Epidemiology and Economic Impact of Meticillin-Resistant *Staphylococcus aureus*

Review and Analysis of the Literature

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Abstract

In the past 2 decades, meticillin-resistant *Staphylococcus aureus* (MRSA) has become an increasingly prevalent problem in healthcare, both in acute care institutions and in the community. MRSA is associated with worse outcomes and higher costs for care than meticillin sensitive *S. aureus* (MSSA). MRSA is a particular problem in several conditions, including hospital-acquired pneumonia (including ventilator-associated pneumonia), skin and soft tissue infections, and diabetic foot infections. Hospitalisation costs associated with MRSA infection are substantially greater than those associated with MSSA infection, and MRSA has wider economic effects that involve indirect costs to the patient and to society. In

several countries, infection control programmes have shown potential economic benefits, as savings accruing from strict and effective control have been shown to outweigh the cost of policy implementation.

Standard therapy is based on glycopeptide treatment, usually with vancomycin, although resistance to this agent has emerged. Alternative available treatments for MRSA include teicoplanin, tigecycline, daptomycin, quinupristin-dalfopristin and the oxazolidinone, linezolid, which has a higher acquisition cost than vancomycin but is available as intravenous and oral formulations. Despite some limitations of analyses to date, linezolid has been shown to be cost effective in the treatment of MRSA and appears to be related, in part, to the drug's potential for facilitating earlier discharge from hospital. Current opinion favours rational prescribing to maximise therapeutic benefit and minimise the risk of further antibacterial resistance.

Gram-positive pathogens, including *Staphylococcus aureus*, are the leading cause of healthcare-associated infections. The increasing prevalence of methicillin-resistant *S. aureus* (MRSA) remains particularly concerning. This pathogen continues to spread across multiple disease states such as pneumonia, bacteraemia and skin and skin structure infections, including surgical site infections (SSIs).^[1] Additionally, MRSA-related infections cause substantial morbidity and mortality.^[1-3] Indeed, MRSA is now the predominant form of *S. aureus* in US hospitals.^[1]

Patients infected with MRSA face worse clinical outcomes than those with methicillin-sensitive *S. aureus* (MSSA) infections.^[4-6] Moreover, multiple reports document that MRSA is associated with increased costs.^[7-9] For example, in primary nosocomial bloodstream infections, MRSA results in an approximate 3-fold increase in direct healthcare costs relative to MSSA.^[7] Furthermore, the mean incremental direct cost of MRSA infection in a case control study in a French ICU with a 4% prevalence of MRSA carriage was \$US9275 (year 1997 values).^[10] On a national as opposed to patient level, one study in Canada^[8] showed that the costs associated with the management of hospitalised patients with MRSA approached \$Can42–59 million annually.

In addition to the burden on healthcare providers, MRSA infections can have wider economic effects that involve indirect costs to the patient and to

society. These include effects on work productivity, household income and costs for social services.^[11]

In short, it is clear that MRSA presents a formidable challenge. As such, MRSA must remain a major source of concern for both clinicians and patients. Since MRSA imposes a significant financial burden on healthcare systems, any effort to improve MRSA-related outcomes must also consider the cost effectiveness of the various options available for prevention and treatment.

1. Epidemiology

S. aureus is a human commensal, and nearly 50% of the population are asymptomatic carriers. A secondary analysis of data from the National Health and Nutrition Examination Survey showed that the prevalence of *S. aureus* and MRSA colonisation in the US population was 31.6% and 0.84%, respectively.^[12] However, these findings are limited, as the analysis is derived from 2001/2 data.^[12] Carriers of *S. aureus*, particularly those with MRSA, have an increased risk of developing infection, but most remain asymptomatic and act as a reservoir for transmission of the organism.^[13] *S. aureus* predominantly colonises the anterior nares, with certain subgroups of patients (including intravenous drug users, patients with HIV infection or insulin-dependent diabetes mellitus and those requiring dialysis) more frequently affected.^[14]

1.1 Healthcare-Associated
(Hospital-Acquired) Meticillin-Resistant
Staphylococcus aureus (MRSA)

Until recently, MRSA was primarily associated with hospitals and long-term care facilities (healthcare-associated MRSA; HA-MRSA). Risk factors for HA-MRSA are listed in table I and generally reflect exposure to healthcare, severity of illness and prior treatment with antimicrobials. Within hospitals, ICUs generally have the highest prevalence of HA-MRSA. Figures from the National Nosocomial Infections Surveillance (NNIS) System, a national database of acute care information from US hospitals, revealed that 59.5% of all *S. aureus* isolated in ICUs during 2003 were MRSA.^[1,15] This represents an increase of 11% compared with figures from 1998–2002^[15] and confirms that MRSA is endemic in all types of ICUs (medical, surgical, mixed). Separate data from the Centers for Disease Control and Prevention Coordinating Center for Infectious Diseases attest to the increasing emergence of MRSA as the dominant form of *S. aureus* in the ICU, with the most recent data indicating that approximately 65% of *S. aureus* isolated in ICUs in the US are now MRSA.^[16]

Despite the recent focus on MRSA, these epidemiologic patterns do not represent a new phenomenon. The prevalence of HA-MRSA has been increasing for the last 2 decades.^[18] Hospital data

summarised throughout the year 1999 showed that the frequency of MRSA rose from <5% of all *S. aureus* from 1976 to 1980, to 20% from 1986 to 1990, and to 28% from 1991 to 1995; by 1996–9, the prevalence had reached 40%.^[18] As HA-MRSA has become endemic in the ICU, it now represents a leading cause of healthcare-associated infections such as pneumonia, bacteraemia and SSIs.^[1,3] Although the specific prevalence of MRSA varies between geographic regions and institutions,^[1,18] nearly all ICUs in the US face issues with MRSA. Outside the US, the pattern is more variable. An analysis of 4065 isolates from 21 hospitals worldwide demonstrated that meticillin resistance was present at low levels (<1%) in hospitals in Northern Europe, whereas prevalence ranged from 6% to 22% in central European countries, New Zealand, Australia and parts of the US, and were highest in Southern Europe (28–63%).^[19]

1.2 Impact of Resistance on Mortality

Mortality is an outcome that appears straightforward, but can be measured in different ways, e.g. as deaths that occur during hospitalisation that are attributable to infection, or as all-cause mortality up to a predefined time after hospital discharge. The differences in these two measures of mortality can impact conclusions drawn from clinical and economic studies and need to be borne in mind.

Data appear to suggest that MRSA infection is associated with higher rates of crude mortality than MSSA infection.^[2,9,20] Several different types of analyses have confirmed this relationship. In a meta-analysis of studies exploring outcomes in bacteraemia, Cosgrove et al.^[2] identified 31 cohorts of patients (total of 3963 individuals) with MSSA or MRSA bacteraemia. Although there was heterogeneity among the studies, pooling the results with a random effects model demonstrated that MRSA bacteraemia nearly doubled the risk for death (odds ratio [OR] 1.93; 95% CI 1.54, 2.42; *p* < 0.001). Limitations to the analysis include that the authors were unable to obtain detailed information about the source of the bacteraemia and the adequacy of antimicrobial therapy. Consequently, they were unable

Table I. Risk factors for healthcare-associated meticillin-resistant *Staphylococcus aureus* (MRSA) (adapted from Tacconelli and Venkataraman,^[17] with permission from Oxford University Press)

Male gender
Non-ambulatory status
Hospitalisation in the previous 6 months
Diabetes mellitus
Chronic haemodialysis
Neoplasm
Intravenous drug use
Presence of a central venous catheter
Skin ulcers at hospital admission
Cellulitis at hospital admission
Previous antibacterial therapy
Previous MRSA infection or colonisation
Previous ICU admission

to fully assess whether these factors were potential confounders in the true relationship between meticillin resistance and mortality. Also, not all of the studies reviewed in the meta-analysis corrected for differences in severity of illness. However, limiting their analysis to reports that did adjust for this important covariate did not alter their conclusions. Furthermore, data from 479 surgical patients in North Carolina confirmed these observations with respect to SSIs.^[9,20] Engemann et al.^[20] showed that SSIs due to MRSA led to greater 90-day mortality (adjusted OR 3.4; 95% CI 1.5, 7.2).

In a review of a large administrative database, rather than an assessment of patient-level data from a single institution, Rubin et al.^[9] noted that, among 1 351 362 non-obstetrical hospital discharges in New York City in 1995, 1% were infected with *S. aureus*. Death rates for patients with MRSA and MSSA were 21% and 8%, respectively.

1.3 Emerging Issues with Community-Acquired MRSA

Although MRSA has been considered as primarily a healthcare-associated pathogen, this organism is now emerging as an important cause of infection in the community.^[1,18,21,22] Community-acquired MRSA (CA-MRSA) is distinct from traditional nosocomially spread MRSA.^[1,18,21-23] Epidemiologically, data from a prospective cohort study of 1100 patients with MRSA infections suggested that the prevalence of CA-MRSA was approximately 12% in people presenting to EDs. CA-MRSA is also unique in that it has differing *in vitro* sensitivities to antimicrobials and possesses unique virulence factors. Given differences in the types of patients infected with CA-MRSA, it appears that this new strain did not originate in the hospital. Sentinel surveillance of 12 hospitals in Minnesota showed 1647 cases of CA-MRSA during 2001/2, which represented between 8% and 20% of all isolates.^[23] Moreover, the prevalence of CA-MRSA is increasing. For example, a survey at San Francisco General Hospital and its associated clinics revealed that the prevalence of CA-MRSA grew from 7% to 29% between 1993 and 1999.^[21]

CA-MRSA differs from HA-MRSA in several important ways. Specifically, there is a tendency for this pathogen to affect younger people, those in lower socioeconomic status groups and cohorts of people living in close proximity (e.g. prison inmates or military personnel).^[1,24] Furthermore, CA-MRSA is frequently associated with skin and soft tissue infections (SSTIs). Of 1100 MRSA infections in one group of patients in the Minneapolis/St Paul area of Minnesota, SSTIs were found to be more prevalent in community-associated cases (75%) than in those associated with healthcare institutions (37%).^[22] Unfortunately, CA-MRSA is now an established cause of *S. aureus*-related SSTI in certain geographical areas. Two clones, designated USA 300 and USA 400, represent the most common strains of CA-MRSA in the US.^[25]

There are genetic and microbiological differences between CA-MRSA and HA-MRSA.^[24,26] For example, CA-MRSA isolates commonly carry genes for the Panton-Valentine leukocidin (PVL) toxin (a virulence factor associated with severe necrotising pneumonia and SSTIs); this is rarely seen in HA-MRSA.^[22,27] CA-MRSA is more likely than HA-MRSA to be susceptible to commercially available antimicrobials, with the exception of the β -lactams.^[22] However, precise recommendations for the treatment of CA-MRSA do not exist as no clinical trials have been specifically conducted for this pathogen and because the results of *in vitro* sensitivity testing may not always correlate with clinical outcomes in CA-MRSA. Specifically, clindamycin may show activity against CA-MRSA. However, resistance while receiving therapy may occur, representing a form of inducible resistance.^[26]

Effective control of CA-MRSA may be more challenging than that of HA-MRSA. First, nasal carriage is not a reliable predictor of subsequent infection. Second, CA-MRSA may show different patterns of spread.^[26] Most disturbingly, there are now reports that CA-MRSA isolates are being introduced into hospitals.^[28,29] An SSTI outbreak affecting seven otherwise healthy newborn babies in a New York maternity unit was reported by Bratu

et al.,^[28] and hospital transmission of CA-MRSA in the postpartum period in eight women has been documented.^[29]

1.4 Epidemiology in Selected Disease States

Although MRSA has been implicated in infections ranging from endocarditis to osteomyelitis, three infections deserve special focus since they account for the majority of infections caused by MRSA: hospital-acquired pneumonia (HAP), SSTIs and diabetic foot infections.

1.4.1 Hospital-Acquired Pneumonia (HAP)

HAP, including ventilator-associated pneumonia (VAP), affects up to 2% of hospitalised patients, and is often associated with poor outcomes.^[30] Crude mortality rates for VAP approach 30%, although controversy remains regarding the attributable mortality of VAP. MRSA is a common cause of both early and late HAP. Results from the NNIS revealed that *S. aureus* now accounts for nearly one in five cases of HAP, and MRSA is implicated in nearly 10% of all HAP cases. In Europe, MRSA has long been a recognised cause of VAP. An epidemiological survey carried out in 135 French ICU patients between May 1993 and June 1995 revealed MRSA in 13.1% of cases,^[31] while figures based on a literature evaluation over the period 1980 to 2001 suggest that *S. aureus* was present in 1689 episodes in 24 clinical studies.^[32] Of these isolates, over half (55.7%) were meticcillin resistant.

Some authors have reported increased mortality in patients with pneumonia caused by traditional nosocomial MRSA as opposed to MSSA.^[5] However, others found no difference after controlling for confounding variables such as differences in patient characteristics and management strategies.^[33] Multiple studies indicate that the timeliness and appropriateness of initial antibacterial therapy is a key determinant of outcome in VAP generally, and particularly so in MRSA VAP. Confirming this, Combes et al.^[34] noted that MRSA VAP was not associated with an increased risk for death compared with MSSA VAP so long as patients received appropriate treatment. They defined appropriate therapy for MRSA as vancomycin 15–20mg/kg twice daily. The

standard 1gm twice daily administration was considered inadequate.

1.4.2 Skin and Soft Tissue Infections

Clinicians frequently encounter SSTIs, both in hospital and community settings. However, wound infections represent the most common adverse events affecting hospitalised post-surgical patients. As is the case in HAP and VAP, MRSA is an increasingly common pathogen in complicated SSTIs (cSSTIs). More importantly, MRSA is now the leading cause of SSIs following cardiovascular and orthopaedic surgery in the US.^[1] Compared with other wound infections, *S. aureus* infections can be associated with worse clinical outcomes. Petti et al.^[35] showed that the risk for bacteraemia following an SSTI is increased in patients with an infection due to *S. aureus*.

Complicating the approach to the treatment of SSTIs is the growing importance of CA-MRSA. Initially, CA-MRSA-related infections were described in outbreaks in specific populations in which crowding, skin-to-skin contact or poor hygiene were common factors.^[24] However, surveillance projects conducted in a large hospital in Georgia and its affiliated clinics during the period 1 August to 15 November 2003 identified 389 episodes of community-associated SSTIs caused by *S. aureus*, with MRSA accounting for 72% of cases. The USA 300 strain was identified as the primary type in 99% of cases.^[25] Similarly, CA-MRSA was described as the most common cause of community-acquired SSTI at a Los Angeles area ED, where the proportion of SSTIs due to CA-MRSA rose from 29% in 2001/2 to 64% in 2003/4.^[36] This trend has been identified in many US cities. The prevalence of MRSA-related SSTI presenting to the EDs of 11 cities across the US during August 2004 was 59% overall (range 15–74%); CA-MRSA accounted for 99% of isolates.^[37] Of the MRSA isolates, 99% were USA 300.

1.4.3 Diabetic Foot Infections

Diabetic foot ulcers frequently become infected. This in turn leads to prolonged morbidity, hospitalisation and, potentially, lower leg amputation.^[38,39] *S. aureus* is the most common Gram-positive aerobe found in infected foot ulcers in diabetic patients,

with an increasing proportion of isolates being methicillin-resistant.^[40-42] For example, MRSA was isolated from 30.2% of 63 patients with positive wound swabs at the Manchester Foot Hospital, UK,^[40] and from nearly 50% of *S. aureus* swabs in a recent series of 84 Greek patients with diabetic foot ulcers.^[42] MRSA diabetic foot infections are associated with longer healing times than those caused by MSSA. Confirming this, an analysis from Greece revealed that the respective mean healing times were 35.4 and 17.8 weeks ($p = 0.03$).^[41] In addition, infection of diabetic foot ulcers with *S. aureus* may increase the risk of death.^[43]

2. Cost Issues

Given the prevalence of MRSA and its clinical burden, appreciating its economic consequences will facilitate efforts to develop preventive and treatment interventions. In other words, by understanding its financial effects, clinicians and policy makers can put MRSA into context relative to other health-care issues. In an effort to be comprehensive as to the state of the current literature regarding the costs of MRSA, we searched the medical publication databases MEDLINE, EMBASE and Chinal (from their inception until January 2006) and noted over 600 reports addressing MRSA and economics (table II). Relevant studies describing the economic burden of MRSA and the cost effectiveness of treatment options for MRSA are described in the following sections of this review.

2.1 The Financial Burden of MRSA Compared with Methicillin-Sensitive *S. aureus* (MSSA)

Three studies reported the costs of MRSA in relation to MSSA. Analysis of the New York State-wide Planning and Research Cooperative System (SPARCS) database of 1 351 362 non-obstetrical hospital discharges in New York City in 1995 revealed direct medical costs per patient of \$US35 300 and \$US28 800, respectively, for community-acquired and nosocomial *S. aureus* infections.^[9] The authors suggested that the societal cost of *S. aureus* infection would be reduced by attempts to lower the incidences of both MRSA and MSSA.

Table II. Literature search of the economic burden and cost effectiveness of treatments for methicillin-resistant *Staphylococcus aureus* (MRSA)

#	Search terms	Results
1	economics.mp.	74 982
2	health economics.mp.	3 786
3	economic evaluation.mp.	6 322
4	cost.mp.	350 460
5	cost benefit analysis.mp.	53 374
6	cost control.mp.	22 817
7	cost effectiveness analysis.mp.	26 848
8	cost minimisation analysis.mp.	153
9	cost utility analysis.mp.	1 707
10	cost of illness.mp.	11 446
11	burden.mp.	71 218
12	resource utilil\$.mp.	5 500
13	MRSA.mp.	14 162
14	methicillin-resistant Staphylococcus aureus.mp.	18 124
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	471 954
16	13 or 14	22 267
17	15 and 16	940
18	limit 17 to English language	861
19	limit 18 to human	786
20	limit 19 to humans	786
21	remove duplicates from 20	602

In a study of primary nosocomial bloodstream infections, the median attributable hospital stay associated with MSSA bacteraemia was 4 days, markedly less than the 12 days for MRSA ($p = 0.023$).^[7] Moreover, in this report, MRSA infection led to a 3-fold increase in direct costs relative to MSSA. Part of this cost differential was because the antibacterials used to treat MRSA were more expensive than those employed against MSSA. However, most of the cost differential arose because of the extensive impact of MRSA on duration of hospitalisation.

In another US study, which focused on mixed types of infections in 90 long-term care facility residents, the median overall infection cost of MRSA was nearly 2-fold that of MSSA.^[44] Significant differences were found in the nursing care and infection management components of the infection cost. The major difference in cost between resistant and susceptible infection was associated with direct patient care rather than pharmaceutical manage-

ment; nursing care was more than 2-fold greater in the MRSA group. Infection management constituted the second largest component of infection cost in the MRSA group and was more than 6-fold higher than in the MSSA group.

Overall, MRSA appears to increase costs in several ways. First, the antibacterials for MRSA tend to be expensive. Second, even with less expensive agents such as vancomycin, either added laboratory studies are needed to ensure adequate administration or central venous access is needed for prolonged infusion. Third, and most important, MRSA adversely affects length of stay (LOS). Each of these factors arises independent of patient severity of illness or of long-term co-morbidities.

2.2 The Financial Burden of MRSA in HAP/Ventilator-Associated Pneumonia

HAP (which includes VAP) is associated with longer LOS in the ICU and hospital, and increased costs versus the absence of developing one of these nosocomial infections.^[32,45-47] In particular, VAP due to MRSA leads to longer stays in the ICU^[6,48] and a longer duration of hospitalisation than MSSA-related VAP.^[48] Two studies^[6,48] have provided estimates of the financial burden of MRSA in HAP/VAP.

An analysis of a multi-hospital US database covering patients with VAP over 24 months showed that patients with MRSA-related VAP consume substantial excess resources. In particular, patients with MRSA consumed an additional 4.4 overall days of mechanical ventilation, and required >5 additional days of ICU care compared with MSSA-related VAP. In terms of excess direct costs, MRSA VAP independently added nearly \$US7731 after controlling for disease severity and other factors.^[48] In a study in French ICUs, those with MRSA VAP had longer median ICU stays than those with MSSA VAP (33 vs 22 days; $p = 0.047$).^[6] Specifically, infection with MRSA also doubled the probability of requiring continued ICU care. Importantly, this finding was independent of multiple confounders, including severity of illness, process of care and appropriateness of initial antibacterials. Of note, all

subjects with MRSA in this analysis were treated with high-dose vancomycin.

2.3 Skin and Soft Tissue Infections

As with other hospital-acquired infections, cSSTIs (which often involve MRSA) are associated with an extended stay in hospital and higher costs.^[49] Moreover, among nearly 480 surgical patients in a US hospital, MRSA-related SSIs were associated with a longer duration of hospitalisation and higher hospital charges than those associated with MSSA.^[20] In this analysis, MRSA was associated with a median 5 additional days of hospitalisation, and patients with MRSA had a 1.2-fold increase in hospital charges ($p = 0.03$) and mean attributable excess charges of \$US13 901 per SSTI (year of value not stated) relative to MSSA.

2.4 Diabetic Foot Infections

Diabetic foot disease is a common co-morbidity in patients with diabetes. Singh et al.^[50] estimated that patients with diabetes face a nearly 25% lifetime risk of developing a foot ulcer. Whilst there were no studies identified that currently quantify the burden of MRSA in this disease state, with the increasing incidence of diabetes, the current substantial economic consequences of diabetic foot ulcers are expected to increase.^[38,39,51-53] Hartemann-Heurtier et al.^[53] found multidrug-resistant organisms to be present in 18% of admission specimens from a specialised diabetic foot unit in France. Approximately one-third of patients with a history of prior hospitalisation for the same wound, and 25% of patients with osteomyelitis, yielded specimens positive for multidrug resistance.

3. Cost Effectiveness of Treatment and Prevention

In addition to the treatment of established infections, the management of MRSA includes preventive measures. Indeed, the effectiveness of isolation has already been shown in more than one centre, and is recommended as a means of reducing costs associated with MRSA.^[10,54]

3.1 Prevention

The incidence of MRSA infection can be reduced substantially through prevention. For example, the introduction of an MRSA policy in a British orthopaedic unit in 2003 required all admissions to be screened for MRSA and then isolated if positive.^[55] The result of this effort was a reduction in the incidence of MRSA infection in both trauma and elective patients.

In addition, prevention is often less costly than treatment. Although cumbersome, surveillance and isolation of patients with MRSA yields lower costs than would otherwise be incurred through the need to treat the same infections.^[55-59] For instance, the orthopaedic unit MRSA policy outlined above reduced the incidence of MRSA infection by 56% in trauma patients (from 1.57% [17/1084] in 2003 to 0.69% [10/1447] in 2004; $p = 0.035$) and by 70% ($p = 0.06$) in elective surgical patients.^[55] Given that MRSA infection more than doubled the mortality rate in these orthopaedic cases previously, the authors concluded that their policy was substantially cost effective. Underscoring this, patients who did develop MRSA-infected proximal fractures of the femur were hospitalised for an additional 50 days, received vancomycin treatment for a further 19 days and had 26 more days of vacuum-assisted closure therapy than did matched controls. This led to additional costs amounting to £13 972 per patient. In light of the fact that the cost of preventing one MRSA infection was only £3200, prevention was clearly the dominant strategy.

Karchmer et al.^[56] evaluated the cost effectiveness of surveillance cultures and barrier precautions for containing MRSA in neonatal units. Conducted in the US, they estimated that direct total costs of controlling a 10.5-month outbreak in neonatal intensive care ranged from \$US48 617 to \$US68 637. In contrast, the estimated attributable excess cost for another outbreak that was not properly controlled was \$US1 306 600, lasting for 51 months and causing 14 deaths.

Even more intensive control programmes appear to be financially worthwhile, regardless of the initial cost.^[60] For instance, the financial value of a so-

called 'search and destroy' policy has been demonstrated in The Netherlands, where an extremely stringent policy to eradicate MRSA was implemented.^[60] Data based on a 10-year survey (1991–2000) at the University Medical Center of Utrecht showed that the implementation of the policy resulted in the loss of 2265 days of hospitalisation, 48 ward closures, temporary leave for 29 healthcare workers and testing of 78 000 additional cultures. The total direct cost was Netherlands guilders (NLG)6 million, equivalent to €2 800 000. However, the authors estimated that the direct costs of an outbreak without these controls would have been at least twice as high.

Two formal cost-benefit analyses found that infection control programmes based on screening and isolation were beneficial in the ICU setting.^[10,61] The findings of Chaix et al.^[10] have already been discussed in the introduction. Other French data from 14 ICUs over 6 months show that universal screening and preventive isolation are economically attractive, with a baseline analysis (4.4% prevalence of MRSA carriage from their study population), translating into a net value (cost-benefit) of \$US600–700.^[61]

The addition of single-bed rooms to hospital facilities could further save costs both by preventing transmission of MRSA and by preventing the functional loss of hospital beds that arises when a single patient requiring isolation is placed in a multi-bed room.^[54] Furthermore, limiting the spread of MRSA can minimise expenditures that would otherwise arise from treating a documented infection. Most strategies currently focus mainly on the healthcare setting since, historically, transmission has taken place largely via nosocomial routes. Measures utilised for prevention include screening for MRSA carriage, hygiene measures, isolation of colonised/infected patients, ward closures and, in some situations, decolonisation (see table III).^[62]

Unfortunately, there are few well designed prospective trials evaluating the economics of MRSA colonisation/infection prevention. Most data come from clinically-based descriptive studies. However, two systematic reviews have reported that the avail-

Table III. Infection control measures to limit transmission of methicillin-resistant *Staphylococcus aureus* (MRSA)^[62]**Take active surveillance cultures to identify the reservoir for spread**

Cultures indicated at time of admission for patients at high risk

Periodic sampling is required for hospitalised patients at high risk

Facility-wide surveys are indicated in facilities with high prevalence on initial sampling

Base frequency of active surveillance on prevalence and risk factors for colonisation

Identify all colonised patients

Always include samples from nasal anterior vestibule, and areas of skin breakdown if present; throat swabs are also useful

Patients with MRSA may be mixed with other like patients, but not if there are differences in other antibacterial sensitivities

Consider social and physical contact implications in nursing homes and psychiatric wards

Hand hygiene

Antiseptic hand washing recommended after all patient contacts

Soap and water required for visibly soiled hands; where not visibly contaminated, alcohol hand rubs are recommended

Monitor hand hygiene compliance

Barrier precautions

Contact precautions include gloves and gowns, with universal use suggested for adjunctive control on high-risk wards among patients with surveillance cultures pending

Masks may be worn to prevent nasal acquisition

Antibacterial stewardship

Avoid inappropriate or excessive use, ensure correct dosages, restrict use of vancomycin

Reduce use to minimum levels necessary to help prevent persistent carriage in institutions where MRSA is endemic

Avoid therapy for colonisation except where suppression or eradication of colonisation is being attempted with an evidence-based approach

Decolonisation or suppression of colonised patients

Consider as an adjunctive measure for selected populations where appropriate; avoid widespread or prolonged use

Initiate routine susceptibility testing

Other measures

Educational programmes

Ensure adequacy of hospital disinfection and cleaning policies

Keep computerised records of long-term isolation indicators

Avoid sharing non-critical patient-care equipment between patients; if unavoidable, clean and disinfect properly

able data support the adoption of infection control measures.^[63,64] Cooper et al.^[63] assessed 46 studies and concluded that there is strong evidence that concerted efforts that include isolation can reduce MRSA carriage and transmission, even when MRSA is endemic. Loveday et al.^[64] concluded, on the basis of their analysis of 24 non-experimental descriptive studies, five economic evaluations and one set of international guidelines, that there is support for prevention and control of MRSA in acute care hospitals and long-term care settings.^[64]

3.2 Treatment

Currently, glycopeptides are utilised for MRSA therapy. Physicians rely on vancomycin most often, although teicoplanin is available in Europe.^[13] How-

ever, *S. aureus* strains that are vancomycin resistant or have reduced susceptibility are emerging.^[13] A recent study^[65] demonstrated that, in MRSA bacteraemia, the rate of clinical cure is related to the vancomycin minimal inhibitory concentration (MIC): when the MIC was ≤ 0.5 $\mu\text{g/mL}$, the outcome was favourable in 55.6% of the cases, against only 9.5% success if the MIC was ≥ 1 $\mu\text{g/mL}$. *Staphylococci* with vancomycin MICs ≤ 4 $\mu\text{g/mL}$ are considered susceptible to the drug according to laboratory criteria.^[66]

Other available treatment options for MRSA include linezolid (an oxazolidinone), daptomycin (a lipopeptide), tigecycline (a glycylcycline antimicrobial) and quinupristin-dalfopristin (a streptogramin). Additional molecules are in active clinical develop-

ment and are now the subject of phase III clinical trials (e.g. ceftobiprole, telavancin, dalbavancin, iclaprim and oritavancin).

Two key, relevant pharmacoeconomic issues that one must consider when evaluating any discussion of cost as it relates to infection are the higher costs associated with administration of intravenous compared with oral formulations of antibacterials and the recognition that the LOS is a key determinant of overall treatment costs.^[67-69]

Almost all of the available pharmacoeconomic data on the drug treatment of MRSA are based on linezolid (generally in comparison with vancomycin), and this drug will be considered in more depth below. Limited pharmacoeconomic data assessing vancomycin, teicoplanin and tigecycline are also available, although these studies did not all relate specifically to MRSA infections.

3.2.1 Vancomycin

Only four studies were identified that have specifically evaluated the cost effectiveness of vancomycin to treat MRSA infection. Of these, two were conducted in Spain, one in Italy and one in the US.

Shah et al.^[70] quantified the direct medical costs associated with using vancomycin in MRSA infections, in four clinical indications: SSTI, bacteraemia, infective endocarditis (IE) and HAP. Their analyses compared the costs of vancomycin in each of the indications but no comparison was made between vancomycin and an alternative treatment option. The authors constructed a decision analytic model to evaluate the costs of administering intravenous vancomycin. Cost inputs included hospitalisation, drug procurement, materials, preparation and administration, renal function and drug monitoring, treating adverse events and treatment failure. Probabilities and LOS and treatment were obtained from the literature, an antimicrobial therapy database and clinical expert opinion. They completed several sensitivity analyses to evaluate their observations. The main outcome measure for the analysis was the cost of using vancomycin in the four indications, including and excluding hospital cost.

Total costs per patient receiving multiple doses in a single course of treatment, excluding hospital

room costs, were \$US779, \$US749, \$US2261 and \$US768, respectively, for SSTI, bacteraemia, IE and HAP.^[70] Total costs, including hospital LOS, were \$US23 616, \$US26 446, \$US48 925 and \$US22 493, respectively, for SSTI, bacteraemia, IE and HAP. In univariate analyses, varying *per diem* hospital costs and LOS had the greatest impact. Results of the multivariate analysis were comparable to the costs in the baseline scenario for all indications. The analysis highlights the importance of capturing all costs beyond simple drug acquisition costs.

Abad et al.^[71] completed a cost-minimisation analysis to compare the economic impact of treatment with either vancomycin or teicoplanin in intensive care patients. Three patients in the teicoplanin arm of the study and 11 patients in the vancomycin arm had infection caused by MRSA. Although personnel, material and monitoring costs were higher in the vancomycin group, the acquisition and total costs were much lower in this group. Resulting total costs per day were equal to €33 for vancomycin-treated patients and €59.5 for teicoplanin-treated patients. This economic study only included those costs directly attributed to the drug treatment, which is a key limitation of the analysis.^[71]

An assessment from Italy^[72] found vancomycin to be cost saving compared with teicoplanin when added to initial empirical amikacin-ceftazidime therapy for Gram-positive cocci infections in patients with neutropenia, reducing the average cost per patient by €168.36 ($p < 0.001$).

Finally, Portoles et al.^[73] prospectively studied costs of treatment with teicoplanin and vancomycin. The study cohort included 201 patients at a Spanish hospital (with any illness), with suspected or reported Gram-positive infection who had been given teicoplanin ($n = 100$) or vancomycin ($n = 101$) for at least 4 days. Costs of acquisition, administration and monitoring by course of treatment (mean $\pm$ SD) were lower in the vancomycin group (teicoplanin; €647.62 $\pm$ 572.75 vs vancomycin; €378.11 $\pm$ 225.90); when total costs (including hospital stay) were considered, no differences were found (teicoplanin; €4432.04 $\pm$ 3383.46 vs vancomycin;

€4364.44 ± 2734.24). Readers should note that indirect costs were not measured in this analysis.

3.2.2 Tigecycline

Only one study reporting the cost effectiveness of tigecycline in treating MRSA was identified. This study by Mallick et al.^[74] focused on the treatment of complicated skin and skin structure infections in the US. The authors analysed the expected cost differences between tigecycline and vancomycin/aztreonam. Using a retrospective analysis of pooled clinical data, the authors suggested that patients with complicated skin and skin structure infections treated with tigecycline cost less to care for than those treated with aztreonam/vancomycin. Specifically, tigecycline resulted in cost savings of \$US1469 per patient. When the evaluation was restricted only to those with documented MRSA, cost savings with tigecycline increased to \$US2239. This study has only been presented as an abstract to date and limitations include a lack of clarity of study perspective and the retrospective nature of the analysis.

3.2.3 Linezolid

A number of publications that have examined the cost effectiveness of linezolid were identified. In each case, linezolid was found to be cost effective relative to vancomycin. These reports employed differing approaches, ranging from decision analytic models to economic analyses based upon prospective randomised controlled trials.

SSTIs

In a prospective, randomised controlled trial of orally administered linezolid compared with intravenous vancomycin for cSSTI, Sharpe et al.^[75] documented that use of linezolid was associated with a 3-day reduction in LOS and a significant reduction in mean total hospital cost per patient. With linezolid treatment, an average of \$US6438 in total hospital charges per patient was avoided. The daily cost of outpatient therapy was \$US97 less with linezolid, and theoretically, the results of the trial would suggest that this would also equate to outpatient cost savings with linezolid of \$US388 per patient.

Modelled analyses for the US and the UK exploring issues from a broader perspective, found that initial use of linezolid as empiric treatment for hospitalised patients with cellulitis was associated with lower total costs than vancomycin.^[76,77] The models were based on the assumption that use of oral linezolid would allow early discharge from hospital. Both analyses were well conducted and reflected a realistic scenario in which empiric therapy for hospitalised patients with cellulitis is started (with one of three possible treatment options), and then treatment is adjusted as necessary on the basis of culture and sensitivity results. In addition, the model covered a wide range of values for the percentage of meticillin-resistant Gram-positive pathogens and for the proportion of inconclusive culture and sensitivity results.

This was also the case for an analysis based just on the US cohort from this study.^[78] Medical resource costs from the various countries in the multinational analysis^[79] were converted to \$US with purchasing power parity adjustments, and both costs and outcomes were risk-adjusted using multivariate methods to account for differences between countries. The mean risk-adjusted cost associated with linezolid was \$US3629 versus \$US4140 for vancomycin ($p < 0.0001$); these data matched with respective predicted cure rates of 92% and 88%, respectively ($p < 0.0001$).

In the US analysis^[78] the mean ± SD cost for intent-to-treat population patients treated with linezolid versus vancomycin was \$US4865 ± 4367 versus \$US5738 ± 5190, respectively ($p = 0.017$), and in the MRSA population was \$US4881 ± 3987 versus \$US6006 ± 5039, respectively ($p = 0.041$). Factors significantly associated with increased cost included vancomycin therapy, age and co-morbidities, including diabetes. After adjusting for all other factors, treatment with linezolid was associated with significantly lower treatment costs than vancomycin. The largest cost advantage was demonstrated in patients with documented MRSA cSSTIs. Limitations to the analysis included the use of clinical protocol medical treatment relative to standard clinical practice and the use of clinical trial data for

economic analyses. Also for consideration is that in clinical practice it is possible that patients treated with intravenous vancomycin could be switched to oral linezolid. However, this was not considered in this analysis, which was designed to demonstrate the superiority of one treatment over another.

A study by Schurmann et al.,^[80] based on a decision-analysis model, also found linezolid to be dominant over vancomycin in the treatment of cSS-TIs due to suspected MRSA. The published abstract based on a German study reported linezolid to be cost saving over vancomycin, with its higher acquisition cost being offset by shorter treatment duration and reduced LOS.

A decision-analytic study from the perspective of a tertiary-care academic medical centre by Patanwala et al.^[81] adds further support to the cost effectiveness of linezolid over vancomycin for treating SSIs caused by MRSA. Three clinical scenarios were considered in the analysis: (i) treatment with intravenous vancomycin during hospitalisation and after discharge with home-care follow-up; (ii) treatment with intravenous vancomycin during hospitalisation, followed by oral linezolid after discharge; (iii) treatment with oral linezolid during hospitalisation and post-discharge. Cost data were obtained from both internal and external sources. Cure rate probabilities for MRSA SSIs were obtained from records at the medical centre and results from a randomised, multicenter trial. Healthcare costs for each scenario were obtained from the medical centre, healthcare buying groups and national databases. Sensitivity analyses were used to evaluate the robustness of the base-case scenario.

Treatment with oral linezolid during hospitalisation and post-discharge (scenario 3) was associated with lower costs (\$US8923, \$US11 479 and \$US12 481, respectively) and greater effectiveness (0.867, 0.787 and 0.707, respectively) compared with the intravenous vancomycin/oral linezolid switch (scenario 2) and intravenous vancomycin (scenario 1), so it dominated the latter options in the base-case incremental cost-effectiveness analysis (\$US10 292, \$US14 486 and \$US17 653 per MRSA SSI cure, respectively).^[81] Sensitivity analysis

demonstrated that intravenous vancomycin/oral linezolid (scenario 2) option would be the expected cost-effective choice only if the LOS for this scenario was <6 days or if the probability of cure with oral linezolid (scenario 3) was ≤ 0.72 ; otherwise, the oral linezolid option was dominant. This study included the use of probability estimates from institutional and published research sources, and success rates obtained from one relatively small randomised, open-label trial. Despite these limitations, the authors concluded that treatment with oral linezolid during hospitalisation and post-discharge is expected to be the most cost-effective approach for treating SSIs caused by MRSA.

Finally, a retrospective cohort study based on 12-month longitudinal claims data from over 80 US healthcare plans and utilising propensity scoring to match 1048 linezolid and 1048 vancomycin recipients found that outpatient treatment with oral linezolid significantly decreased resource utilisation and medical costs compared with vancomycin.^[82] During the 35-day follow-up period, mean total cost was \$US4630 less for linezolid patients (\$US8922, vs \$US13 552 for vancomycin; $p < 0.0001$).

Overall, each of these analyses has assumed one provides the anti-MRSA agent empirically. In other words, either linezolid or vancomycin is prescribed initially. The clinical trials comparing these two agents against each other all utilised an empiric treatment approach rather than a strategy that withheld MRSA treatment until the presence of MRSA was documented. Hence, the data from these trials that populate the models described above and those presented in the following section reflect the scenario most resembling the way the trials were completed. The benefits of linezolid with respect to either cure rate or LOS have only been seen when given initially for suspected MRSA. Although it might seem intuitive to 'save' this agent for only documented MRSA infection, that approach has never been studied formally in clinical trials. Therefore it is inappropriate to assume that the benefits seen in trials of empiric treatment strategies would also be noted if one took a more conservative approach. As a corollary, applying outcomes data from such trials

Table IV. Cost-effectiveness analyses comparing linezolid (LIN) with vancomycin (VAN) in healthcare-acquired meticillin-resistant *Staphylococcus aureus* (MRSA) ventilator-assisted pneumonia (VAP). Summary of fully published studies using decision-analysis models

Parameter	Spanish analysis ^[83]	Brazilian analysis ^[66]
Study perspective	Spanish public health system	Brazilian university hospital
Time horizon	Length of hospitalisation (costs) and lifetime (QALY)	Duration of hospitalisation
Year of costing	2003	2004 (May)
Source of efficacy data	Combined analysis ^[84] of two key clinical studies ^[85,86]	Combined analysis ^[84] of two key clinical studies ^[85,86]
Costs accounted for	Drugs; VAN monitoring; days of stay in ICU; resources used in clinical failure	Drugs; administration equipment and materials (syringes, etc.); other costs (e.g. hospital stay) assumed to be equivalent between treatments
IC per LYG for LIN	All VAP: €1501 VAP (Gram-positive): €828 VAP (<i>S. aureus</i>): €955 VAP (MRSA): €290	NR
IC per QALY gained for LIN	All VAP: €1804 VAP (Gram-positive): €997 VAP (<i>S. aureus</i>): €1149 VAP (MRSA): €349	NR
Total cost per patient	NR	LIN: \$Brz4829.66; Brand-name VAN: \$Brz2805.11; Generic VAN: \$Brz2390.85
Amount invested per patient cured	NR	LIN: \$Brz7764.72 Brand-name VAN: \$Brz13 231.65 Generic VAN: \$Brz11 277.59

IC = incremental cost; LYG = life-year gained; NR = not reported; \$Brz = Brazilian real.

to models that violate the paradigm used in those trials would be methodologically inappropriate and could lead to spurious estimates of linezolid’s cost effectiveness.

HAP/VAP
Several cost-effectiveness studies have been carried out to compare linezolid with vancomycin in HAP (generally VAP) caused by suspected or proven MRSA.

Decision-analysis models applied in studies in Spain^[83] and Brazil^[66] have shown linezolid to be a cost-effective alternative to vancomycin for the treatment of suspected or proven MRSA-associated VAP (table IV). Clinical efficacy data for both analyses were drawn from a pooled analysis^[84] of two major clinical studies.^[85,86] The Spanish analysis^[83] considered life expectancy of survivors after hospital discharge but not costs incurred after the period of hospitalisation; sensitivity analyses were also applied and showed the results to be robust. Results from this analysis showed that the additional cost per QALY gained with treatment with linezolid

rather than vancomycin was well below the stated acceptable threshold in Spain for cost effectiveness (€30 000/QALY gained).

The decision analysis model created for the Brazilian study^[66] was simpler than that used by the Spanish authors and included options for cure or death only. Costs directly related to medicines and their administration were included in the analysis, as the authors assumed that other costs would be similar in each group. Other indirect costs were not explicitly considered. Information on materials and pricing was drawn from interviews with nursing staff at a São Paulo medical facility, and vancomycin was priced on the basis of both brand-name and generic variants. In terms of the simple outcome of expenditure per patient cured, linezolid was superior to either version of vancomycin (table IV). Some caution should be observed when interpreting these data as no sensitivity analyses were conducted and some of the methods used to assess costs were unclear.

A report by Mullins et al.^[87] also used a decision-analytic model and claims data from a large health plan to compare the cost effectiveness of linezolid and vancomycin in the treatment of patients with nosocomial pneumonia caused by MRSA. Efficacy estimates for linezolid versus vancomycin were taken from the same pooled analysis utilised in other reports.^[86] Additionally, the authors extracted hospital claims information for patients in the health plan with suspected nosocomial pneumonia. The authors then determined the daily billed (submitted) hospital charges for four mutually exclusive potential health outcomes of linezolid or vancomycin treatment: survival with bacteraemia, survival without bacteraemia, non-survival with bacteraemia and non-survival without bacteraemia. Daily billed hospital charges were weighted by the probabilities of each outcome developing. Drug acquisition costs were then incorporated, and the difference in expected total costs relative to the difference in rates of survival between the linezolid and vancomycin arms was used to calculate the incremental cost-effectiveness ratio (ICER) for linezolid.

Costs were higher for non-surviving patients than for surviving patients. Estimated median daily billed treatment charges were \$US2888 for linezolid and \$US2993 for vancomycin. Based on Monte Carlo simulations, the respective 95% CIs were \$US2671 to \$US3106 and \$US2615 to \$US3372. Using mean treatment durations of 11.3 and 10.7 days, respectively, these investigators concluded that expected total hospitalisation charges with linezolid treatment equalled \$US32 636 (95% CI 30 182, 35 098), compared with \$US32 024 (95% CI 27 978, 36 078) for those treated with vancomycin. The ICER for linezolid per life saved was \$US3600. The higher acquisition cost of linezolid was almost completely offset by improved survival and a reduction in healthcare costs associated with improved survival. As a result, linezolid was almost cost-neutral compared with vancomycin in the treatment of nosocomial pneumonia caused by MRSA.^[87]

Other cost-effectiveness analyses (reported as abstracts) for the US^[88] and Germany^[89] concur with these findings showing linezolid to be cost effective

compared with vancomycin in the treatment of suspected MRSA nosocomial pneumonia.

Kuznik et al.^[88] reported an ICER of \$US3847 per life saved relative to vancomycin on the basis of drug and hospital charges for 2002/3. Similar findings have been reported from the German healthcare perspective: Grünewald et al.^[89] documented incremental costs per life-year gained and death avoided with linezolid relative to vancomycin of €371 and €5124, respectively. The authors' conclusions did not change after variation by up to 25% of the proportion of MRSA cases and costs accrued by patients who died.

A further decision-analysis model based on a US perspective indicated that linezolid is a cost-effective alternative to vancomycin for the empiric treatment of VAP caused by *S. aureus* (MSSA or MRSA) [figure 1].^[90] The researchers were conservative in their assumptions and biased the model against linezolid. Shorr et al.^[90] noted that the cost per added QALY with linezolid was approximately \$US30 000. An extensive sensitivity analysis included concomitantly skewing all of the model variables against linezolid, including lowering the relative risk reduction of linezolid and reducing the value of an added year of life in terms of quality.

Fig. 1. Cost effectiveness of linezolid compared with vancomycin for the empirical treatment of ventilator-associated pneumonia in the US. Incremental cost per life-year gained (LYG) and QALY gained.^[90] Results shown are for the base-case analysis and for best- and worst-case scenarios as shown by multivariate sensitivity analysis (reproduced from Plosker and Figgitt,^[91] with permission).

This yielded a 'worst-case' cost-effectiveness ratio of approximately \$US100 000 per QALY gained (2001 values). In other words, with every variable in the model simultaneously skewed to the farthest extreme of the data range, linezolid still appeared cost effective. A Monte Carlo simulation based on 10 000 runs resulted in a 95% CI of 23 637, 42 785 for the ICER.

3.2.4 Teicoplanin Study

Literature regarding costs associated with teicoplanin is sparse. A retrospective audit of treating 55 cases of bone and joint infections was completed by Nathwani et al.^[92] Their analysis showed that the mean cost of care per episode of infection was less with treatment in the ambulatory setting (£1749.15) than in the in-patient setting (£11 400) or compared with the hypothetical situation of treatment with oral linezolid in the home setting (£2546). Teicoplanin therapeutic drug monitoring appears to be valuable in establishing optimal serum levels, which seem to correlate with good clinical outcomes. The potential for alternative day or thrice-weekly administration with teicoplanin may offer further cost advantages whilst maintaining equivalent clinical effectiveness.

4. Conclusions

The increasing prevalence of MRSA, together with the morbidity and mortality associated with infections caused by this pathogen, underscores why MRSA infection represents a considerable economic burden. In particular, the increasing prevalence of CA-MRSA will aggravate the clinical situation and complicate matters. It is clear that all practical steps should be taken to control and contain MRSA. Advances in diagnostics to enable early detection of MRSA will permit timely implementation of infection control programmes to prevent its spread. This has been shown ultimately to cost less than treatment of the additional infections that would otherwise result.

For established MRSA infections, glycopeptides are currently used routinely. Nevertheless, the need for alternative treatment options is clear. In addition, most drugs that are effective against MRSA carry implications for healthcare workloads and patient

comfort because they are available for intravenous administration only. The oxazolidinone linezolid is an effective therapy for MRSA infections that has been supported by a number of pharmacoeconomic publications in an arena in which there is a general paucity of economic literature relating to treatments. Unique in that it is available as both intravenous and oral formulations, linezolid has been studied in a number of disease states and has been found to be either non-inferior to or superior to vancomycin.

Due to limitations within some of the studies, the results relating to the cost effectiveness of linezolid need to be treated with some caution; however, analyses have demonstrated how oral linezolid allows for treatment on an outpatient basis, which may facilitate early discharge from hospital. Earlier discharge along with the avoidance of costs related to home intravenous infusion raises the potential for reductions in overall treatment costs, despite a higher drug acquisition cost. In other disease states, such as HAP, where oral formulations are less likely to be employed, linezolid remains financially attractive given its efficacy relative to vancomycin. Additional studies are needed to document the benefit of newer antimicrobial agents and other innovative interventions on healthcare cost and resource utilisation.

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