Recent initiatives to reduce the spread of meticillin-resistant *Staphylococcus aureus*

Recent initiatives have achieved marked reductions in meticillin-resistant* Staphylococcus aureus *bacteraemias. However, the relative effectiveness of prevention interventions is unclear. Initiatives to control meticillin-resistant* Staphylococcus aureus *have tended to ignore the benefits of altering antimicrobial prescribing.

There is a notably wide variation in the frequency of infection caused by meticillin-resistant *Staphylococcus aureus* (MRSA) between developed countries. For example, in Europe in 2004, the prevalence of MRSA (i.e. the proportion of invasive *S. aureus* infections that are caused by MRSA as opposed to meticillin-susceptible strains) varied from 0–70%, and the incidence of MRSA bloodstream infections ranged from 0.12 (per 100 000 patient days) in Norway to 19.29 in Malta; the incidence rate in the UK was 9.56 per 100 000 patient days (European Antimicrobial Resistance Surveillance System, 2005). Such differences in infection rates are likely to reflect the many differences in practice that exist between health systems, including health-care facility design, rigour of infection control approach, qualitative and quantitative antibiotic prescribing, and overall resourcing of health care and indeed infection intervention measures.

Mandatory reporting of MRSA bacteraemias (bloodstream infections), which represent the severe end of the spectrum of infections caused by MRSA, was introduced in England in 2001. MRSA bacteraemias are simple to detect and measure consistently, and cause significant morbidity and mortality, thus are a useful infection surveillance target. However, bloodstream infections represent the tip of the MRSA iceberg. MRSA is also a common pathogen in infections of skin, including surgical wounds and intravascular catheters, soft tissue, bone and joints, and an occasional cause of urinary tract infections and pneumonia that is associated with poor outcome.

For infections where MRSA is isolated from non-sterile sites, distinguishing between infection and colonization is particularly problematic. In 2005, the Department of Health in England set a target for a national 50% reduction in the number of cases of bacteraemia over a 3-year period (actually this meant a 60% for the majority of hospitals), although there was neither a rationale for such a level of reduction nor evidence that it was achievable in the designated time frame. Initial progress towards meeting this target was modest, but subsequent progress was impressive. For example, there was a 30% decrease in the number of reported MRSA bacteraemias in the financial year 2007–8 compared to financial year 2006–7 (the infection rate decreased from 1.67 to 1.19 cases per 10 000 bed days). In the latest reported figures (April–September 2008) the number and rate of MRSA bacteraemias fell to 1562 and 0.84 cases per 10 000 bed days, respectively; in the same period in 2005 the corresponding figures were 3570 and 1.78. Thus, there have been decreases of 56% and 53% in the number of cases and the rate of MRSA bacteraemias, respectively (Health Protection Agency, 2009).

How has this been achieved?

The key unanswered question is how has this reduction in infection rates been achieved? Frustratingly, it remains uncertain what the key changes in practice were that led to the reduction in MRSA bacteraemias. Unfortunately, information on the timing of specific interventions was not collected. In reality, successful infection prevention and control strategies are invariably multi-factorial.

A key likely factor in UK MRSA reduction has been the concerted approach across the country so that patient transfers between hospitals are less likely to lead to new clusters. The concept of bundled interventions (e.g. high impact interventions) is founded on the premise that implementation of one or a few components of the bundle is unlikely to yield much reduction in infection incidence. Maximal infection risk reduction requires that all, or almost all, components are implemented. Many interventions were launched, promoted, and indeed exhorted. Some (abandoning white coats, bare below the elbows, and deep cleaning programmes) had little evidence to sustain an effectiveness argument, but fast became high-profile public, political and clinical issues.

However, when seen in the context of providing safe environments and patient pathways it is unreasonable to argue that these do not have potential merit, and importantly carry few, if any, genuine risks. The most logical major contributors to the falling MRSA bacteraemia rates are improvements in compliance with hand hygiene, alongside optimized management of intravenous access devices.

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Screening

Most recently, the Department of Health (2008) in England has mandated that MRSA screening is implemented, initially for all elective patients (from April 2009), and as soon as practicable thereafter (but by November 2010) for all acute admissions, in whom the risk of MRSA bacteraemia is actually greater. Ironically, this controversial mandate for universal screening comes after the major reductions in MRSA bacteraemia have been achieved. Robust evidence to support the cost effectiveness of universal MRSA screening followed by decolonization (e.g. with topical chlorhexidine and mupirocin) is lacking, which is important given the sheer organizational implications of implementing and sustaining such a programme.

Notably, as infection rates fall, cost-effectiveness issues will likely become more prominent (as there are fewer opportunities to reduce infection risk by screening). The delays inherent in culture-based approaches to MRSA screening can now be overcome by rapid detection methods, but these are considerably more expensive. Preadmission screening is an alternative approach but is only applicable to elective, primarily surgical, patients. Unfortunately, the risk of MRSA carriage is often greatest in acute admissions because of the higher prevalence of comorbidities.

Controlled data on MRSA screening from the UK and Switzerland have not demonstrated a benefit of universal or rapid screening (Harbarth et al, 2008; Jeyaratnam et al, 2008), thus emphasizing the need for robust cost-effectiveness analyses (Wilcox, 2008). Despite their impressive design and execution, these studies had some weaknesses, such as prospective isolation of new admissions, thus limiting the potential benefit of rapid screening (Jeyaratnam et al, 2008), and poor compliance with decolonization therapy (Harbarth et al, 2008).

Prescribing

With the possible exception of restricted prescribing to reduce the risk of *Clostridium difficile* infection, conventional infection control measures to reduce the prevalence of health-care-associated pathogens have generally not included altering antimicrobial prescribing. This omission has been referred to as the 'missing care bundle' (Cooke and Holmes, 2007), in recognition of the vogue for the implementation of health-care bundles, i.e. key elements that when grouped together improve the delivery of clinical care, in this case the reduction of health-care-associated infection risk. Broadly, such an approach can be divided into antibiotic prescribing measures that aim to reduce the selective pressure for MRSA and those directed at optimization of treatment.

Prescribing of fluoroquinolones and third-generation cephalosporins in particular provides a selection pressure for MRSA; thus, as these antibiotics are used more frequently, so the prevalence of MRSA in hospitalized patients increases (Wilcox, 2005; Tacconelli et al, 2008). This occurs primarily because of the lack of activity of these antibiotics against MRSA, coupled with their broad-spectrum activity against commensal bacterial flora, resulting in a clear field for MRSA that is already present, or soon acquired, to proliferate.

There are numerous retrospective, observational and modelling studies that describe the association between MRSA and prior exposure to fluoroquinolones and cephalosporins, but controlled intervention studies to determine effects of altering antimicrobial prescribing on the prevalence of MRSA are lacking. A French study found that the rate of MRSA isolation in one hospital decreased significantly, in comparison with three control hospitals, when fluoroquinolone use was restricted for 1 year (32.3% *vs* 36.8% of *S. aureus* isolates were MRSA; odds ratio 0.82; 95% confidence interval 0.69–0.99; P=0.036) (Charbonneau et al, 2006). A study in Switzerland described a temporal correlation between MRSA incidence and the consumption of several classes of antibiotics, and at the same time demonstrated the effectiveness of a hand hygiene promotion campaign (Vernaz et al, 2008). A mathematical model was developed to map the effect of alcohol hand rub and antibiotic use on preventing and promoting, respectively, MRSA incidence. This explained 57% of the variance in rates.

Treatment of MRSA infection has conventionally centred on the use of a limited number of intravenous antibiotics, typically vancomycin or teicoplanin. In recent years, a number of new antibiotics that are effective at treating MRSA infection have become available (e.g. daptomycin, linezolid and tigecycline). Most of these also have to be administered intravenously, but linezolid can also be given orally (because it has 100% oral bioavailability) without compromising the levels of antibiotic that are achieved in tissues. However, there have been concerns over the toxicity associated with longer term use (e.g. thrombocytopenia), and administration is usually limited to 28 days. Older orally available antibiotics such as tetracylines, rifampicin and fusidic acid have variable activity against MRSA, but these may also be used to treat less severe MRSA infections (Gemmell et al, 2006).

The reliance on intravenous antibiotics for the treatment of MRSA infection has invariably meant that patients receive their therapy predominantly as inpatients. It is clear, however, that a significant proportion of hospitalized patients with MRSA infection can be treated outside hospital with oral antibiotics or, alternatively, dedicated (outpatient antimicrobial therapy) services can be used to provide intravenous antibiotics at home, although their provision is very variable between hospitals. Providing the patient with MRSA infection is stable, it is possible and indeed may be preferable to treat or continue treatment at home. Studies in the UK and USA reported that approxi-

mately 30% of patients with MRSA infection could potentially be switched from intravenous to oral antibiotic treatment and discharged from hospital (Parodi et al, 2003; Desai et al, 2006).

There may also be advantages intrinsic to switching from intravenous to oral therapy, for example to reduce the risk of bacteraemia secondary to intravascular catheter infection. People with MRSA infection are not a danger to healthy people and indeed MRSA infection is not a reason to stop admission to a residential or nursing home. Treating MRSA infection outside hospital may be preferred by patients and, not surprisingly, has also been shown to be cost-effective for the hospital. Furthermore, treating patients with MRSA outside of the hospital removes the risk of spread of that strain to other inpatients. Many NHS hospitals have only a small proportion of beds in single rooms (typically about one in every five beds), thus compromising the ideal of being able to nurse all patients who have a potential health-care-associated infection, such as MRSA, in isolation. A study found that the likelihood of not being able to isolate a patient, even when it was believed to be necessary by the infection control team, varied between 0% and 57% in different clinical specialities (Wigglesworth and Wilcox, 2006). For all these reasons, the former 'inevitability' of treating MRSA infection as an inpatient with intravenous antibiotics should be reviewed on a case-by-case basis.

Conclusions

Recent initiatives to reduce MRSA infection in England have had significant success. We should not be complacent, however. Reducing cross-infection in hospitals involves many potential interventions, and repeated reviews of these options, including the evidence for their effectiveness, should be undertaken to ensure that no stones are left unturned. **BJHM**

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Charbonneau P, Parienti JJ, Thibon P et al (2006) Fluoroquinolone use and methicillin-resistant *Staphylococcus aureus* isolation rates in hospitalized patients: a quasi experimental study. *Clin Infect Dis* **42:** 778–84

Cooke FJ, Holmes AH (2007) The missing care bundle: antibiotic prescribing in hospitals. *Int J Antimicrob Agents* **30:** 25–9

Department of Health (2008) Code of practice for the prevention and control of healthcare associated infections. Department of Health, London (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4139336 accessed 16 April 2009)

Desai M, Franklin BD, Holmes AH, Trust S, Richards M, Jacklin A, Bamford KB (2006) A new approach to treatment of resistant Gram positive infections: potential impact of targeted IV to oral switch on length of stay. *BMC Infect Dis* **6:** 94

European Antimicrobial Resistance Surveillance System (2005) *EARSS Annual Report 2004.* EARSS, Bilthoven, The Netherlands (www.rivm.nl/earss/Images/EARSS%20annual%20report%202004%20webversie_tcm61-25345.pdf accessed 20 February 2009)

Gemmell CG, Edwards DI, Fraise AP et al (2006) Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK. *J Antimicrob Chemother* **57:** 589–608

Harbarth S, Fankhauser C, Schrenzel J et al (2008) Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* **299:** 1149–57

Health Protection Agency (2009) *Quarterly results from the mandatory surveillance of MRSA bacteraemia, 2008.* Health Protection Agency, London (www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1229502459877 accessed 20 February 2009)

Jeyaratnam D, Whitty CJ, Phillips K, Liu D, Orezzi C, Ajoku U, French GL (2008) Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* **336:** 927–30

Parodi S, Rhew DC, Goetz MB (2003) Early switch and early discharge opportunities in intravenous vancomycin treatment of suspected methicillin-resistant staphylococcal species infections. *J Manag Care Pharm* **9:** 317–26

Tacconelli E, De Angelis G, Cataldo MA, Pozzi E, Cauda R (2008) Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* isolation? A systematic review and meta-analysis. *J Antimicrob Chemother* **61:** 26–38

Vernaz N, Sax H, Pittet D, Bonnabry P, Schrenzel J, Harbarth S (2008) Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA and *Clostridium difficile*. *J Antimicrob Chemother* **62:** 601–7

Wigglesworth N, Wilcox MH (2006) Prospective evaluation of hospital isolation room capacity. *J Hosp Infect* **63:** 156–61

Wilcox MH (2005) Antibiotic prescribing as a risk factor for MRSA. *Hosp Med* **66:** 180–4

Wilcox MH (2008) Screening for MRSA. *BMJ* **336**: 899–900

KEY POINTS

- Recent initiatives in England have achieved marked reductions in meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemias.
- There is controversy regarding the relative effectiveness of MRSA prevention interventions.
- These controversies include the value (cost-effectiveness) of conventional and rapid screening for MRSA.
- Initiatives to control MRSA have tended to ignore the benefits of altering antimicrobial prescribing, including to reduce MRSA selection pressure.
- Treatment options are available that decrease dependence on hospital management of MRSA infection, potentially freeing up resources.