it was characterized as methodologically weak. Nonetheless, based on the literature, the following assumptions were incorporated into the economic modelling for a 775 bed tertiary referral hospital setting over a 5 year period: a MRSA prevalence of 7% among patients admitted to acute inpatient care in the UK; sensitivity and specificity values of 68% and 94%, respectively, for agar culture from swabs, 98% and 94% for enrichment broth culture from swabs, and 92% and 91% for PCR from swabs; that swab screening of patients with at least one risk factor for MRSA colonisation would expose 65% of patients to screening and identify 88% of the MRSA carriers; and that decolonisation of MRSA positive patients would be successful 53% of the time. With no screening and the presence of one isolation room per high-risk speciality unit, the MRSA prevalence would be reduced from 7% to 6% over a 5 year modelling period; increasing the isolation rooms to three would reduce the prevalence from 7% to 5%. With respect to screening strategies, swab screening of all patients admitted to high and low risk specialty units was most effective at reducing the prevalence of MRSA. Similar reductions were associated with swab screening using broth enrichment culture (5.6% decline) or PCR (5.3% decline) but a smaller reduction was associated with agar culture (4% decline). The impact of MRSA on hospital resources was estimated as the additional number of days needed to treat patients whose hospital stay was prolonged due to MRSA infection. Not implementing a screening and isolating policy would result in 8,166 MRSA infections and an additional 52,779 bed days over a 5 year period. Screening all patients using the enrichment broth method was most cost-effective. Specifically, for a total cost of £17.2 million, 5,905 MRSA infections and 42,714 bed days were prevented producing the lowest cost per bed day saved (£403/bed day). Conversely, screening all patients using the PCR method cost £20.3 million, prevented 5,068 infections, and saved 33,900 bed days producing a cost per bed day saved of £598. Hence, enrichment broth screening cost less, prevented more infections and saved more bed days than PCR screening. Similar findings were seen when modelling was applied to the large general hospital scenario. Sensitivity analyses indicated the following factors to be influential: changes in the spontaneous community decolonisation rate; colonisation pressure within a ward; the sensitivity and specificity for carriage assessment; and the number of single-bed isolation rooms per ward. The authors stated the resource costs for PCR screening of swabs was high, limiting its ability to replace culture methods, but that rapid PCR testing might be useful for emergency admissions to high-risk speciality units or emergency admissions at high colonisation risk. The HTA concluded that all patients admitted to hospital should be screened using a test with comparable sensitivity and specificity to enrichment broth testing, and that at least 3 single-bed isolation rooms would be required to accommodate MRSA-positive patients in a 25 bed ward. The primary limitation of this HTA was the methodologically weak clinical literature upon which the economic modelling was based.

Systematic Reviews or Meta-analyses
No systematic reviews or meta-analyses were identified.
Guidelines
Two Canadian provincial guidelines\textsuperscript{8,15} and one United Kingdom guideline\textsuperscript{16} were identified. An Alberta provincial MRSA working group, comprised of infection prevention and control experts and representation from Health Canada’s First Nations and Inuit Health Branch, the provincial public health laboratory, and Council of Medical Officers of Health, developed MRSA infection prevention/control guidelines for Alberta’s acute care settings or hospitals. The development process involved sharing and discussing regional guidelines and resources, conferring on best practices, and identifying key components of the guideline. With respect to admission screening, the group recommended that individuals with a history of hospitalization or institutionalization (e.g. longterm care, correctional facility) for at least 24 hours within the past 6 months should be routinely screened on admission to an acute care facility, and patients previously identified as MRSA positive should be screened on re-admission. They suggested screening a maximum of two sites including the anterior nares and one of the following: perianal or groin, skin lesions or open wounds, invasive devices, urine specimen if a urinary catheter is present, or the umbilicus if a neonate. No recommendations regarding the screening test were offered.\textsuperscript{8}

Similarly, a multidisciplinary committee of infection prevention and control specialists developed the Manitoba Guidelines for Prevention and Control of Antibiotic Resistant Organisms. Included was an admission MRSA screening statement for acute care facilities and surgical centres. It suggested that all patients hospitalized for more than 24 hours in an acute care hospital or emergency room within the past 6 months in Winnipeg or outside of Manitoba should be screened for MRSA on admission. It was further recommended that previously positive patients whose status was presently unknown, patients known to be positive, and patients identified as an MRSA contact (a person exposed to a case in which transmission could occur) should also be screened on admission. Again, no recommendations regarding a preferred screening test were provided.\textsuperscript{15}

Finally, using a more rigorous, documented approach which involved a systematic review and appraisal of published literature, grading of recommendations, and extensive consultation, a multi-disciplinary group developed guidelines for the control and prevention of MRSA in healthcare facilities.\textsuperscript{16} The working group recommended screening for MRSA carriage in selected patients and clinical areas according to locally agreed criteria based upon assessment of the risks and consequences of transmission and infection. Specifically, certain high-risk patients should be screened routinely, and certain high-risk units should be screened at least intermittently in all hospitals. Detailed descriptions of high-risk patients and units, and the anatomical sites that should be sampled were provided (p.S3-S4). This guidance was categorized as “suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale”. Based on a lack of evidence, routine screening of all admissions to hospital was not advocated, but the working group acknowledged that local conditions may justify such a policy, perhaps temporarily. Consistent with recent Alberta and Manitoba guidelines, no recommendations were provided with respect to the screening test to be used.

Randomized Controlled Trials
No randomized controlled trials were identified.

Observational Studies
Accuracy Studies
Fifteen studies\textsuperscript{7,17-30} were identified which examined the diagnostic accuracy of rapid PCR testing relative to culture methods. They are presented in chronological order starting with the
de San et al. examined the accuracy of a PCR assay (IDI-MRSA™) compared to optimized selective culture methods for detecting MRSA in 1000 swabs taken from the nares (522 swabs), throat (212 swabs), perineum (206 swabs), and skin wounds (60 swabs) of 466 patients admitted to high-risk medico-surgical departments in a tertiary care teaching hospital in Belgium. Accuracy was estimated using swab- and person-based analyses. In a swab-based analysis, the swab is the unit of analysis and one patient can contribute multiple swabs, each of which can be MRSA-positive or negative. In a person-based analysis, the person is the unit of analysis and they are designated as MRSA-positive or negative if at least one or none of their swabs are positive, respectively. Swab-based analysis indicated a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 81%, 97%, 75%, and 97.9% respectively, while the corresponding estimates for a person-based analysis were 89.4%, 95.2%, 67.7%, and 98.8% respectively. With respect to discordant results, of the 26 patients who were culture-negative but PCR-positive, 11 were considered to be probable MRSA carriers because of recent history of MRSA carriage. PCR tests on nasal swabs were significantly more sensitive than those based on other samples (90.6% vs 76.5%, p<0.01) whereas the specificity was similar (97.1% vs 96.8% respectively). Overall, 0.3% of PCR tests were “inhibited” (i.e., failed to produce a result). The median (range) turnaround time was 19 hours (4 to 27 hours) for PCR results versus 3 days (1 to 9 days) for agar culture and 6 days (2 to 9 days) for enrichment culture. The authors concluded that the IDI-MRSA™ was rapid, sensitive, and specific for MRSA colonisation, but that PCR-positive samples should be confirmed by culture to avoid unnecessary contact isolation.

Paule et al. examined the accuracy of a PCR assay (BD GeneOhm™, formerly IDI-MRSA™), implemented with an in-house achromopeptidase lysis method, compared to culture for detecting MRSA from nasal swabs obtained during a universal surveillance program testing all admissions to a three hospital academic organization in Chicago, Illinois. Of 1107 PCR-negative samples, culture recovered MRSA from only one sample producing a negative predictive value of 99.9% (95% confidence interval (CI): 99.4%, 100%). Of 215 PCR-positive samples, 119 samples were positive on basic culture, 15 samples were positive on culture after an enrichment broth, and 24 samples were from patients with a history of MRSA within the last year. Including those with a MRSA history as true positives, the authors calculated a PPV of 73.5% (95%CI: 67%, 79.2%) for the PCR assay. Overall, 0.53% of PCR tests were inhibited. The authors concluded that the BD GeneOhm™ was a rapid and accurate way to detect MRSA colonisation and that their data suggested that culture-based surveillance was less sensitive.

Rajan et al. examined the accuracy of a PCR assay (IDI-MRSA™) compared to a variety of basic and enrichment culture methods for detecting MRSA in 170 nasal swabs taken from 65 patients in a general ICU of a university hospital in Dublin, Ireland. Patients were screened on admission and twice weekly thereafter. Patients without a MRSA-positive history were excluded. Relative to culture methods considered in aggregate, sensitivity, specificity, PPV and NPV were 86.7%, 88.4%, 56.5%, and 80.6% respectively. PCR testing had a laboratory turnaround time of 2.25 hours compared to 48 to 96 hours for the various culture methods. Laboratory costs for the study, which excluded overhead and staff time, totalled €7590 for PCR, €366 for CHROMagar MRSA™ (enrichment culture €461.34), and €170 for blood agar (enrichment culture €200.92). The authors concluded that PCR facilitated rapid detection of MRSA and has the potential to contribute to preventing spread, but should be used in conjunction with culture until further studies indicate when and where it can be used alone for MRSA screening.
Rossney et al.\textsuperscript{19} examined the accuracy of a PCR assay (IDI-MRSA\textsuperscript{™}) compared to direct culture, enrichment culture, and combined direct and enrichment culture for detecting MRSA. A total of 606 swabs were taken from the nose, throat, and groin/perineum for routine MRSA screening of 202 consecutive high-risk patients attending an adult tertiary university teaching hospital in Ireland. When considering all swab sites simultaneously, sensitivity was highest when the assay was compared to direct culture (91\%) and declined when compared to enrichment culture (84\%) and combined direct and enrichment culture (82\%). Using combined direct and enrichment culture as the reference, the sensitivity, specificity, PPV, and NPV with 95\% CIs were 82\% (76\%, 89\%), 96\% (94\%, 97\%), 82\% (75\%, 89\%), and 96\% (94\%, 98\%) respectively. Site-specific analyses indicated that diagnostic accuracy was relatively consistent for swabs taken from the nose (90\%, 97\%, 92\%, 97\% respectively), throat (89\%, 99\%, 98\%, 97\% respectively), and groin/perineum (88\%, 99\%, 93\%, 98\% respectively). More detailed investigations of the discordant results indicated that culture did produce some false positives and negatives. After incorporating the more detailed investigations, the overall sensitivity, specificity, PPV and NPP with 95\% CIs increased to 88\% (83\%, 94\%), 99\% (97\%, 100\%), 94\% (90\%, 98\%), 97\% (95\%, 98\%) respectively. Approximately 0.5\% of PCR tests were inhibited. With respect to timeliness, overall assay time, including sample preparation, took approximately 2.5 hours for batches of 12 specimens. The authors concluded that IDI-MRSA\textsuperscript{™} can provide a rapid preliminary screen for MRSA, but that culture is still required until the sensitivity of the assay is improved.

van Hal et al.\textsuperscript{20} examined the accuracy of two molecular methods (IDI-MRSA\textsuperscript{™} PCR Assay and GenoType MRSA Direct\textsuperscript{™} PCR Assay) and three selective MRSA agars (MRSA ID\textsuperscript{™}, MRSASelect\textsuperscript{™}, and CHROMagar MRSA\textsuperscript{™}) for detecting MRSA from swabs taken from 205 patients (101 nasal, 52 groin, 52 axillary) admitted to a hospital in Sydney, Australia. Screening targeted consecutive patients known to be previously MRSA infected or colonised. The reference value for comparison was derived using an algorithm based on all PCR and culture method results. Overall, IDI-MRSA\textsuperscript{™} demonstrated the greatest sensitivity for MRSA. IDI-MRSA\textsuperscript{™} sensitivity, specificity, PPV, and NPV were 90\%, 96\%, 93\%, and 94\% respectively. Site-specific sensitivities were also greatest for the IDI-MRSA\textsuperscript{™} (nasal 94\%, non-nasal 80\%). The proportion of inhibited IDI-MRSA\textsuperscript{™} tests was 1.5\%. For the GenoType MRSA Direct\textsuperscript{™}, the sensitivity, specificity, PPV, and NPV were 69\%, 96\%, 92\% and 82\% respectively, and the inhibited rate was 4.4\%. The cost per test was $53.60, $144.80 and approximately $10.00 (Australian dollars) for the IDI-MRSA\textsuperscript{™}, GenoType MRSA Direct\textsuperscript{™} and selective agars respectively. This cost estimate included the cost of the test, additional consumable/reagent cost, and processing time. The authors concluded that although IDI-MRSA\textsuperscript{™} was more expensive than conventional selective agars, it provided rapid turnaround times of 2 to 3 hours, and greater detection of MRSA colonisation than conventional selective agars and the GenoType MRSA Direct\textsuperscript{™}, irrespective of swab site.

Bishop et al.\textsuperscript{21} examined the accuracy of a PCR assay (IDI-MRSA\textsuperscript{™}) compared to routine cultures for detecting MRSA from nasal swabs, groin swabs, and combined nasal and groin swabs from 211 adult inpatients in a tertiary care university teaching hospital. PCR assays of nose swabs had a sensitivity, specificity, PPV and NPV of 90\%, 91.7\%, 56.3\%, and 98.8\% respectively. Similarly, values using groin swabs were 83.3\%, 90.2\%, 46.9\% and 98.1\% respectively, and values using combined nose and groin swabs were 88.0\%, 91.6\%, 61.1\% and 98.1\% respectively. Additional testing on PCR-culture discordant results suggested that PCR testing was actually more sensitive than routine cultures in detecting MRSA colonisation. The overall proportion of inhibited PCR tests was 5.5\%. With respect to PCR processing times, each batch of 14 samples took approximately 2.5 hours to complete. The authors concluded that IDI-MRSA\textsuperscript{™} assay of a combined nose-groin specimen has an accuracy similar to that of the currently recommended nasal method, provides results in a clinically useful time frame, and
may be more cost effective given the reduction in the number of IDI-MRSA™ assays required and scientist processing time.

Davidson et al.\textsuperscript{22} examined the accuracy of a PCR assay (IDI-MRSA™) compared to culture for detecting MRSA on nose, throat, and perineum swabs taken from 75 new routine hospital admissions. All three swabs were pooled for culture and the nose and throat swabs were subsequently combined in a single PCR assay. Patient-based analysis revealed a sensitivity, specificity, PPV and NPV of 89%, 97%, 80%, and 98% respectively. Because of the high cost of PCR kits relative to culture and the inability of PCR testing to replace culture with respect to antibiotic susceptibility testing and typing, the authors stated that it would be necessary to target the use of the PCR assay to high-risk patients.

Holfelder et al.\textsuperscript{23} examined the accuracy of a PCR assay (GenoType MRSA Direct™) compared to selective culture methods for detecting MRSA in 508 swab specimens (nose 209, throat 101, skin 80, groin 46, axilla 12, wound 34, other sites 26) obtained from 242 high-risk patients during admission to 12 hospitals in Germany. Exclusion criteria included treatment for MRSA colonisation or infection within the previous 4 weeks. Sensitivity, specificity, PPV, and NPV were 94.6%, 98.7%, 85.4%, and 99.6% respectively. The authors concluded that GenoType MRSA Direct™ was accurate and timely, requiring approximately 4 hours to complete, but that simultaneous culture of the same swab was recommended.

Drews et al.\textsuperscript{24} examined the accuracy of a PCR assay (IDI-MRSA™) compared to traditional culture for detecting MRSA from 307 swabs (26 perineal, 8 rectal, 88 wound, 21 axillary-groin, and 164 nasal plus axillary-groin-perineal) collected during surveillance at Toronto, Ontario hospital(s). Overall sensitivity and specificity with 95% CIs were 96% (89%, 99%) and 93% (88%, 96%) respectively. Further investigation of discordant results indicated that 7 of the 15 samples initially identified as culture-negative and PCR-positive were determined to be true positives. After incorporating the results of more detailed investigation, sensitivity and specificity were 96% (90%, 99%) and 96% (92%, 98%) respectively. Although not discussed by the authors, anatomic site-specific sensitivities and specificities could be derived from the provided data. Site-specific sensitivities ranged from 89% for the perineum to 100% for the axilla/groin and rectum while specificities ranged from 82% in the perineum to 100% in the axilla/groin and rectum. The overall proportion of inhibited PCR tests was 6%. The authors concluded that IDI-MRSA™ assay may be implemented directly on swabs from nonnasal body sites while retaining high sensitivity.

Lucke et al\textsuperscript{25} examined the accuracy of a PCR assay (IDI-MRSA™) relative to enriched culture for identifying MRSA in 691 swabs (nasal, throat, axilla, groin, vagina, annus/rectum, wound) collected from 300 high-risk patients admitted to hospitals in central Switzerland. Sensitivity, specificity, PPV, and NPV were 80.0%, 97.5%, 66.6%, and 98.8% respectively. The proportion of inhibited PCR tests was 0.29%. Due to the frequency of false positives, the authors recommended back-up cultures. The author’s concluded that the high costs of IDI-MRSA™ was justified by the “extremely” high costs of patient isolation and other infection control measures, and that the test efficiently helps to prevent pathogen transmission within the hospital. However, neither of these conclusions were substantiated with cost or MRSA transmission rate data.

Oberdorfer et al.\textsuperscript{26} examined the accuracy of a PCR assay (IDI-MRSA™) relative to conventional culture for identifying MRSA on nasal swabs taken from 320 patients admitted to ICUs in a tertiary university hospital in Germany. Cultures were completed for swabs from the nose, throat and, where present, wounds. Using cultures from nose swabs as the reference, sensitivity, specificity, PPV and NPV were 100%, 98.6%, 75%, and 100% respectively. Using
cultures from the nose, throat, and wound swabs as the reference, the estimates were 92.3%, 98.6%, 75%, and 99.6% respectively. Approximately 5% of the PCR tests were inhibited. It was observed that inhibition occurred more frequently in swabs that were contaminated macroscopically with blood or nasal secretions. With respect to time requirements, on weekdays, PCR tests were initiated at 11 am and results were forwarded to the ICU between 2 to 5 pm the same day whereas culture results were communicated in 3 days. The authors concluded that accurate results were obtained with IDI-MRSA™ even when referenced against swabs of multiple sites in a low MRSA prevalence (4%) patient population. In addition, they recommended that further work be directed at reducing the inhibition rate and elucidating the cause of false-positives, and that positive IDI-MRSA™ results be confirmed with culture.

Huletsky et al.\textsuperscript{27} compared the accuracy of a PCR assay (Smart-Cycler™) with standard culture for detecting MRSA on 331 nasal swabs obtained from 162 high-risk patients identified during a hospital surveillance program. Patients who had received a MRSA-decolonisation protocol were excluded from the study. After repeat testing to resolve discrepancies, sensitivity, specificity, PPV, and NPV with 95% CIs were 100% (94.4%, 100%), 98.4% (95.7%, 99.5%), 95.3% (87.7%, 98.5%) and 100% (98.1%, 100%) respectively. Repeat testing indicated that MRSA carriers were detected more often by PCR than by culture. The proportion of inhibited PCR tests was 1.5%. The time requirements for PCR assay and culture were reported as less than 1 hour and at least 48 hours respectively. The authors concluded that MRSA carriers can be identified rapidly and accurately by PCR testing of nasal specimens.

Warren et al.\textsuperscript{28} examined the accuracy of a PCR assay (IDI-MRSA™) compared to selective culture for detecting MRSA on nasal swabs from 288 currently and newly admitted high-risk inpatients in an academic tertiary hospital in St. Louis, Missouri. Exclusion criteria included decolonisation treatment within the past 14 days or contraindications to nasal sampling. The sensitivity, specificity, PPV and NPV with 95% CIs were 91.7% (85.3%, 98.1%), 93.5% (90.2%, 96.8%), 82.5% and 97.1% respectively (CIs were not provided for the latter two estimates). The proportion of inhibited PCR tests was 0.7%. Using batch mode processing (8-10 specimens), the time from start of specimen processing to generation of results was approximately 1.5 hours. The authors concluded that the IDI-MRSA™ assay was a sensitive and specific test for detection of MRSA directly from nasal swabs.

François et al.\textsuperscript{29} examined the accuracy of a PCR assay (qMRSA™) compared to optimized culture for detecting MRSA from 219 samples taken from the nares, inguinal region, wounds or pooled sites of surgical ICU patients. Sensitivity, specificity, PPV, and NPV were 84%, 94%, 70%, and 97% respectively. The authors stated that the majority of PCR-positive and culture-negative patients were either previously identified as MRSA carriers and/or were screened as MRSA culture positive at another sampling site during the same hospital stay. It was concluded that qMRSA™ was a promising procedure for detecting MRSA carriers within 6 hours and that the overall sensitivity might be improved by analyzing a larger fraction of the sample extract.

Finally, in a brief abstract, Huletsky et al.\textsuperscript{30} described a study examining the accuracy of a PCR assay (AmpliMRSA™) compared to culture for detecting MRSA from 142 nasal swabs collected during a hospital surveillance program. Sensitivity, specificity, PPV, and NPV were 97.1%, 92.6%, 80.5%, and 99.0% respectively. The authors concluded that the AmpliMRSA™, which took less than 1 hour to complete, was a powerful method for detecting MRSA carriers directly from nasal specimens.

Several limitations were common in the accuracy studies and should be acknowledged when interpreting the results. First, is the lack of a true gold standard reference test as demonstrated by those studies conducting a more detailed examination of discordances and/or using various
culture methods. 7,17-22,24-27,29  Second, is the lack of information regarding patient populations, inclusion, and exclusion criteria. 7,17,20-22,24,25,29,30  Third, is some small sample sizes with two studies including less than 100 patients. 18,22  Fourth, is the uncertainty regarding the degree of blinding of those performing and interpreting the results of PCR and reference tests which may introduce bias. 7,17-20,22,24-30  Fifth, is the sample rather than person-based analyses which violate the independence of observations assumption. 17-19,23-25,27,29,30  Sixth, is the lack of anatomic site-specific diagnostic accuracy estimates when samples have been taken from multiple body sites. 23,25,29  Seventh, is the conflicts of interest such as industry sponsorship. 17,21,23,27,28  Eighth, is the general lack of diagnostic accuracy information relevant to paediatric populations.  Last, is the preponderance of research (11 of the 15 studies) focussing on the BD GeneOhm™ (formerly IDI-MRSA™, License No.: 63391), which is the only PCR assay discussed in this report that is currently approved for use in Canada. 31

Clinical-Effectiveness Studies

Two studies were identified which examined the clinical-effectiveness of rapid PCR testing compared to culture for identifying MRSA in hospitalized patients. Cunningham et al. 32 examined the impact of an admission and discharge MRSA screening program using same-day PCR testing (IDI-MRSA™) instead of conventional culture in a mixed medical and surgical adult critical care unit within a teaching hospital in southwest England. Pilot testing of 174 patients by culture and PCR in parallel showed a sensitivity and specificity of 100% and 92% respectively. Standard MRSA culture methods were used to screen 612 patients during the first 5 months of the study and the PCR test was used to screen 693 patients during the subsequent 5 months. Standard infection control precautions were instituted after positive results were obtained, regardless of method of identification, but PCR results were reported as provisional until confirmed by culture. The overall pre-admission carriage rate throughout the period of study was 7% with no significant difference between the culture and PCR testing phases. Time to test results was 3 working days for culture and less than 1 working day for PCR. The incidence rate of MRSA transmission (critical care unit acquired cases) significantly (p<0.05) decreased from 13.89 per 1000 patient-days during the culture testing phase to 4.9 per 1000 patient-days during the PCR testing phase resulting in an absolute reduction of 8.98 transmissions per 1000 patient-days (95% CI: 8.56, 9.42). The authors concluded that PCR screening for MRSA on admission to critical care units is feasible in routine clinical practice, provides quicker results than culture-based screening, and is associated with a significant reduction of MRSA transmission. Suggested reasons for the reduction in MRSA transmission included earlier use of decolonisation regimens, earlier use of appropriate antibiotics, earlier isolation, and better compliance with hand hygiene procedures. The major limitation of this study was its observational nature, which precludes definitively attributing the positive results to the initiation of PCR testing. Nonetheless, the authors were unable to identify any other changes which could explain the study results.

Harbarth et al. 10 examined the impact of an MRSA admission screening program using a quick multiplex immunocapture-coupled PCR (qMRSA™) combined with pre-emptive contact isolation for all patients admitted for longer than 24 hours to adult surgical and medical intensive care units (ICU) within a university hospital in Switzerland. A pre-emptive isolation day was defined as a day spent under contact precautions while awaiting MRSA screening results. The diagnostic performance of the qMRSA™ had been previously evaluated in critically ill patients with a prevalence of MRSA carriage on admission of 14%. Sensitivity, specificity, PPV and NPP were 84%, 94%, 70%, and 97% respectively. The effectiveness of the intervention was assessed through comparison with a historical control period. In the surgical ICU, usual practice consisted of screening of high-risk patients using conventional culture techniques and pre-emptive isolation whereas usual practice in the medical ICU involved only the screening component. During the intervention period, the on-admission prevalence of MRSA was 6.7%
(71/1053) and without systematic on admission screening, 55 previously unknown MRSA carriers would have been missed on admission. Relative to the historical control period, median time from surgical ICU admission to notification of test results decreased from 87 to 21 hours (p<0.001), and 245 MRSA-negative patients would have spent an additional 1227 days in pre-emptive isolation had culture-based screening methods been employed for systematic on-admission screening. Poisson regression indicated that systematic qMRSA™ screening on admission had no significant impact on the incidence rate of ICU-acquired MRSA infections in the surgical ICU (relative risk=1.0; 95% CI: 0.6, 1.7; p=0.97). In the medical ICU, median time from medical ICU admission to notification of test results decreased from 106 to 23 hours (p<0.001). The introduction of systematic screening using qMRSA™ did not significantly decrease the risk of acquired MRSA infections, but combined systematic on-admission qMRSA™ screening and pre-emptive isolation significantly decreased the risk of acquired MRSA infections in the medical ICU (relative risk=0.3; 95% CI: 0.1, 0.7; p=0.004). Specifically, the risk of acquiring an MRSA infection in the medical ICU decreased by 70% after implementing the combined intervention. Poisson regression analyses adjusted for colonisation pressure by including a variable which documented the number of admitted previously known MRSA carriers. The authors concluded that ICU admission prevalence of previously unknown MRSA carriers was high; that the qMRSA™ test decreased the overall time to notification allowing rapid identification of previously unknown MRSA carriage; and that a substantial decline in MRSA infections was observed in the medical ICU by combining qMRSA™ admission screening with pre-emptive isolation. Furthermore, although no effect on MRSA infection rates was observed in the surgical ICU, a large number of pre-emptive isolation days could be saved by incorporating qMRSA™ testing. Explanations for the contradictory findings across ICUs included differences in antibiotic use, case mix, frequency of patient movements outside the ICU, compliance with standard precautions and isolation practices, or staffing levels. None of these factors were adjusted for in Poisson regression modelling. Interestingly, the authors never discussed the possibility that pre-emptive isolation, newly introduced to the medical ICU only, was actually the key ingredient for success. Additional limitations included the confounding associated with changing both the screening policy and screening test during the intervention period; the inability to measure intervention impact on overall MRSA transmission rates because of lack of discharge screening throughout the study period; and the competing interests of two of the authors who are the developers and patent holders of the qMRSA™.

Conclusions and Implications for Decision or Policy Making:

MRSA is a growing, costly problem in Canadian hospitals, and confusion exists regarding the best screening tests and policies to minimize its impact. Screening guidelines generally advocate a targeted approach where high-risk patients and units are screened for MRSA carriage, but they are silent on the actual screening test to employ. Rapid PCR diagnostic accuracy studies have demonstrated a range of values for sensitivity (69% to 100%), specificity (88.4% to 98.7%), PPV (46.9% to 95.3%) and NPV (80.6% to 100%), and several studies have suggested that PCR testing may be more sensitive than culture methods.\textsuperscript{7,17,21,24,27,29} Factors contributing to this variability include previously detailed study limitations; differences in the diagnostic accuracy of PCR assays;\textsuperscript{20} differences in the diagnostic accuracy of the reference culture methods;\textsuperscript{19} the actual anatomic site sampled;\textsuperscript{21,26} differences in the technologies being compared with one detecting genetic material and the other viable organisms;\textsuperscript{19} and the prevalence of MRSA carriage in the screened population.\textsuperscript{33} With respect to the last factor, the positive predictive value of PCR tests will be affected by the prevalence of MRSA carriage in the population tested. Specifically, assuming a constant diagnostic sensitivity and specificity, the PPV of PCR testing will increase as the prevalence of MRSA carriage increases.\textsuperscript{33} Because of the imperfect diagnostic accuracy of rapid PCR tests, their inhibition rate (ranging from 0.29% to 6% in the accuracy studies reviewed), and the fact that PCR cannot replace culture with respect
to susceptibility testing and typing, cultures cannot be eliminated completely and back-up cultures continue to be recommended for PCR-positive results.\textsuperscript{7,19,22,23,25,26}

Clinical-effectiveness evaluations for rapid PCR testing are few, observational in nature, and have differed with respect to screening/infection control policies and the primary outcomes captured. Nonetheless, they suggest promising impacts such as a decrease in turnaround time for test results, a decline in pre-emptive isolation days for facilities implementing such a policy, and a decline in MRSA transmission and infection rates.\textsuperscript{10,32} Obviously, well-conducted large cluster randomized controlled trials, which allow for thorough economic evaluation, are needed to inform the optimal screening policy/test. Recommended study endpoints include: the number of unisolated MRSA patient-days avoided; the number of unnecessary pre-emptive isolation days avoided; the increase in the MRSA decolonisation rate; the decrease in the MRSA transmission and infection rate; the decrease in MRSA-related mortality; the cost-savings associated with shorter hospital and ICU stays; and the decreased use of glycopeptides.\textsuperscript{9}

Finally, it should be remembered that screening is not a control measure in itself. Rather, it is one component of an infection control program which requires infection prevention and control specialists, laboratory professionals, doctors, nurses, and allied health professionals to coordinate their efforts for success.

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