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Reduction in the rate of methicillin resistant *Staphylococcus aureus* acquisition in surgical wards by rapid screening for colonisation – a prospective, cross-over study.

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Abstract
Identification of patients colonised with methicillin resistant *Staphylococcus aureus* (MRSA) and subsequent isolation and decolonisation is pivotal to the control of cross infection in hospitals. The aim of this study was to establish if early identification of patients using rapid methods alone reduces transmission. A prospective, cluster, two period cross-over design was used. Seven surgical wards at a large hospital were allocated to two groups, and for the first eight months four wards used rapid MRSA screening and three wards used a standard culture method. The groups were reversed for the second eight months. Regardless of the method of detection all patients were screened for nasal carriage on admission and then every four days. MRSA control measures remained constant. Results were analysed using a log linear Poisson regression model. A total of 12,682/13,952 patient ward episodes (PWE) were included in the study. Admission screening identified 453 (3.6%) MRSA positive patient ward episodes, with a further 268 (2.2%) acquiring MRSA. After adjusting for other variables, rapid screening was shown to statistically reduce MRSA acquisition with patients being 1.49 times (p=0.007) more likely to acquire MRSA in wards where they were screened using the culture method. Screening of surgical patients using rapid testing resulted in a statistically significant reduction in MRSA acquisition. This result was achieved in a routine surgical service with high bed occupancy and low availability of isolation rooms, making it applicable to the majority of health-care systems worldwide.

Introduction

Methicillin resistant *Staphylococcus aureus* (MRSA) is an important hospital acquired infection, the prevalence of which has increased, despite the introduction of multifaceted control measures (1;2). Successful control measures have mainly relied upon the identification and isolation of colonised and infected patients to prevent them acting as a reservoir of infection and onward transmission (3-6). The important unanswered question, addressed by this study, is whether a more rapid diagnosis of colonisation or infection confers additional benefits over traditional culture-based methods (7).

Recently developed molecular methods, using polymerase chain reaction (PCR) have the potential to confirm or refute colonisation and infection of individual patients within two hours. One such commercially available real-time PCR test links *mecA*, the gene responsible for methicillin resistance, to a *S. aureus* genomic background, thereby avoiding false positives (8). Several studies have evaluated this test and shown it to have both high sensitivity and negative predictive value (9-12).

We have designed and executed a prospective controlled cross-over study within the surgical wards of a single large hospital to test the hypothesis that early identification of MRSA colonised and infected patients reduces onward transmission of MRSA compared to traditional culture based methods.

Materials and Methods

Study setting and design

The study was based in a large teaching hospital of 1,200 beds and carried out in seven surgical wards (number of wards); general surgery (2), thoracic (1), ear, nose and throat (ENT) (1), trauma and orthopaedic (2) and urology (1). Each ward had between 20 and 34 beds, arranged in bays of six beds and two to five single isolation rooms.

A prospective, cluster two-period cross-over design was used, with the only difference between the two periods being the method of MRSA detection (13). The study compared the use of rapid MRSA testing with the BD GeneOhm^{TM} molecular test (BD Diagnostics - GeneOhm, CA, USA) with a standard direct inoculation culture method using chromogenic (MRSA ID) media (Biomerieux, Marcy, l'Etoile, France). Wards were assigned to one of two groups (A to D and E to G), with wards of a similar speciality being placed in opposite groups. An initial two month pilot period, following group assignment and introduction of test methods, was conducted according to the study protocol. This was followed by two eight-month cross-over periods, with one month follow up of study patients at the end of the final period.

A screening protocol was implemented, requiring all adult patients admitted for >24h to have a nasal sample taken on admission. In order to identify transmission events and acquisition whilst on the ward, all patients who were negative on admission were re-screened every four days until discharge. Patients known to be positive from previous admission were still screened on admission.

Laboratory procedures and reporting

On receipt in the laboratory all swabs, including those from the wards where the samples were being tested using the rapid test, were inoculated directly onto chromogenic culture media. Subsequently the swabs requiring the rapid test were processed according to the manufacturer's instructions. Rapid results were reported immediately on completion of the

test and did not await a culture result. Culture plates were read after 18h incubation and MRSA isolates confirmed the following day using standard methods (14). Mupirocin sensitivity was carried out on all isolates according to British Society Antimicrobial Chemotherapy methods. Where there were discrepant results between rapid and culture tests, samples were placed in broth enrichment, incubated overnight and then sub-cultured onto chromogenic media. Results from all tests were entered on the hospital reporting system and all positive MRSA results, rapid and culture, were telephoned. A seven day per week service was provided.

Infection control procedures

All wards were provided with the same infection control guidelines which remained unchanged for the duration of the study. Only upon a positive test result were patients placed under control measures. These included placing the patients in an isolation room if available and placement of an isolation precaution sign detailing the infection control measures, including hand hygiene and the wearing of an apron, that should be taken either on the entry to the room or above the bed space. Gloves were only required when handling blood, body fluids, secretions, excretions and contaminated materials. All patients were commenced on decolonisation treatment (nasal mupirocin or naseptin for strains with high level mupirocin resistance and triclosan body wash (Aquasept®) administered three times a day for five days).

Data collection

Dedicated staff collected a comprehensive set of data for all patients admitted to the study wards. This included demographic information, risk factors, source of admission, antibiotic usage, length of stay, bed movements and type of surgery. For all patients who were colonised or infected with MRSA, the times of implementation of infection control measures and decolonisation treatment were also recorded. Turnaround times for MRSA screening results, from taking a sample to reporting, were recorded for all samples.

Outcome measures

The primary outcome of the study was the acquisition rate of MRSA colonisation. Due to differences in sensitivity between the rapid and culture tests, acquisition rates were calculated using only culture results which were obtained consistently in all arms of the study. A patient was deemed to be colonised with MRSA on admission to a ward if MRSA was isolated within 48h of admission. If a patient did not have an admission sample, but a negative sample was taken within four days of the ward admission, the patient was regarded as not being colonised with MRSA on admission. Patients were excluded from the analysis if they had no samples taken or if they had a positive four day sample, but no admission sample (Figure 1).

In order to account for colonisation pressure, acquisition rates were calculated as the ratio of the number of patients acquiring MRSA on the ward to the number of patients who were MRSA positive on admission. Analysis was carried out at ward level and, to take account of the fact that during the study some patients moved between study wards, analysis was carried out using patient ward episodes (PWE), i.e. each separate ward admission for the same patient was counted. A patient was regarded as being colonised with MRSA from the point at which it was first detected and then for the duration of their admission.

Statistical Analysis

A log-linear Poisson regression model was used to analyse counts of new MRSA acquisitions on each ward during each study period. The analysis was carried out in SPSS v.15. The log of the number of MRSA colonisations on admission to each ward in each period was included in the model as an offset variable so that model parameters correspond to estimates of the MRSA acquisition rate. A stepwise model fitting approach was adopted to investigate the effects of the potential confounding factors, including age, length of stay in the ward, proportion of patients undergoing elective or emergency surgery, source of admission, critical care admission and antibiotic usage, enabling adjustment of the effect of test method (rapid vs. culture) on the number of new MRSA colonisations. Overall model improvement was assessed after adding each of the potential confounders and the final model retained those variables that were significant at the 5% level. For comparison, MRSA incidence rates per 100 bed days were calculated for each study period. The rates were compared using a log-linear Poisson regression model, adjusted for ward, period and test method.

Results

During the study period (Jan ’05 to Apr ’07) a total of 10,934 patients were admitted to the study wards amounting to 13,952 patient ward episodes (PWE). A total of 1,270 (9.1%) PWE were excluded from the analysis; 32 (0.2%) had no admission sample taken and 1,238 (8.8%) had no samples taken. These patients had a shorter length of stay (mean 3 days) than patients included in the study. Characteristics of the patient groups across the study periods are shown in Table 1. Overall, there were 453 (3.6%) PWE in which the patient was MRSA culture positive on admission to the ward; 187 (2.8%) in the culture arm and 266 (4.4%) in the rapid arm. Based on culture results only MRSA was acquired during 157 (2.4%) PWE in the culture arm and 111 (1.9%) PWE in the rapid arm.

A total of 808 PWE were positive with the rapid test, of which 377 were positive using direct culture and a further 140 using broth enrichment.

The final fitted model for MRSA acquisition rate included terms for ward, period (pre or post cross-over), log of the mean length of stay on a ward, log of proportion of patients undergoing emergency surgery and test method (rapid vs. culture). Logs were taken of the two continuous variables (mean length of stay on ward and proportion of patients undertaking emergency surgery) to reflect the log link in the Poisson model. There was a significant ward effect in the model and a significant period effect after adjusting for all other factors (Table 2). Both length of stay on the ward and the proportion of emergency surgical procedures carried out on a ward significantly increased the likelihood of MRSA acquisition. After adjusting for all other variables in the model, the test method (rapid vs. culture) was shown to have a significant effect on the numbers of patients acquiring MRSA during a ward stay, with an estimated rate ratio of 1.49 (95% confidence interval 1.115-2.003; p=0.007). This shows that patients on wards during the culture period were 1.49 times more likely to acquire MRSA than during the rapid period. The incidence rates per 100 bed days for the rapid and culture periods were respectively 0.286 and 0.410 (p=0.002).

Six of the seven wards saw a decrease in the number of MRSA acquisitions during the periods of the study when the rapid test was utilised (Table 3). Ward B, an ENT ward which has rapid turnover of patients and a low rate of acquisition, saw an increase in the

acquisition rate (Table 4 and S3). There was a minor change to the admission policy on ward B during the study which resulted in an increase of short stay patients (Table S1).

Turnaround times and compliance with isolation procedures

The time from sample taking to result reporting was calculated for all samples. The mean time for reporting positive results for the rapid test was 0.9 days versus 3.3 days for the culture test (Table 4). The mean time from result reporting to decolonisation treatment was comparable between the two study periods (Table 4). The percentage of MRSA colonised patients nursed in isolation rooms was low in both study arms (Table 4).

Discussion

The present study has shown, within the rigorous constraints of a controlled trial, that rapid MRSA screening significantly reduces MRSA transmission within surgical wards of a large hospital when compared with standard culture based techniques. This finding has important implications for the control and management of MRSA in institutions where MRSA is endemic and there is limited availability of isolation rooms. The shortened turnaround time to MRSA result ensures that the risk of transmission occurring from a patient not known to be colonised is reduced (6).

In most UK hospitals there are small numbers of single rooms available for patient isolation. This explains the very low compliance with isolation in both arms of the study (approx 17%) meaning that the dominant intervention was early patient identification; resulting in the implementation of infection control precautions and decolonisation treatment. Early notification of MRSA in the rapid arm resulted in a greater percentage of patients receiving decolonisation treatment, with a higher percentage of the culture arm being discharged before the result was available and therefore receiving no decolonisation treatment.

Since the introduction of rapid molecular tests other studies have been published investigating the impact of these tests on MRSA transmission and infection rates (15-22). The majority of these have a retrospective, time intervention study design which does not control for confounding variables. Our study adopted a prospective cross-over design, enabling the elimination of sampling biases and ensuring, as far as possible, that there were no changes to the ward environment or practices during the study. Although the wards were not randomised, they were matched as far as possible to ensure that seasonal bias was not introduced. No wash out period was used as no operational changes were required, but this did result in an altered length of reporting for 68 (0.5%) patients.

Two other studies have used a cross-over design; the first assessed the impact on infection rates of screening patients rapidly on admission versus no screening (20). The second assessed the impact of rapid screening versus conventional culture and had a high compliance with admission screening (93.4%), but a larger number of patients were lost to follow up (17.8%) so that transmission rates may have been underestimated (21). In addition, pre-emptive isolation of patients (i.e before microbiological screening) at high risk of MRSA colonisation was used (21). We believe these two factors resulted in a much lower detected transmission rate, 0.36 as opposed to 0.84 in our study.

Elucidation of the impact of rapid screening in previous studies has been hampered by the introduction of multiple interventions, for example the introduction of rapid screening and pre-emptive isolation (19).

Re-screening patients every four days may well have contributed to the effectiveness of rapid testing, with new acquisitions being identified more promptly. All of the other published studies reporting the effects of rapid testing have focused on admission screening and used the availability of clinical or discharge samples as evidence of transmission. There is evidence that using either clinical samples or discharge screening to determine transmission events will result in an under reporting (23-25). Harbarth and colleagues used only passive surveillance and, as they acknowledge, this may have resulted in some MRSA infections being missed, which they felt the cross-over design would account for (20). However, only patients in the test group were screened for MRSA possibly resulting in an increased awareness and reporting of infection in this group.

As has been reported in other studies, some samples were positive using the rapid test and we were unable to grow MRSA using direct culture (16). This is partly due to the increased sensitivity of molecular tests, with direct inoculation being known to be less sensitive than broth enrichment. Interestingly, unlike Conterno and colleagues who deemed all samples that were positive using the rapid test and negative using culture to be false positives and ceased to isolate and decolonise the patient, the present study continued to treat the patient as positive (16), which may account for the differing results from the two studies.

Our study provided a challenging test of the value of rapid versus slower culture based methods for MRSA screening because of the limited availability of isolation rooms (26). We conclude that the introduction of MRSA screening using rapid tests and the protocol we have described can significantly reduce MRSA transmission on wards that have a limited number of isolation rooms.

Acknowledgements Section

Authors contributions
P M Hawkey and A Szczepura conceived the idea and were involved in the study design with K J Hardy, R Davies, S Gossain and A Bradbury. The study was set up and run by K J Hardy and P M Hawkey. S Shabir and C McMurray collected and cleaned the data. N Stallard and C Price extracted data and completed the statistical analysis. K J Hardy wrote the manuscript which was modified after review by all authors.

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Role of the funding source
The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and for the decision to submit for publication.

Conflict of interest statement
Grants received: P M Hawkey (Becton Dickinson]

Substantial contributions
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Figure 1: Flow of patients through the study

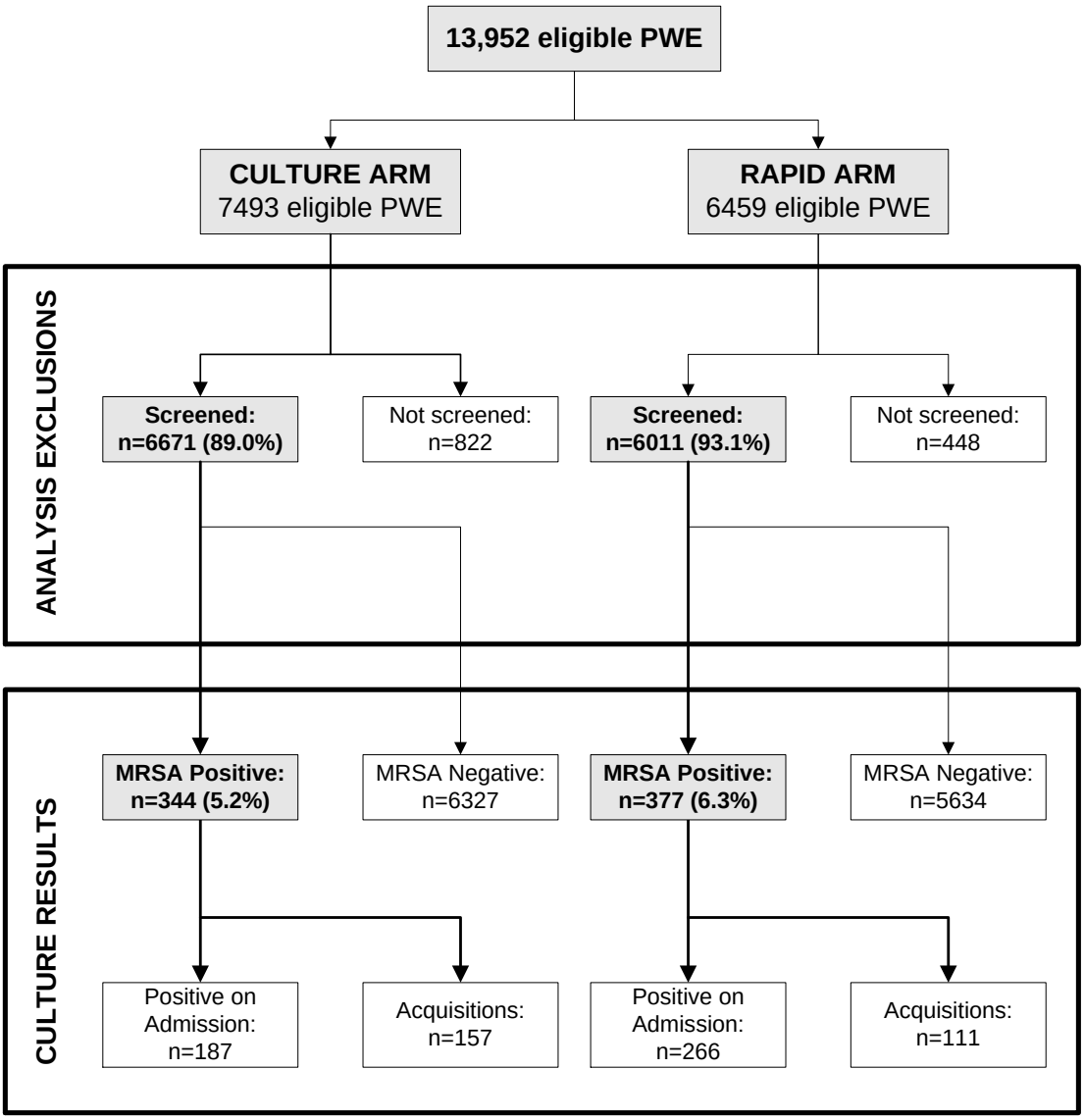

Table 1: Patient characteristics from the two study periods, all of the above data, apart from total number of patients relates to patient ward episodes.

	STUDY PERIOD		p-value
	CULTURE	RAPID	
Total number of patient ward episodes (PWEs)	7493	6459	<0.001
Number of PWEs excluded from analysis	822 (11.0%)	448 (6.9%)	<0.001
Number of admission samples	6671	6011	<0.001
Number of post admission samples	8516	9292	<0.001
Age (mean, years)	57.1	59.1	0.157
Male	3663 (54.9%]	3425 (57.0%]	0.005
Patients admitted from nursing home	68 (1.0%]	76 (1.3%]	0.505
Patients admitted from other hospital ward	1053 (15.8%]	1016 (16.9%]	0.416
Mean length of stay on ward (days)	6.5	7.2	0.374
Mean length of hospital stay (days)	9.7	10.6	0.365
Patient undergoing surgical procedure	2807 (42.1%]	2989 (49.7%]	0.017
Emergency surgery	1429 (21.4%]	1411 (23.5%]	0.736
Antibiotic prophylaxis	1700 (25.5%]	1779 (29.6%]	0.180
Antibiotics (excluding prophylaxis)	1258 (18.9%]	1223 (20.3%]	0.482
Ward episode followed by admission to critical care	551 (8.3%]	558 (9.3%]	0.455
Ward episode following discharge from critical care	665 (10.0%]	638 (10.6%]	0.834

Log-linear Poisson models, adjusted for ward, were used to compare counts in the two arms. Two-sample t-tests were used to compare the within-ward differences in lengths of stay and mean ages, allowing for ward and period effects. These were carried out in SPSS V.15. A random effects logistic regression model was used to compare the proportion of PWE excluded from the two arms using SAS v.9.1.

Table 2: Parameter estimates and rate ratios for the fitted log-linear model.

Parameter	Estimated rate ratio	95% C.I.	*p*-value
Period (Pre or post cross over]	0.356	(0.230, 0.701)	< 0.001
log(mean length of stay on ward]	89.971	(13.782, 587.362)	< 0.001
log(emergency surgery]*	27.694	(4.260, 180.058)	0.001
Test method: culture (rapid test is reference level]	1.494	(1.115, 2.003)	0.007

*log(emergency surgery] = log(proportion of patients undertaking emergency surgery on each ward]

Table 3: MRSA transmission rates for each study period (culture vs. rapid) based on culture positive sample (* Wards which were in the molecular arm of the study first)

Ward	Speciality	**CULTURE**				**RAPID**			
		Number of patient ward episodes	MRSA positive on admission to ward	MRSA acquired during ward admission	MRSA acquisition ratio	Number of patient ward episodes	MRSA positive on admission to ward	MRSA acquired during ward admission	MRSA acquisition ratio
A *	Thoracic	997	18	36	**2.0**	1088	58	18	**0.31**
B *	Ear, nose, throat	1933	27	4	**0.15**	894	22	6	**0.27**
C *	General surgery	1050	32	20	**0.63**	1070	60	34	**0.57**
D *	Trauma and orthopaedics	543	16	11	**0.69**	479	17	8	**0.47**
E	Urology	638	29	36	**1.24**	788	43	15	**0.35**
F	General surgery	1065	41	38	**0.93**	1171	49	23	**0.47**
G	Trauma and orthopaedics	445	24	12	**0.50**	521	17	7	**0.41**
Total	All	6671	187	157	**0.84**	6011	266	111	**0.42**

Table 4: Compliance with infection control guidelines. The rapid arm calculations are made using data only from those patients who were positive by both the rapid test and culture.

	STUDY PERIOD		**p-value**
	CULTURE	**RAPID**	
MRSA colonisation on admission	187	266	<0.001
MRSA acquisition	157	111	0.005
Total colonised with MRSA	344	377	0.219
Mean length of time on the ward to MRSA acquisition (days]	13.0	12.9	0.894
Percentage isolated in isolation rooms	16.3% (56/344)	17.5% (66/377)	<0.001
Percentage prescribed decolonisation treatment	41.3% (142/344)	71.1% (268/377)	<0.001
Mean length of time to MRSA positive result reporting (days]*	3.3	0.9	<0.001
Mean length of time from reporting to prescribing decolonisation treatment (days]	0.7	0.7	1.000

* Denominator figures represent ward episodes in which MRSA colonisation was first detected

** Log-linear Poisson models, adjusted for ward, were used to compare counts in the two arms. Two-sample t-tests were used to compare the within-ward differences in lengths of time, allowing for ward and period effects.

SUPPLEMENTARY TABLES

Table S1: Number of patients/corresponding patient ward episodes (PWEs) and number of samples tested on each ward for each of the study periods.

Ward	CULTURE							RAPID						
	Patients	Patient ward episodes	Excluded PWE's	PWE's included in analysis	Admission samples	Post-admission samples	Total samples	Patients	Patient ward episodes	Excluded PWE's	PWE's included in analysis	Admission samples	Post-admission samples	Total samples
A	904	1048	51 (4.9%)	997 (95.1%)	997	1611	2608	1014	1132	44 (3.9%)	1088 (96.1%)	1088	1755	2843
B	1981	2121	188 (8.9%)	1933 (91.1%)	1933	1283	3216	958	1016	122 (12.0%)	894 (88.0%)	894	735	1629
C	1116	1248	198 (15.9%)	1050 (84.1%)	1050	1025	2075	1048	1159	89 (8.5%)	1070 (92.3%)	1070	1569	2639
D	603	616	73 (11.9%)	543 (88.1%)	543	967	1510	509	526	47 (8.9%)	479 (91.1%)	479	1116	1595
E	600	709	71 (10.0%)	638 (90.0%)	638	1004	1642	673	808	20 (2.5%)	788 (97.5%)	788	1298	2086
F	1163	1260	195 (15.5%)	1065 (84.5%)	1065	1372	2437	1147	1267	96 (7.6%)	1171 (92.4%)	1171	1689	2860
G	481	491	46 (9.4%)	445 (90.6%)	445	1254	1699	535	551	30 (5.4%)	521 (94.6%)	521	1130	1651

Table S2: Patient demographics, source of admission to ward and length of stay (ward and hospital] on each ward between the two study periods.

Ward	CULTURE								RAPID							
	Age (mean, years]	Gender		Source of admission to ward			Length of stay (mean, days]		Age (mean, years]	Gender		Source of admission to ward			Length of stay (mean, days]	
		Male	Female	Own home	Nurse home	Hosp ward	Ward	Hosp		Male	Female	Own home	Nurse home	Hosp ward	Ward	Hosp
A	57.2	626 (62.8%]	371 (37.2%]	771 (77.3%]	1 (0.1%]	225 (22.6%]	7.4	9.1	56.9	702 (64.5%]	386 (35.5%]	853 (78.4%]	3 (0.3%]	232 (21.3%]	7.1	9.3
B	52.2	974 (50.4%]	959 (49.6%]	1808 (93.5%]	5 (0.3%]	120 (6.2%]	2.0	3.0	53.9	420 (47.0%]	474 (53.0%]	835 (93.4%]	1 (0.1%]	58 (6.5%]	3.7	5.7
C	59.4	543 (51.7%]	507 (48.3%]	766 (73.0%]	14 (1.3%]	270 (25.7%]	6.8	10.5	60.9	566 (52.9%]	504 (47.1%]	895 (83.6%]	14 (1.3%]	161 (15.0%]	7.6	11.4
D	58.8	273 (50.3%]	270 (49.7%]	429 (79.0%]	11 (2.0%]	103 (19.0%]	10.5	17.6	60.1	256 (53.4%]	223 (46.6%]	367 (76.6%]	15 (3.1%]	97 (20.3%]	13.0	22.4
E	64.2	442 (69.3%]	196 (30.7%]	529 (82.9%]	11 (1.7%]	98 (15.4%]	8.0	11.7	64.4	546 (69.3%]	242 (30.7%]	638 (81.0%]	10 (1.3%]	140 (17.8%]	5.8	7.8
F	56.7	613 (57.6%]	452 (42.4%]	911 (85.5%]	11 (1.0%]	143 (13.4%]	7.2	11.2	58.7	717 (61.2%]	454 (38.8%]	907 (77.5%]	13 (1.1%]	251 (21.4%]	6.5	9.6
G	62.1	192 (43.1%]	253 (56.9%]	336 (75.5%]	15 (3.4%]	94 (21.1%]	14.3	21.8	61.2	218 (41.8%]	303 (58.2%]	424 (82.3%]	20 (3.8%]	77 (14.8%]	10.8	16.2

Table S3: Adherence to infection control procedures upon detection of an MRSA positive patient for each ward for each of the two study periods.

Ward	CULTURE					RAPID				
	Mean length of time on ward to MRSA acquisition (days]	Mean length of time to MRSA positive result reporting (days]	Mean length of time from reporting to decolonisation treatment (days]	Number of patients isolated in side rooms	Number of patients prescribed decolonisation treatment	Mean length of time on ward to MRSA acquisition (days]	Mean length of time to MRSA positive result reporting (days]	Mean length of time from reporting to decolonisation treatment (days]	Number of patients isolated in side rooms	Number of patients prescribed decolonisation treatment
A	12.8	3.3	0.6	17 (32.1%]	22 (41.5%]	10.7	0.8	0.6	35 (22.3%]	117 (74.5%]
B	8.3	3.3	0.2	0 (0.0%]	6 (19.4%]	14.2	0.6	0.6	14 (19.2%]	44 (60.3%]
C	13.8	2.9	0.6	14 (28.6%]	22 (44.9%]	15.4	0.8	0.7	18 (12.0%]	111 (74.0%]
D	9.7	3.0	0.1	1 (4.8%]	7 (33.3%]	19.3	0.7	1.2	6 (8.6%]	58 (82.9%]
E	13.4	3.4	0.9	6 (10.2%]	32 (54.2%]	8.1	1.0	0.3	11 (10.7%]	82 (79.6%]
F	13.8	3.6	0.7	8 (10.7%]	35 (46.7%]	13.4	0.7	0.6	23 (16.1%]	112 (78.3%]
G	13.4	3.3	1.0	4 (13.3%]	19 (63.3%]	6.4	0.7	0.5	9 (15.3%]	52 (88.1%]

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