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# Speed of molecular detection techniques for meticillin-resistant *Staphylococcus aureus* admission screening in an acute care hospital

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SUMMARY

Active surveillance for meticillin-resistant *Staphylococcus aureus* (MRSA) carriers is considered an essential component of MRSA control strategies in acute care hospitals. Recently, molecular assays for MRSA screening have been proposed with significant reduction of the sample processing time. Using a time analysis model, we investigated the time gain after the introduction of a molecular assay and compared this with a preceding control period, using culture-based techniques. During a four-month period all high risk patients ($N = 44$) and all known MRSA-positive patients readmitted to the hospital ($N = 41$) were screened for MRSA upon admission. In both groups the long pre-analytical phase – time from admission to sampling and transportation of samples to the laboratory – was the determining factor in the entire process. A substantial reduction of the sample processing time was achieved using molecular assays, compared with conventional culture. Due to the long pre-analytical phase, in addition to the high costs associated with polymerase chain reaction (PCR) testing, molecular techniques were not introduced for the admission screenings. In the group of the readmission screenings, however, a fast test result could save a substantial number of unnecessary isolation days, resulting in an economic benefit for the hospital. PCR testing might be of interest for the readmission screenings. In conclusion, local policies for MRSA screening should be investigated before introducing expensive PCR technology.



## Introduction

Meticillin-resistant *Staphylococcus aureus* (MRSA) is one of the major nosocomial pathogens responsible for increased morbidity, mortality and prolonged hospital stay.[1]

The additional length of stay, the need for isolation or cohorting patients, the requirement for additional investigations and the use of more expensive and toxic antibiotics contributes to the significant impact on healthcare costs of MRSA infections.[2] Current Belgian recommendations advise contact isolation for MRSA-positive patients, decolonisation protocols, appropriate hand hygiene and continuous education of healthcare workers. MRSA carrier screening may contribute to early identification and thus result in a tangible reduction of the MRSA transmission rate.[3]

Conventional culture-based detection of MRSA with selective chromogenic agars requires at least 24–48 h for presumptive MRSA detection, leading to delayed or unnecessary isolation precautions.[4,5] Although several commercialised molecular assays promise MRSA detection within a few hours, the broad use of these assays is hampered by the high costs for polymerase chain reaction (PCR), compared with culture.[6]

The aims of this study were: (i) to make a time analysis of the whole sample flow, from the time of arrival of the patient at the hospital, until the time of reporting to the wards and the moment that MRSA-positive patients are isolated; (ii) to evaluate the time gain after the introduction of rapid PCR tests compared with a preceding control period when patients were screened using a traditional culture-based method.

## Methods

### *Study population*

AZ Sint-Lucas Ghent is an 807-bed acute care hospital in Belgium. Annually, the hospital admits ± 28 000 patients and the

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average length of stay is eight days. All high risk patients and known MRSA-positive patients (previously colonised or infected) readmitted to our hospital were screened for MRSA upon admission. A high risk admission was defined as: (i) a patient with a previous admission to a healthcare facility for more than 14 days within the last year; (ii) a patient transferred from a long term care facility; or (iii) a patient receiving domiciliary care for more than two months.

During a four-month period (from 16 February until 16 June 2009) MRSA detection was performed using a molecular-based assay. These results were compared with a preceding control period (16 February until 16 June 2008) where the detection of MRSA was culture-based.

*Specimen collection*

For admission screening, nasal and wound swabs were taken, for readmission screening, nose, throat, perineum and wounds were sampled. The ESwab® (Copan Diagnostics, Brescia, Italy), a nylon flocked swab, was used for sampling. This type of swab was chosen for its higher release of bacteria.[7] All swabs were transported to the laboratory at room temperature, stored at 4 °C and processed within 1–16 h after collection. Collection of the samples from the wards occurred at regular time intervals. A small section of the hospital has a pneumatic hospital transport system (PHTS), for direct sample transport.

*PCR-based MRSA screening*

During the study period, MRSA screening was performed with one of both qualitative real-time PCR assays, either the BD GeneOhm™ MRSA real-time PCR system (BD Diagnostics, Franklin Lakes, NJ, USA), or the GeneXpert® System (Cepheid, Sunnyvale, CA, USA).

*BD GeneOhm™ MRSA (BDGO)*

The BDGO PCR system detects simultaneously the staphylococcal cassette chromosome *mec* (SSC*mec*) and a *Staphylococcus aureus*-specific sequence located within the *orfX* gene.[8]

The BDGO assay has previously been validated for nasal, throat, perineal and wound testing.[9] The turnaround time (TAT) of the BDGO MRSA assay, including the extraction procedure, is about 180 min.

*GeneXpert® System Cepheid (Xpert)*

The PCR MRSA assay targets DNA sequences in the chromosomal *orfX*-SCC*mec* junction. The Xpert real-time MRSA PCR is US Food and Drug Administration-approved for nasal, skin and soft tissue samples. The Xpert system is a closed and fully automated platform that combines board sample preparation with real-time PCR amplification and reading. The sample preparation time is minimal and the TAT of the MRSA assay on the Xpert is 75 min.

*Choice of the PCR assay*

The choice of the assay depended upon the arrival time of the swab in the laboratory. All sample swabs arriving in the laboratory from Monday to Friday, between 20:00 and 12:00, were collected and analysed in the molecular laboratory, using the less expensive BDGO assay. For the BDGO assay, batch testing is recommended and specialised molecular laboratory staff are required. Samples arriving after 12:00 or at the weekend were processed on the Xpert in the microbiology laboratory. As the extraction was included in the test, direct testing was possible, significantly reducing the TAT of the analytical process.

*Sample processing*

All swabs were processed between 08:00 and 20:00 on working days and on Sunday. On Saturday, sample evaluation was performed between 08:00 and 18:00. The swabs were vortexed thoroughly for 5 s to release the sample from the swab tip into the liquid Amies transport medium. For the Xpert and the BDGO, respectively 100 and 200 μL transport medium was transferred in a single tube. After pooling, the tube was again vortexed for 5 s. For further PCR testing, respectively 150 and 2.8 μL was used for the Xpert and the BDGO.

Only positive PCR results were confirmed with culture. These molecular assays have high negative predictive values of 98%, compared with culture, and are therefore excellent screening tests.[10]

*Sample pooling*

In response to the high costs associated with molecular detection, a sample pooling strategy was set up. The samples of high risk patients taken on admission were pooled up to four samples: four nasal swabs from four different patients were pooled. If a wound swab was taken, the nasal swab and the wound swab from one patient were pooled. When a set of pooled nasal swabs tested positive, each individual sample was re-evaluated with a second molecular test, in order to define the positive patient within an acceptable time period. The swabs taken from the readmission screenings were pooled per patient.

*Control period*

During the control period the detection of MRSA was culture-based, by transferring 100 μL transport medium into a 5 mL enrichment trypticase soy broth (TSB) (BD Diagnostics). After overnight incubation at 35 °C, 50 μL TSB was subcultured on a selective chromogenic medium, chromID™ MRSA agar (bioMérieux, Marcy l'Etoile, France), incubated at 35 °C ambient air and examined after 24 h of incubation. If no growth or coloration was obtained after overnight incubation, plates were further incubated for another 24 h.

All new MRSA isolates were confirmed with a latex agglutination test (Oxoid PBP 2′ test) for the detection of penicillin binding protein 2′. For the confirmation of known MRSA positives an oxacillin screen agar (BD Oxacillin Screen Agar) was used, requiring an additional overnight incubation.

Additionally, each new MRSA strain was confirmed with a triplex PCR, targeting the 16S rRNA, mecA and nuc genes, according to the recommendations of the Belgian reference laboratory.[11]

*Time analysis*

We set up a time analysis model to investigate the overall period from patient admission to the onset of isolation precautions and to determine the time gain attributable to molecular assays. The whole diagnostic process was divided into four different time frames. The time of admission of the patient to the hospital was traceable in the electronic medical record system. Organisationally, it was not possible to differentiate between the time of sampling the patient and the arrival of the sample in the laboratory. Time of sample arrival and registration in the laboratory was traceable in the laboratory information system (LIS). When multiple samples are processed from one patient, the first registered sample was used. The exact time of the start of sample processing was automatically registered by the instrument software. The time at which

the technician confirms the result in the LIS was also traceable. At that time, an automatic e-mail alert was sent to the infection control team and the microbiologists. They contacted nursing staff to start the isolation procedure. The patient's transfer into a single room was registered in the electronic medical record system and was used as marker for the initiation of isolation precautions. For patients already in a single room, the recording of MRSA positivity in the electronic nursing record was taken as a surrogate marker.

## Results

During a four-month period, 44 positive admission screenings and 41 readmission screenings were consecutively included. The time frame of the whole process, from the moment of admission of the patient until the onset of the isolation precautions, was registered. The overall time frame was divided into four parts (A–D) (Table I).

The period from admission of the patient until the sample arrival and labelling in the laboratory (A) was comparable for both groups, and took on average 16.9 h for the admission screenings and 17.0 h for the readmission screenings. Once the sample was registered, the time necessary to start sample processing (B) was rather short and again similar for both groups. Furthermore, it took on average 3–4 h from the moment the sample processing started until the time the results were registered in the LIS (C). This time span included the time necessary for pooling the samples, the extraction procedure for the BDGO assay and for individually retesting the positive pools with another molecular assay.

When comparing these results with the preceding control period, using culture technique, we found a substantial reduction of the analytical processing time using molecular assays. During the control period we needed on average 36.8 h to isolate newly admitted MRSA-positive cases, using culture-based techniques. For the readmission screenings, the average time was even longer, 54.9 h. By contrast with the new MRSA-positive cases, an oxacillin screen agar was used for MRSA confirmation, requiring an additional overnight incubation period.

Once the result was reported in the LIS, the average time necessary to isolate the patient (D) was 1.8 h (median: 0.9 h) for the admission screenings. In the group of the positive readmission screenings, all patients with the exception of one patient were correctly isolated at the time of admission.

Period A included patient sampling, sample transport to the laboratory and sample registration. In our hospital, patients were not screened in the emergency department, thus already introducing a delay in sampling. Furthermore, only a small part of the hospital has a pneumatic hospital transport system (PHTS), covering 30.5% of the overall sample transport. Over a five-week period, time segment A was registered for all ($N = 265$) (negative as well as positive) MRSA results. Samples transported with the pneumatic hospital transport system (PHTS) needed on average 9.1 h to arrive in the laboratory, compared with 20.6 h for samples coming from wards without a PHTS. A PHTS constitutes an important gain in time in the sample transport in a hospital.

**Table I**
Overview of the average and median times (in hours) for each segment of the diagnostic process[a]

| Time segment | | Admission | | Readmission | |
|---|---|---|---|---|---|
| | | Molecular assays ($N = 44$) | Culture ($N = 43$) | Molecular assays ($N = 41$) | Culture ($N = 34$) |
| A. Time from admission until the sample arrival in the laboratory | Median | 16.6 | 17.7 | 16.7 | 15.2 |
| | Average | 16.9 | 21.7 | 17.0 | 17.8 |
| B. Time from laboratory arrival until start of sample processing | Median | 2.5 | 1.3 | 1.5 | 1.2 |
| | Average | 4.2 | 2.0 | 2.6 | 3.1 |
| C. Time from sample processing until result confirmation | Median | 2.1 | 26.5 | 1.8 | 47.4 |
| | Average | 4.1 | 36.8 | 3.2 | 54.9 |
| D. Time from confirmation until start of isolation precautions | Median | 0.9 | 2.0 | NA | NA |
| | Average | 1.8 | 3.2 | NA | NA |

NA, not applicable.
[a] Both molecular assays compared with culture.

## Discussion

Culture-based screening methods have been shown to be cheap and sensitive; unfortunately these methods usually require 24–48 h before MRSA identification. Therefore the introduction of rapid screening tests such as PCR testing can be considered as an alternative.[12]

Several commercial molecular assays have recently been launched on the market, offering a test result within 2–6 h. Our time analysis study indicates that the first step in the sample process, time from admission to sampling and transport to the laboratory, is the determining step in the entire process. Screening of patients in the emergency department could not be organised in our hospital. Patients are, however, screened upon arriving on the assigned ward. Due to the absence of a PHTS in a major part of the hospital, this pre-analytical time segment of the diagnostic process is further increased. Organisationally, it was not possible to register sampling time and time of sample arrival in the laboratory. To remove this limitation, we tried to assume the importance of swift transport on the duration of this pre-analytical time segment. Our data clearly indicate that the presence of a PHTS might be very useful. Furthermore, pooling samples introduced a delay in the sample processing time, therefore this might only be of interest in a low prevalence setting. Factors outside the laboratory may hamper the whole time interval from admission to isolation of the patient.

Due to the limited study period, the impact of rapid PCR screening test on nosocomial MRSA transmission could not be evaluated. The data from literature are contradictory on this topic. Harbarth *et al.* could not show a positive effect of rapid transmission screening on the MRSA infection rate.[12] On the other hand, Cunningham *et al.* demonstrated that MRSA admission screening by PCR could reduce the nosocomial transmission of MRSA on an intensive care unit.[13] It is likely that the compliance with local hygiene standards plays an important role and that the study results cannot be extrapolated to other institutions with different MRSA epidemiology and different compliance rates for infection control measures.

A substantial reduction of the sample processing time is achieved using molecular assays, compared with conventional culture, but does not compensate for the long pre-analytical phase. Due to local policy and the absence of a PHTS in most of the hospital, there is no opportunity in the near future for improving the speed of patient sampling and sample transport to the laboratory. Therefore we decided to go back to using culture methods for the admission screenings.

The situation is different for the readmission screenings. Our local algorithm for isolating known MRSA-positive patients at the time of readmission is based on the assumption that pre-emptive isolation is the most beneficial, due to the high prevalence (42%) of MRSA carriers in this group. Rapid screening, compared with conventional culture, could save 540 isolation days, resulting in a substantial economic benefit to the hospital.

In conclusion, before introducing expensive PCR technology, the time involved in sampling the patient and transporting the specimen to the laboratory should first be shortened. As these assays are much more expensive than conventional tests, further controlled trials will be needed to determine the potential medical and economic benefit of control strategies using this technology in an acute care setting.

**Conflict of interest statement**
None declared.

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