Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study

Jorge A Cepeda, Tony Whitehouse, Ben Cooper, Janeane Hails, Karen Jones, Felicia Kwaku, Lee Taylor, Samantha Hayman, Barry Cookson, Steve Shaw, Chris Kibbler, Mervyn Singer, Geoffrey Bellingan, A Peter R Wilson

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Department of Clinical Microbiology, University College London Hospitals, London W1T 4JF, UK (J A Cepeda MRCP, B Cooper PhD, S Hayman BSc, A P R Wilson FRCP); **Bloomsbury Institute of Intensive Care Medicine, Department of Medicine, University College London, London W1T 3AA, UK** (T Whitehouse FRCA, J Hails RGN, F Kwaku MSc, Prof M Singer FRCP, G Bellingan FRCP); **Department of Medical Microbiology** (B Cooper, C Kibbler FRCP), **and Intensive Care Unit** (K Jones RGN, L Taylor RGN, S Shaw FRCA), **Royal Free Hospital, London NW3 2QG, UK; and Specialist and Reference Microbiology Division, Health Protection Agency, London NW9 5HT, UK** (Prof B Cookson FRCP)

Correspondence to:
Dr A Peter R Wilson, Department of Clinical Microbiology, Windeyer Institute of Medical Sciences, University College London Hospitals, 46 Cleveland Street, London W1T 4JF, UK
peter.wilson@uclh.nhs.uk

Summary

Background **Hospital-acquired infection due to meticillin-resistant *Staphylococcus aureus* (MRSA) is common within intensive-care units. Single room or cohort isolation of infected or colonised patients is used to reduce spread, but its benefit over and above other contact precautions is not known. We aimed to assess the effectiveness of moving versus not moving infected or colonised patients in intensive-care units to prevent transmission of MRSA.**

Methods **We undertook a prospective 1-year study in the intensive-care units of two teaching hospitals. Admission and weekly screens were used to ascertain the incidence of MRSA colonisation. In the middle 6 months, MRSA-positive patients were not moved to a single room or cohort nursed unless they were carrying other multiresistant or notifiable pathogens. Standard precautions were practised throughout. Hand hygiene was encouraged and compliance audited.**

Findings **Patients' characteristics and MRSA acquisition rates were similar in the periods when patients were moved and not moved. The crude (unadjusted) Cox proportional-hazards model showed no evidence of increased transmission during the non-move phase (0·73 [95% CI 0·49–1·10], p=0·94 one-sided). There were no changes in transmission of any particular strain of MRSA nor in handwashing frequency between management phases.**

Interpretation **Moving MRSA-positive patients into single rooms or cohorted bays does not reduce crossinfection. Because transfer and isolation of critically ill patients in single rooms carries potential risks, our findings suggest that re-evaluation of isolation policies is required in intensive-care units where MRSA is endemic, and that more effective means of preventing spread of MRSA in such settings need to be found.**

Introduction

Hospital-acquired infections—a fifth of which are caused by meticillin-resistant *Staphylococcus aureus* (MRSA)—are estimated to cost the UK National Health Service (NHS) £1 billion per year.[1] The incidence of MRSA is especially high within intensive-care units, with one in six patients in English units being colonised, infected, or both.[2] National guidelines for preventing the spread of MRSA recommend contact precautions and isolation of infected or colonised patients in a single room or cohort—ie, grouping them geographically with designated staff, though without the benefit of a physical barrier.[3–5] Although workers on several reports have suggested a benefit from single-room isolation or cohort nursing, in a systematic review no well-designed studies were noted that allowed the role of isolation measures alone to be assessed.[6] Such reports[6] have been predominantly retrospective, lacking in proper statistical analysis, and generally undertaken in response to outbreaks rather than within intensive-care units of high endemicity. Moreover, isolation was generally introduced within a package of measures, variably including surveillance, improved handwashing compliance, reduction in ward activity, and addition of other treatments.[6]

The continuing rise in MRSA infection rates, the endemicity of MRSA in many countries, the inconsistency in current approach (eg, 24% of English intensive-care units do not isolate affected patients),[2] and the ongoing debate and scarcity of conclusive evidence on the use of infection control measures[3,7,8] all raise important questions about the value of isolation strategies. The implications for resource use and, in particular, potential risks to the critically ill patient inherent in transfer and isolation[7–9] mandate the need for definitive studies. We thus aimed to assess the benefit on MRSA transmission of isolation in single rooms or cohorts, over and above standard precautions.

Methods

Patients

We undertook a prospective study in three general medical-surgical intensive-care units of two central London teaching hospitals for 1 year from June, 2000, in accordance with a prespecified protocol. All patients needing intensive care for more than 48 h were included, because this period was the minimum for MRSA screening to become available. We obtained ethics committee approval in both hospitals. Each committee agreed that patients' consent (or relatives'

Figure 1: **Plan of intensive-care units of hospital A (upper) and hospital B (lower)**
Light blue bars indicate doors.

agreement) did not need to be sought because no compelling evidence was available to adopt one or other practice, as shown by the wide and clear variation in use of isolation in British intensive-care units.[2] We always informed patients and their next-of-kin about infection with MRSA.

Procedures

In hospital A, an 18-bed unit consisted of four single rooms, four bays of three beds, and one bay of two beds. A four-bed unit had three beds in the main area and one single room (figure 1). The distance from bed centre to bed centre was a median of 3·2 m (IQR 3·0–4·6). Hospital B had a ten-bed unit with four single rooms, a bay of four beds, and a bay of two beds, with a median distance from bed centre to bed centre of 2·7 m (IQR 2·1–5·3; figure 1). All single rooms were at negative pressure.

The study consisted of three phases. During the first 3 months (phase 1) and the last 3 months (phase 3), any patient colonised or infected with MRSA (MRSA-positive) was moved to a single room or cohort-isolated in an open bay with other MRSA patients (move phase). In the middle 6-month period (phase 2, non-move phase), MRSA-positive patients were only moved to a single room or cohort area if they were carrying other multiresistant or notifiable pathogens, or needed protective isolation—eg, for neutropenia. At the end of every phase, existing MRSA patients were treated as new admissions—eg, moved to a bay or single room if in a cohort phase.

Disposable aprons were worn throughout each nursing shift. Gloves were worn for all invasive procedures, washing and turning the patient, contact with mucous membranes or body fluids, and disposal of body fluids, whether patients were known to have MRSA or not. This practice falls between contact and standard precautions (panel) and we thus term it standard plus. The policy for dealing with the environment did not differ between phases: removal of gloves and hand hygiene were required between patient and environment, together with cleaning of the environment both daily and after discharge of the patient. Gloves and aprons were removed and disposed of before contact with shared surfaces (eg, telephones) and were changed when moving between bed spaces. We encouraged use of the recommendations of the US Hospital Infection Control Practices Advisory Committee and UK Working Party[3,5,9] throughout the study, other than not moving MRSA-positive patients in the middle 6-month period. Nurse cohorting was required for all patients with multiresistant pathogens and, during the move phase, for all patients with MRSA. During breaks, nurses from adjacent bed spaces within the same cohort would cross-cover. One staff member was dedicated to specifically relieve nurses in single isolation rooms. All bed spaces had ready access to a handwash sink, alcohol handrub, chlorhexidine, povidone-iodine, and paper towels. We encouraged handwashing (including hand hygiene with alcohol handrub) through regular education sessions to all staff and visitors. Separate devices (eg, stethoscopes) were provided at every bed space.

We calculated the incidence of MRSA colonisation and infection from screening samples (nose or groin swabs)[3] taken from all patients within 24 h of admission, weekly thereafter, and at discharge, and from samples taken when clinically indicated—eg, sputum, wound, and blood cultures. We informed intensive-care staff about the results of these cultures. Before the study began, only hospital B undertook admission and weekly screening.

We defined colonisation with MRSA by its presence in nose, groin, sputum, wound, or other sites but that did not require treatment with an appropriate antibiotic. Infection with MRSA was described as the presence of MRSA in any clinical isolate coinciding (within 5 days) with treatment with an appropriate antibiotic (a glycopeptide, linezolid, or combination treatment with rifampicin and trimethoprim). A consultant microbiologist assessed every case in which MRSA infection was treated.

We recorded details of potentially important confounders, including demographic data, severity and dependency scoring (first 24 h acute physiology and chronic health evaluation II score, daily therapeutic intervention severity score),[10] and length of intensive-care unit and hospital stay. Factors affecting preadmission acquisition—eg, previous hospital stay—were not included. All antibiotic use and daily staffing levels were noted. Two independent observers assessed hand hygiene compliance unobtrusively during periods of high and low activity for both hospitals over 4 months during phases 1 and 2, using Pittet's method.[11,12] Nurse compliance with apron wearing was measured separately over the three study phases.

Microbiological specimens

We identified both meticillin-sensitive *S aureus* (MSSA) and MRSA with salt agar media. Screening swabs were inoculated onto one plate containing mannitol salt agar (with oxacillin) and into salt broth. After overnight incubation, the broth was subcultured onto mannitol salt agar (without oxacillin). Suspect colonies on the original plate at 24 h and 48 h were identified and subcultured to a blood agar plate with oxacillin disc and incubated at 30ºC overnight. We incubated the salt broth subculture for a further 24 h and re-examined it on day 4. Intermediate oxacillin results were confirmed with an oxacillin E test (AB Biodisk, Solna, Sweden).

All isolates were initially phage-typed with the 23 phages of the basic international set 1 at 100× routine test dilution, plus the four experimental UK phages 88A, 90, 83C, and 9322.[13] Isolates of MRSA and MSSA that were likely to represent new acquisitions or reinfection (as defined below) were further typed by pulsed-field gel electrophoresis (PFGE; Laboratory of Hospital Infection, HPA Colindale, London, UK).[13] We used the enzyme *Sma*I for DNA restriction and analysed the banding patterns by BioNumerics software (Applied Maths, Ghent, Belgium) to calculate Dice coefficients.[14] These coefficients calculate relatedness between banding patterns of related strains. A dendrogram was generated by the unweighted pair group method using arithmetic averages (UPGMA) clustering. We interpreted chromosomal DNA restriction patterns by applying set criteria for bacterial strain typing, as formulated by Tenover and coworkers designed for short-term epidemiological studies.[15,16] Profiles were taken as indistinguishable if two bands or fewer were different and similar if seven bands or fewer were different.

Statistical analysis

We analysed data in accordance with a prespecified plan. The primary outcome measure was time to acquisition of MRSA from time of admission to the intensive-care unit. Any MRSA-positive isolate arising after the first 48 h from admission was judged to constitute acquisition, provided: (1) the patient had no previous MRSA isolates documented; and (2) there was at least one previous negative screen during the current episode. Timing was recorded to the nearest day, and we judged patients present if their stay exceeded 12 h. Acquisition was assumed to happen at the midpoint between the last negative and first positive swabs. For calculation of colonisation pressure, patients not known to be MRSA-positive before admission who were found to be positive on the first isolate were assumed to be MRSA-positive from the day of admission. We did several sensitivity analyses under different assumptions to assess the effect of these assumptions on the results. Patients not acquiring MRSA were regarded as censored at the time of the last screening sample.

We analysed data with a Cox proportional-hazards model with the non-move intervention incorporated as a time-dependent covariate (1 non-move phase, 0 move phase). The model adjusted for potential ward-level and patient-level confounders. We derived the colonisation pressure covariate for every patient from the number of

***Panel:* Standard and contact precautions**

Standard precautions[5]

- Wash hands with plain soap after touching blood, body fluids, excretions, or contaminated items whether or not gloves are worn.
- Wear gloves when touching blood, body fluids, excretions, and contaminated items.
- Put on clean gloves before touching non-intact skin or mucous membranes.
- Change gloves between procedures on the same patient involving contact with high concentration of organisms.
- Remove gloves and wash hands before touching the environment or other patients.
- Wear mask and eye protection and gown during procedures causing splashes of blood or body fluid.

Contact precautions

As standard precautions, plus

- Patient placed in single room or in a room with patients who have active infection with the same microorganism but no other infection (cohorting).
- Wear gloves when entering the room.
- Change gloves after contact with high concentration of microorganisms.*
- Remove gloves and wash hands with antiseptic agent when leaving patient's environment.*
- Wear gown in the room if in contact with patient, environment, or if patient incontinent.*
- Remove gown before leaving room.*
- Avoid sharing of patient equipment.*

*Indicates those criteria that formed standard plus, except that aprons were used instead of gowns, and gloves were not worn for simple comfort contact.

	Hospital A		Hospital B	
	Move	Non-move	Move	Non-move
Patients*				
Patient-days	3914	3591	1541	1593
Median (IQR) age (years)	60 (44–70)	59 (39–70)	52 (36–67)	53 (39–67)
Women	112 (36%)	115 (40%)	60 (45%)	54 (41%)
Admission diagnosis				
Medical	209 (68%)	195 (67%)	84 (63%)	72 (54%)
Surgical	100 (32%)	95 (33%)	50 (37%)	61 (46%)
Urgent or emergency	52 (17%)	32 (11%)	29 (22%)	37 (28%)
Elective or scheduled	48 (16%)	63 (22%)	21 (16%)	24 (18%)
Median (IQR) white-cell count $\times 10^9$/L)	10·3 (5·5–13·6)	9·5 (6·0–13·5)	9·7 (5·8–14·1)	9·8 (4·9–14·4)
Median (IQR) APACHE II score	18 (14–24)	19 (14–24)	17 (12–21)	18 (13–22)
Median (IQR) hospital stay before intensive-care unit (days)	1 (0–11)	1 (0–6)	3 (0–14)	4 (0–13·5)
Median (IQR) intensive-care unit stay (days)	5·8 (3·0–11·0)	6·0 (3·2–12·3)	6·8 (3·6–14·9)	7·1 (3·8–13·1)
Median (IQR) TISS	23 (20–27)	23 (20–27)	32 (29–35)	31 (28–34)
MRSA screening swabs per patient-day†	0·24, 0·23 (0·24)	0·23	0·46, 0·24 (0·35)	0·47
Patient-days isolated for other pathogens‡	201 (5%)	113 (3%)	71 (5%)	92 (6%)
Antibiotic use (% of patient-days)				
Anti-MRSA antibiotics	810 (21%)	733 (20%)	481 (31%)	494 (31%)
Anti-MSSA antibiotics	1296 (33%)	1436 (40%)	566 (37%)	507 (32%)
Other antibiotics	1092 (28%)	1002 (28%)	629 (41%)	671 (42%)
Median (IQR) number of intravascular catheters per patient-day	2 (1–2)	2 (1–2)	3 (3–4)	3 (3–3)
Nursing				
Total nursing shifts	11 676	10 840	7756	6444
Agency nursing shifts	2588 (22%)	2002 (18%)	1476 (19%)	1294 (20%)
Median (IQR) nurse/patient ratio over 24 h	3·3 (2·8–3·5)	3·3 (2·8–3·6)	4·3 (3·6–5·2)	3·7 (3·5–4·0)

APACHE II=acute physiology and chronic health evaluation II. TISS=therapeutic intervention severity score. *Characteristics are for patients staying for 48 h or longer (hospital A: move, 309/680; non-move 290/666; hospital B: move, 134/167; non-move 133/163). †Data are phase 1,3 (overall) or phase 2. ‡Patient-days of source isolation for pathogens other than MRSA expressed as a percentage of patient days at risk of acquiring MRSA.

Table 1: **Study characteristics**

other MRSA-positive patients present on a given day, including those staying fewer than 48 h, assuming clearance of carriage after two negative screens and no subsequent positive screens. Nurse hours were calculated for every day on each unit on the basis of the patient census and documented staffing levels. We included antibiotic use as three time-varying covariates corresponding to treatment with antibiotics with predefined (1) activity against MRSA, (2) activity against MSSA but not MRSA, and (3) other antibiotics. The number of intravascular catheters for every patient was also included as a time-dependent covariate, as was the therapeutic intervention severity score after subtracting the contribution attributable to the vascular catheters. Interactions between covariates and both survival time and setting (hospital A or B) were considered and retained in the final model if significant at the 5% level. The model was fitted with the Efron method for ties and a robust variance estimator to account for patient-episode level clustering, using Stata 7.0 software (College Station, TX, USA). The proportional-hazards assumption was assessed with log-log survival plots and, formally, with scaled Schoenfeld residuals (Stata). We stratified data with variables that did not satisfy this assumption—ie, elective surgery and hospital.

A prestudy power calculation suggested there was an 80% chance of detecting as significant at the one-sided 5% level an increase in MRSA prevalence from 11% to 16% when single room or cohort isolation was withdrawn. This calculation was based on the recorded prestudy MRSA prevalence and assumed 900 patients in every 6-month period and independent outcomes. Screening during the study showed the prevalence to be considerably higher than assumed and the analysis plan subsequently changed after recognition of the importance of dependencies in outcome data. This power estimate might therefore be misleading. However, since the interpretation of outcome data should be based on CIs and not on power calculations,[17] this has no bearing on the findings of this study.

We used a one-sided test to increase the chance of detecting a small or moderate beneficial effect of moving patients. We judged failure to detect any increase in transmission resulting from moving patients a much lesser concern because, in the absence of any beneficial effects of this policy, the other known negative effects of moving critically ill patients would be sufficient reason for abandoning the policy.

Role of the funding source

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

Results

Patients' characteristics were similar between the move and non-move phases within hospitals (table 1, figure 2), although more elective admissions and fewer admissions for emergency operations took place in hospital A during the non-move phase. Patients in hospital A were more likely to be older, non-surgical admissions, and to have lower therapeutic intervention severity scores, shorter stays in the intensive-care unit, and shorter hospital stays before admission to the intensive-care unit.

Admission screening cultures were taken in 80–87% of patients and discharge screens were done in 71–75% of patients in both hospitals over the three phases, and culture results were consistent by phase and hospital. Similar MRSA acquisition rates were seen in the move and non-move phases (figure 3). No major changes were noted in incidence or prevalence between phases, nor was there seasonal variation (figure 4). Both hospitals were always able to isolate colonised or infected patients into single rooms or cohort bays during the move phases, even when the prevalence of MRSA was high.

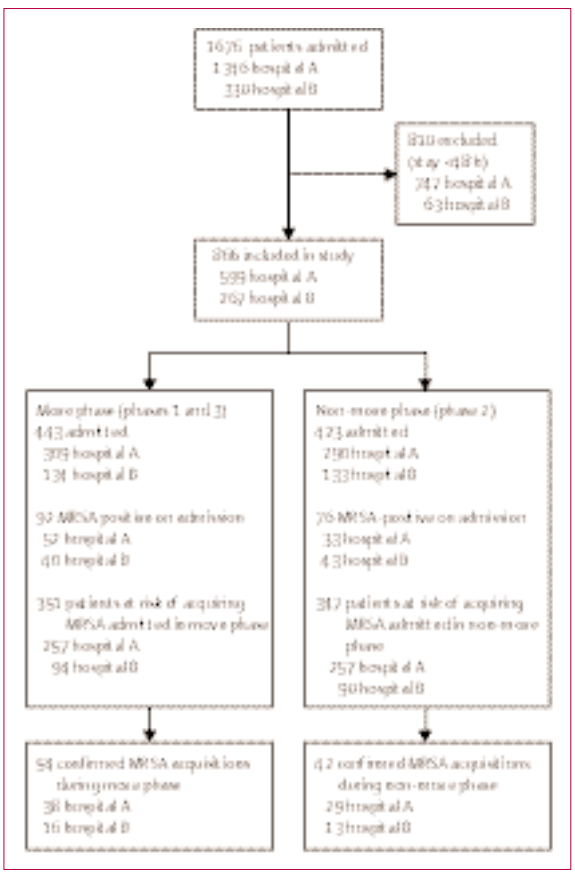

Figure 2: **Patient disposition in every phase**

The crude (unadjusted) Cox proportional-hazards model showed no evidence of increased transmission during the non-move phase compared with the move phases. This finding was true both for the combined data stratified by hospital (hazard ratio 0·73 [95% CI 0·49–1·10], p=0·94 one-sided) and for hospital A and B individually (0·72 [0·44–1·17], p=0·91 and 0·76 [0·37–1·58], p=0·77). The upper 95% CI of 1·10 indicates that we can be confident there was not a striking increase in the hazard for acquiring MRSA in the non-move phase.

After adjusting for potential confounders (table 2) and accounting for the non-independence of outcomes by adjusting for colonisation pressure, we still recorded no evidence of increased transmission in the non-move phase for combined data (0·79 [0·51–1·22]), for hospital A (0·73 [0·42–1·26]), and for hospital B (1·37 [0·36–5·18]). Non-independence means that the risk to one patient of becoming colonised could depend on the number of other colonised patients.

The sensitivity analyses produced similar results irrespective of whether MRSA acquisition was assumed to occur the day after the last negative swab (0·72 [0·46–1·12]) or on the day before the first positive swab (0·81 [0·52–1·25]). Likewise, the result was not affected if patients without an admission swab were assumed to have acquired MRSA in the intensive-care unit if the first available swab grew MRSA. This finding was seen whether conversion was assumed to occur at the earliest possible time (0·69 [0·46–1·05]), the latest possible time (0·72 [0·48–1·10]), or at the midpoint of negative and positive swabs, as in the main analysis (0·74 [0·49–1·12]). Because the possibility of short-term carryover effects could not be entirely excluded, the main analysis was also repeated allowing for 2-week washout periods at the start of the non-move phase and the final move phase. This reanalysis led to similar results (0·72 [0·45–1·13]). The analysis was repeated for the two commonest MRSA types (EMRSA15 and EMRSA16) to assess whether any variation existed between strains. No increase was noted in the rate of acquisition of either type when patients were not moved (0·92 [0·39–2·19] and 0·91 [0·40–2·09]).

Table 3 shows the frequency with which patients became newly colonised or infected with MRSA while on the intensive-care unit during the different management phases. For patients staying more than 48 h, 38 (12%; hospital A) and 16 (12%; hospital B) patients became colonised during the move phases compared with 29 and 13 (10%; both hospitals) when they were not moved. The frequency of isolating MRSA from different body sites, and the number of patients who died while receiving treatment for MRSA, were also similar between phases.

PFGE typing was available in 81 of 96 possible acquisitions. There was no specific increase in transmission of any phage or PFGE type during any management phase in either hospital (table 4). In 74 of these 81 (91%) MRSA acquisitions (as defined in the main analysis), one or more possible patient sources on the ward were identified—overlapping stays and carrying an MRSA strain with a PFGE pattern differing by two bands or fewer. Of patients who acquired MRSA

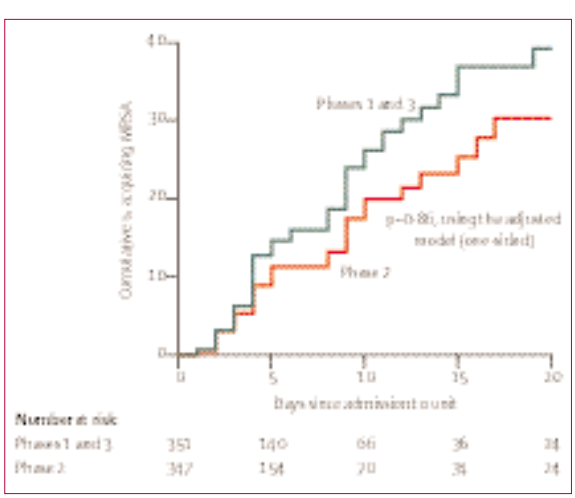

Figure 3: **MRSA acquisition in intensive-care unit by study phase**
Data are for both hospitals combined.

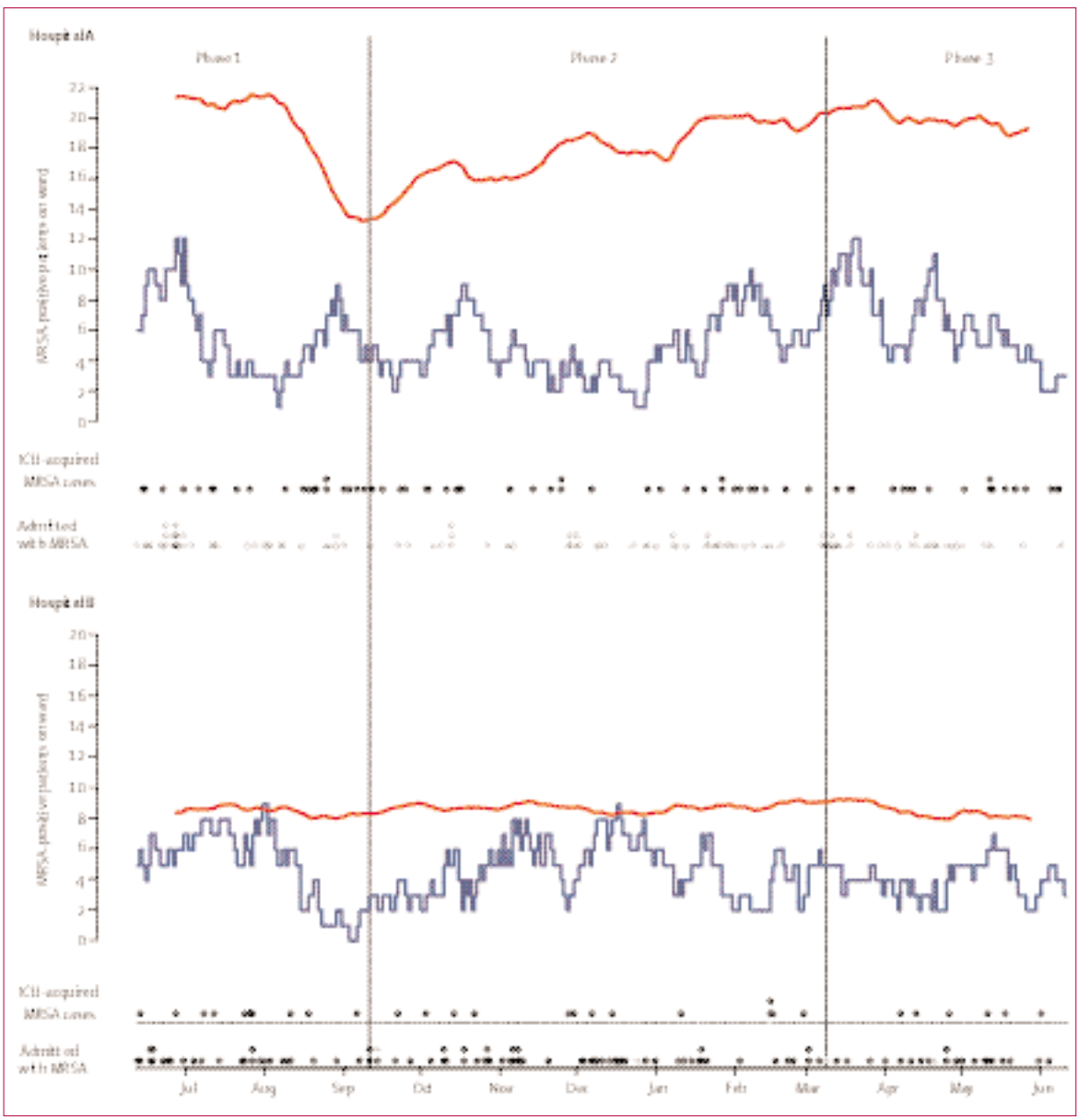

Figure 4: **MRSA colonisation and infection at the two study centres**
Open circles indicate days of assumed acquisition of MRSA or admission. Grey circles indicate patients assumed to be MRSA-positive on admission in the main analysis, but where admission swabs were missing and the first swab taken was positive. Red line represents the smoothed total patient census on the intensive-care units (31-day moving average). Blue line represents the number of MRSA-positive patients on the ward.

in the intensive-care unit, the distribution between phases did not differ by much. There were no well-demarcated peaks of incidence at either hospital of a particular phage or PFGE type during the year when examining every 2-month period. A high proportion of strains overlapped because patients carrying different strains were usually present for long periods. Clearance of MRSA was unusual except in some patients treated with linezolid.[18] Two patients were colonised with strains of both EMRSA15 and EMRSA16 that shared a similar PFGE profile in the move phase, compared with six patients in the non-move phase, of whom four shared a similar profile.

The median time to prepare and undertake a bed move was 27 min (n=93; IQR 18–36), and this time did not differ between phases or hospitals. Fewer bed moves took place for MRSA during the non-move phase than for the move phases in hospitals A and B (61 *vs* four and 17 *vs* 0). Four patients with MRSA were inadvertently moved in the early stage of the non-move phase but adherence to moving or cohorting was otherwise complete. Similar numbers of patients in the move and

non-move phases were moved into source isolation for other multiresistant pathogens (hospital A, 18 *vs* 21; hospital B, six *vs* eight). The nurse/patient ratio was between 3·3 and 4·3 over a 24-h period (table 1), allowing a high degree of adherence to cohorting of staff.

Hand hygiene frequency and use of standard plus precautions remained stable during the study period at both sites. In 80 unobtrusive observation periods of 20 min, 534 handwashing opportunities were noted (one every 3 min); of these, 237 (8·9 per h) were high-risk—eg, moving between patients[12]—and hand hygiene was undertaken on 50 occasions (21% compliance). Risk, dependency, cohort isolation, staff ratio, and staff seniority did not affect compliance. Aprons were worn by nursing staff on 400 of 403 (99%) observed occasions.

Discussion

While not excluding a small effect, and contrary to the expectation of many experts, we recorded no evidence that moving MRSA-positive patients into single rooms or cohorted bays was associated with a reduction in crossinfection. The similar finding in both hospitals, which had different patient populations, different lengths of stay in the intensive-care units, different MRSA rates, and different endemic MRSA strains, adds further weight to these findings.

	Hazard ratio (95% CI)
Ward-level covariates	
Phase 2 (non-move)	0·79 (0·51–1·22)
Nurse hours per patient	
1st quartile	Reference
2nd quartile	1·04 (0·59–1·85)
3rd quartile	0·82 (0·44–1·55)
4th quartile	1·24 (0·68–2·27)
Constant patient-level covariates	
Sex	
Women	Reference
Men	0·75 (0·49–1·14)
APACHE II	
1st quartile	Reference
2nd quartile	1·22 (0·61–2·45)
3rd quartile	1·13 (0·56–2·28)
4th quartile	0·92 (0·43–1·95)
Urgent or emergency surgery	1·64 (0·97–2·78)
Age	
1st quartile	Reference
2nd quartile	1·25 (0·65–2·38)
3rd quartile	1·24 (0·66–2·33)
4th quartile	1·30 (0·64–2·65)
Time-dependent patient-level covariates	
Modified TISS	
1st quartile	Reference
2nd quartile	0·57 (0·29–1·11)
3rd quartile	0·92 (0·49–1·73)
4th quartile	0·68 (0·27–1·72)
Isolated for other pathogens	1·12 (0·44–2·84)
Anti-MRSA antibiotics	0·81 (0·42–1·58)
Anti-MSSA antibiotics	0·59 (0·37–0·93)
Other antibiotics	0·76 (0·48–1·21)
Colonisation pressure*	1·19 (0·86–1·65)
Number of intravascular catheters	1·24 (0·92–1·66)

Hazard ratios greater than 1 indicate increased risk. *Colonisation pressure defined as $\log_e$(1+number of other patients with MRSA on unit).

Table 2: **Hazard ratios for MRSA acquisition estimated from the Cox proportional-hazards model**

Hospital-acquired infection, in particular due to MRSA, is a major problem in many intensive-care units in Europe[8,19] and other developed countries.[20–22] Findings of the 1999–2001 European antimicrobial resistance surveillance survey showed a wide variation in MRSA rates across Europe, ranging from 37% of blood isolates in the UK to less than 3% in the Netherlands, Sweden, Denmark, and Iceland.[23] The high prevalence of MRSA colonisation or infection on admission to intensive care in our study exceeds that of many other countries,[24,25] but it is representative of the UK[2,26] and intensive-care units in other countries[27–30] where MRSA is endemic.

Previous reports suggesting benefit from a policy of isolating MRSA-positive patients have been uncontrolled, retrospective, and generally found within a package of infection control measures.[6,31] The use of gown and gloves in immune-compromised patients delays development of nosocomial infection.[32] On the other hand, isolation of critically ill patients in single rooms is not without risk, whether related to the transfer process[33] or to reduced clinical input.[34] Despite higher illness severity scores, isolated patients are visited half as often as are non-isolated patients (5·3 *vs* 10·9 visits per h),[35] and are twice as likely to have adverse events (31 *vs* 15 events per 1000 patient-days).[36]

Previous work has not been designed to specifically show benefit from single room isolation.[6] Reports include a description of an outbreak,[37] a retrospective study in which the intervention was active surveillance rather than a change in isolation practice alone,[38] a retrospective cohort study of national guidelines that also included screening and eradication measures,[39] and one that included handwashing, topical eradication, and screening of staff and patients.[40]

We noted that not moving critically ill patients who were colonised or infected with MRSA did not lead to any detectable increase in specific strains, as shown by phage-typing or PFGE. Our finding accords with the interpretation that this type of isolation does not further reduce the transmission of MRSA within this environment, which is perhaps occurring at a low level from a fairly large pool of MRSA strains. We do not address the value of source isolation during a confirmed point source outbreak of MRSA involving a single strain, as discussed elsewhere.[41,42]

We took extensive measures to document potential confounders that might have masked any beneficial effects of moving MRSA patients, and plausible threats to validity were dealt with systematically. Infection control measures were reinforced throughout the study and no temporal change in hand hygiene or barrier compliance was noted. We recorded no difference between the phases in either staff carriage or

	Hospital A		Hospital B	
	Move	Non-move	Move	Non-move
Total admissions (stay ⩾48 h)	680 (309)	666 (290)	167 (134)	163 (133)
MRSA-positive on admission to intensive-care unit (% of total)				
All patients	63 (9%)	46 (7%)	50 (30%)	55 (34%)
Patients staying ⩾48 h	52 (17%)	33 (11%)	40 (30%)	43 (32%)
MRSA acquisitions (colonisation or infection)	38 (12%)	29 (10%)	16 (12%)	13 (10%)
Incidence (MRSA acquisitions per 1000 patient-days at risk)	20·6	15·5	28·2	22·2
Median (IQR) number of MRSA-positive patients on ward [% of beds]	6 (4–8) [27%]	4·5 (4–6) [20%]	5 (3–6) [50%]	5 (3–6) [50%]
Number of patients not colonised on admission but developing MRSA infection (not colonisation) in intensive-care unit	7+3 (3%)	9 (3%)	5+0 (4%)	2 (2%)
Respiratory	6+3 (3%)	8 (3%)	1+0 (2%)	2 (2%)
Wound	1+0 (0·3%)	4 (1%)	1+0 (1%)	0
Blood	1+0 (0·3%)	3 (1%)	1+0 (1%)	1 (1%)
Other	1+0 (0·3%)	1 (0·3%)	0	0
Number of patients colonised on admission but developing MRSA infection in intensive-care unit	9+13 (7%)	23 (8%)	6+3 (7%)	8 (6%)
Respiratory	1+2 (1%)	4 (1%)	1+1 (1%)	2 (2%)
Wound	3+5 (3%)	9 (0.5%)	0	1 (1%)
Blood	4+5 (3%)	8 (3%)	5+2 (5%)	5 (4%)
Other	1+1* (1%)	2 (1%)	0	0
Number of patients dying on active treatment for MRSA†	5+4 (3%)	14 (5%)	13+6 (14%)	13 (10%)
Number of patients dying with MRSA not under treatment	11+7 (6%)	4 (1%)	4+2 (4%)	9 (7%)

*More than one site in some patients. †Defined as antibiotics up to 48 h before death.

Table 3: **Colonisation with or acquisition of MRSA in every study phase**

	Typed by PFGE		Typed by bacteriophage		Other phage types	Total
	EMRSA15	EMRSA16	EMRSA15	EMRSA16		
Hospital A						
Move phase						
PGFE 1	36	31	..	..	..	67
PGFE 2	6	1	..	..	..	7
PGFE 3	8	0	..	..	..	8
Total	50	32	28	31	23	82
Non-move phase						
PGFE 1	23	22	..	..	..	45
PGFE 2	5	3	..	..	..	8
PGFE 3	5	0	..	..	..	5
Total	33	25	19	22	17	58
Hospital B						
Move phase						
PGFE 1	3	15	..	..	..	18
PGFE 2	2	0	..	..	..	2
PGFE 3	6	0	..	..	..	6
Total	11	15	3	15	8	26
Non-move phase						
PGFE 1	5	12	..	..	..	17
PGFE 2	3	1	..	..	..	4
Total	8	13	5	12	4	21

PFGE subgroups consisted of isolates with seven or fewer different bands in the gel profile.

Table 4: **PFGE typing of MRSA during every study phase (excluding repeat isolates on same patient)**

environmental contamination with MRSA, MSSA, or other pathogens (data not reported). The disappointing handwashing adherence rate is nevertheless comparable with the median 31% rate reported in other studies.[12,43] In the environment of the intensive-care unit, hands need to be washed or disinfected so frequently (20–30 times per h) that a low adherence rate is inevitable. While it is possible that hand hygiene was less carefully adhered to for patients not known to be MRSA-positive, unit policy did require hand hygiene irrespective of MRSA status, and cohort isolation had no relevant effect on adherence in our unobtrusive surveys. Laboratory staff did not know from which study phase screening and diagnostic samples were taken. There was a 3-day delay between collection of screening cultures and results becoming available. MRSA-positive patients might therefore have been a potential source of spread during this time unless carriage had been reported previously. In practice, this delay is always present and so we do not think that bias was introduced when all patients were managed with standard plus precautions. Units that practise full isolation of all new admissions until MRSA status is confirmed might want to be careful about adopting a policy of not moving patients to isolation. The introduction of molecular tests for MRSA might reduce this delay in future.

Acquisition rates reflected the high prevalence of MRSA in UK intensive-care units compared with other countries.[27,30] Admission screens were obtained in 80–87% of patients and discharge screens in 71–75%, and no change in screening compliance took place over the study period. Although there was a risk of some MRSA carriers being undetected and potentially transmitting the bacterium, all patients with suspected infection had cultures taken. The apparent protective effect of anti-MSSA antibiotics during treatment against acquisition of MRSA could be attributable to the activity of some drugs (eg, imipenem) against some strains. Suppression of nasal flora might then result in acquisition at the end of treatment. In this critically ill high turnover population, colonisation pressure and severity of illness were not significant factors in acquisition. The use of standard plus precautions for all patients might have reduced the effect of prevalence of MRSA colonisation on acquisition.

Our study does not address practices on general wards; further study is needed to clarify best practice and best resource use in this setting. In terms of generalisability to other intensive-care units, several factors should be considered, such as unit layout, nurse/patient ratios, MRSA endemicity, and infection control adherence.[19,44,45] If, as widely believed, carer-borne spread is the predominant mode of transmission, extensive staff cohorting could have a profound effect, even without any physical segregation of patients.[46] We did not record details of contact patterns between health-care workers and cohorted patients. The results

might have differed had hand hygiene adherence been higher than it was, yet this objective has proved difficult to consistently achieve in intensive-care units in view of the sheer volume of hand-washing opportunities presented by caring for critically ill patients. An eight-fold increase in MRSA acquisition rate was reported by a Hong Kong intensive-care unit during the SARS crisis, where infection control was a major consideration of the health carers.[47] The authors suggested that strict contact precautions with continuous wearing of gloves and gowns could have led to the increase in transmission. Other studies show reduced hand-hygiene adherence among glove users.[48,49] Nevertheless, intensive-care units that feel they are able to maintain high levels of hand-hygiene adherence might want to assess the validity of our findings in their environment before changing practice.

In conclusion, our findings challenge the prevailing view that isolation of intensive-care unit patients who are colonised or infected with MRSA in single rooms or cohorts reduces the transmission of MRSA, over and above the use of standard precautions, in an environment in which it is endemic. We greatly reduced the number of bed moves for this reason, thereby allowing better resource use and minimising risk from both the transfer and isolation itself. We used a prospective interrupted time-series design in only two hospitals. This design is widely regarded as one of the strongest quasi-experimental designs, provided it is well conducted and threats to validity are addressed.[6] Ideally, our findings should be confirmed by a cluster-randomisation trial in many centres. Although this exercise would be costly, we hope our findings will provide the necessary impetus for this study to take place.

Contributors

J A Cepeda and T Whitehouse undertook data collection and analysis and J A Cepeda undertook PFGE typing. B Cooper did the statistical analysis. J Hails, K Jones, F Kwaku, and L Taylor undertook data collection and supervised sample collection. B Cookson supervised strain analysis. S Hayman did most of the laboratory identification work. S Shaw and C Kibbler supervised the intensive-care unit and laboratory running of the trial at the Royal Free Hospital. G Bellingan, M Singer, and A P R Wilson had the original idea, supervised the trial in the intensive-care unit and laboratory of University College London Hospital, and wrote the main part of the paper. All authors gave useful comment on the analysis of data and text of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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References

1 National Audit Office. The management and control of hospital-acquired infection in acute NHS trusts in England: report by the Comptroller and Auditor General. London: Stationery Office, 2000: paragraphs 15–16.

2 Hails J, Kwaku F, Wilson AP, Bellingan G, Singer M. Large variation in MRSA policies, procedures and prevalence in English intensive care units: a questionnaire analysis. *Intensive Care Med* 2003; **29:** 481–83.

3 British Society for Antimicrobial Chemotherapy, Hospital Infection Society and the Infection Control Nurses Association. Revised guidelines for the control of methicillin-resistant *Staphylococcus aureus* infection in hospitals. *J Hosp Infect* 1998; **39:** 253–90.

4 O'Connell NH, Humphreys H. Intensive care unit design and environmental factors in the acquisition of infection. *J Hosp Infect* 2000; **45:** 255–62.

5 Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals, part II: recommendations for isolation precautions in hospitals. *Am J Infect Control* 1996; **24:** 32–52.

6 Cooper BS, Stone SP, Kibbler CC, et al. Isolation measures in the hospital management of methicillin-resistant *Staphylococcus aureus* (MRSA): systematic review of the literature. *BMJ* 2004; **329**: 533–41.

7 Barrett SP, Mummery RV, Chattopadhyay B. Trying to control MRSA causes more problems than it solves. *J Hosp Infect* 1998; **39:** 85–93.

8 National Audit Office. Improving patient care by reducing the risk of hospital acquired infection: a progress report. London: Stationery Office, 2004.

9 Garner JS. Guideline for isolation precautions in hospitals, part I: evolution of isolation practices, Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1996; **24:** 24–31.

10 Cullen DJ, Nemeskal AR, Zaslavsky AM. Intermediate TISS: a new therapeutic intervention scoring system for non-ICU patients. *Crit Care Med* 1994; **22:** 1406–11.

11 Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Lancet* 2000; **356:** 1307–12.

12 Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. *Ann Intern Med* 1999; **130:** 126–30.

13 Aucken HM, Westwell K. Reaction difference rule for phage typing of *Staphylococcus aureus* at 100 times the routine test dilution. *J Clin Microbiol* 2002; **40:** 292–93.

14 Murchan S, Kaufmann ME, Deplano A, et al. Harmonization of pulsed-field gel electrophoresis protocols for epidemiological typing of strains of methicillin-resistant *Staphylococcus aureus*: a single approach developed by consensus in 10 European laboratories and its application for tracing the spread of related strains. *J Clin Microbiol* 2003; **41:** 1574–85.

15 Tenover FC, Arbeit RD, Goering RV, et al. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. *J Clin Microbiol* 1995; **33:** 2233–39.

16 Duck WM, Steward CD, Banerjee SN, McGowan JE Jr, Tenover FC. Optimization of computer software settings improves accuracy of pulsed-field gel electrophoresis macrorestriction fragment pattern analysis. *J Clin Microbiol* 2003; **41:** 3035–42.

17 Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Ann Intern Med* 1994; **121:** 200–06.

18 Cepeda JA, Whitehouse T, Cooper B, et al. Linezolid versus teicoplanin in the treatment of gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. *J Antimicrob Chemother* 2004; **53:** 345–55.

19 Fluit AC, Verhoef J, Schmitz FJ. Frequency of isolation and antimicrobial resistance of gram-negative and gram-positive bacteria from patients in intensive care units of 25 European university hospitals participating in the European arm of the SENTRY Antimicrobial Surveillance Program 1997–1998. *Eur J Clin Microbiol Infect Dis* 2001; **20:** 617–25.

20 Takeda S, Yasunaka K, Kono K, Arakawa K. Methicillin-resistant *Staphylococcus aureus* (MRSA) isolated at Fukuoka University Hospital and hospitals and clinics in the Fukuoka city area. *Int J Antimicrob Agents* 2000; **14:** 39–43.

21 Cook PP, Catrou PG, Christie JD, Young PD, Polk RE. Reduction in broad-spectrum antimicrobial use associated with no improvement in hospital antibiogram. *J Antimicrob Chemother* 2004; **53:** 853–59.

22 Marshall C, Wolfe R, Kossmann T, Wesselingh S, Harrington G, Spelman D. Risk factors for acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA) by trauma patients in the intensive care unit. *J Hosp Infect* 2004; **57:** 245–52.

23 Bronzwaer SL, Buchholz U, Kool JL, Monen J, Schrijnemakers P. EARSS activities and results: update. *Euro Surveill* 2001; **6:** 2–5.

24 Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost-benefit analysis in an intensive care unit. *JAMA* 1999; **282:** 1745–51.

25 de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003; **362:** 1011–16.

26 Theaker C, Ormond-Walshe S, Azadian B, Soni N. MRSA in the critically ill. *J Hosp Infect* 2001; **48:** 98–102.

27 Marshall C, Harrington G, Wolfe R, Fairley CK, Wesselingh S, Spelman D. Acquisition of methicillin-resistant *Staphylococcus aureus* in a large intensive care unit. *Infect Control Hosp Epidemiol* 2003; **24:** 322–26.

28 Lucet JC, Chevret S, Durand-Zaleski I, Chastang C, Regnier B. Prevalence and risk factors for carriage of methicillin-resistant *Staphylococcus aureus* at admission to the intensive care unit: results of a multicenter study. *Arch Intern Med* 2003; **163:** 181–88.

29 Warren DK, Nitin A, Hill C, Fraser VJ, Kollef MH. Occurrence of co-colonization or co-infection with vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* in a medical intensive care unit. *Infect Control Hosp Epidemiol* 2004; **25:** 99–104.

30 Korn GP, Martino MD, Mimica IM, Mimica LJ, Chiavone PA, Musolino LR. High frequency of colonization and absence of identifiable risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) in intensive care units in Brazil. *Braz J Infect Dis* 2001; **5:** 1–7.

31 Gastmeier P, Schwab F, Geffers C, Rilden H. To isolate or not to isolate? Analysis of data from the German Nosocomial Infection Surveillance System regarding the placement of patients with methicillin-resistant *Staphylococcus aureus* in private rooms in intensive care units. *Infect Control Hosp Epidemiol* 2004; **25:** 109–13.

32 Klein BS, Perloff WH, Maki DG. Reduction of nosocomial infection during pediatric intensive care by protective isolation. *N Engl J Med* 1989; **320:** 1714–21.

33 Waddell G. Moving the critically ill. *Nurs Times* 1975; **71:** 1937–39.

34 Kirkland KB, Weinstein JM. Adverse effects of contact isolation. *Lancet* 1999; **354:** 1177–78.

35 Evans HL, Shaffer MM, Hughes MG, et al. Contact isolation in surgical patients: a barrier to care? *Surgery* 2003; **134:** 180–88.

36 Stelfox HT, Bates DW, Redelmeier DA. Safety of patients isolated for infection control. *JAMA* 2003; **290:** 1899–905.

37 Thompson RL, Cabezudo I, Wenzel RP. Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982; **97:** 309–17.

38 Boyce JM, Landry M, Deetz TR, DuPont HL. Epidemiologic studies of an outbreak of nosocomial methicillin-resistant *Staphylococcus aureus* infections. *Infect Control* 1981; **2:** 110–16.

39 Esveld MI, de Boer AS, Notenboom AJ, van Pelt W, van Leeuwen WJ. [Secondary infection with methacillin-resistant *Staphylococcus aureus* in Dutch hospitals (July 1997–June 1996)]. *Ned Tijdschr Geneeskd* 1999; **143:** 205–08.

40 Jernigan JA, Titus MG, Groschel DH, Getchell-White S, Farr BM. Effectiveness of contact isolation during a hospital outbreak of methicillin-resistant *Staphylococcus aureus*. *Am J Epidemiol* 1996; **143:** 496–504.

41 Christensen A, Scheel O, Urwitz K, Bergh K. Outbreak of methicillin-resistant *Staphylococcus aureus* in a Norwegian hospital. *Scand J Infect Dis* 2001; **33:** 663–66.

42 Farrington M, Redpath C, Trundle C, Coomber S, Brown NM. Winning the battle but losing the war: methicillin-resistant *Staphylococcus aureus* (MRSA) infection at a teaching hospital. *QJM* 1998; **91:** 539–48.

43 Boyce JM, Pittet D. Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HIPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *Am J Infect Control* 2002; **30:** S1–46.

44 Gastmeier P, Sohr D, Geffers C, Nassauer A, Dettenkofer M, Ruden H. Occurrence of methicillin-resistant *Staphylococcus aureus* infections in German intensive care units. *Infection* 2002; **30:** 198–202.

45 Moreno R, Reis Miranda D. Nursing staff in intensive care in Europe: the mismatch between planning and practice. *Chest* 1998; **113:** 752–58.

46 Nijssen S, Bonten MJ, Franklin C, Verhoef J, Hoepelman AI, Weinstein RA. Relative risk of physicians and nurses to transmit pathogens in a medical intensive care unit. *Arch Intern Med* 2003; **163:** 2785–86.

47 Yap FH, Gomersall CD, Fung KS, et al. Increase in methicillin-resistant *Staphylococcus aureus* acquisition rate and change in pathogen pattern associated with an outbreak of severe acute respiratory syndrome. *Clin Infect Dis* 2004; **39:** 511–16.

48 Thompson BL, Dwyer DM, Ussery XT, Denman S, Vacek P, Schwartz B. Handwashing and glove use in a long-term-care facility. *Infect Control Hosp Epidemiol* 1997; **18:** 97–103.

49 Khatib M, Jamaleddine G, Abdallah A, Ibrahim Y. Hand washing and use of gloves while managing patients receiving mechanical ventilation in the ICU. *Chest* 1999; **116:** 172–75.