

## Has decolonization played a central role in the decline in UK methicillin-resistant *Staphylococcus aureus* transmission? A focus on evidence from intensive care

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The UK has seen a dramatic reduction in methicillin-resistant *Staphylococcus aureus* (MRSA) infection and transmission over the past few years in response to the mandatory MRSA bacteraemia surveillance scheme. Healthcare institutions have re-enforced basic infection control practice, such as universal hand hygiene, contact precautions and admission screening; however, the precipitous decline suggests other contributing factors. The intensive care unit (ICU), with its high endemic rates and complex patient population, is an important reservoir for seeding MRSA around the hospital and has understandably been at the forefront of MRSA control programmes. Recent studies from the UK and elsewhere have identified decolonization with agents such as chlorhexidine and mupirocin as having an important and perhaps underappreciated role in reducing ICU MRSA transmission, although evidence is incomplete and no prospective randomized studies have been performed. Chlorhexidine particularly is being recommended in the ICU for an increasing number of indications, including decolonization, universal patient bathing, oropharyngeal antiseptics in ventilated patients and vascular catheter insertion sites. Likewise, although there is little published evidence on decolonization efficacy or practice on UK general wards, it is now recommended for all MRSA-colonized patients and uptake is probably widespread. The recent observation that MRSA strains carrying the antiseptic resistance genes *qacA/B* can be clinically resistant to chlorhexidine raises a note of caution against its unfettered use. The dissemination of chlorhexidine-resistant MRSA would have implications for the decolonization of individual patients and for preventing transmission.

**Keywords:** chlorhexidine, infection control, mupirocin, MRSA

### Introduction

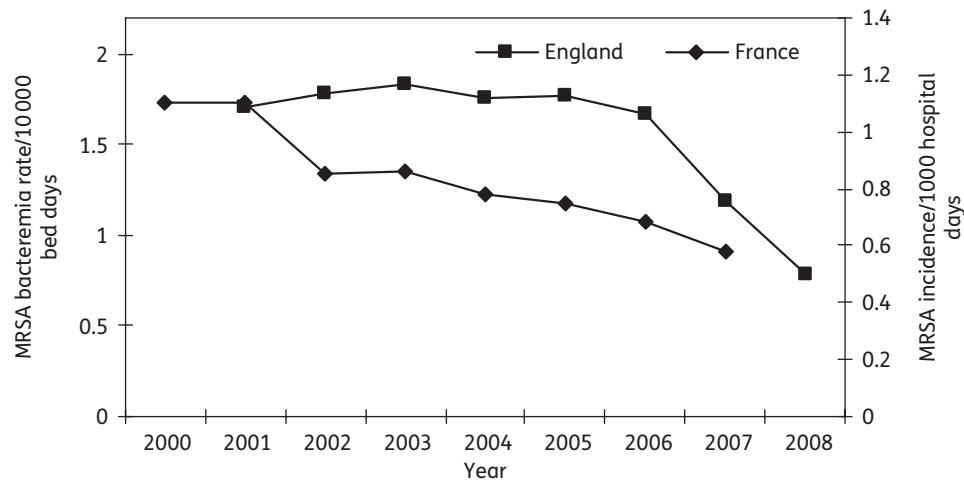
In April 2001, the UK Government introduced mandatory reporting of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia rates by all English NHS hospitals in the face of a national epidemic due to healthcare-associated MRSA sequence types (STs) 22 and 36, commonly referred to as EMRSA-15 and EMRSA-16, respectively. At that time, the UK had some of the highest rates of MRSA in Europe, with >40% methicillin resistance in *S. aureus* bacteraemia isolates.<sup>1</sup> In November 2004, the Health Secretary set what at first sight appeared to be an extremely ambitious task of halving the national MRSA bacteraemia rate by April 2008. This target was made a priority from central government through the Department of Health to Trust Boards, their infection prevention and control (IPC) teams, front-line clinicians and managers. Additional resource was made available to re-enforce IPC teams, and there was external inspection of Trusts deviating from the target trajectory. Observers remarked on a new performance management culture, of 'Board to Floor' accountability and a

dramatically increased profile of the IPC team as being key changes in many hospitals.

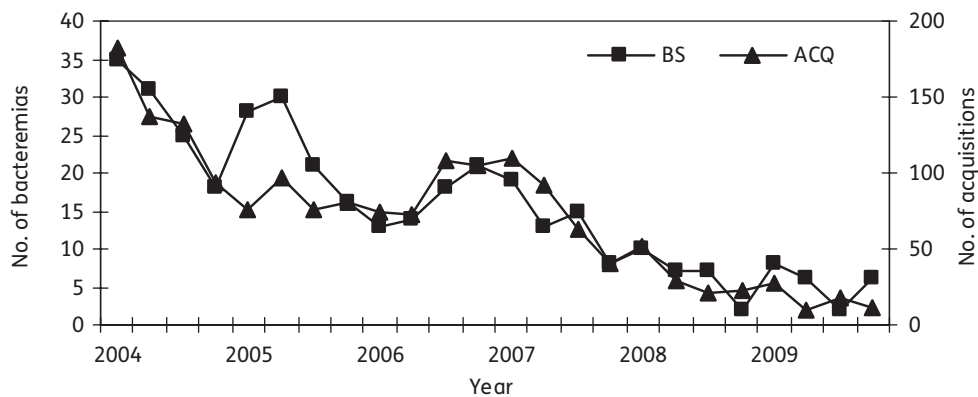
During the first 2 years there was minimal change in bacteraemia rates; however, from September 2006 onwards, rates declined dramatically to reach a reported 57% reduction by April–June 2008 (Figure 1).<sup>1</sup> Rates have continued to fall since, with perhaps a greater contribution due to a reduction in EMRSA-16.<sup>2</sup> It is important to understand how NHS hospitals achieved this goal. Success can have many parents, perhaps not inappropriately so in this case, but it is important to identify the key contributors so that we can most effectively plan to maintain these low rates.

### The intensive care unit (ICU) as a reservoir for MRSA transmission

The national decline in MRSA bacteraemias can be linked to a parallel reduction in MRSA transmission, as exemplified by data from one institution (Figure 2). This close association presumably reflects the fact that many of the basic IPC measures re-enforced



**Figure 1.** Comparison between the reduction in MRSA bacteraemia rates in English hospitals and MRSA incidence reported at 38 French hospitals. English data (financial year) expressed as MRSA bacteraemia rate/10000 hospital bed days in all English NHS hospitals extracted from [http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb\\_C/1233906819629](http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1233906819629) on 21 May 2010. French data (calendar year) expressed as MRSA incidence/1000 hospital days at 38 hospitals within the Assistance Publique-Hopitaux de Paris, extracted from reference 37.



**Figure 2.** Comparison between trend reductions in MRSA bacteraemias and MRSA acquisitions at a single UK hospital. Quarterly number of MRSA bacteraemias (BS) reported to the UK mandatory surveillance scheme, and quarterly MRSA acquisitions (ACQ) defined as first isolation of MRSA being >48 h after admission by the hospital surveillance team at Guy's and St Thomas' Hospitals.

as part of an MRSA campaign (such as hand hygiene, contact precautions and patient isolation) primarily target transmission.

Prior to the recent fall in UK MRSA rates, between 8% and 12% of patients were colonized or infected with MRSA on admission to UK ICUs and an equivalent proportion acquired MRSA while on the ICU.<sup>3-6</sup> Comparing published data from ICU and general ward studies conducted during an overlapping time period at the same UK hospital,<sup>7,8</sup> the prevalence of MRSA on admission to ICU is higher than on general wards (11.3% versus 6.7%, respectively;  $P < 0.0001$ ), as is the MRSA acquisition rate {11.7/1000 [95% confidence interval (CI): 10.5–13.0] versus 6.7/1000 (95% CI: 5.9–7.5) at-risk days, respectively;  $P < 0.0001$ }. Furthermore, MRSA-colonized ICU-discharged patients ( $n=651$ ) spend a median [interquartile range (IQR)] and mean  $\pm$  SD of 14 (2–36) and  $25 \pm 34$  days, respectively, on general wards after discharge, which is significantly longer than MRSA-colonized patients admitted to general wards without a prior ICU stay ( $n=629$ ) [7 (3–15) and

$11 \pm 15$  days, respectively;  $P < 0.0001$ ]. The ICU, in effect, acts as a reservoir for generating and then seeding the rest of the hospital with MRSA-colonized patients, making it logical to target control on the ICU as a first priority for any health-care institution aiming to reduce the burden of MRSA. Such an approach is supported by published evidence that an effective ICU control programme can lead to reduced MRSA acquisition across the rest of the hospital.<sup>9</sup> For these reasons, it is instructive to review recent evidence on preventing MRSA transmission in ICUs, particularly in the UK during this period of effective national control.

## Infection prevention and control strategies in the ICU

For many years, the main approach to MRSA control on the ICU has been the identification of colonized patients and

implementation of contact isolation precautions, on a background of re-enforcing universal hand hygiene practice.<sup>10,11</sup> It has been estimated that implementing contact isolation reduces the risk of MRSA transmission 16-fold.<sup>12</sup> It is unclear whether there is additional benefit in the ICU of moving colonized patients into isolation rooms or into a cohort with other colonized patients.<sup>4</sup> Some basic MRSA control programmes have been successful in single-room-only units, but such facilities are rarely available in the UK.<sup>13</sup>

The identification of colonized or infected patients through the culture of clinical samples misses >50% of the MRSA-colonized population that only have MRSA at carriage sites.<sup>14–16</sup> A number of ICU studies have reported reductions in MRSA transmission and infections after the introduction of active surveillance cultures (ASC) on admission to the ICU,<sup>8,13,17</sup> and this approach is endorsed by national guidelines.<sup>10,11</sup> In the UK, the Department of Health recommended ASC for all ICU admissions as part of the ‘Saving Lives’ initiative in 2007.<sup>18</sup> However, doubt remains about the cost-effectiveness of ASC in the ICU, as there have been reports of successful MRSA control without the use of ASC,<sup>19</sup> some groups have had disappointing results with ASC alone<sup>8,14,20,21</sup> and there are concerns about the evidence upon which the recommendations have been made.<sup>22,23</sup>

There are two main additional considerations pertaining to an ASC programme: which sites to screen; and the laboratory method used to detect MRSA. Both are based on the assumption that the sooner all MRSA-colonized patients can be identified, the sooner interventions can be implemented. Also, the assessment rests on the effectiveness and cost-effectiveness of incremental improvements. The dominant site of MRSA colonization is the anterior nares and probably all ASC programmes will recommend screening this site. Debate rests on which additional sites to swab, such as throat, axilla, groin/perineum or rectum.<sup>24–28</sup> A number of these studies have shown that the throat and rectum are important additional hidden colonization sites, and, indeed, one study has shown that together they contribute significantly to increasing the sensitivity of an ICU screening protocol.<sup>27</sup>

Traditional laboratory agar-based culture systems have taken between 3 and 4 days to identify *S. aureus* and perform susceptibility testing to detect methicillin resistance. Given that the median (IQR) length of stay for patients admitted to 180 UK NHS adult ICUs in the 2008–09 financial year was only 2.1 (1.0–5.2) days,<sup>29</sup> only a minority of MRSA-colonized patient days would be managed under contact isolation if patient identification was based on traditional culture alone. Turnaround time can be reduced using either specialized chromogenic agar, which generally gives a negative result within 24 h and a confirmed positive within 48 h,<sup>30</sup> or rapid PCR-based tests that take only a few laboratory hours to perform, but when transport and result reporting are included this extends to ~20 h.<sup>7,20</sup> The benefit of PCR-based testing compared with either chromogenic agar or conventional culture has not been clearly defined either on general wards<sup>7,31</sup> or in the ICU environment in the UK health-care setting.<sup>32,33</sup> One UK study that observed a benefit after the introduction of PCR-based testing on the ICU did not exclude the possibility of a trend reduction prior to the use of PCR.<sup>33</sup> The drawback of a 20 h turnaround time for laboratory-performed MRSA PCR assays could be overcome with a point-of-care assay, and it will be interesting to assess whether such a test has greater impact on reducing MRSA transmission.

## Strategies involving the use of antiseptics and antimicrobials to prevent MRSA transmission

A further distinct strategy for preventing MRSA transmission is the use of antiseptics or antimicrobials as surface decolonization agents, to reduce the bacterial load available for transmission. It has the additional potential benefits of reducing endogenous infection in colonized patients,<sup>34</sup> and transmission and infection due to other antibiotic-resistant bacteria, such as vancomycin-resistant enterococci.<sup>35</sup> It is distinct from the target of eradication, which is probably not realistically achievable in ICU patients that have multiple skin breaches and multisite colonization, and which has been the subject of a recent systematic review.<sup>36</sup> Decolonization is contentious, because of concerns about developing resistance, cost-effectiveness and that its use might lead to complacency with other basic IPC measures. Detractors can point to successful IPC strategies that have not included the use of antiseptics and antimicrobials.<sup>9,22,37</sup>

The two most commonly used decolonization agents are mupirocin for nasal carriage<sup>38</sup> and chlorhexidine for skin carriage, the latter applied either as a daily bath after dilution in water,<sup>3,34</sup> where there is potential for variability in the applied concentration, or as disposable cloths saturated in 2% chlorhexidine.<sup>35</sup> Triclosan, octenidine dihydrochloride or tea tree oil are alternatives to chlorhexidine.<sup>3,8,9,39–41</sup> Some groups have advocated the use of vancomycin as a decolonization agent in the ICU to clear ‘hidden MRSA’ in the throat and gastrointestinal tract, applied as a paste or enterally, respectively.<sup>42,43</sup>

Many studies have reported successful control of endemic and epidemic MRSA in an ICU setting with the use of decolonization agents, usually as part of a raft of interventions;<sup>8,44–50</sup> although, one study observed no effect.<sup>51</sup> There is huge variability in application protocols and simultaneous use or introduction of other IPC measures. Studies where the timing of introducing antiseptics for decolonization can be associated with reported changes in MRSA transmission are presented in Table 1. Some have restricted the use of decolonization agents to patients identified as MRSA carriers through ASC,<sup>44,46,49</sup> whereas others have applied chlorhexidine skin cleansing to all patients.<sup>8,34,50</sup> In the latter case, there might be an added effect of ‘colonization resistance’ due to residual antiseptic on the skin of non-colonized patients. None of the studies has used cluster randomization, although some have been conducted in multiple ICUs concurrently.<sup>34</sup> These studies analysed rates of acquisition or infection before and after interventions, using in some cases quasi-experimental Poisson regression analysis of interrupted time series data to assess trend and step changes. Overall, the absence of randomized studies in part prevents international guidelines from making a clear recommendation on decolonization<sup>10,52</sup> and, indeed, one systematic review recommends against decolonization.<sup>53</sup> Nonetheless, the use of antiseptic washing with chlorhexidine is undoubtedly widespread in Europe, with two-thirds of 526 ICUs across 10 European countries reporting its use even in 2004, prior to the publication of many of these articles.<sup>54</sup>

Four studies have reported on successful MRSA control in UK ICUs and in each case a decolonization strategy was included as part of a package of interventions.<sup>8,33,45,50</sup> In one study, there was an immediate 70% reduction in the transmission of

**Table 1.** Overview of studies reporting on use of antiseptics as part of decolonization protocols to control MRSA transmission and infection on intensive care units

Reference	Setting	Population	Measures pre-intervention	Intervention	Outcomes
46	13 bed general ICU	2200 adm., 16.5% MRSA carriers	not stated	ASC (nose); CHX bathing and nasal mupirocin for colonized patients	trend reduction in MRSA infection (year 1 versus year 5: 8.2% versus 2.8%; $P=0.001$ )
44	10 bed general ICU	667 adm. before, 1995 adm. after	no specific interventions	ASC (nose); contact precautions, CHX bathing and nasal mupirocin for colonized patients	MRSA infection rate (before versus after: 3.5 versus 1.7/1000 patient days; $P=0.0023$ )
49	16 bed coronary medical ICU	845 adm. before, 736 adm. after	ASC (nose)	CHX bathing and nasal mupirocin for colonized patients	MRSA incidence density (before versus after: 8.5 versus 4.1/1000 patient days; $P=0.048$ )
51	8 bed medical and 14 bed surgical ICU	653 adm. with length of stay >24 h	not stated	ASC <sup>a</sup> (nose); contact isolation and topical betaine polyhexamide for colonized patients <sup>b</sup>	MRSA infection incidence rate (before versus after: in surgical ICU, 3.8 versus 3.0/1000 patient days; $P=0.057$ ; in medical ICU, 1.4 versus 1.7/ 1000 patient days)
8	30 bed general ICU	2480 adm. before, 2090 adm. after	ASC (nose, axilla, groin), contact precautions, isolation or cohorting	CHX bathing <sup>c</sup> plus CHX applied to nose, tracheostomy and skin creases for all patients	incident rate ratio (95% CI) for CHX-susceptible strains before versus after: 0.3 (0.19–0.47)
50	16 bed general ICU	1232 adm. before, 1421 adm. after	contact precautions for clinically identified cases	ASC (nose, throat, axilla, groin); CHX bathing and nasal anti-MRSA preparations for all patients	MRSA cases (before versus after: 16% versus 6%) time series analysis showed immediate effect— reduction of 11.38% (95% CI: 19.2%–3.54%; $P<0.001$ )
34	2 medical, 2 surgical and 2 mixed ICUs from 4 centres	2670 adm. before, 2650 adm. after	ASC (nose)	CHX bathing for all patients	MRSA acquisitions (before versus after: 5.04 versus 3.44/1000 patient days; $P=0.046$ )

Adm., admissions; ASC, active surveillance testing; CHX, chlorhexidine.

<sup>a</sup>Detected by PCR.

<sup>b</sup>Topical treatment for all patients implemented midway through study.

<sup>c</sup>Non-MRSA colonized patients received triclosan to skin instead of CHX.

susceptible MRSA strains with the introduction of a universal chlorhexidine-based antiseptic protocol, after ASC and an educational campaign had failed to reduce rates.<sup>8</sup> The Department of Health's high-impact interventions MRSA screening best practice guideline endorsed full MRSA decolonization of all ICU patients in 2007.<sup>18</sup>

Few studies have reported on the efficacy or practice of decolonization to prevent MRSA transmission on general wards in the UK. In two studies, decolonization was linked with an enhanced screening programme and reduced transmission was observed.<sup>31,55</sup> The high-impact interventions guideline also recommends decolonization for all hospital patients.<sup>18</sup> The uptake of decolonization guidelines on UK ICUs and general wards is probably high, given the intense scrutiny of IPC practice, but it would require a national audit to confirm this.

The likely efficacy of decolonization in a high-endemic setting gains some support from the experience in the Netherlands and Scandinavian countries that have low rates of healthcare-associated MRSA (<2%). A national MRSA 'search and destroy' policy was introduced in the Netherlands in 1988, involving pre-emptive isolation and screening of high-risk groups, active outbreak management, and elimination of carriage in both patients and healthcare workers. Decolonization is considered an important part of this strategy,<sup>56-58</sup> but, again, the introduction of this policy without any randomized study evidence leaves doubt as to the relative importance of each intervention. Of note, when an institution-wide MRSA surveillance programme that included recommending decolonization for carriers was introduced into three US hospitals, there was a 70% reduction in hospital-wide MRSA infections within 2 years.<sup>43</sup>

## Potential for emergence of chlorhexidine resistance

Chlorhexidine is a safe and effective antiseptic that has been in use for >50 years.<sup>59</sup> Recently, there has been a notable rise in the proposed uses for chlorhexidine in ICUs. In addition to its role in MRSA decolonization discussed above, it is being used for skin antisepsis prior to blood culture collection and the insertion of vascular catheters;<sup>60</sup> applied to the catheter exit site in the form of impregnated sponges;<sup>61</sup> impregnated into vascular catheters to prevent bloodstream infections;<sup>62</sup> and for oropharyngeal antisepsis to prevent ventilator-associated pneumonias.<sup>63</sup> Much of this broader use has been predicated on the notion that resistance is either restricted to certain non-fermenting Gram-negative bacteria or where potentially transferable resistance mechanisms are identified, they are not clinically significant.<sup>64</sup> This increased use of chlorhexidine in ICUs does, however, raise concerns about selecting for resistance. In one UK ICU study, it was observed that a chlorhexidine-based antiseptic protocol failed to prevent the transmission of an MRSA strain (ST239-TW) carrying *qacA/B* genes.<sup>8</sup> ST239-TW body site colonization was also not reduced in contrast to a reduction seen for ST22 and ST36 strains. The *qacA/B* genes encode multicomponent efflux pumps conferring resistance to a variety of antiseptics, including quaternary ammonium compounds and biguanides such as chlorhexidine.<sup>65</sup> The activity of these pumps leads to only a modest increase in the MBC *in vitro*, which was hitherto not thought to reflect clinical resistance. The *qacA/B* genes are found in ~5%–10% of UK MRSA

strains,<sup>64,66</sup> but in 60% of European strains<sup>67</sup> and up to 80% of strains in some other countries,<sup>68,69</sup> implying that the potential exists for selection with intensive chlorhexidine use.

## Summary

It is important to identify the interventions associated with the dramatic reduction in MRSA transmission in the UK over the past 5 years. Hand hygiene, contact precautions and ASC have surely played an important role; however, it is of note that a French study reporting on the effect of implementing such measures in 38 hospitals indicated that this leads to only a gradual reduction in MRSA burden over many years (Figure 1).<sup>37</sup> UK rates fell by >50% over 2 years. This might reflect a truly heroic national effort implementing basic infection control measures, but perhaps a more likely explanation is the contribution of other intervention(s). Available evidence on the efficacy of decolonization, predominantly from ICU studies, combined with the introduction of national guidelines endorsing its implementation as part of a new performance management culture in the NHS, supports the proposal that the widespread uptake of decolonization has made the key additional contribution.

Of concern for the future would be the emergence of resistance to decolonization agents. Mupirocin resistance is well known,<sup>38</sup> but chlorhexidine resistance in MRSA is an emerging threat and of additional concern. If *qacA/B*-positive MRSA strains are clinically resistant to chlorhexidine and selected for in response to its use in MRSA control programmes, this would have important implications for the many uses of chlorhexidine in preventing MRSA transmission and infection. It highlights the importance of maintaining careful surveillance during practice changes and, ideally, the need to ensure that new IPC interventions are supported by evidence from well-conducted prospective studies. Only with such measures will we be able to learn from our successes and plan confidently for the future.

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