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American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Review of a major epidemic of methicillin-resistant *Staphylococcus aureus*:
The costs of screening and consequences of outbreak managementAnneke van der Zee PhD^{a,*}, Willem D.H. Hendriks MD, PhD^b, Lieuwe Roorda^a,
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Key Words:

MRSA
PCR
High-throughput screening
Cost**Background:** A major outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) occurred in locations C and Z of our hospital and lasted for several years. It affected 1,230 patients and 153 personnel. **Methods:** Outbreak management was installed according to the Dutch “search and destroy” policy. A rapid, high-throughput method for molecular screening of potential MRSA carriers was implemented. Outbreak isolates were retrospectively genotyped by pulsed field gel electrophoresis. Costs of molecular screening were compared with screening by culture.**Results:** Genotyping results revealed 4 distinct epidemic MRSA clones. Three were present in hospital C. Because of a merger of hospitals, these clones spread to hospital Z. Another clone of MRSA affected other health care-related institutions in the region. Because of the implementation of strict containment measures of the “search and destroy” policy, the annual number of tests decreased from 100,000 to 18,000. The disposables and reagents used in polymerase chain reaction technology are more expensive than those of conventional methods. However, the clinical and economic benefits of fast results in regard to expenses of the hospital clearly outweigh the higher costs of screening.**Conclusion:** The implementation of a rapid, high-throughput molecular screening system greatly contributed to the effectiveness of strict containment measures of the “search and destroy” policy. The major epidemic clones of MRSA in the outbreak were eradicated by this strategy.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is, worldwide, one of the most important pathogens known to frequently cause nosocomial infections.¹ The clonal spread of highly epidemic MRSA strains within hospitals or between hospitals has been well described.^{2,3} Outbreaks of MRSA in a hospital are often difficult to control, and eradication of epidemics may take several years.⁴ In The Netherlands, MRSA is approached by a “search and destroy” policy that has proven to be successful.^{5,6} This policy has been implemented in other countries as well.⁷ It has been shown that, with extended infection control strategies of screening of patients at admission and discharge, and screening of all health care workers, outbreaks could be contained more rapidly.

We experienced a major epidemic of MRSA in both locations, C and Z, of our hospital, which was recognized in November 2001. This particular strain of MRSA initially escaped detection because of its very low minimum inhibitory concentration for oxacillin. Using disc diffusion, these strains were initially reported as methicillin-sensitive *S aureus*. Consequently, this MRSA strain was able to spread freely in our hospital and affected both patients and personnel. Extensive measures were taken to control the epidemic, as was described by Van Trijp et al,⁸ covering hospital C from 2002 to 2005. Here, we report the analysis of the epidemic over a time span of 8 years. We report on the spread of epidemic clones in both hospital locations and its spread to other health care-related facilities in the region outside of our hospitals. We analyze the factors contributing to the successful eradication of the epidemic clones. Furthermore, we compare fully automated molecular screening for MRSA with conventional culture and provide estimates of costs controlling the outbreak. We show that the implementation of molecular screening led to considerable hospital savings.

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Conflicts of interest: None to report.

Table 1
Numbers of screening by culture and PCR from 2002 to 2009

Year	Culture/patients		Culture/personnel		PCR/patients		PCR/personnel		Results/patients		Results/personnel	
	Patients, n	Screenings, n	Personnel, n	Screenings, n	Patients, n	Screenings, n	Personnel, n	Screenings, n	Suspect, n	Confirmed positive, n	Suspect, n	Confirmed positive, n
2002	10,508	53,773	1,124	24,738						374		96
2003	15,470	86,045	1,228	27,030						320		35
2004	14,954	83,634	7,650	16,830						97		5
2005	16,669	72,382	2,964	6,612						162		5
2006					15,618	72,515	566	1,231	1,073	101	28	1
2007					14,979	71,821	591	1,323	541	89	13	5
2008					3,907	16,716	751	1,631	325	42	72	2
2009					3,745	17,794	350	787	401	45	36	4
Total										1,230		153

NOTE. MRSA screen by PCR was implemented on March 16, 2005. Screening on admission and discharge of patients was abolished as from January 2008. Repeated screening was counted.

MATERIALS AND METHODS

Samples and culture

From hospital personnel and patients, nose and throat swabs were taken. In addition, perineum swabs were taken from patients, and, if indicated, swabs from wounds, sputum, and catheters were taken (Transwab, Medical Wire & Equipment Co Ltd, Corsham, Wilts, England). No extra action or sampling was requested than that medically indicated. Informed consent was not asked, and no ethical approval was required, in conformity to the guidelines of the Dutch Central Committee on Research involving Human Subjects (www.healthlaw.nl/humsub.pdf).

To verify correct sampling, swabs were plated onto 5% sheep blood agar to count commensal bacteria. To ensure compliance with appropriate sampling, swabs should at least produce 15 colonies. Therefore, when swabs produced less than 15 colonies, they were rejected. In these cases, a repeat sample was requested. Subsequently, swabs were inoculated into 5 mL phenyl mannitol broth containing ceftizoxime and aztreonam for overnight incubation.⁹ After >18-hour overnight incubation, 100 µL was plated onto blood agar for MRSA isolation. All colonies suspected for *S aureus* were tested by slide agglutination (Staphaurex Plus, Remel Europe Ltd, Dartford, England). If positive, antibiotic sensitivity testing was performed by agar diffusion (Isosensitest; Oxoid, Ltd, Hampshire, United Kingdom), according to the Clinical and Laboratory Standards Institute protocol. Strains that were resistant to oxacillin (from 1-1-2006 cefoxitin; Clinical and Laboratory Standards Institute, Wayne, PA), erythromycin, or ciprofloxacin were tested by agglutination for PBP2a (Oxoid). Colonies were sampled from the edge of the oxacillin inhibition zone for penicillin binding protein PBP2a. If the slide test was positive, Accuprobe (Gen-Probe Inc, San Diego, CA) confirmation of the determination of *S aureus* was done. Confirmed MRSA isolates were sent to the National Institute of Public Health and the Environment, Bilthoven, The Netherlands, for further genotyping by pulsed-field gel electrophoresis (PFGE).

Implementation of molecular screening of MRSA

The measures taken to control the epidemic according to the Dutch "search and destroy" protocol led to huge numbers of specimens for screening. Consequently, automated methods were sought to limit the laborious and time-consuming number of cultures. A fully automated novel DNA extraction method for MRSA was adopted that virtually prevents polymerase chain reaction (PCR) inhibition and requires no centrifugation.¹⁰ The real-time PCR-based detection was presented by extended multiplex PCR.¹⁰ This PCR specifically targets the junction between a conserved open reading frame *orfX* in *S aureus* and the staphylococcal cassette

chromosome containing the *mecA* gene (*SCCmec*). This system was designed to detect MRSA DNA in enrichment broth incubated overnight. The detection process was fully automated for high through-put of clinical materials, and a digitized data work flow was installed in 2005.

Calculation of costs and savings

All data of screening by conventional culture and by automated molecular methods were used to calculate the costs. Because the PCR screening system was evaluated during 2005 and was fully operational since 2006, data over the year 2005 were omitted from the calculations.

The data listed in Table 1 were used to estimate costs: (1) the number of MRSA screening tests per year per patients and personnel, (2) the number of patients and personnel suspect for infection or carriage of MRSA, and (3) the number of MRSA-positive patients or health care workers.

The mean number of screening tests per patient was 4.9 and 2.2 per health care worker. Other parameters used were as follows:

- Culture screening costs, €7. Average cost of a conventional culture was €7 per sample. It included culture media, hands-on time of technicians, and input of staff and administrative personnel.
- PCR screening costs, €19. Costs include a 5-year period of depreciation and maintenance of the fully automated extraction/PCR system and the cost of the proportion of positive PCRs (10%, Table 1) that were subsequently subjected to culturing.
- Duration of culture screening, 5 days. Traditional culture takes 5 days before both a positive or a negative result is available because oxacillin susceptibility tests have to be performed.
- Duration of PCR screening, 2 days. With PCR detection of the *MecA* gene, a negative result can be obtained within 2 days. PCR-positive screenings have to be cultured to determine whether PCR positivity was due to MRSA or to a combination of MSSA and coagulase negative Staphylococci.
- Duration positive patients isolation (culture), 20 days. Isolation was ended when 3 subsequent cultures were negative.
- Duration positive patients isolation (PCR), 7 days.
- Isolation costs per day, €500
- HCW salary costs per day, €160
- Correction for patients, 15%. To provide a reliable overall cost estimate, it was assumed that 15% of patients were involved. The 15% was carefully derived to (1) minimize the effect of each counted screening (repeated counting by consecutive screenings of MRSA positive patients), (2) to compensate for cohort isolation of patients, (3) to correct for admitted patients who were not suspect for carrying MRSA.

MRSA positive 2002 - 2009

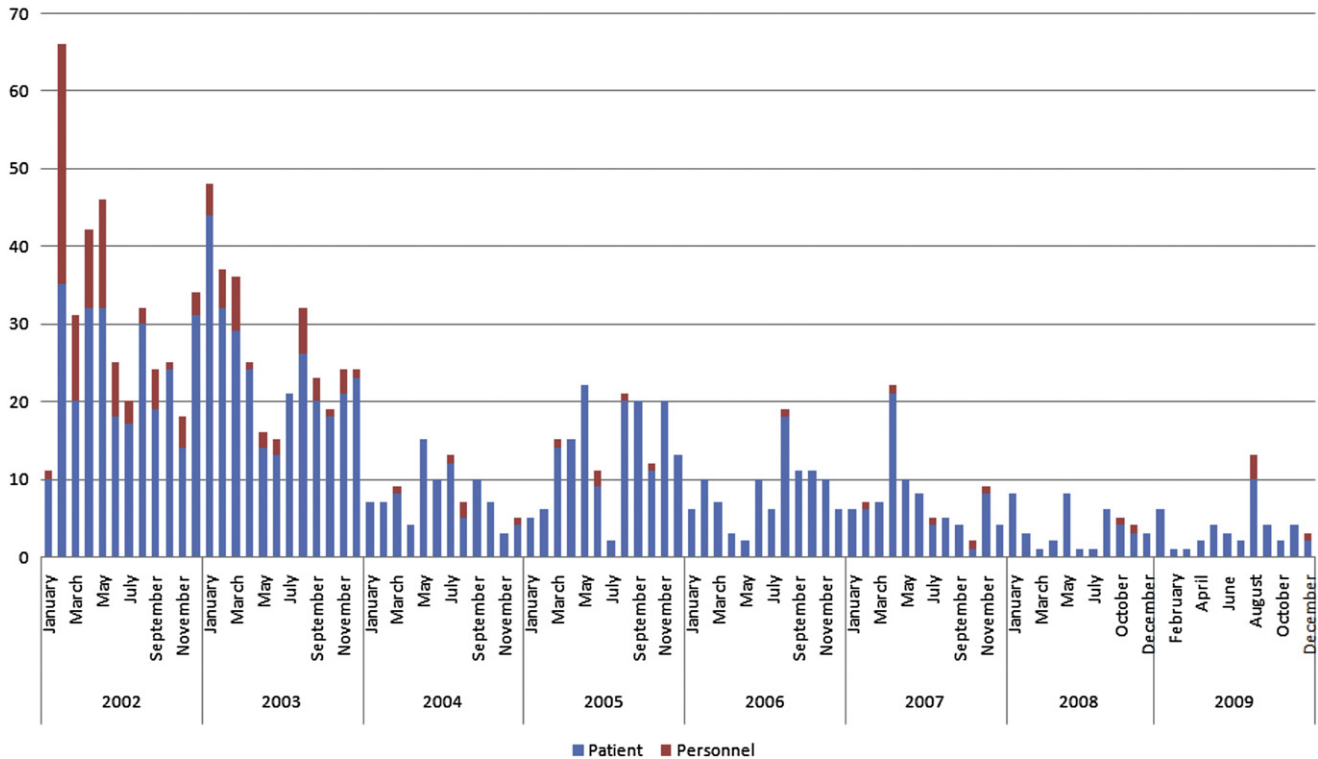


Fig 1. The monthly incidence of MRSA among patients and personnel (as indicated) during and after the outbreak.

RESULTS

The course of the epidemic

The outbreak of MRSA was initially recognized in November 2001, and soon a large number of colonized patients and hospital personnel were detected (Fig 1). Because of the measures taken as described previously,⁸ the number of new infections decreased during the following 2 years (2002-2003), followed by a slight increase in 2005. The slight increase in the number of infections in 2005 was probably due to increased spread of MRSA in health care institutions in the region of the hospital as is shown in Figure 2 by the increase in genotype 18. A further decline in the number of infections in later years led to the level that was seen in our hospital before the outbreak. An outbreak is defined when 2 or more patients share the same MRSA strain or by transmission of 1 MRSA strain between 2 or more patients. In fact, 3 epidemic strains were found to have spread in hospital C as was revealed by retrospective genotyping results and PFGE-type assignment. In 2002, PFGE types 16, 37, and 38 were the major clones in hospital C. Other MRSA genotypes only disseminated minimally and were considered as bystanders.

Distribution of MRSA genotypes

We analyzed samples from both locations C, and Z, from other hospitals in our region as well as various health care related institutions as nursing homes, care centres and general practitioners. The distribution of major genotypes 16, 37, 38, and 18, is shown in Figure 2. Of minor genotypes 98% was only seen once. Minor genotypes were evenly distributed over locations C, Z, and X and over time. The outbreak started in location C of our hospital (Fig 2).

Because of a merger of hospital C and hospital Z in 2001, the epidemic spread to location Z by lateral transfer of patients and health care workers. It subsequently appeared to have spread to other health care locations in the region. For example, MRSA genotype 18 was present in 1 patient in 2002 in location C. It was not recognized as an epidemic type of strain within hospital C because it did not spread in this location. However, as is shown in Figure 2, MRSA with PFGE genotype 18 appeared to be most widespread and most persistent because its presence covered all locations and years from 2002 to 2007. After 2004, the epidemic clone of PFGE genotype 38 was no longer found. After 2005, genotype 37 was eradicated and PFGE genotype 16 after 2006. After 2007, all the major epidemic clones could no longer be found. Many MRSA strains were found because of new introductions with a sporadically occurring genotype.

Analysis of costs and savings

The yearly numbers of MRSA screening among patients and personnel are listed in Table 1, as well as the number of patients and personnel who were suspect by PCR for infection or carriage of MRSA and the number of positive cultures in each group. A comparison of costs between screening by traditional culture and by automated molecular method was carried out. The parameters mentioned in the Materials and Methods section contribute to an approximate figure of yearly savings in hospital costs (Table 2).

When screened by traditional culture, patients had to be kept in isolation and/or were not allowed to be transferred or discharged for at least 5 days, and personnel was sent home for at least 5 days awaiting the outcome of the cultures. In case of a positive culture, patients had to be kept in isolation for at least 20 days until cultures

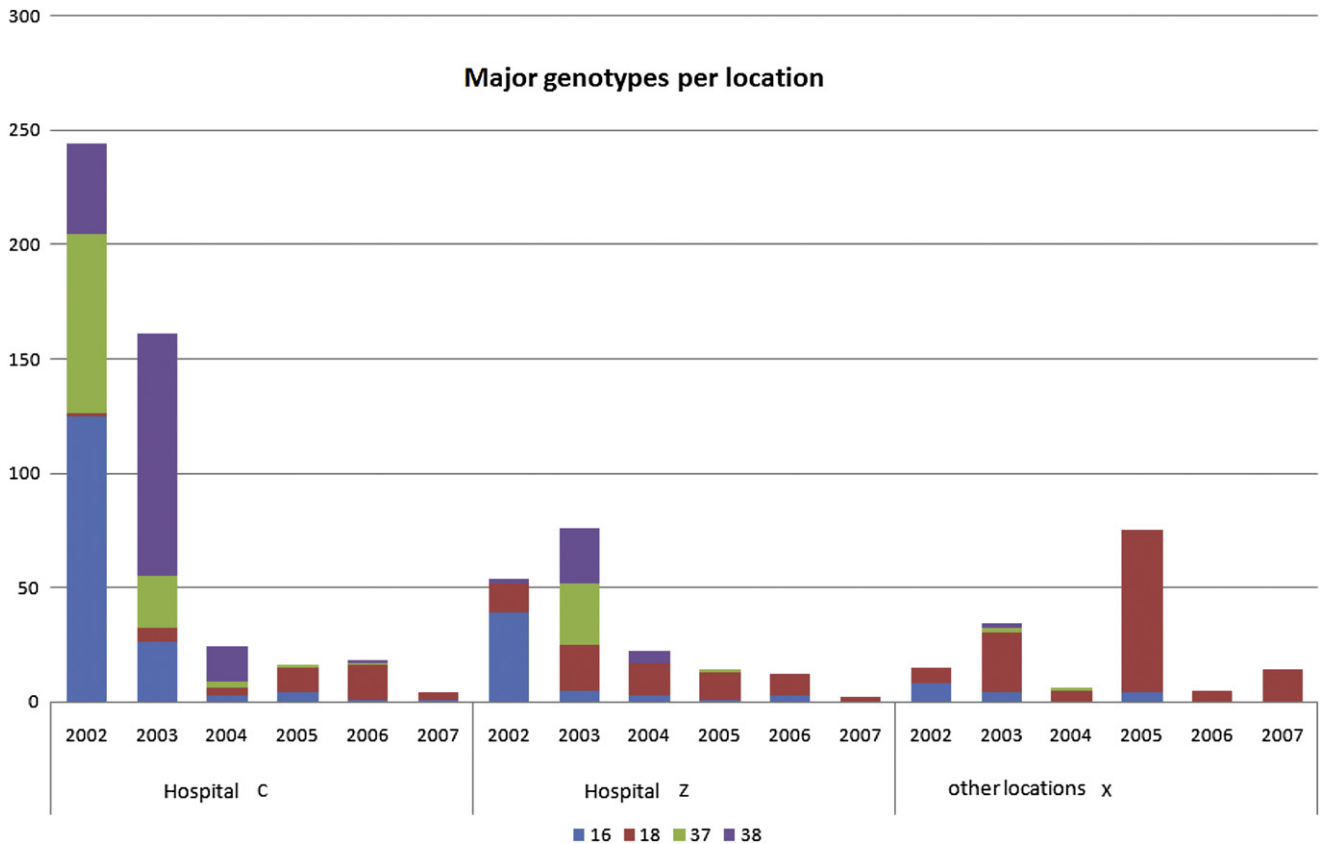


Fig 2. Spread of major epidemic MRSA clones with indicated PFGE genotypes 16, 18, 37, and 38. C and Z comprise both locations of our hospital. X includes all other health care facilities in our region.

Table 2
Calculations of costs and savings based on comparison of screening by culture and screening by PCR

Year	A		B		C		D		E		F		G	
	Costs test/patients		Costs test/personnel		Isolation costs/patients (15%)		Absence costs/personnel		Savings/patients		Savings/personnel			
	Culture	PCR	Culture	PCR	Culture	PCR	Culture	PCR	Culture	PCR				
2002	€376,411		€173,166		€4,361,250		€169,440							
2003	€602,315		€189,210		€6,161,250		€159,960							
2004	€585,438		€117,810		€5,716,875		€919,800							
2005	ND		ND		ND		ND							
2006	€507,605	€1,377,785	€8,617	€22,998	€6,828,875	€3,096,050	€455,200	€228,000	€2,862,645	€212,819				
2007	€502,747	€1,364,599	€9,261	€24,706	€6,473,750	€2,759,000	€484,800	€321,920	€2,852,898	€147,435				
2008	€117,012	€317,604	€11,417	€30,015	€1,869,375	€853,875	€605,600	€346,880	€814,908	€240,122				
2009	€124,558	€338,086	€5,509	€14,301	€1,837,500	€868,500	€289,600	€238,720	€755,472	€42,088				
Subtotal savings											€7,285,923		€642,464	

ND, not done.

NOTE. A and B: number of screenings (Table 1) × costs, respectively, culture and PCR, patients and personnel. C: [(number of patients – MRSA positives) × 5 days × €500 × 15%] + number of positives × 20 days × €500. D: [(number of patients – MRSA suspects) × 2 days × €500 × 15%] + (number of suspects – number of positives) × (2 + 5 days) × €500 × 15% + (number of positives × 10 days × €500). E: [(number of patients – MRSA positives) × 5 days × €500] + number of positives × 20 days × €500. F: [(number of patients – MRSA suspects) × 2 days × €500] + (number of suspects – number of positives) × (2 + 5 days) × €500 + (number of positives × 10 days × €500). G: (cost culture – cost PCR) + (isolation/absence because of culture – isolation/absence because of PCR positives, culture confirmed MRSA suspects, PCR positives).

were 3 times negative, and personnel was not allowed to resume work for at least 20 days.

With MRSA screening by automated PCR, negative results are known after 2 days. PCR-positive results are considered suspect for MRSA until proven by traditional culture. Patients suspect for MRSA were therefore kept in isolation for 7 days. MRSA-positive results from culturing were kept in isolation for at least 10 days until 3 negative PCR and/or cultures were obtained.

The time span required for each method to yield a result (5 or 2 days) thus contributes to saving hospital costs. Implementation of

MRSA screening by automated PCR was estimated to save a total of €7.3 million in hospital costs for patients over the years 2006 to 2009 (Table 2). Savings involving personnel was estimated at €642,000.

DISCUSSION

In 2002, the largest epidemic of MRSA known to have ever occurred in The Netherlands, occurred in our hospital. The 2 locations C and Z are spaced by 1 km and merged in 2001 into 1

organization. The outbreak started in hospital location C by a MRSA strain with a methicillin-sensitive phenotype (PFGE type 16). It has been shown by multilocus sequence typing¹² that this particular clone was found in Germany from 1993 and has since been observed in various European countries.^{3,13}

Subsequently, 2 more epidemic clones were found to be present in hospital C (types 37 and 38), with phenotypes that differed from each other and from type 16. It is not clear why these MRSA clones could disseminate so fast. On the other hand, type 18 initially did not spread. Although it was detected in a patient repeatedly admitted to hospital C, this strain apparently lacked the capacity to spread in location C or did not spread because of a low number of contacts. This patient was discharged and received home care. Because of the merger of hospital C and Z in 2001, patients and personnel were transferred between 2 locations, and the outbreak of MRSA subsequently shifted to location Z and also to health care facilities outside of the hospital. In location Z, PFGE type 18, which was not recognized as being epidemic in hospital C, was most predominant. This finding suggests that, in case of an epidemic in 1 location, related institutions should also strictly abide to the "search and destroy" policy to prevent these shifted outbreaks. This also applies for workers who provide home care because results suggest that MRSA PFGE type 18 may have been first transmitted outside of the hospital.

Genotyping of MRSA presents a resource for identification of epidemic clones and recognition of transmission routes. Genotyping was performed by the reference laboratory of the National Institute of Public Health and the Environment in The Netherlands, which takes time before results are available. A local typing system for MRSA and timely results could assist in defining a smaller group of contacts to be screened and in localization of environmental sources.

When the outbreak was recognized, the prevalence of MRSA in the Dutch community was less than 1%.¹¹ In addition to the measures of the Dutch guideline for infection control, the following measures were taken to contain the outbreak.

In 2002, the hospital board decided that all patients were to be screened for the presence of MRSA on admission and on readmission if no previous negative culture result was available. In addition, all patients were to be screened for MRSA on discharge. The decisions were based on the following principles: (1) to prevent new MRSA clones from entering the hospital, (2) to prevent further spread to other institutions and to eliminate the concern of other hospitals on the transfer of patients, and (3) to be able to recognize patients at high risk for carrying MRSA on readmission.

In addition, strict measures were applied for personnel. Preferably, they were screened at the start of shifts, between shifts, and when changing departments in the same shift.

In addition, the implementation of a rapid high-throughput molecular MRSA screening system contributed to speed up results. It markedly reduced the time of isolation of patients and sick leave of personnel. As a result, the number of suspected contacts was less and hence the number of necessary screening tests and isolation days.

The huge number of screening tests led to very high costs for the hospital and huge pressure on personnel. To be able to perform screenings much faster and more efficiently, a high-throughput molecular detection method was implemented for MRSA. Negative screening test results are known after overnight incubation and automated PCR analysis. Isolation procedures for approximately 90% of patients can be omitted. According to the hygiene policy in The Netherlands, patients at risk of being colonized with MRSA are isolated in a closed single room until negative cultures for MRSA are available. In such cases, an earlier MRSA-negative result by a rapid PCR-based screening test, as presented in this study, will help to reduce patient isolation time and therefore the costs for the

hospital. The same applies for health care workers, of which 90% can resume their work in 2 days. In addition to limiting the costs, an epidemic can be contained much faster. The rapid molecular identification of MRSA proved to be of major importance for the rapid eradication of the epidemic both in our hospitals and in the region. In a model to quantify the effectiveness of different infection control measures,¹⁴ it has been shown that isolation of MRSA carriers identified by clinical cultures was insufficient to control MRSA. This finding indeed underscores the importance of rapid diagnostic testing.

Outbreak control screening for MRSA has been shown to be cost-effective in comparison with no containment measures.^{15,16} We compared the costs of automated molecular screening and traditional screening cultures. The costs of automated PCR screening are much higher than the costs of traditional culture. Only when the number of patients to be screened is less than approximately 500 per year, cost-effectiveness of automated PCR screening diminishes compared with culture. When the number of patients exceeds 500, the clinical and economic benefit of saving time in regard to expenses of the hospital are in favor of rapid automated molecular methodology.

Acknowledgment

The authors thank all technicians for their dedicated technical assistance with this work and John Vriens for sharing data.

References

- Johnson AP, Aucken HM, Cavendish S, Ganner, Wale MC, Warner M, et al. Dominance of EMRSA-15 and -16 among MRSA causing nosocomial bacteraemia in the United Kingdom: analysis of isolates from the European Antimicrobial Resistance Surveillance System (EARSS). *J Antimicrob Chemother* 2001; 48:143-4.
- Deplano A, Witte W, van Leeuwen WJ, Brun Y, Struelens MJ. Clonal dissemination of epidemic methicillin-resistant *Staphylococcus aureus* in Belgium and neighboring countries. *Clin Microb Infect* 2000;6:239-45.
- Witte W, Kresken M, Bräulke C, Cuny C. Increasing incidence and widespread dissemination of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals in central Europe, with special reference to German hospitals. *Clin Microbiol Infect* 1997;4:414-22.
- Jernigan JA, Clemence MA, Stott GA, Titus MG, Alexander CH, Palumbo CM, et al. Control of methicillin-resistant *Staphylococcus aureus* at a university hospital: one decade later. *Infect Control Hosp Epidemiol* 1995;16:686-96.
- Vos MC, Behrendt MD, Melles DC, Mollema FP, De Groot W, Parlevliet G, et al. Five years of experience implementing a methicillin-resistant *Staphylococcus aureus* search and destroy policy at the largest university medical center in The Netherlands. *Infect Control Hosp Epidemiol* 2009;30:977-84.
- Vos MC, Ott A, Verbrugh HA. Successful search-and-destroy policy for methicillin-resistant *Staphylococcus aureus* in The Netherlands. *J Clin Microbiol* 2005;43:2034-5.
- Bocher S, Skov RL, Knudsen MA, Guardabassi L, Mølbak K, Schouenborg P, et al. The search and destroy strategy prevents spread and long-term carriage of methicillin-resistant *Staphylococcus aureus*: results from the follow-up screening of a large ST22 (E-MRSA 15) outbreak in Denmark. *Clin Microbiol Infect* 2010;16:1427-34.
- van Trijp MJCA, Melles DC, Hendriks WDH, Parlevliet GA, Gommans M, Ott A. Successful control of widespread methicillin-resistant *Staphylococcus aureus* colonization and infection in a large teaching hospital in The Netherlands. *Infect Control Hosp Epidemiol* 2007;28:976-82.
- Wertheim H, Verbrugh HA, van Pelt C, de Man P, van Belkum A, Vos MC. Improved detection of methicillin-resistant *Staphylococcus aureus* using phenyl mannitol broth containing aztreonam and ceftiozime. *J Clin Microbiol* 2001; 39:2660-2.
- van der Zee A, Roorda L, Hendriks WDH, Ossewaarde JM, Buitenvierf J. Detection of novel chromosome-SCCmec variants in methicillin-resistant *Staphylococcus aureus* and their inclusion in PCR-based screening. *BMC Res Notes* 2011;4:150.
- Wertheim HF, Vos MC, Boelens HA, et al. Low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission in the Netherlands: the value of search and destroy and restrictive antibiotic use. *J Hosp Infect* 2004;56:321-5.
- Wannet WBJ, Spalburg E, Heck MEOC, Pluister GN, Willems RJJ, de Neeling AJ. Widespread dissemination in The Netherlands of the epidemic Berlin methicillin-resistant *Staphylococcus aureus* clone with low level resistance to oxacillin. *J Clin Microbiol* 2004;42:3077-82.

13. Enright MC, Ashley Robinson DA, Randle G, Feil EJ, Grundmann H, Spratt BG. The evolutionary history of methicillin resistant *Staphylococcus aureus* (MRSA). *Proc Natl Acad Sci USA* 2002;99:7687-92.
14. Bootsma MCJ, Diekmann O, Bonten MJM. Controlling methicillin-resistant *Staphylococcus aureus*: quantifying the effects of interventions and rapid diagnostic testing. *Proc Natl Acad Sci U S A* 2006;103:5620-5.
15. Rubinovitch B, Pittet D. Screening for methicillin-resistant *Staphylococcus aureus* in the endemic hospital: what have we learned? *J Hosp Infect* 2001;47: 9-18.
16. Simoons S, Ophals E, Schuermans A. Search and destroy policy for methicillin-resistant *Staphylococcus aureus*: cost-benefit analysis. *J Adv Nurs* 2009;65: 1853-9.