

# Laboratory tools and strategies for methicillin-resistant *Staphylococcus aureus* screening, surveillance and typing: state of the art and unmet needs

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## Abstract

The public health burden caused by methicillin-resistant *Staphylococcus aureus* (MRSA) infections is now widely recognized, and is a cause of public alarm. Effective MRSA risk management in the healthcare system as well as in the community should rely on accurate detection of reservoirs and sources of transmission, as well as on close monitoring of the impact of interventions on disease incidence and bacterial dissemination. MRSA carrier screening and disease surveillance, coupled with molecular typing, are key information tools for integrated MRSA control and individual risk assessment. These tools should be tailored to the distinct needs of local interventions and national prevention programmes. Surveillance schemes should primarily inform local staff and serve as quality assurance about MRSA risk management. New technologies, including the use of selective culture media and real-time PCR assays, allow faster detection of MRSA carriers upon admission or during stay in healthcare institutions. More research is needed to ascertain their cost-effectiveness for MRSA control. Likewise, tremendous progress has been made concerning molecular typing methods, with optimization and standardization of sequence-based technologies offering broad applicability and high throughput. However, no single *S. aureus* typing method is yet providing fully reliable information within the range of discrimination needed for public health action. Further refinement of genotyping methods and international harmonization of surveillance and typing schemes must be achieved to facilitate global MRSA control.

**Keywords:** Carrier state, cross-infection, cross-over studies, DNA typing, epidemiology, incidence, infection control, mass screening, methicillin resistance, patient admission, PCR, prevention and control, prospective studies, review, standards, staphylococcal infections, *Staphylococcus aureus*, surveillance

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## Introduction

The magnitude of the health threat caused by antibiotic-resistant bacteria in general and methicillin-resistant *Staphylococcus aureus* (MRSA) in particular is increasingly appreciated by public health agencies, the media, and governments [1,2]. Reports on the increasing incidence of infections caused by community-acquired MRSA (CA-MRSA) and healthcare-associated MRSA in many parts of the world have raised concern about the failure of current control strategies. On the other hand, several countries have reported persistently low or decreasing incidence rates of MRSA disease. Many guidelines

produced by national professional bodies and health agencies have advocated a range of strategies to contain the transmission of MRSA in healthcare facilities and the community; these combine improvement of basic hygiene with targeted surveillance and control measures based on screening individuals for carriage of MRSA [3]. Controversy exists about their effectiveness and general applicability.

In this consensus statement, practitioners from different European countries with experience in the surveillance and control of MRSA have appraised the best strategies available and outlined the criteria that may help in selecting and applying laboratory and epidemiological tools for MRSA detection, surveillance, and typing. Readers are referred to other

sources for detailed descriptions of the evidence base, where available.

## Active Surveillance of MRSA Carriers

Active surveillance (or screening) for MRSA carriers is the systematic use of microbiological tests able to detect mucocutaneous carriage of MRSA by individuals without clinical infection. This is an essential component of MRSA control strategies in acute-care hospitals, and it is also potentially useful in other healthcare facilities, in both MRSA-endemic and low-incidence settings. This is based on the well-established fact that more than half of the reservoir of MRSA-colonized patients admitted to hospitals will go undetected by sampling of clinical specimens for routine diagnostic testing, unless swab samples of the nares, skin, wounds and, possibly, rectum and throat are tested specifically for MRSA using selective culture and/or DNA amplification methods [3,4]. These MRSA carriers may act as a source of transmission to other patients in the facility, unless they are readily identified and cared for with additional isolation precautions. Mathematical modelling supports the view that, without active carrier screening, implementation of isolation and carrier decolonization precautions will fail to decrease transmission of MRSA in acute-care hospitals [5,6]. Moreover, during outbreaks, admission screening differentiates 'imported cases' (positive culture/PCR within 48 h after admission) from new cases of hospital-acquired colonization or infection (first positive culture/PCR more than 48 h after admission). This differentiation is essential for monitoring of the effect of control measures.

In addition, screening of MRSA or *S. aureus* carriage before planned surgery may be beneficial to the individual patient in reducing the risk of surgical site infection by allowing targeted *S. aureus* preoperative topical decolonization and/or perioperative prophylaxis [7]. Active surveillance of MRSA also provides information about colonization status, which may help clinicians to choose appropriate antibiotic therapy in cases of infection.

Several conditions must be met to effectively implement active surveillance of MRSA at the hospital level. First, it should be driven by need, in other words, evidence that MRSA transmission and/or surgical site infection occurs locally in spite of good compliance by healthcare staff with standard precautions such as hand hygiene and prophylaxis. Second, the extent of active surveillance according to department or type of patient should be adjusted to the patient isolation capacity and the effectiveness in controlling spread and preventing infection. The effectiveness of active

surveillance should be periodically checked by local risk assessment.

An unresolved aspect is the decision about who should be screened upon hospital admission. Options range from universal screening (performed for all admitted patients) to screening of a selection of high-risk groups. Mathematical models suggest that universal screening would be most effective [5,8]. Indeed, some recent observational studies have documented a major reduction in the incidence of MRSA infection after the introduction of universal surveillance and isolation of carriers in all cases of admission to tertiary-care hospitals [9] or to surgical wards [10]. However, selective screening is the usual practice, for reasons of cost and logistics. Which, then, are the particular patient groups or care settings that can be proposed for screening? Single-centre and multicentre studies have identified risk factors that predict MRSA carriage upon admission. They include older age, transfer from or previous stay in another hospital, admission from a long-term-care facility, and underlying health conditions such as wounds or diabetes [11]. By application of a multi-criteria risk score, a higher yield of positive tests can be achieved, but with a sensitivity below c. 80%. However, this approach is difficult to implement routinely because of the limited compliance of nursing staff in performing the extensive review of medical history required to assess the risk profile of each individual before taking surveillance samples.

Another pragmatic approach that has been widely field-tested is to target patient-care services and departments caring for patients at high risk of MRSA transmission and/or invasive infections. Targeted patient groups include those in adult and neonatal intensive-care, dialysis, cardiothoracic, vascular and orthopaedic surgery units. In high-risk units such as intensive care, where the pretest probability of MRSA carriage can reach 10–30% of admissions, the strategy of pre-emptive isolation and screening of all patients followed by release from isolation after negative test findings for MRSA (also called the 'guilty until proven innocent' strategy) can be considered. In this setting, the use of a rapid screening test such as PCR offers clear advantages, although, when it was implemented in two intensive-care units, somewhat discrepant results were obtained [12].

In any event, a local policy of admission screening for MRSA should be developed by the infection control team, based on the identification of local high-risk units and patient groups. Compliance with screening and isolation policies must be audited. Adequate compliance depends heavily on continuing education of all involved healthcare workers, as well as on the regular feedback of results.

Infections caused by CA-MRSA strains are currently far less common in Europe than in North America. To maintain this low incidence, vigilance must be maintained to promptly identify cases of CA-MRSA carriage and infection as they occur. This requires more extensive microbiological testing of skin and soft tissue infections in both general and emergency-care practice. MRSA screening upon hospital admission should be considered for patients transferred from foreign hospitals or those who have travelled to a foreign country. This is routine practice, and forms an integral part of national MRSA control policy in low-incidence countries such as The Netherlands and Scandinavia. When Panton–Valentine leukocidin (PVL)-producing MRSA strains are detected, further contact tracing is warranted to identify and decolonize MRSA carriers and individuals with skin infections among family and close social contacts. This approach has been found to limit the community spread of imported PVL-producing MRSA strains [13,14]. Opinions vary as to whether such screening and contact tracing should be performed in every sporadic case of PVL-producing MRSA infection/colonization or only in those producing severe invasive infection or clusters of disease. More research is needed in this area.

Finally, 'livestock-associated' strains of MRSA, most frequently belonging to the ST398 clonal lineage, have recently emerged in several countries, including France, The Netherlands, Denmark, Germany, and Belgium. Individuals living in these countries and who are frequently exposed to farm animals such as pigs and calves, because of either their professional occupation or their place of residence, should also be considered to be at high risk for MRSA carriage and eligible for screening upon admission to healthcare facilities [15,16].

In addition to active surveillance for MRSA upon admission, further surveillance of patients during MRSA outbreaks, or, when a single case is detected in low-incidence settings, periodic (e.g. weekly) screening of patients in the ward or institution concerned can be useful to rapidly identify, isolate and/or decontaminate patients newly colonized by MRSA. Furthermore, post-admission screening is essential to determine the transmission epidemiology of MRSA among patients transferred within or between wards and facilities.

The issue of screening for MRSA carriage among healthcare workers is ethically sensitive, because positive results may jeopardize an individual's ability to safely perform clinical duties and may oblige them to undergo medical treatment. In low-incidence countries, screening of all staff in contact with a case of MRSA infection or colonization, and decolonization of all carriers, is part of the standard 'search-and-destroy' policy, the value of which has been amply demonstrated in protecting these healthcare systems

against the MRSA pandemic. In endemic settings, where MRSA cases are encountered by clinical staff on a daily basis, this is impracticable. Furthermore, in the vast majority of cases, carriage by healthcare workers is transient, and spontaneously resolves within hours. Nevertheless, outbreaks can be initiated or maintained by staff members who become chronic carriers and 'human disseminators'. Such a phenomenon usually occurs in people who suffer from skin disease or upper respiratory tract inflammation. Surgical and intensive-care personnel are the most frequently involved [17]. When epidemiological and molecular typing evidence points to a common source for a cluster of deep-seated infections (e.g. of surgical sites), it may be useful to screen staff and treat chronic carriers until MRSA is eradicated.

### Laboratory Tools for MRSA Screening

The optimal procedures for screening for MRSA mucocutaneous carriage are currently under investigation. These include the choice of the anatomical sites to be sampled, the sampling method, and the laboratory methods for processing and testing of the samples. These aspects are discussed below, and key areas for research are outlined.

Screening for MRSA carriage is generally performed by swabbing the anterior nares or multiple superficial sites, including nares, throat, and perineum [4]. Additional samples may be taken from the rectum, sputum of ventilated patients, wounds, and/or catheter insertion sites. Nasal screening is reported to have a sensitivity of over 80%, which can increase to 95% when additional sites are screened, although, in some series, screening in up to one-third of carriers was restricted to either the throat or rectum.

Sterile cotton or Dacron swabs can be used, and should be placed in a buffered medium for transportation to the laboratory. The use of liquid rather than gel transport medium may increase the recovery of bacteria from the swab, and the sensitivity of detection.

Conventional MRSA detection methods rely on selective culture in liquid and/or on solid media. Recent chromogenic, cefoxitin-based selective agar media have demonstrated superior selectivity, specificity and faster time to detection for MRSA screening than non-chromogenic media [4], and several chromogenic commercial media have performed well in clinical evaluations [18]. MRSA is detected in 20–48 h with most of these media, and negative results are usually reliable at 24 h. The use of a pre-enrichment step in selective broth medium increases the sensitivity of these media by 15–30%, but increases the cost and delays the results by an additional

18–24 h. Therefore, the practical value and cost-effectiveness of using an enrichment step needs further study.

Rapid (same-day) MRSA detection is potentially relevant for patient management [19]. It can be achieved by using several commercial or in-house nucleic acid amplification and hybridization assays [18–20].

Although these 'rapid' methods offer a turn-around time to results ranging between 75 min and 6 h, one should keep in mind that other delays in the diagnostic process comprise time from admission to sampling, from sample collection to laboratory reception, from laboratory reception to testing, and from test result production to ward reporting and implementation of isolation precautions. Pre-analysis and post-analysis steps typically make these rapid test results available for action, at best, within 24 h after admission, or later if testing is not performed 7 days a week and 24 hours a day [12]. Ideally, these tests should be accurate, rapid (<2 h process time), random access, robust, accessible to laboratory workers with basic skills, and affordable for high-volume use. Recent health technology assessment studies showed the promising performance of several commercial tests [18–20].

In addition to validation of test robustness and diagnostic accuracy, future health technology assessment research should establish the added medical value of these molecular detection systems, such as decreased MRSA nosocomial transmission and improved patient outcome, as compared with best-in-class conventional screening methods.

The need to measure this benefit by performing multicentre, national intervention trials in countries and hospitals with low, medium and high MRSA prevalence levels must be stressed. These trials should be controlled by comparing multiple intervention arms based on PCR vs. conventional testing, including, where appropriate, the use of pre-emptive isolation measures. Studies should preferably follow a cluster-randomized, cross-over design. Adherence to protocol should be closely monitored, and appropriate adjustments should be made for key confounding factors, including other control measures, hand hygiene compliance, colonization pressure, and antibiotic exposure. Relevant primary outcomes are incidence rates of nosocomial MRSA acquisition (as defined by temporal sequence after admission and molecular typing evidence) and incidence rates of nosocomial MRSA infection. Secondary outcomes of interest include length of patient stay, days of isolation, and days of antibiotic therapy. An evaluation of cost-effectiveness should also be part of these investigations. However, should any of the rapid MRSA detection assays prove to be cost-effective, the local benefit would still need to be further validated by interrupted time-series analysis before and after introduction into routine practice.

The results of two well-designed and strictly controlled trials have been published [21,22] since the consensus conference being reported here took place. Unfortunately, both studies concluded that there is a lack of demonstrable benefit of rapid PCR detection of MRSA upon admission to medical and surgical wards, in a tertiary-care centre in England in one study, and in patients undergoing clean surgery in a tertiary-care hospital in Switzerland in the other. More intervention studies of this quality are needed to ascertain the cost-effectiveness of rapid MRSA screening in relevant patient populations and healthcare systems.

### Surveillance Methods at Local, National and International Levels

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The most robust and clinically relevant surveillance indicators for monitoring MRSA control programmes are incidence rates of community-acquired and hospital-acquired infections. For the latter population, incidence of MRSA bacteraemia is probably the most objective and readily comparable indicator for longitudinal risk assessment, at both local and multi-hospital levels. These indicators must be monitored prospectively by adequately trained personnel, using standard case definitions and validated microbiological test results.

The rate of MRSA bacteraemia is a clinically relevant quality indicator that is also sensitive to the other preventive measures applied to intravenous catheter use, surgery, and intensive care. However, the rate of MRSA bacteraemia is influenced by many factors other than infection control, including the case mix and the rate of transfer from other institutions. Laboratory utilization rates should be measured to adjust this indicator for potential ascertainment bias. The relative frequency of MRSA among non-duplicate *S. aureus* clinical isolates by specimen type is a more easily accessible surrogate marker, and is used for international MRSA surveillance by the EARSS programme. However, the absence of a record of epidemiological factors to allow classification into the categories of community-onset, community-acquired and hospital-acquired cases may obscure proper interpretation of rates. Likewise, it would be desirable to adjust for the colonization pressure by relating healthcare-associated MRSA infection to the prevalence of MRSA carriage upon admission. Without universal admission screening, this is not generally applicable, but it can be attempted in special care settings, such as critical-care units, where screening has become standard practice.

From an operational standpoint, local surveillance can make possible the estimation of the incidence rate of

nosocomial MRSA acquisition (number of new cases of MRSA colonization detected on day 3 (or later) of hospital stay/1000 patient-days) as a sensitive indicator of control measures. It can be further refined by excluding from the denominators all patients with a short duration of stay (<48 h) and those already colonized upon admission. However, such an indicator is greatly affected by ascertainment bias, unless extensive patient screening is performed upon admission, during stay, and at discharge from the facility. A surrogate marker for this indicator that has been used for crude inter-hospital comparison is the counting of only new cases detected after performance of clinical cultures.

It is essential that the results of these surveillance indicators be fed back regularly to practitioners at ward level. Use of multiple indicators and analysis methods is preferable. Examples of feedback formats include root cause analysis of single cases of MRSA bacteraemia, quarterly/yearly rates of nosocomial MRSA acquisition and infection interpreted with statistical process charts or temporal trend analysis, and analysis of clusters of cases according to time, person, exposure, and genotype.

### Typing Tools for MRSA Outbreak Investigation and Surveillance

An overview of the most popular *S. aureus* typing methods, with their respective strengths and weaknesses, is shown in Table 1. Because *S. aureus* has a highly clonal population structure, many different chromosomal markers indexing polymorphism in coding or noncoding regions will provide largely congruent classifications of isolates into

clonal lineages, albeit with differing levels of resolution, depending on the number of loci analysed and their molecular clocks. This is true for DNA restriction polymorphism as well as for variable number of tandem DNA repeat data, inter-repeat element spacer polymorphism, and single-nucleotide polymorphism (SNP) [21–25]. Multilocus sequence typing, by indexing allelic polymorphism in seven neutral housekeeping genes, is the reference method for defining the core genetic population structure of *S. aureus*, which is dominated by a dozen major clonal complexes and comprises several hundred clonal lineages or sequence types (STs) [26]. However, for epidemiological typing, MLST has only moderate discriminatory power, and it remains too labour-intensive and costly for use as a primary typing tool. In addition to defining the bacterial chromosomal background, additional molecular tests should be applied to subtype the mobile methicillin resistance element, called the staphylococcal chromosomal cassette *mec* or *SCCmec*, which differentiates MRSA clones of common ancestry but distinct epidemiological origin [27].

For over a decade now, pulsed-field gel electrophoresis of genomic macrorestriction fragments has been widely used for local outbreak investigation and as part of typing systems for long-term surveillance of MRSA infections at regional and national levels. It is a highly discriminatory tool, for which epidemiologically validated interpretation criteria have been published for the investigation of local transmission of MRSA strains and outbreak management [28]. However, it is a technically demanding and low-throughput method, with limited portability owing to technical challenges in achieving interlaboratory comparability and standardization. In addition, attribution of pulsed-field gel electrophoresis clusters to

**TABLE 1.** Comparison of the main currently available methicillin-resistant *Staphylococcus aureus* molecular typing methods

Method	Principle/target	Strengths	Weaknesses
Multilocus sequence typing (MLST)	Sequence determination of allelic variants of housekeeping genes	Phylogenetic structure of core genome Interlaboratory portability Standard nomenclature High discriminatory power	Limited discriminatory power Low throughput Cost
Macrorestriction pattern analysis (PFGE)	Restriction polymorphism of the whole chromosome		Technically demanding Slow Limited interlaboratory portability Multiple nomenclatures
<i>spa</i> -sequence typing	Polymorphism of number and sequence of repeat elements of the hypervariable gene	Rapid High throughput Interlaboratory portability Standard nomenclature Attribution of MLST STs by BURP algorithm	Moderate discriminatory power Misclassification of particular STs due to recombination/homoplasy
Rep-PCR typing	Polymorphism in chromosomal inter-repeat element spacers	Rapid High throughput	Limited discriminatory power No validated interpretation criteria No standard nomenclature
Multilocus VNTR analysis (MLVA)	Polymorphism in number of chromosomal VNTR elements	Rapid High throughput	Limited discriminatory power No validated interpretation criteria No standard nomenclature

PFGE, pulsed-field gel electrophoresis; ST, sequence type; VNTR, variable number of tandem DNA repeat.

genetic lineages may be problematic, and some strains, such as the 'livestock-associated' ST398 strains, are non-typeable by standard protocols, owing to restriction site methylation.

The determination of sequence polymorphism in the variable X region of the *spa* gene encoding the staphylococcal surface protein A (*spa* sequence typing) has become the most popular MRSA typing system. Its popularity is attributable to its many practical advantages, including high throughput and full portability of data, thanks to its absolute reproducibility, which allows internet-based type assignment and comparison with a worldwide database [29,30]. It has therefore become one of the primary typing methods for regional and national MRSA surveillance schemes. Nevertheless, this technique also has limitations, which necessitate the use of additional tests for reliable typing in some circumstances. Indeed, *spa* types do not allow reliable inference of particular genetic ST lineages (e.g. ST1, ST8, and ST80). In these cases, the use of PCR for the analysis of additional markers, such as toxin and antibiotic resistance genes located on clone-specific mobile genetic elements, is needed for correct ST delineation and assignment [23,30]. Repeat-based *spa* locus polymorphism is subject to misclassification bias, owing to both horizontal DNA transfer and recombination (e.g. in ST239) and homoplasy (e.g. in ST5 subclones) [31].

Other high-throughput MRSA typing techniques include rep-PCR typing and multilocus variable tandem repeat analysis (MLVA). The former was shown to be variably discriminative but poorly reproducible among laboratories when based on in-house protocols [32]. A kit-based rep-PCR assay combined with a commercial fingerprint analysis platform (Diversilab; Bacterial BarCodes, Houston, TX, USA) showed excellent reproducibility but moderate discrimination, and remains impeded by the lack of validated criteria for interpretation and type nomenclature [33]. MLVA schemes share the rep-PCR advantages of rapid turn-around times and high throughput, but their discriminatory power depends on the number and types of variable number of tandem DNA repeat/Staphylococcal interspersed repeat units (SIRUs) loci analysed. As with rep-PCR, no standard MLVA protocol or international nomenclature is yet available for type assignment.

Typing of SCCmec elements should be performed for multi-centre surveillance and analysis of interhospital or international MRSA strain transmission and evolution, especially among the ST5, ST8 and ST398 lineages, which harbour a diversity of cassette types and subtypes. Several methods, which rely either on PCR mapping of cassette elements (such as the *ccr* complex, *mec* complex and J regions) or on sequence determination of an internal fragment of the recombinase gene *ccrB*, are available for this purpose. A combination of these two approaches is recommended for reliable typing.

Finally, SNP detection methods offer an efficient alternative to the above-mentioned typing methods. These methods have been developed for rapid identification of major *S. aureus* clonal complexes and STs as well as for detailed discrimination of regionally emerging MRSA subclones [31]. Additional mutation discovery studies in different *S. aureus* lineages should allow the development of a standard hierarchical SNP catalogue that could be used for high-throughput, scalable-resolution SNP typing systems. In the meantime, PCR-based or microarray-based detection of clone-specific SNPs, genes or genomic islands can be useful for rapid identification of epidemiologically important MRSA clones (such as ST1, ST80, ST8-'USA300', and ST398).

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## Conclusion

MRSA carrier screening, surveillance and molecular typing are pivotal information tools for integrated MRSA control programmes. New technologies offer tremendous potential for more effective and timely interventions. There is an urgent need for health professionals, *in vitro* diagnostics companies and policy-makers to work together to assess the cost-effectiveness of these tools for safer care of patients and protection of the public against the tide of MRSA. In addition, greater international harmonization of surveillance and typing schemes is needed to facilitate cooperation in an effort to control the MRSA pandemic.

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