MAJOR ARTICLE

Efficacy and Limitation of a Chlorhexidine-Based Decolonization Strategy in Preventing Transmission of Methicillin-Resistant *Staphylococcus aureus* in an Intensive Care Unit

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(See the editorial commentary by Jarvis, on pages 218–20.)

Background. Surface-active antiseptics, such as chlorhexidine, are increasingly being used as part of intervention programs to prevent methicillin-resistant *Staphylococcus aureus* (MRSA) transmission, despite limited evidence and potential for resistance. We report on the effect of an antiseptic protocol on acquisition of both endemic MRSA and an outbreak strain of MRSA sequence type 239 (designated TW).

Methods. Interrupted time-series data on MRSA acquisitions in two 15-bed intensive care units were analyzed using segmented regression models to estimate the effects of sequential introduction of an educational campaign, cohorting, and a chlorhexidine-based antiseptic protocol on transmission of TW and non-TW MRSA strains. Representative TW and non-TW MRSA strains were assessed for carriage of *qacA/B* genes and antiseptic susceptibility.

Results. The antiseptic protocol was associated with a highly significant, immediate 70% reduction in acquisition of non-TW MRSA strains (estimated model-averaged incidence rate ratio, 0.3; 95% confidence interval, 0.19–0.47) and an increase in acquisition of TW MRSA strains (estimated model-averaged incidence rate ratio, 3.85; 95% confidence interval, 0.80–18.59). There was only weak evidence of an effect of other interventions on MRSA transmission. All TW MRSA strains (21 of 21 isolates) and <5% (1 of 21 isolates) of non-TW MRSA strains tested carried the chlorhexidine resistance loci *qacA/B*. In vitro chlorhexidine minimum bactericidal concentrations of TW strains were 3-fold higher than those of non-TW MRSA strains, and in vivo, only patients with non-TW MRSA demonstrated a reduction in the number of colonization sites in response to chlorhexidine treatment.

Conclusion. A chlorhexidine-based surface antiseptic protocol can interrupt transmission of MRSA in the intensive care unit, but strains carrying *qacA/B* genes may be unaffected or potentially spread more rapidly.

The optimum set of interventions required to prevent methicillin-resistant *Staphylococcus aureus* (MRSA) transmission in an intensive care unit (ICU) is unclear [1]. The mainstay of infection control is prompt identification of MRSA-colonized patients and institution of contact precautions while enforcing compliance with universal hand hygiene practice [2–4]. Guidelines also recommend active surveillance cultures be obtained from high-risk patients, allowing earlier initiation of contact precautions, although the need for surveillance cultures is debated [3, 5]. Isolation or cohorting is also practiced to facilitate contact nursing, although the benefit in the ICU remains unclear [6]. Studies have reported a benefit of using surface antiseptics, such as chlorhexidine [7–11], and guidelines recommended their use for high-risk groups in which basic interventions have failed to reduce rates of MRSA infection to acceptable levels for decolonization [2, 3] and routine cleansing of all patients [2, 12]; however, given the

Received 28 April 2009; accepted 17 August 2009; electronically published 10 December 2009.

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Clinical Infectious Diseases 2010;50:210–7
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1058-4838/2010/5002-0008$15.00
DOI: 10.1086/648717

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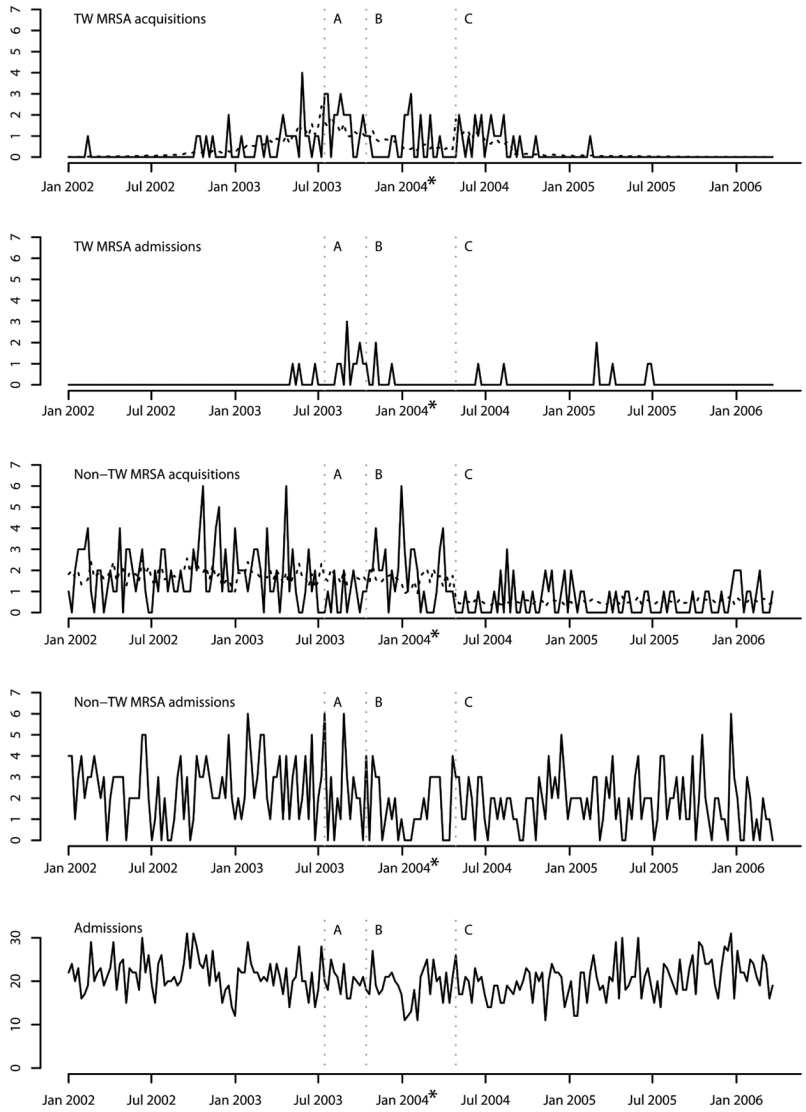

Figure 1. Weekly total number of admissions and number of patients admitted with or acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) in the intensive care unit during the study. Time of introducing interventions A, B, and C are shown. The expected number of outbreak strains of MRSA sequence type 239 (TW) and non-TW MRSA acquisitions generated using the best-fitting segmented regression models (model 1 in Table 2) are represented by a broken line. *The TW MRSA outbreak was first recognized in January 2004.

limited evidence of eradication, some reviews recommend against routine decolonization to prevent MRSA transmission [1, 13].

Emerging resistance is a particular concern with the use of antimicrobials and antiseptics as decolonization agents. MRSA can develop clinically significant resistance to mupirocin [14–16], and some MRSA strains carry genes that confer increased minimum bactericidal concentrations (MBCs) to antiseptics [17]. The plasmid-borne *qacA/B* genes code for multidrug efflux pumps [18, 19] found in 10%–20% of UK [20, 21], 63% of European [18], 80% of Brazilian [22], and 55% of Taiwanese MRSA strains [23], the last being predominantly sequence type (ST) 239. Such strains have a 2-fold to 4-fold increase in MBCs for antiseptics, such as chlorhexidine [20], although because the MBC remains well below the concentrations used to treat patients, the clinical significance of *qacA/B* carriage remains unclear [21].

We recently reported measures introduced to control MRSA transmission in an ICU where there was high-level endemic MRSA transmission, mostly due to ST-22 and ST-36, and a 2-year outbreak with a novel variant of ST-239 called TW [24]. Here, we assess the effect of the chlorhexidine-based antiseptic protocol introduced during the TW MRSA outbreak using a retrospective interrupted time-series study.

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Table 1. Clinical and Microbiological Characteristics of Patients Admitted to the Intensive Care Unit (ICU) before and after Introduction of the Antiseptic Protocol

Characteristic	Pre-antiseptic protocol (n = 2480)	Postantiseptic protocol (n = 2090)	P
Age, mean years (±SD)	60 ± 17	59 ± 18	.09
Male sex	1507 (61)	1308 (63)	.21
Specialty			
General medical	1444 (58)	1316 (62)	.001
General surgical	518 (21)	416 (20)	
Cardiothoracic surgery	518 (21)	358 (17)	
Admission APACHE II score, mean value (±SD)	16.2 ± 8.6	15.9 ± 8.3	.19
Length of ICU stay,[a] median days (IQR)	4 (2–11)	4 (2–10)	.68
ICU mortality	581 (23)	442 (21)	.07
Admitted to ICU with MRSA	291 (12)	226 (11)	.37
Daily staff-to-bed occupancy rate, median value (IQR)	1.07 (1.02–1.1)	1.04 (1.02–1.09)	.001
Renal replacement	584 (24)	496 (24)	.91
Mechanical ventilation	2027 (82)	1704 (82)	.89

NOTE. Data are no. (%) of patients, unless otherwise stated. APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation.

[a] Median values (IQR) are presented where data are not normally distributed.

METHODS

Clinical setting and infection control practice. The St Thomas' Hospital site has two 15-bed ICUs on adjacent floors. All patients admitted to the ICUs from 1 January 2002 through 20 April 2006 were included in this study. Throughout, alcohol gel was at every bed space and contact precautions were in place. MRSA screening swab samples (of the nose, perineum, and axilla) were obtained from all patients at admission to the ICU and every Monday morning before the first application of antiseptics. After 1 November 2005, axilla swabs were stopped, and throat and rectal swab samples were added to the screening [25]. Other samples were obtained when the infection was clinically suspected. In response to high rates of MRSA transmission, the infection control committee instigated sequential additional measures, as previously reported [24]. An educational campaign initiated on 15 July 2003 focused on reenforcing hand hygiene and barrier nursing, covert audit of hand hygiene and barrier nursing practice on ward rounds (66%–77% compliance on 3 documented occasions), and monthly feedback on rates of MRSA infection (intervention A). Beginning 15 October 2003, MRSA-colonized patients were nursed in side rooms or in pairs (intervention B). Beginning 26 April 2004, a surface antiseptic protocol was introduced: patients with known MRSA infection had 1% (weight/volume) chlorhexidine gluconate (Hibitane; Derma) applied to the nostrils, around the mouth, and at tracheostomy sites 4 times daily; had 1% chlorhexidine acetate powder (CX Antiseptic Dusting Powder; Adams Health) applied to groin, axillae, and skinfolds daily; and were washed daily with 4% chlorhexidine (Hibiscrub; SSL International) applied by a wet cloth. Patients who had test results that were negative for MRSA had the same protocol apart from Hibitane use twice daily and 2% (weight/volume) triclosan (Aquasept; Medlock Medical) instead of Hibiscrub (intervention C). Mupirocin was not used because of resistance concerns [11, 26, 27]. Retrospective review revealed that 12% of MRSA-positive patients harbored a mupirocin-resistant strain.

Data collection and definitions. Clinical, demographic, microbiological, antimicrobial treatment, intervention, bed occupancy, and staffing level data were extracted from intensive care (CareVue; Philips), microbiology (MC&S; GSTT), and electronic patient administration systems (iSoft) to form the anonymized Guy's and St Thomas' Staphylococcal Transmission and Antimicrobial Record database, with approval from the hospital ethics committee [28]. Integrity of data extraction was validated for completeness and accuracy by abstracting 2% of data and comparing it manually with the original source data. The following data were used for this study: age, sex, specialty, admission Acute Physiology and Chronic Health Evaluation (APACHE) II score, length of ICU stay, ICU mortality rate, dates of isolation of MRSA from any sample and its antibiotic resistance profile, dates of ventilation and renal replacement, and staffing levels. A patient was defined as importing MRSA if MRSA was cultured from any sample taken within the first 48 h after ICU admission and acquiring MRSA if MRSA was isolated for the first time from any sample taken after 48 h in the ICU.

Laboratory techniques. Samples were processed using standard laboratory techniques. MRSA was identified in screens using tube-coagulase and disk-diffusion testing with methicillin disks [24, 25]. The antimicrobial resistance pattern of the first

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Table 2. Estimated Parameters from the Poisson Segmented Regression Applied to the Non-TW and TW Methicillin-Resistant *Staphylococcus aureus* (MRSA) Data

	Full model		Model 1		Model 2		Model 3	
Variable	IRR (95% CI)	*P*	IRR (95% CI)	*P*	IRR (95% CI)	*P*	IRR (95% CI)	*P*
Non-TW MRSA								
Intervention A	0.32 (0.05–1.31)	.16			0.45 (0.21–0.85)	.03		
Intervention B	2.39 (0.72–10.30)	.19			2.52 (1.27–5.66)	.01		
Intervention C	0.37 (0.15–0.89)	.03	0.31 (0.22–0.43)	<.001	0.26 (0.17–0.40)	<.001	0.33 (0.23–0.47)	<.001
Trend before interventions	1.00 (0.99–1.01)	.96						
Change in trend after intervention A	1.06 (0.88–1.28)	.55						
Change in trend after intervention B	0.93 (0.76–1.12)	.43						
Change in trend after intervention C	1.02 (0.98–1.06)	.33						
Non-TW MRSA in previous week	1.04 (0.97–1.12)	.28					1.05 (0.98–1.13)	.18
Posterior model *P* value[a]	<.01		0.54		0.11		0.09	
TW MRSA								
Intervention A	2.01 (0.77–5.02)	.14					2.12 (1.09–4.26)	.03
Intervention B	0.73 (0.20–2.71)	.64						
Intervention C	3.23 (1.14–10.23)	.04	4.37 (1.76–11.37)	.002	1.70 (1.86–16.43)	.002	6.69 (2.43–19.05)	<.001
Trend before interventions	1.05 (1.03–1.08)	<.001	1.06 (1.04–1.08)	<.001	1.07 (1.05–1.09)	<.001	1.05 (1.03–1.08)	<.001
Change in trend after intervention A	0.88 (0.78–0.98)	.03	0.91 (0.88–0.94)	<.001	0.89 (0.86–0.91)	<.001	0.89 (0.86–0.92)	<.001
Change in trend after intervention B	1.07 (0.95–1.22)	.26						
Change in trend after intervention C	0.93 (0.87–0.99)	.03	0.95 (0.91–0.99)	.02				
TW MRSA in previous week	1.10 (0.90–1.32)	.34						
Posterior model *P* value[a]	<.01		0.24		0.14		0.13	

NOTE. Results from 4 models are shown: a full model containing all covariates and 3 models with the highest posterior model probability selected by the Bayesian model averaging procedure (models 1–3). IRRs of covariates included in each model are shown. Intervention A is the education program; intervention B, patient cohorting; and intervention C, anticeptic protocol. The 95% CIs were always between 0 and 0.004 for the outbreak strain of methicillin-resistant *Staphylococcus aureus* (MRSA) sequence type 239 (TW) models and were always between 0.04 and 0.12 for the intercepts of the non-TW models. CI, confidence interval; IRR, incidence rate ratio.

[a] The posterior model *P* value measures the degree to which the data support the model (the closer these values are to 1, the greater the evidence in favor of the model).

patient isolate defined them as having either TW (resistant to methicillin, erythromycin, ciprofloxacin, gentamicin, neomycin, tetracycline, and trimethoprim) or non-TW MRSA (all other resistance patterns) [24, 25]. Restriction-modification analysis [29] showed that all available TW isolates ($n = 34$) were CC8/239, consistent with previous microarray analysis [24], and 169 of 174 non-TW isolates were CC22 or CC30, consistent with local and national epidemiology data (data not shown). A total of 21 TW and 21 non-TW isolates were randomly selected to determine carriage of the *qacA/B* genes from all cluster acquisitions occurring before introduction of the antiseptic protocol. A cluster acquisition was defined as >1 acquisition of a strain with the same resistance pattern for >1 month. DNA was extracted using the ChargeSwitch DNA kit (Invitrogen) according to the manufacturer's protocol. Single primer pair sequences were used to detect *qacA/B*, as described elsewhere [18]. Polymerase chain reactions (PCRs) were performed in 50 μL of Platinum Blue Supermix (Invitrogen) containing 25 ng of DNA, according to the manufacturer's protocol. The PCR was performed at 96°C for 10 min, then 35 cycles of 94°C for 30 s, 52°C for 30 s, 74°C for 30 s, and final elongation at 72°C for 10 min. Products were analyzed by 2% agarose gel electrophoresis. Five *qacA/B* PCR-positive TW and 5 *qacA/B* PCR-negative non-TW isolates were selected for determination of biocide MBCs using a modified Clinical and Laboratory Standards Institute protocol [30]. Briefly, 5×10^5 colony-forming units (CFUs) from an overnight culture were incubated at 37°C for 24 h in serial dilutions of heat- and filter-sterilized chlorhexidine gluconate 20% (weight/volume) or 2% triclosan (weight/volume) (Sigma) in Mueller-Hinton broth. After 24 h, broths were subcultured onto Mueller-Hinton agar for colony counting. The MBCs were calculated as the concentration producing a 99.9% kill. Broths were reincubated and plated in the same fashion after an additional 24 h to confirm lack of growth. Each experiment was performed in triplicate and repeated twice.

Statistical analysis. TW and non-TW MRSA acquisition data were analyzed using separate segmented regression models. Specifically, the weekly number of acquisitions was analyzed using Poisson models with a log link function accounting for extra-Poisson variation and variations in exposure caused by changes in the weekly number of ICU admissions. Independent variables were week number (to model secular log-linear trends), week number after interventions A-C (to estimate changes in trends), which continued to the end of the study in each case, and indicator variables for the 3 interventions (to

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Table 3. Estimated Bayesian Model-Averaged Incidence Rate Ratios (IRRs) for TW and Non-TW Methicillin-Resistant *Staphylococcus aureus* (MRSA) Acquisitions

	Non-TW MRSA		TW MRSA	
Variable	IRR (95% CI)	Probability $\neq 1$[a]	IRR (95% CI)	Probability $\neq 1$[a]
Intervention A	0.91 (0.53–1.58)	15	1.12 (0.63–2.01)	17
Intervention B	1.12 (0.60–2.09)	18	0.71 (0.18–2.88)	25
Intervention C	0.30 (0.19–0.47)	100	3.85 (0.80–18.59)	83
Trend before interventions	1.00 (1.00–1.00)	4	1.06 (1.03–1.08)	100
Change in trend after intervention A	1.00 (1.00–1.00)	4	0.93 (0.85–1.02)	75
Change in trend after intervention B	1.00 (1.00–1.00)	4	0.99 (0.92–1.06)	15
Change in trend after intervention C	1.00 (1.00–1.00)	4	0.96 (0.88–1.05)	57

NOTE. Incidence rate ratios (IRRs) were derived from model averages taken from the best 9 and 17 models fitting the non–outbreak strain of methicillin-resistant *Staphylococcus aureus* (MRSA) sequence type 239 (non-TW) and TW MRSA acquisition data, respectively (models with posterior probabilities less than one-twentieth that of the most likely model were excluded). Intervention A was the education program, intervention B was patient cohorting, and intervention C was anticeptic protocol. CI, confidence interval.

[a] The columns headed Probability $\neq 1$ give estimated probabilities for an effect associated with each parameter. Low values indicate little evidence of an effect, and values close to 100 indicate increasingly strong evidence.

estimate sudden changes). The number of TW or non-TW cases during the previous week was included as an independent variable to account for autocorrelation. Parameter estimates were obtained using Bayesian model averaging (with equal prior probabilities for possible models) to account for model uncertainty [31]. Analysis was performed using the BMA package in R, version 2.6, averaging over all models with posterior probabilities greater than one-twentieth of the most likely model [32]. Numerical data are presented as mean values ($\pm$ standard deviations [SDs]) and median values, unless otherwise indicated. Numerical variables were compared using Student's *t* test or Mann-Whitney *U* test. All simple analyses were performed using Stata software, version 10 (StataCorp).

RESULTS

Clinical and epidemiologic characteristics. A total of 4570 patients were admitted to the ICU for a total of 44,505 days. Of these patients, 517 (11%) were admitted with MRSA infection, and 347 of 3073 susceptible patients staying >48 h acquired MRSA during their stay. Figure 1 shows the weekly number of ICU admissions and acquisitions of TW and non-TW strains. The educational campaign (intervention A), cohorting (intervention B), and antiseptic protocol (intervention C) are indicated with vertical dotted lines. Introduction of the antiseptic protocol appeared to be associated with an immediate reduction in acquisition of non-TW, but not TW, strains, although there was no apparent effect after the educational campaign or cohorting. This association was investigated further. Demographic, clinical, and other factors with the potential to influence MRSA acquisitions were compared before and after introduction of the antiseptic protocol (Table 1). No significant reduction was found in the proportion of patients admitted with MRSA. In addition, we found no obvious decrease in patient disease severity that might prompt fewer staff hand contacts, as measured by admission APACHE II score, ventilation, renal replacement, and length of stay. The daily nursing staff to bed occupancy ratio, which has been associated with MRSA acquisitions when reduced [33], deteriorated after introduction of the antiseptic protocol, although it remained >1. We explored whether the reduction in patients undergoing surgery might have contributed to the reduction in transmission by reducing the number of skin breaches available for acquisition. We saw no reduction in skin breach sampling after introduction of the antiseptic protocol and therefore considered this to be an unlikely explanation for the reduction in MRSA transmission.

Estimating the impact of interventions on transmission of MRSA. Segmented regression analysis was used to assess step changes and trends associated with the interventions. This provided strong evidence of a large (~3-fold) instantaneous reduction in the risk of acquiring non-TW strains after introduction of the antiseptic protocol. This result was identified in the full model (all covariates), in the 3 best models (Table 2), and when model selection uncertainty was accounted for (Table 3). In contrast, there was little evidence that other inter-

Table 4. Chlorhexidine and Triclosan Minimum Bactericidal Concentrations (MBCs) for Selected TW and Non-TW Methicillin-Resistant *Staphylococcus aureus* (MRSA) Acquisition Isolates

Isoalte	Triclosan MBC, g per 100 mL	Chlorhexidine MBC, g per 100 mL
TW MRSA	0.0025	0.0078 $\pm$ 0.0004
Non-TW MRSA	0.0025	0.0026 $\pm$ 0.0008

NOTE. The minimum bactericidal concentrations (MBCs) are reported as mean $\pm$ SD of 5 outbreak strains of methicillin-resistant *Staphylococcus aureus* (MRSA) sequence type 239 (TW) of non-TW MRSA acquisition isolates.

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Table 5. Methicillin-Resistant *Staphylococcus aureus* (MRSA) Isolation Sites from Patients Discharged from the Intensive Care Unit (ICU) before and Admitted to the ICU after Introduction of the Antiseptic Protocol

Variable	Before antiseptic protocol	After antiseptic protocol	*P*
TW MRSA			
No. of patients	82	28	
Screen sites[a]	28 (34)	11 (39)	.31
Respiratory tract[b]	52 (63)	15 (53)	.18
Catheter tips[c]	41 (50)	12 (43)	.26
Skin breaches[d]	45 (55)	16 (57)	.42
Non-TW MRSA			
No. of patients	480	274	
Screen sites	359 (75)	140 (52)	<.001
Respiratory tract	261 (54)	97 (36)	<.001
Catheter tips	81 (17)	32 (12)	.03
Skin breaches	145 (30)	59 (22)	.005

NOTE. Data are no. (%) of patients from whom MRSA was isolated at the indicated site at any time during their stay in the ICU. Patients whose ICU stay spanned the day when antiseptics were introduced are excluded. TW indicates outbreak strain of MRSA sequence type 239.

[a] Screen sites were anterior nares, axillae, perineum, and throat (rectal swabs are excluded).

[b] Respiratory tract samples were sputum, bronchial lavage or washings, and tracheal aspirates.

[c] Catheter tips were from all central venous and arterial catheters.

[d] Skin breaches were predominantly surgical wounds, including tracheostomy sites, drain sites, and ulcers.

ventions had any effect on non-TW strains in the full model, the best single models (Table 2), or when model uncertainty was accounted for (Table 3). However, the short interval between the educational campaign and cohorting means that the uncertainty is substantial, and model 2 (Table 2) indicates it is possible, although relatively unlikely, that the educational campaign caused a large reduction in transmission of non-TW MRSA, whereas cohorting had the opposite effect. The posterior model probability indicates that this model was 5 times less likely than model 1, which attributed all changes to the antiseptic protocol (Table 2).

Analysis of the TW data showed strong evidence of an initial increasing trend in acquisitions before any interventions (Table 2 and Table 3). There was strong evidence that the educational campaign and/or cohorting reduced acquisitions of TW by causing a reduction in either trend or level (the cumulative posterior probability of models not showing a reduction in transmission associated with at least 1 of these interventions was <1%), and the 3 models with the greatest support (Table 2) all suggested a decreasing trend after the educational campaign. However, after accounting for model uncertainty, there was only weak evidence in support of either intervention on its own, although a reversal of the increasing trend in TW MRSA associated with the educational campaign was estimated to be more likely than not (Table 3). Interestingly, the full model and the 3 best-fitting models all indicated a sudden increase in transmission of TW MRSA associated with the antiseptic protocol, although the estimated magnitude of the effect varied greatly (Table 2). Accounting for model uncertainty weakened the evidence in support of this effect, but nonetheless the estimated probability remained >80% (Table 3). In summary, regression analysis provided strong evidence that the antiseptic protocol caused an immediate reduction in transmission of non-TW MRSA and moderate evidence of an immediate increase in transmission of TW MRSA.

Carriage of* qacA/B *and biocide MBCs of TW and non-TW MRSA strains. This apparent diverging effect of the antiseptic protocol on transmission of TW and non-TW MRSA strains raised the possibility that they differed in their susceptibility to either or both chlorhexidine and triclosan. This was assessed first by detecting carriage of *qacA/B*. Twenty-one temporally distinct acquisition isolates of TW and non-TW strains were assessed for carriage of *qacA/B*. All TW MRSA strains and only 1 of 21 non-TW isolates carried both *qacA/B* genes. Chlorhexidine and triclosan MBCs for 5 TW MRSA and 5 *qacA/B*-negative non-TW MRSA were assessed (Table 4). The TW MRSA strains had a 3-fold higher chlorhexidine MBC than the non-TW MRSA strains, whereas triclosan MBCs of TW and non-TW MRSA strains were identical.

Anatomical sites of MRSA isolation. To assess whether increased chlorhexidine MBCs of TW strains translate into reduced efficacy in vivo, a comparison was made of TW and non-TW site colonization before and after introduction of the antiseptic protocol. The percentage of patients from whom non-TW strains were isolated at screening, respiratory, skin breach, and wound sites was significantly reduced after introduction of the antiseptic protocol, whereas there was no significant reduction in TW isolation (Table 5).

DISCUSSION

This study demonstrates that introduction of a chlorhexidine-based surface antiseptic protocol into an ICU where MRSA prevalence is stable at ~20% can lead to an immediate and sustained reduction in transmission of susceptible MRSA stains. Although basic infection control interventions were already in place and actively reenforced, this does not mean that a more sustained and effective campaign would not have had an effect comparable to that of the antiseptic protocol. However, the data contribute to a body of evidence indicating that use of antiseptics, either as part of a decolonization strategy for known MRSA-colonized patients or administered to all ICU patients, can be useful in controlling MRSA [8–14]. It is recognized that surface antiseptics have only limited efficacy at eradicating MRSA in multisite-colonized patients [13, 34–37], at least in part prompting systematic reviews to recommend against their use to prevent MRSA transmission [1, 38]; however, the evi-

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dence suggests that the suppression of colonization, evidenced by a reduction in colonization sites after introduction of antiseptics rather than attainment of culture negativity, can reduce transmission. All patients received an antiseptic at multiple sites, so determining the relative benefit of individual components would require detailed prospective studies. The contribution of triclosan as a skin cleanser in MRSA-negative patients is also unclear; however, the fact that MBCs of TW and non-TW strains were identical suggests that it did not make a major contribution.

Interrupted time-series studies are the strongest quasi-experimental designs for assessing longitudinal effects of interventions, and segmented regression analysis is recommended for their analysis [39]. However, when several interventions are introduced close in time, accurately assessing the effect of each is difficult because multicolinearity can lead to unreliable estimates. One possible approach is to eliminate covariates using standard model selection algorithms (such as backward and forward selection). However, these are known to generate estimates that are too precise and *P* values that are too small, because they ignore uncertainty in model choice [31, 40]. We overcame this problem by using a Bayesian model averaging approach, which accounts for model uncertainty when obtaining parameter estimates by combining results of multiple models weighted by the posterior probability that they are correct. This reduces the chance of making type I errors. Even after accounting for such model uncertainty, the estimated effect of the antiseptic protocol on non-TW acquisition remained highly significant (Table 3).

One concern about the use of antiseptics is the lack of effect on and, therefore, selection of resistant strains, which was consistent with observations in this study. The TW strains carried *qacA/B* genes, demonstrated 3-fold increased chlorhexidine MBCs in vitro (similar to previously published *qacA/B*-positive MRSA strains [21]), and were not affected in anatomical site colonization or transmissibility after introduction of the antiseptic protocol. Indeed, all models provided evidence that the antiseptic protocol increased transmission of TW MRSA, although this was less clear when model uncertainty was fully accounted for. The MBC of TW MRSA was, however, still well below the chlorhexidine concentrations used, which might be explained by greater activity and/or expression of *qacA/B* on body surface localized TW MRSA and, therefore, a higher MBC in vivo than was demonstrated in vitro. Alternative explanations, such as ineffective application or inactivation on skin, seem less likely, because it is hard to envisage how this would translate into such a markedly different effect on TW and non-TW strains when their MBCs were so close. This continued transmission of TW strains cautions against widespread use of chlorhexidine in situations in which prevalence of *qacA/B* is high. It will be interesting to hear about experiences with chlorhexidine use in countries where *qacA/B* strains are more highly endemic and whether the carriage of *qacA/B* can account for some of the decolonization failures observed in randomized studies in which chlorhexidine is used as part of the protocol [12, 13, 15, 36, 37].

The TW MRSA models provided some evidence that hand hygiene or cohorting may have reduced TW MRSA acquisitions; however, this may be an artefact because the exponential increase in TW MRSA is clearly not sustainable in a small ICU. A better assessment of the effect of interventions on transmission of MRSA in small units would make use of individual-level data within a mechanistic transmission model to account for the fact that, as the numbers colonized increase, fewer patients remain at risk. This is an important area for further research.

This article and our previous report [24] on the TW MRSA strain together demonstrate that hospital MRSA strains can differ in their virulence and response to infection control interventions. That such strains exist should be borne in mind when extrapolating effectiveness of infection control interventions from one situation to another. The storage and analysis of MRSA strains identified in intervention studies may help to develop a more targeted approach to introduction of enhanced infection control measures.

Acknowledgments

We thank Dr Jodi Lindsay and Joshua Cockfield for restriction modification typing of the MRSA strains.

Financial support. Guy's and St Thomas' Charity (to R.B. and J.D.E), Department of Health, via the National Institute for Health Research comprehensive Biomedical Research Centre award to Guy's and St Thomas' National Health Service Foundation Trust in partnership with King's College London (to J.D.E.). R.B. receives 50% salary support in the form of an unrestricted educational grant from Novartis UK.

Potential conflicts of interest. All authors: no conflicts.

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