Economic Features of Antibiotic Resistance: The Case of Methicillin-Resistant *Staphylococcus aureus*

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Abstract This paper analyses and updates the economic information regarding methicillin-resistant *Staphylococcus aureus* (MRSA), including information that has been previously reviewed by other authors, and new information, for the purpose of facilitating health management and clinical decisions. The analysed articles reveal great disparity in the economic burden on MRSA patients; this is mainly due to the diversity of the designs of the studies, as well as the variability of the patients and the differences in health care systems. Regarding prophylactic strategies, the studies do not provide conclusive results that could unambiguously orientate health management. The studies addressing treatments noted that linezolid seems to be a cost-effective treatment for MRSA, mostly because it is associated with a shorter length of stay (LOS) in hospital. However, important variables such as antimicrobial

susceptibility, infection type and resistance emergence should be included in these analyses before a conclusion is reached regarding which treatment is the best (most efficient). The reviewed studies found that rapid MRSA detection, using molecular techniques, is an efficient technique to control MRSA. As a general conclusion, the management of MRSA infections implicates important economic costs for hospitals, as they result in higher direct costs and longer LOS than those related to methicillin-susceptible *S. aureus* (MSSA) patients or MRSA-free patients; there is wide variability in those increased costs, depending on different variables. Moreover, the research reveals a lack of studies on other related topics, such as the economic implications of changes in MRSA epidemiology (community patients and lineages associated with farm animals).

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Key Points for Decision Makers

Methicillin-resistant *Staphylococcus aureus* (MRSA) implicates significant costs in its management, when compared with MSSA or with no infection processes; if we compare MRSA patients and MSSA patients, the incremental length of stay (LOS) is in the range of 2–10 days, and the direct costs are 1.5 to 3 times greater (in the range of approximately €1,200–50,000).

Rapid detection techniques based on molecular methods have proven to be an efficient diagnostic tool, given that they allow prescription of the right antibiotic treatment earlier than would otherwise be the case, as well as adoption of decisions regarding the clinical management of the patient, which usually means a shorter LOS for hospitalized patients and lower overall costs.

Prophylactic policies, which are usually based on isolation and decolonization, have sometimes been shown to be cost saving, while others have obtained positive cost-effectiveness ratios (below €50,000), depending on the way those procedures have been implemented and on the different settings that have been analysed.

Switching patients from intravenous to oral antimicrobial treatments has been shown to be a cost-effective decision in the majority of the analysed papers. Most studies have considered the short-term effects of savings in the LOS and increases in drug costs, but other aspects such as the impact on selection of antibiotic resistance (depending on the antibiotic that is used) need further evaluation.

1 Introduction

Antimicrobial resistance constitutes a growing health care problem with important economic implications, and methicillin-resistant *Staphylococcus aureus* (MRSA) is a prevalent bacterium that has caused concern in hospital settings. Recently, a variety of policies have been implemented in some countries to reduce the rate of MRSA [1, 2]. There has been an encouraging decrease, but the percentages detected in health care facilities are still excessive, and this microorganism has also increased its prevalence in other settings (community patients and lineages associated with farm animals) [3].

There is an increasing body of scientific literature dealing with the economic implications of MRSA resistance. It is aimed at attracting the attention of health authorities, and society in general, to this topic. In addition, it is aimed at supporting the relevant decision-making processes by providing useful information regarding the efficiency of the implemented policies to cope with this resistance.

During the last 10 years, several reviews on this topic have described the economic aspects of MRSA infections by summarizing the published papers from different perspectives; they have focused on the specific sites of the infections (cost of illness and control) [4, 5]; epidemiology and various economic issues [6]; epidemiology and the cost of illness [3]; prophylaxis applied to different settings and sites, such as orthopaedic and surgical infections [7–10]; rapid detection techniques [11]; and the efficiency of treatment options [12–15]. However, given that the evolution of the infection is continuing and that the health care sector is adopting new forms of responses, it is important to update, analyse and summarize recently published studies that have highlighted some of the epidemiological findings, as well as the economic and managerial implications. As is shown in Table 1, taking into account the topics that have already been reviewed by other authors, the current update addresses new papers that have been published during the last 2–8 years, together with other texts that our research team found—which, for whatever reason, were not included in the previous reviews—for a total of 69 papers.

This paper is aimed at analysing the economic features or economic information regarding antibiotic resistance and, specifically, regarding MRSA. By ‘economic information’, we mean the results that, from this perspective, can be useful to facilitate health management and clinical decisions (i.e. studies on the economic burden of the disease, as well as economic evaluations of several prophylactic and therapeutic options). Specifically, we address five questions with economic implications in this area: how costly is MRSA; what additional costs are associated with MRSA versus MSSA; is the application of prophylaxis for MRSA beneficial; are rapid detection techniques efficient; and what is the most efficient therapeutic option, if any, to treat MRSA patients?

This review first introduces the global problem of MRSA, emphasizing the epidemiological factors, and second it demonstrates its economic implications, as studied by different authors.

2 Global Problem of MRSA

Antimicrobial resistance is an important global problem, which is increasing all over the world. In the European Union, approximately 111,000 deaths each year are due,

Table 1 Summary of the review studies related to economic aspects of methicillin-resistant *S. aureus* (MRSA) infections^a

Reference/ number of economic revised papers/ period	Subject	Main conclusions
Cost of illness and control		
Gould [4] 49 papers Up until 2006	Costs of HA-MRSA and its control: Costs to the patient Costs to the hospital Costs to society Costs of control	Huge costs of MRSA at all levels The costs of not controlling MRSA are much greater than the costs of control While the CE of control strategies, even in the short term, should not be in doubt, it is proving difficult to mobilize the finances necessary to kick-start the process. The reasons for this are complex but need to be addressed urgently before community-acquired MRSA, GISA and VRSA complicate the issue and create even greater problems
Gould et al. [5] 23 papers 2006–2010	Costs of HA-MRSA and its control (update): Costs to hospitals Costs of infection control Costs to patients and society QALYs	There is a consistent message from these studies that admission surveillance cultures and barrier precautions for MRSA-positive patients are both efficacious in control of MRSA and are also likely to be highly CE. The more screening there is, the larger the reduction in MRSA that is likely to be achieved, and the higher the prevalence of MRSA, the greater the impact of screening will be
	Estimating costs to inform policy decision-making	Control of MRSA is highly worthwhile for reducing the clinical burden of MRSA and for improving treatment of other infections through the ability to avoid the use of glycopeptides Future research should concentrate on more methodical, well-designed and robust intervention studies rather than the largely observational, uncontrolled studies that fill the existing literature
Epidemiology and different economic issues		
Shorr [6] 56 papers Up until January 2006	Epidemiology and economic impact of MRSA; among economic issues, it was focused on: MRSA vs MSSA MRSA in HA pneumonia/VAP, SSTI, diabetic foot infections CE of treatment and prevention	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 Glycopeptides are used routinely for MRSA infections, but the need for other treatment options is clear LZD is an effective therapy for MRSA infections, which has been supported by several pharmacoeconomic publications. LZD has been studied in a number of disease states and has been found to be either non-inferior or superior to VAN Because of limitations within some of the studies, the results relating to the CE of LZD need to be treated with some caution. However, analyses have demonstrated how oral LZD allows for treatment on an outpatient basis, which may facilitate early discharge from hospital

Table 1 continued

Reference/ number of economic revised papers/period	Subject	Main conclusions
Epidemiology and cost of illness		
Köck et al. [3] 5 papers 2001–2009	Epidemiology and cost; it was more focused on epidemiology aspects than on economic issues; however, it included a financial burden section	Besides effects on mortality, several studies, mainly from the USA, have indicated that MRSA infections cause a significant additional financial burden compared with MSSA infections after adjustment for co-morbidities, which is largely the result of greater LOS and occupation of isolation rooms Successful MRSA control in some countries and facilities offers opportunities for identifying effective interventions and reassessment of best practice
Prophylaxis applied to different settings		
Chen et al. [7] 25 papers Up until 2013	To determine whether <i>S. aureus</i> S&D reduce SSIs in orthopaedic patients and whether implementing this protocol is CE	Preoperative S&D of <i>S. aureus</i> in orthopaedic patients is a CE means to reduce SSIs There was lack of uniformity between studies The results could not be stratified by type of surgery and were not always statistically significant The studies included in this review were unable to determine if different swab sites were more sensitive for detecting <i>S. aureus</i> colonization Infection control interventions reported in the available literature usually show highly favourable cost–benefit calculations. This is true also for high MRSA endemicity settings Unresolved economic issues include rapid screening using molecular techniques and universal vs targeted screening Data were reported in the primary studies without CIs or other measures of precision There is a need for guidance on how to conduct and report economic analyses of infection control interventions in primary studies that will allow for comparison between studies and increase external validity of individual studies
To examine the cost and cost–benefit of infection control interventions against MRSA and to examine factors affecting economic estimates		
Farbman et al. [8] 36 papers 1987–2011		
To assess the medical and health economics of prevention and control measures related to MRSA infections or colonizations at hospitals		
Korczak and Schöffmann [9] 8 papers 2004–2009		Application of rapid tests seems to be recommendable only for ‘risk patients’ and high MRSA prevalence Improvement of compliance with hand hygiene should be the basis of any prevention strategy Antibiotic management programmes are effective as well The eight studies were of limited quality. The break-even point of CE prevention and control measurements could not be finally clarified There is a need for additional cost–benefit analyses

Table 1 continued

Reference/ number of economic revised papers/period	Subject	Main conclusions
McGinagle et al. [10] 20 papers Up until 2007	To observe the possible efficacy and CE of ASCs to control increasing numbers of infections due to MRSA in published papers	Evidence from multiple observation-based studies suggests that use of ASCs reduces the incidence of MRSA infection, but the overall quality of the evidence is poor None of the studies were of good quality Important gaps in the literature were identified, including a need for a clear definition of ASCs, a clear implementation protocol and rigorous economic evaluations
Rapid detection techniques		
Brown and Paladino [11] 12 papers 1995–2008	To evaluate the effect of a rapid PCR assay on mortality and economics, compared with traditional empirical therapy, using a literature-derived model	Rapid MRSA PCR testing appears to reduce mortality rates and can be expected to be CE in the EU and USA across a wide range of MRSA prevalence rates and test costs It was assumed that all clinicians would react to the results of the rapid PCR test and implement a respective therapeutic change The base model did not include the costs of negative blood tests in the overall costs of the different strategies These findings require prospective study and further elucidation
Treatment options		
Ager and Gould [12] 4 papers Up until 2012	To perform a clinical update on LZD for treatment of Gram-positive bacterial infections, including a CE section	The high oral bioavailability of LZD and its equivalent intravenous-to-oral formulations lead to ease of dosing and administration and, combined with its good clinical outcomes, make it a CE option, allowing early discharge from hospital Relatively high incidence of adverse effects, particularly with long-term use There are currently only low resistance rates, although long-term use may be complicated by development of resistance
Gurusamy et al. [13] 3 papers Up until 2013	To compare the benefits (such as decreased mortality and improved quality of life) and harms (such as adverse events related to antibiotic use) of all antibiotic treatments in people with non-surgical wounds with established colonization or infection caused by MRSA	No trials were found comparing use of antibiotics with no antibiotic for treating MRSA-colonized non-surgical wounds; therefore, no conclusions could be drawn for this population In trials that compared different antibiotics for treating MRSA-infected non-surgical wounds, there was no evidence that any one antibiotic was better than the others Further well-designed RCTs are necessary

Table 1 continued

Reference/ number of economic revised papers/period	Subject	Main conclusions
Watkins et al. [14] 7 papers Up until September 2012	To provide an up-to-date evaluation of the clinical evidence for using LZD to treat MRSA infections and to analyse the CE of LZD vs other agents	Additional large studies are needed to clarify whether LZD is more or less CE than other agents and to better define the role of LZD in treating certain conditions (e.g. sepsis, endocarditis) and in different patient populations (e.g. patients with HIV/AIDS) While LZD-resistant strains of MRSA remain rare, ongoing surveillance is important to optimize infection control measures to prevent their spread Although most patients tolerate LZD well, clinicians must be cognisant of potential adverse reactions LZD seems to be more effective than VAN for treating people with SSTIs, including SSTIs caused by MRSA The available evidence is at high risk of bias and is based on studies that were supported by the pharmaceutical company that makes LZD Further well-designed, independently funded RCTs are needed to confirm the available evidence
Yue et al. [15] 9 papers Up until 2013	To compare the effects and safety of LZD and VAN for treating people with SSTIs	

^a Abbreviations used in the table: *AIDS* acquired immunodeficiency syndrome, *ASC* active surveillance culture, *CE* cost effective/cost effectiveness, *CI* confidence interval, *GISA* glycopeptide-intermediate *S. aureus*, *HA* hospital-acquired, *HIV* human immunodeficiency virus, *LOS* length of stay, *LZD* linezolid, *MSSA* methicillin-susceptible *S. aureus*, *PCR* polymerase chain reaction, *QALY* quality-adjusted life-year, *RCT* randomized controlled trial, *S&D* screening and decolonization, *SSI* surgical site infection, *SSTI* skin and soft-tissue infection, *VAN* vancomycin, *VAP* ventilator-associated pneumonia, *VRSA* vancomycin-resistant *S. aureus*

directly or indirectly, to hospital-acquired infections, and many of these infections are caused by antimicrobial-resistant bacteria (about 25,000 deaths are attributed to five specific antimicrobial-resistant bacteria, including MRSA) [16]. In the USA, resistant bacteria affect approximately 2 million people, and they seem to be the cause of more than 23,000 deaths [17]. Although the data from the EU and the USA are not comparable, because the studies have focused on different bacteria, these numbers point out the large human burden attributable to antimicrobial resistance. Moreover, according to a study carried out by the European Centre for Disease Prevention and Control (ECDC), the direct cost of infections that are due to some of the most important antimicrobial-resistant bacteria in the EU, Iceland and Norway has been approximately €1.5 billion per year during the last decade. [16]. In the USA, the figure rises to \$55 billion, as calculated for 2013, if both direct and indirect costs are considered [17]. With respect to the most prevalent antimicrobial-resistant bacteria, there has been, during recent decades, a high level of concern about the increase in MRSA, which has been considered to be one of the most important nosocomial pathogens worldwide. According to the latest data from the European Antimicrobial Resistance Surveillance System (EARSS) regarding the prevalence of bacteraemic MRSA isolates recovered in different EU countries, a north-to-south gradient has been reported, with the highest proportions found in the Mediterranean countries (25–50 %) [18].

The first detection of strains of *S. aureus* that were resistant to methicillin emerged shortly after the clinical use of this antibiotic; they were able to produce a modified penicillin-binding protein (PBP), encoded by the gene *mecA*, which presented low affinity for β -lactams (named PBP2a) [3]. Recently, a novel *mecA* homologue gene, named *mecC* [19, 20], has been described. This gene is also responsible for methicillin resistance, but it is not detectable by the conventional methods that are currently used to identify MRSA strains in hospital settings, with the consequent risks that such misdiagnoses entail. MRSA strains are resistant to most β -lactams, with the exception of a few cephalosporins; this implies a serious therapeutic problem, as it severely limits the treatment options. Moreover, MRSA strains are able to acquire multiple genes that confer resistance to other non- β -lactam agents (such as aminoglycosides, macrolides and fluoroquinolones, among others), which often present a multi-resistance phenotype. The current alternatives for treatment of MRSA, such as glycopeptides, linezolid or daptomycin, could, in some cases, be problematic because of reduced susceptibilities or emerging mechanisms of resistance [21, 22].

S. aureus, in most cases of methicillin-susceptible *S. aureus* (MSSA) but also in cases of MRSA, can colonize the noses of humans and animals [23]. It has been observed

that *S. aureus* infections (by MSSA or MRSA) are frequently preceded by colonization [24]. A reduction in the level of MRSA colonization in specific settings has been associated with a reduction in MRSA infections [25].

In recent years, changes in the epidemiology of this microorganism have occurred. First, this pathogen spread rapidly in hospital environments (hospital-acquired MRSA [HA-MRSA]) [16]. Since the 1990s, the emergence of MRSA in people in the community has altered the idea that this microorganism was a phenomenon observed only in health care settings. These community-acquired MRSA (CA-MRSA) strains are, in general, more susceptible to other antimicrobials (different from β -lactams), but they are more virulent, and many of them produce Panton–Valentine leukocidin (PVL) [26]. These strains are now also emerging in hospital settings, and the differentiation of HA-MRSA and CA-MRSA strains is now more complicated [27].

In addition, in recent years, a new variant of MRSA associated with farm animals has emerged worldwide. These strains comprise the so-called livestock-associated MRSA (LA-MRSA), and the ST398 clone is the most prevalent. This new variant is mainly found in pigs and other farm animals [28]. There have been reports of the presence of ST398 in pets, in foods and also in healthy humans, or causing human infections and outbreaks [28–33]. It is clear that LA-MRSA has an important effect on the economy, not only because of its health effects on humans but also because of its effects on livestock animal health and food safety.

3 Literature Review Method

To identify the literature in the area related to MRSA and the economic information related to it, we conducted a search in the PubMed database up to 15 October 2014. The search terms used were ‘MRSA’ AND ‘economic evaluation’ OR ‘economic cost’ OR ‘budget’ OR ‘mortality cost’ OR ‘length of stay and cost’. To date, as mentioned in the introduction, there have been several general and specific review articles that have covered some aspects of the economic implications of MRSA. As a consequence, we decided to eliminate the papers included in those reviews from the current review and, hence, we are only presenting an update on the current literature findings (the aforementioned 69 new papers).

Five tables (one for each question) have been compiled to describe each reference, the year and location of the study, the objectives, materials and methods, and the main economic results of each article (Tables 2, 3, 4, 5, 6). We have included two additional columns to show the study authors’ conclusions, and the limitations and observations

Table 2 Summary of the 11 studies related to methicillin-resistant *S. aureus* (MRSA) vs methicillin-resistant *S. aureus* (MSSA) costs^a

Reference/ study period ^b / location	Objectives	Methods	Economic results ^c	Conclusions of the authors	Limitations and observations acknowledged by the authors
Abramson and Sexton [34] 1993–1995 Durham, NC, USA	To determine the attributable hospital stay and costs of nosocomial MSSA and MRSA primary BSIs	Pairwise- matched (1:1) nested case- control study	MRSA vs MSSA: (a) 12 vs 4 days ($P = 0.023$) (d) \$27,083 vs \$9,661 per case ($P = 0.043$)	Nosocomial primary BSI due to <i>S. aureus</i> significantly prolongs the LOS. Primary nosocomial BSIs due to MRSA result in 3-fold increase in direct cost, compared with those due to MSSA	Potential risk factors that were not collected may have affected hospital costs or LOS The generalizability of the findings may be limited given the small size of the study
Anderson et al. [35] 1998–2003 Durham, NC, USA	To determine clinical and financial outcomes of SSTIs directly attributable to MRSA and MR	Retrospective analysis Multicentre matched- outcome study	MRSA vs MRSA-free: (a) 23 days (95 % CI 19–26) (d) \$61,681 per case (95 % CI 23–100) Probability of (n): yes (OR 35, 95 % CI 17–70) Excess (c): yes (OR 7, 95 % CI 2–18) MRSA vs MSSA: (a) 5.5 days (95 % CI 1–9) (d) \$24,113 per case (95 % CI 4–43) Probability of (n): no (OR 0.4, 95 % CI 0.2–0.8) Excess (c): no (OR 1.7, 95 % CI 0.7–4) YA: 2003	The attributable impact of <i>S. aureus</i> and MR on outcomes of surgical patients is substantial. Preventing a single case of SSTI due to MRSA can save hospitals as much as \$60,000	The study included only deep incisional and organ/space infections. Thus, the findings cannot be generalized As indirect medical costs, the authors considered only indirect in-hospital costs but no other indirect costs, so their charge estimates were probably underestimations of the true financial impact of these infections
Ben-David et al. [36] 2000–2003 RI, USA	To study the impacts of MRSA in hospitals on mortality, LOS and costs, and to compare it with MSSA BSI	Retrospective cohort study Used multivariable adjustment and PSA	MRSA vs MSSA: (a) 20.5 vs 10.5 days (d) \$113,852 vs \$42,137 per case (o) \$51,492 vs \$17,603 per case Multivariable adjustment: excess (a), (d), (o): yes PSA: excess (a), (d), (o): no YA: 2003	On the basis of PSA, they found that MR did not independently increase hospital cost or LOS after onset of <i>S. aureus</i> BSI They believe that use of PSA in a comparable subset of patients may be a better method than multivariable adjustment in cohort studies	They included all patients who developed nosocomial <i>S. aureus</i> BSI during their hospital stay. Thus, patients with various admission diagnoses were included in the cohort

Table 2 continued

Reference/ study period ^b / location	Objectives	Methods	Economic results ^c	Conclusions of the authors	Limitations and observations acknowledged by the authors
Erdem et al. [37] 1996–2007 HI, USA	To determine osteomyelitis admission rates and to describe characteristics of osteomyelitis associated with MSSA and MRSA infections	Retrospective inpatient chart reviews	MRSA vs MSSA: Excess (a), (p), (q), (r): NS Excess (d), (s): yes ($P = 0.0045$ and $P = 0.018$, respectively)	MRSA-infected patients had frequent surgical procedures and systemic complications	The retrospective nature of the study did not allow them to support any possible association between osteomyelitis and a prior history of SSTIs or close contact with an infected or colonized person The isolates were not available to study the role of virulence factors
Filice et al. [38] 2004–2006 MN, USA	To determine differences in health care costs between cases of MSSA and MRSA infection in adults	Retrospective study	MRSA vs MSSA: (c) 23.6 vs 11.5 % (d) \$34,657 vs \$15,923 per case YA: 2007	MRSA was independently associated with increased costs. Effective antimicrobial stewardship and infection prevention programmes are needed to prevent these costly infections	It was only performed at a single hospital The extra costs of private rooms, gowns, gloves and labour for MRSA-infected patients were not included
Kaye et al. [39] USA	To compare MRSA- and VRE- infected patients with non- infected or MSSA- and VSE- infected patients	Case-control study	MRSA vs MRSA-free: (a) 29.1 vs 6.1 days (c) 20.7 vs 2.1 % (d) \$118,414 vs \$34,395 per case MRSA vs MSSA: (a) 22.0 vs 13.2 days (c) 20.7 vs 6.7 % (d) \$118,414 vs \$73,165 per case	The impact on clinical outcomes was 2-to 3-fold greater when patients with MRSA SSTI were compared with an uninfected control group as opposed to being compared with control patients infected with MSSA SSTI	Cost results are not directly comparable. The studies were performed in two different geographical sites and used slightly different analytical methods
Kopp et al. [40] 1999–2000 AZ, USA	To determine the clinical and economic implications of MRSA vs MSSA infections across a variety of infection sites and severity of illnesses	Retrospective case-control analysis	MRSA vs MSSA: (a) 15.5 vs 11 days ($P = 0.05$) (e) common in MRSA patients (j) \$16,575 vs \$12,862 ($P = 0.11$) per case (u) 10 vs 7 days ($P = 0.003$) [NS]	Patients with MRSA infections had worse clinical and economic outcomes than patients with MSSA infections	They had to rely on the accuracy of documentation because of retrospective study design Unbalanced differences in co-morbid conditions may exist and might have altered the study findings The sample size was small Some patient data were lacking

Table 2 continued

Reference/ study period ^b / location	Objectives	Methods	Economic results ^c	Conclusions of the authors	Limitations and observations acknowledged by the authors
Kraker et al. [41] 2007–2008 EU	To estimate the excess mortality and LOS associated with MRSA BSI in European hospitals	Multicentre, prospective, parallel matched- cohort study	[1] MRSA vs MRSA/ MSSA-free: Excess (a) 9.2 days (5.2–13.5) Excess (c): yes [2] MSSA vs MRSA/ MSSA-free: Excess (a) 8.6 days (CI 6.8–10.4) Excess (c): yes [1] vs [2]: Excess (a): no Excess (c): yes in 30-day mortality	Irrespective of methicillin susceptibility, <i>S. aureus</i> BSI has a significant impact on morbidity and mortality. In addition, MRSA BSI leads to a fatal outcome more frequently than MSSA BSI. Infection control efforts in hospitals should aim to contain infections caused by both MRSA and MSSA	Potential distortion of results due to discrepancies between hospitals, such as variations in blood culture frequencies or local differences in clinical management Exclusion of exposed patients with excessive LOS before infection resulted in problems of bias They had to exclude exposed patients with excessive LOS before infection, because they were unable to find appropriate controls
Lodise and McKinnon [42] 1999–2001 Detroit, MI, USA	To determine the morbidity, mortality and hospital costs attributable to MR in patients with SAB	Retrospective cohort study using ANCOVA	MRSA vs MSSA: (a) 20.1 vs 13.7 days (c) 30.6 vs 15.3 % (e) 59.6 vs 33 % (d) \$22,735 vs \$11,205 per case Using ANCOVA: (a) 19.1 vs 14.2 days (d) \$21,577 vs \$11,668 per case	MRSA has a slower clinical response Patients with MRSA have an elevated risk of delayed treatment Antibiotics with reliable MRSA activity should be initiated in patients at risk of MRSA, with appropriate adjustment once sensitivity results are available	The results may be unique to the patient population studied It may be difficult to extrapolate the cost findings to other institutions They did not examine the relationship between the specific antibiotic administered and patient outcomes For indirect medical costs, they considered only costs derived from departments that do not provide direct patient care services, but not other indirect costs
Rubio-Terrés et al. [43] 2005 Spain	To calculate the impact of MRSA vs MSSA bacteraemia on health care resources and associated costs in Spain	Retrospective cohort study Univariate sensitivity analyses	MRSA vs MSSA: Excess (a) 2.2 days Excess (d) €1,205 per case Excess (p) 3.1 days Excess (t) 7.6 % YA: 2006	There were additional costs due to resistant strains. MRSA was associated with higher costs in bacteraemia patients, which was attributable to the greater rate of ICU admissions and increased LOS	Because of its retrospective design, some data in the clinical histories were lacking MRSA-infected patients were older, with a higher incidence of nosocomial bacteraemia

Table 2 continued

Reference/ study period ^{b/} location	Objectives	Methods	Economic results ^c	Conclusions of the authors	Limitations and observations acknowledged by the authors
Shorr et al. [44] 2002–2003 USA	To gain better understanding of the clinical and economic outcomes associated with MRSA infection in patients with early-onset VAP	Retrospective cohort analysis	MRSA vs MSSA: Excess (a) 3.8 days Excess ICU (a) 5.3 days Excess MV (a) 4.4 days Excess (d) US\$7,731 per case	Diagnosis of MRSA-related VAP is a determinant of excess hospital LOS, ICU LOS and attributable costs, compared with MSSA infection It is necessary to develop effective strategies for diagnosis, treatment and prevention of MRSA related VAP	They only identified early-onset VAP cases within 5 days of hospitalization Because they used positive culture to define cases, they were unable to estimate potential VAP cases in general and MRSA cases in particular The generalizability of their findings may be limited

^a Abbreviations used in the table: ANCOVA analysis of covariance, *BSI* bloodstream infection, *CE* cost effective/cost effectiveness, *CI* confidence interval, *EU* European Union, *ICER* incremental cost-effectiveness ratio, *ICU* intensive care unit, *LOS* length of stay, *MR* methicillin resistance, *MV* mechanical ventilation, *NS* not statistically significant, *OR* odds ratio, *PSA* propensity score approach, *SAB S. aureus* bacteraemia, *SSTI* skin and soft-tissue infection, *VAP* ventilator-associated pneumonia, *VRE* vancomycin-resistant enterococci, *VSE* vancomycin-susceptible enterococci, *YA* year of adjustment

^b If the original paper did not include the year of the study, the relevant cell in the table does not mention this detail

^c (a) LOS; (b) economic impact; (c) mortality; (d) direct cost; (e) treatment failure; (f) institutionalization; (g) functional impairment at discharge; (h) indirect cost; (i) survival; (j) treatment cost; (k) cost saving; (l) cost of isolation and management of colonized patients; (m) costs of screening; (n) readmission; (o) cost after infection; (p) length of treatment; (q) chronic health problems; (r) total duration of fever; (s) systemic complication rate; (t) rates of admission to ICU; (u) longer antibiotic-related LOS; (v) saving in LOS; (w) saving in deaths; (x) cost of the strategy; (y) failure of treatment; (z) cure rate; (A) CE; (B) cost-benefit; (C) median saving-to-cost ratio; (D) saving-cost difference; (E) efficacy of prevention measures; (F) risk ratio; (G) ICER

^d The reference year for the adjustment of the estimated costs (YA) is indicated; if the original paper did not include the reference year, the relevant cell in the table does not mention the YA data

that they acknowledged in their studies. We also compiled a table showing the main conclusions of the previous reviews in this field (Table 1).

4 Analysis of MRSA Costs (Versus MSSA and Versus No MRSA)

4.1 Costs of MRSA Versus MSSA

Eleven studies addressing the cost of MRSA versus MSSA were found using the selected search terms [34–44] (Table 2). The analysed research generally considered the differences in the utilization of resources for MRSA and MSSA patients. A few articles established an additional control group of uninfected patients to calculate the incremental costs due to infections (regardless of whether *S. aureus* is or is not resistant) [35, 39, 41]. The majority of the studies referred to the US context and showed a wide range of economic values, depending on the setting of the specific study. For instance, Lodise and McKinnon [42] found mean direct costs of US\$22,735 versus US\$11,205, corresponding to an LOS of 20.1 versus 13.7 days at the beginning of last decade, while Kaye et al. [39] found an LOS of 22 versus 13 days, representing a mean cost per case of US\$118,414 versus US\$73,165. It was common to find large cost differences between the MRSA group and the MSSA group—with the costs of the MRSA group being up to three times greater. The number of additional days in the LOS was in the range of 2–10 [36, 43], and most of the differences were statistically significant.

Regarding the different types of hospital resources, again, few papers dealt with intensive care units (ICUs) and regular wards separately, to fix the total costs, and they tended to consider only the incremental LOS resulting from the MRSA infection and to multiply the average per diem cost, independently of the type of ward to which patients were admitted. Furthermore, there was evidence of mortality due to MRSA in several databases collected by the authors; however, the economic consequences of these deaths were not well stated in those papers (either those deaths were explicitly left out and only the costs of the patients that survived were calculated—see, for instance, Gómez-Pavón et al. [45]—or the reviewed papers simply did not address that issue, i.e. they did not discuss how those deaths affected their calculations). In pure economic terms, there is a kind of contradiction, in the sense that patients who die from MRSA soon after admission result in lower costs than those who are cured after a long LOS in the hospital. This element was barely discussed in the reviewed papers. Another statistical aspect is the sample size of the primary data that were collected. Some papers based their analysis on rather small samples [34, 36, 40],

i.e. fewer than 40 patients. Sample size has implications for the reliability of statistical tests in an examination of the differences between MRSA and MSSA patients, and it might explain the greater variability of the results. Again, this issue was scarcely discussed in the papers.

All of the reviewed articles calculated only those costs that were related to hospital resources. The source of information was primarily internal hospital data; these data had several origins: (a) hospital charges (frequently, a general coefficient is applied to transform them into costs); (b) fixed and variable costs related to treatment of the infection, as obtained from hospital accounting; and (c) direct and indirect costs, defined as those related to treatments and those capturing the opportunity costs of foregone revenues (those due to the isolation of patients in specific wards), respectively.

The study by Shorr [6] was a very comprehensive review on the epidemiology and economic impact of MRSA up to 2007; after reviewing articles that compared MRSA cases and MSSA cases (targeting diabetic foot infections, pneumonia, and skin and soft-tissue infections [SSTIs]), he also noted the higher costs associated with MRSA. Seven years after that study, our findings with respect to the 11 reviewed studies highlight that LOS is also the major cost driver and that MRSA generates an important economic burden on hospital care and, hence, on society. Interestingly, this research topic has been extended in scope in recent years, and the cost calculations have also addressed other pathologies and settings that were not covered in Shorr's review (e.g. bloodstream infections, osteomyelitis, geriatric institutions and neonatal care).

Given that MRSA can appear in different hospital settings, the heterogeneity of the studies was quite wide. The variety of therapeutic areas where patients are treated makes it difficult to generalize and to yield a common or average value of the incremental costs derived from methicillin resistance in *S. aureus* infections. Furthermore, almost every article defined its own target variable (such as drug treatment costs, LOS, institutionalization needs, total duration of fever, cure rate and failure of treatment), after which an estimation of costs was performed; the variety of approaches permits us to understand the issue from different perspectives, but it also makes it difficult to produce a narrow range of values for the additional costs induced by the resistance.

In summary, we can mention that the variations in the total costs of MRSA are triggered by the heterogeneity of the patients, the clinical management of their conditions and the cost structures of the centres where they are treated.

4.2 MRSA Costs

A total of 17 studies reported the costs attributed to MRSA infections [45–61] (Table 3). Methodologically, these

Table 3 Summary of the 17 studies related to methicillin-resistant *S. aureus* (MRSA) costs^a

Reference/ study period ^b / location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Athanasakis et al. [46] Greece	To conduct a cost analysis and a budget impact analysis relative to different management scenarios for MRSA-cSSTIs from a hospital perspective	Economic model	Total: (d) €29,196,218 LZD vs VAN vs DAP vs TIG vs TEI: (a) 9.2 vs 12.5 vs 10.3 vs 13.0 vs 14 days (d) €2,457 vs €2,762 vs €2,850 vs €3,494 vs €3,094 per case YA: 2013	Development of hospital strategies that facilitate early discharge, such as introduction of clinical criteria and guidelines for switching from intravenous to oral MRSA-cSSTI therapy, could result in substantial savings for the Greek hospital budget	The study design assumed equal effectiveness among the different treatment schedules. This probably led to conservative estimations Lack of Greek-specific pharmaceutical use and MRSA cSSTI prevalence data Results may not be fully transferable to other treatment settings
Angelis et al. [47] 2004–2006 Switzerland	To use an MM method to estimate the excess of LOS associated with MRSA colonization and infection in surgical patients	MM Used the Aalen-Johansen estimator of the matrix of transition probabilities	MRSA-infected vs MRSA-free: Excess (a) 14.5 [95 % CI 7.8–21.3] days MRSA carriers vs MRSA-free: Excess (a) 5.9 (95 % CI 0.1–11.7) days	MM is a promising statistical method Nosocomial MRSA infection significantly extends LOS, particularly in acute care wards	Possible selection bias induced by the exclusion of hospital readmissions among patients with MRSA SSTIs Low generalizability of the results to centres without long-term care and rehabilitation wards Unadjusted nature of the excess LOS analysis Lack of information on HA infections due to other pathogens and adjustment for other time-varying covariates, such as the severity of illness
Goetghebuer et al. [48] 1995–2005 Canada	To estimate the current cost of MRSA in Canada and to assess the magnitude of this public health issue	Analysis of the literature	(d) \$12,216 per case YA: 2005	MRSA is a costly public health issue that needs to be tackled. Coordinated leadership, compliance with barrier precautions, use of efficacious first-line antimicrobials and guidelines for proper use of the new ones are some available avenues	Lost revenue from hospital rooms used for isolation and indirect costs were not considered Most data were from tertiary care hospitals and not representative of Canadian hospitals The study only used one source of incidence data (CNISP) and may have underestimated MRSA rates The cost of antimicrobial administration was underestimated

Table 3 continued

Reference/ study period ^b / location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Gómez-Pavón et al. [45] 2001–2006 Madrid, Spain	To determine the risk of mortality, functional decline and institutionalization, as well as the hospital costs associated with MRSA infection in an AGU	Retrospective study	MRSA vs MRSA-free: (a) 22.15 vs 10.64 days ($P < 0.001$) (c) 25.5 vs 7.7 % ($P < 0.001$) (d) €7,517.71 vs €3,611.21 ($P < 0.001$) per case (f) 29 vs 9 % ($P < 0.001$) (g) Barthel index 39.43 vs 55.24 ($P < 0.01$)	MRSA infection in the AGU is associated with higher mortality, worse functional status at discharge and a higher incidence of institutionalization, as well as significantly longer LOS and higher hospital costs	The retrospective character of this study prevented adjustment for co-morbidity and diagnosis-related groups
Hübner et al. [49] 2011 Greifswald, Germany	To determine the real costs associated with MRSA cases from the hospital perspective	Retrospective study	(a) 22.75 days (d) €8,673.04 per case	More cost studies, preferably with a multicentre and prospective study design, are required	General limitations of retrospective and monocentre studies They used a conservative approach and included only direct costs that are attributable to identified cases
Kanerva et al. [50] 2003–2004 Helsinki, Finland	To establish costs of an outbreak of MRSA in the surgical and internal medicine units of a hospital	Retrospective study	MRSA infections vs MRSA colonization vs exposed to MRSA but with status inconclusive vs exposed and negative for MRSA: (d) Additional total costs of MRSA: €386,062 Costs due to MR in treatment: €16,000	The high cost of MRSA screening underlines the importance of appropriate screening methods The model for analysing costs that was used might be useful for other hospitals after adaptation of variables	Indirect medical costs were not assessed
Kim et al. [51] 1996–1998 ON, Canada	To determine the costs associated with the management of hospitalized patients with MRSA, and to estimate the economic burden associated with MRSA in Canadian hospitals	Retrospective study	Excess (a) 14 days (range 6–112) Excess (j) \$287,200 (\$14,360 per patient) Excess (l) \$128,095 (\$1,363 per admission) Excess (m) \$109,813 Excess annual hospital cost of MRSA in Canada: \$42–59 million	These results indicate that there is a substantial economic burden associated with MRSA in Canadian hospitals	A number of factors may affect the cost projections for hospitals across the country The analysis did not include any additional costs that may be incurred in the investigation or management of a nosocomial MRSA outbreak

Table 3 continued

Reference/ study period ^b / location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Kraker et al. [52] 2007 31 countries (EARSS): EU, Croatia, Turkey and Israel	To determine the excess number of deaths, bed-days, and hospital costs associated with BSIs caused by MRSA and third-generation cephalosporin-resistant <i>E. coli</i> (G3CREC)	Prospective cohort studies	MRSA or MSSA vs absence of <i>S. aureus</i> bacteraemia: MRSA: Excess (a) 255,683 days Excess (c) 5,503 deaths (d) €44.0 million total MSSA: Excess (a) 691,400 days Excess (c) 7,261 deaths (d) €129.0 million total (d) \$1,933.71 per case (e) 21 % of total patients/27 % of patients in the moderate or cSSTI group/11 % of patients in the mild or uncomplicated group ($P = 0.08$) YA: 2011	Excess mortality associated with BSIs caused by MRSA is significant, and the longer LOS imposes a considerable burden on health care systems	The incidence of resistant BSIs reported by EARSS hospitals may differ from the national average, because of the size, different standards of care and/or different local epidemiology of EARSS hospitals The study did not consider the impact of a delay in appropriate therapy
Labreche et al. [53] 2009–2011 TX, USA	To measure the incidence of treatment failure and associated costs in patients with MRSA SSTIs	Prospective observational study	Baseline risk stratification and new treatment approaches are needed to reduce treatment failures and costs in the primary care setting	Only patients in South TX Only studied SSTIs Patients who did not return to the clinic were counted as treatment successes Clinicians may have changed their behaviour to fit expected results (Hawthorne effect) Indirect medical costs were not assessed	
Lee et al. [54] 2009–2011 USA	To develop an 'economic simulation model' to quantify the costs associated with CA-MRSA infection from the societal and third-party payer perspectives	Classified patients as having SSTI, pneumonia or other invasive infection	Third-party payer perspective: Per CA-MRSA case: (d) \$2,277–\$3,200 Total in USA: \$478 million to 2.2 billion Societal perspective: per CA-MRSA case: (d) + (h) \$7,070–\$20,489 Total in USA: \$1.4–13.8 billion YA: 2011	The considerable economic burden of CA-MRSA infections may justify further investment in prevention and control Much of the overall burden stems from productivity losses Early identification and appropriate treatment of infections could save considerable costs	The model's parameter values came from studies with varying rigour and study populations (which may not be comparable) and may change as new studies emerge Infections were classified into discrete syndromic categories, while infections may involve multiple categories or other severe manifestations They were conservative and probably underestimated the economic burden of CA-MRSA They did not account for all possible procedures (permanent disability, control interventions for CA-MRSA carriers, etc.)

Table 3 continued

Reference/ study period ^b / location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Macedo- Viñas et al. [55] 2009 Switzerland	To estimate the health-economic burden of MRSA infections at a Swiss university hospital, using different analytical approaches	MM and MA	MRSA-infected vs MRSA carriers vs MRSA-free: (a) 37.3 vs 33 vs 8.8 days Excess (a) MM: 11.5 days/MA: 15.3 days (b) Cost per MRSA episode: CHF 4,929–1,313,355 Average additional daily cost of MRSA: CHF 800 YA: 2009	This study demonstrates the importance of accounting for time-dependent bias and confirms that MM is a valid strategy	They did not consider the presence of other nosocomial infections Costs attributable to the extra LOS were calculated from the average bed-day cost for the total acute care episode rather than only the period after onset of infection
Ramanathan et al. [56] 2005 TX, USA	To know the total and itemized health care costs at their facility that were associated with catheter-related sepsis due to Gram-positive and Gram-negative bacteria	Retrospective study Kaplan–Meier analysis	MRSA vs another organism: (a) 13 vs 9 days Additional (d) of \$5,806 per case (i) Worse survival rates on Kaplan–Meier analysis ($P < 0.004$)	This study confirmed the tremendous overall economic burden of catheter-related bacteraemia and specifically identified hypalbuminaemia and MRSA bacteraemia as risk factors associated with higher health care costs	A large fraction of veterans undergo HD at private health care units and they are admitted to the facility that was studied only for inpatient care Other unknown medical conditions could have led to low serum albumin levels and possibly influenced the duration of LOS and resultant expenditure All studied subjects were men The lack of statistical difference between groups could be caused by the small sample size
Resch et al. [57] 2004 Germany	To study the mortality, LOS and cost of MRSA patients at 11 German hospitals	Retrospective matched-pairs analysis	MRSA vs MRSA-free: Excess (a) 11 days per case Excess (c) 7 % Excess (d) € 8,198 per case Total excess (d) €761,516,569	They demonstrated that MRSA patients stayed in hospital longer and showed higher mortality. MRSA patients also caused higher costs	Indirect medical costs were not assessed

Table 3 continued

Reference/ study period ^b / location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Schultz et al. [58] 2004–2006 Durham, NC, USA	To determine the economic impact of MRSA-colonized neonates in a level III NICU	Prospective study	MRSA-colonized vs non- MRSA colonized: (a) According to weeks of gestation at birth [1] <28 weeks: 118 ± 9.0 days vs 68 ± 3.5 days ($P < 0.001$) [2] 28–31 weeks: 48 ± 7.1 vs 25 ± 1.7 days ($P < 0.001$) [3] <31 weeks: 33 ± 8.1 days vs 8 ± 0.4 days ($P < 0.001$) Excess of total (d) \$6,901,180	There is substantial need to increase the ability of the level II NICU to accommodate MRSA-colonized patients	This analysis ignored the difficulty in staffing the cohorted MRSA- positive neonates, resulting in less efficient staffing ratios and decreased numbers of nurses available to care for new admissions
Smith et al. [59] UK	Macroeconomic approach to tackling antimicrobial resistance	Evaluation of three 'macro' policies Study of the effects of MRSA on the health care sector, labour productivity and GDP, among other items, in the UK	Antimicrobial resistance is likely to have a far greater impact on the national economy than would be estimated by concentrating on the health care sector alone	The permit system appears to offer the most efficient 'solution' to optimize antimicrobial consumption and, hence, reduce the development of resistance	It was assumed that, with one type of consumer/household, policies and costs affect every household uniformly
Watters et al. [60] Dublin, Ireland	To assess the morbidity and cost associated with treatment of head and neck cancer patients who become colonized or infected with MRSA following major surgical procedures	Retrospective analysis	MRSA vs MRSA-free: (a) 3 times greater in MRSA group (d) 3 times higher in MRSA group Excess (j) £2,470 per case	The extra stay in hospital, extra days in ICU, extra medical and nursing care and additional costly antibiotic treatment led to major cost implications and loss of health service resources in the unit	It is not generalizable to patients with other pathologies

Table 3 continued

Reference/ study period ^{b/} location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Weigelt et al. [61] 2003–2007 USA	To examine the causative pathogens, mortality and economic burden among patients rehospitalized for SSTIs	Retrospective analysis	MRSA vs other pathogens: (a) 6 vs 5 days ($P < 0.001$) (c) 1.4 vs 0.8 % ($P = 0.03$) (d) \$7,036 vs \$6,134 ($P < 0.0001$) per case	SSTIs caused by MRSA increased significantly and were independently associated with economic burden Admission illness severity, transfer from another health care setting and recent hospitalization were associated with increased mortality, LOS and costs	They did not know whether the MRSA strains were colonizers from the original surgical admission or acquired in the outpatient health care setting The data from the original surgical admission are limited to the same hospital admission Many factors such as the care process after patients were admitted to the hospital could influence LOS and cost. Unfortunately, information regarding the care process was not in the database

^a Abbreviations used in the table: *AGU* acute geriatric unit, *BSI* bloodstream infection, *CA* community-acquired, *CE* cost effective/cost effectiveness, *CI* confidence interval, *CNIS* Canadian Nosocomial Infection Surveillance Program, *cSSTI* complicated skin and soft-tissue infection, *DAP* daptomycin, *EARSS* European Antimicrobial Resistance Surveillance System, *GDP* gross domestic product, *HA* hospital-acquired, *HD* haemodialysis, *ICER* incremental cost-effectiveness ratio, *ICU* intensive care unit, *LOS* length of stay, *LZD* linezolid, *MA* matched analysis, *MM* multi-state modelling, *MR* methicillin resistance, *MSSA* methicillin-susceptible *S. aureus*, *NICU* neonatal intensive care unit, *SSTI* skin and soft-tissue infection, *TEI* teicoplanin, *TEL* telavancin, *TIG* tigecycline, *VAN* vancomycin, *YA* year of adjustment

^b If the original paper did not include the year of the study, the cell in the table does not mention this detail

^c (a) LOS; (b) economic impact; (c) mortality; (d) direct cost; (e) treatment failure; (f) institutionalization; (g) functional impairment at discharge; (h) indirect cost; (i) survival; (j) treatment cost; (k) cost saving; (l) cost of isolation and management of colonized patients; (m) costs of screening; (n) readmission; (o) cost after infection; (p) length of treatment; (q) chronic health problems; (r) total duration of fever; (s) systemic complication rate; (t) rates of admission to ICU; (u) longer antibiotic-related LOS; (v) saving in LOS; (w) saving in deaths; (x) cost of strategy; (y) failure of treatment; (z) cure rate; (A) CE; (B) cost-benefit; (C) median saving-to-cost ratio; (D) saving-cost difference; (E) efficacy of prevention measures; (F) risk ratio; (G) ICER

^d The reference year for the adjustment of the estimated costs (YA) is indicated; if the original paper did not include the reference year, the relevant cell in the table does not mention the YA data

Table 4 Summary of the 20 studies related to methicillin-resistant *S. aureus* (MRSA) prophylactic alternatives^a

Reference/ study period/ location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Clancy et al. [62] 2006–2010 Pittsburgh, PA, USA	To model the CE and economic value of routine perioperative <i>S. aureus</i> S&D of lung and heart–lung transplant recipients from hospital and third-party payer perspectives	Retrospective study	Hospital perspective vs third-party payer perspective: (k) \$73,567–\$133,157 vs \$10,748– \$16,723 per case, varying with the probability of colonization, infection and decolonization efficacy YA: 2012	The data support routine <i>S. aureus</i> S&D of lung and heart–lung transplant patients	The decolonization protocol was not mandatory during the study period, and they did not have data on compliance within the cardiothoracic ICU They could not draw definitive conclusions about the clinical impact of S&D in their patient population Computer models are simplifications of real life and cannot represent all situations Their model utilized colonization and infection rates from a single centre The analysis included the 1-year time course, not taking into account the long-term effects
Courville et al. [63] 2007–2008 USA	To perform a CE analysis to evaluate preoperative use of mupirocin in patients with TJA	‘Simple decision tree model’	[1] Preoperative screening for all patients + mupirocin for positive patients [2] Mupirocin for all patients [3] No mupirocin or screening [1] and [2] had lower costs and greater benefits than [3]	Empirical treatment with mupirocin or use of a screen- and-treat strategy before TJA is a simple, safe and CE intervention	It was limited by the paucity of literature on <i>S. aureus</i> decolonization and SSTI in patients who undergo orthopaedic procedures The study did not consider the possible selection of mupirocin resistance
Diller et al. [64] 2004 Münster, Germany	To evaluate the CE of preadmission MRSA screening and subsequent decolonization of patients admitted to the Department of General Surgery at the University Hospital of Münster	Prospective study	d) €6,000–10,000 for each infected patient (k) €20,000 for detecting and successfully decolonizing a total of 5 patients through preadmission screening The strategy was CE	Preadmission screening for MRSA is an effective method to reduce the hospital burden of MRSA- colonized patients, and the savings due to consistent decolonization before elective admission outweigh the screening costs	Additional costs due to the increased morbidity and mortality of MRSA carriers and possible spread of MRSA through unrecognized colonization were not included

Table 4 continued

Reference/study period ^b /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Elliott et al. [65] Nottingham, UK	To explore whether there is a threshold of MRSA prevalence at which switching to routine glycopeptide-based antibiotic prophylaxis becomes CE	Indicative model to explore CE of VAN, CEP or a combination in patients undergoing primary hip arthroplasty	If the MRSA infection rate is ≥ 0.25 % and the rate of other infections with CEP prophylaxis is ≥ 0.2 %, use of combined antibiotic prophylaxis is optimal	The indicative model provides a framework for evaluation	Outcomes were not clearly defined The main cost driver appeared to be LOS. However, LOS was not measured directly and the data were not corrected for confounding factors Collection of additional data would be essential for modelling in this area
Goldsack et al. [1] 2013 Newark, NJ, USA	To investigate the clinical, patient experience and cost impacts of performing active surveillance on known MRSA-positive patients admitted to 7 medical-surgical units of a large regional hospital, specifically to allow discontinuation of contact isolation	Retrospective study	Only 19.8 % (32/162) were still colonized (k) \$101,230 total per year across the 7 study units	Screening programme targeting patients with a history of MRSA who would otherwise be placed in isolation has the potential to improve outcomes and patient experience and reduce costs	They used culture-based screening with CHROMagar MRSA rather than real-time PCR screening. Cultures are less sensitive than PCR and also require a longer turnaround time Individuals may be only intermittently colonized, and the programme tested patients only at a certain moment in time The programme evaluation did not consider the impact of clearing these patients on future admissions subsequent to their study period
Gurieva et al. [66] 2010 The Netherlands	To evaluate the effects and costs of four S&I strategies and to identify the critical parameters for this outcome	Mathematical model	[1] S&I of previously documented carriers ('flagged') [2] S&I of flagged and ICU admissions [3] S&I of flagged and 'frequent' patients [4] S&I of all admissions [1], [2], [3] or [4] vs doing nothing: (k) [1] and [2] > (k) [3] and [4] (E) 10 % for [1], 25 % for [2], 50 % for [3] and 100 % for [4]	Universal screening hardly prevents more infections than S&I of flagged and frequent patients; S&I of flagged and ICU patients was the most cost-saving strategy. Whether an intervention is cost saving within 10 years depends on costs/infection in ICU, screening costs and isolation efficacy	Inclusion of some assumptions that could modify the results. For example: Pathogens predominantly spread in health care settings (is not applicable for CA-MRSA) All isolation measures were equally effective in all isolated patients and all measures were executed with equal efficacy

Table 4 continued

Reference/study period ^b /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Huang et al. [67] 2012 Orange, CA, USA	To compare 3 strategies for reducing BSIs in ICU: MRSA nares S&I, TD and UD	Cost analysis using decision modelling	S&I vs TD vs UD: (a) 4,391 vs 4,377 vs 4,362 (d) \$19,320,000 vs \$19,250,000 vs \$19,170,000 for every 1,000 ICU admissions UD vs SI/TD: (k) \$171,000 for every 1,000 ICU admissions YA: 2012	UD for patients admitted to ICU would reduce BSIs and likely reduce health care costs, compared with the other strategies	The estimated cost per ICU-day that they used was based on hospital charges that were then adjusted downwards by cost-to-charge ratios Their analysis was conservative since they did not include any productivity or time costs associated with reduced morbidity The use of a static model also meant that sensitivity analyses were not dynamically linked to other parameters
Lee et al. [68] 2008 USA	To determine the economic value of the testing and decolonization strategy before vascular operations	Decision analytic computer simulation model	Decolonization strategy was CE (Δ ratio <\$50,000/QALY) when MRSA prevalence was ≥ 0.01 and decolonization success rate was ≥ 0.25	Testing and decolonizing MRSA patients before vascular surgery may be CE over a wide range of MRSA prevalence and decolonization success rates	Data came from different studies of varying quality The model did not fully reflect the sociodemographic and clinical heterogeneity of vascular surgery patients The model also focused on MRSA, which has disproportionately higher morbidity and mortality, compared with MSSA The study used a culture from a single anterior nares sample, and this surveillance was not 100 % sensitive for nasal carriage of MRSA
Lee et al. [69] 2009 USA	To estimate the economic value of preoperative MRSA S&D for cardiac surgery patients	Monte Carlo decision analytic computer simulation model	Strategy was CE (\$15,000/QALY) when MRSA prevalence was ≥ 0.01 and decolonization success rate was ≥ 0.25 YA: 2009	Routine preoperative screening of cardiac surgery patients could provide economic value to third-party payers and hospitals over a wide range of MRSA prevalence, decolonization success rates and surveillance costs	The findings may not be applicable to patients undergoing emergency cardiac surgery, as the urgency of surgery may not allow enough time for preoperative S&D

Table 4 continued

Reference/study period ^b /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Lee et al. [70] 2009 USA	To estimate the economic value of routine preoperative MRSA S&D of orthopaedic surgery patients	Stochastic decision analytic computer simulation model	Strategy was CE (\$6,000/QALY) when MRSA prevalence was ≥ 0.01 and decolonization success rate was ≥ 0.25 YA: 2009	Routine preoperative S&D of orthopaedic surgery patients may, in many circumstances, save money while providing health benefits	Data came from different studies of varying quality The findings may not be applicable to patients undergoing emergency orthopaedic surgery, because the urgency of treatment obviates screening
Lee et al. [71] 2010 USA	To evaluate the economic value of routine periodic testing and decolonization of HD patients for MRSA	Construction of a 'Markov computer simulation model' to evaluate the economic value of two routine testing: agar-based and PCR	MRSA surveillance was CE (Δ ratio $\leq \$50,000/\text{QALY}$) for all conditions tested Agar-based was dominant at MRSA prevalence $\geq 10\%$ and decolonization success rate $\geq 25\%$ PCR was dominant at MRSA prevalence $\geq 20\%$ and decolonization success rate $\geq 75\%$ YA: 2010	Routine periodic testing and decolonization of HD patients for MRSA may be a CE strategy over a wide range of MRSA prevalence rates, decolonization success rates and testing intervals	Selection of the most common clinical outcomes for which data were available The data inputs of the model came from different studies of varying quality and may not fully reflect the sociodemographic and clinical heterogeneity of HD patients Results may not be generalizable to younger HD patients, as the model considered only patients ≥ 61 years of age The selection of mupirocin resistance was not considered Not quantification of how information from routine testing may help public health officials, administrators and researchers to monitor MRSA spread and the effectiveness of interventions
Mueller and Krebsbach [72] 2004–2006 Lincoln, NE, USA	To calculate the impact of an antimicrobial-impregnated gauze dressing on SSIs, including MRSA infections	Prospective study	(k) \$508,605 total per year YA: 2007	Significant reduction in SSTIs, resulted from a simple change from plain sterile gauze to a sterile comparable antimicrobial dressing. This change reduced morbidity and mortality, shortened LOS and reduced costs	During the study period, there were external variables which could affect the results of the study, e.g. demolition and remodelling of the operating rooms

Table 4 continued

Reference/study period ^b /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Nelson et al. [73] Switzerland	To compare the clinical outcomes and economic costs associated with several MRSA control strategies implemented at the facility level	Decision analytic model One-way and two-way sensitivity analyses and Monte Carlo simulations	[1] Surveillance + decolonization [2] Surveillance only [3] No surveillance Base-case analysis/Monte Carlo simulations: (A) [1] > (A) [2] > (A) [3] Sensitivity analyses: if direct decolonization benefit is low (1–4 %), [1] was not dominant	These results provide a strong economic argument for adding an MRSA decolonization protocol to the current Veterans Health Administration active surveillance strategy	The static model did not capture the dynamic elements of decolonization, including resistance, compliance with contact precaution protocol and herd immunity effects The effectiveness measures were infections and deaths avoided, rather than QALY The time interval between tests and results was not explicitly modelled in the decision tree
Noskin et al. [74] 2003 USA	To evaluate the economic impact of performing rapid testing for <i>S. aureus</i> colonization before admission in inpatients who are scheduled to undergo surgery and subsequent decolonization therapy	‘Budget impact model’ with probabilistic sensitivity analysis	(k) \$231,538,400 total per year (v) 364,919 days (w) 935 in-hospital deaths per year Sensitivity analysis: 64.5 % probability that there would be cost savings to US hospitals YA: 2004	Addition of preadmission testing and decolonization therapy to standard care would result in significant cost savings, even after accounting for variations in model input values	It is likely that the cost savings for individual hospitals may vary on the basis of patient differences and other factors The analysis focused on screening patients for carriage of all strains of <i>S. aureus</i> rather than just MRSA The model focused on <i>S. aureus</i> colonization in the nares and not at any other body sites It assumed no rescreening for <i>S. aureus</i> nasal carriage among patients who received decolonization treatment
Nulens et al. [2] 2000–2004 The Netherlands	To retrospectively establish the cost of the search-and-destroy policy at University Hospital Maastricht and to determine the threshold of MRSA prevalence at which the search-and-destroy policy would still be CE	Retrospective study	(a) 39.9 days (d) €2,736,762 total per year (x) €1,383,200 total per year (B) when MRSA prevalence is ≤8 %	From an economic point of view, the search-and-destroy policy is the best alternative for maintaining an endemic MRSA level of <1 %	The cost of lost hospitalization days and non-performed surgery was not included

Table 4 continued

Reference/study period ^b /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Olechanski et al. [75] USA	To compare the impacts of different MRSA screening test options and programme characteristics on the clinical outcomes and budget of a typical US hospital	Excel-based decision analytic model Multivariate sensitivity analysis	(k) \$12,158–\$76,624 per month (m) PCR \$112,012 < (m) selective media \$113,742 < (m) non-selective media Multivariate sensitivity analysis: PCR testing of high-risk patients resulted in fewer infections	All screening options showed reductions in infection rates and cost impact improvement over no screening programme Among the options, PCR testing for high-risk patients slightly edged out the others in terms of fewest infections and greatest potential cost savings	Certain costs (cost of antimicrobials, medical/legal costs) and adverse publicity following HA infections were not included in the model The model did not include the costs and potential reimbursement associated with readmitting patients The model did not include all possible approaches to implement infection control programmes The model focused only on MRSA and did not assess the impacts of other screening or isolation programmes on MRSA infections or the influence of a MRSA screening programme on transmission of other resistant pathogens
Petlin et al. [76] 2008–2011 St Louis, MO, USA	To examine the impact of a bathing protocol using CHG on MRSA acquisition in 5 adult ICUs and the cost differences between CHG bathing by using the bath-basin method vs using CHG-impregnated wipes	Pre-/post-intervention study	Before CHG vs after CHG: 132 patients acquired MRSA in 34,333 patient days (rate ratio 3.84) vs 109 patients acquiring MRSA in 41,376 patient days (rate ratio 2.63). Bath-basin method vs CHG-impregnated wipes: (d) \$3.18 vs \$5.52 per case	The CHG bathing protocol is easy to implement, is CE and led to decreased unit-acquired MRSA rates in a variety of adult ICUs	Only one bathing protocol was examined There were differences in the surveillance protocols for MRSA in the ICUs

Table 4 continued

Reference/study period ^b /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Robotham et al. [77] England and Wales, UK	To assess the CE of screening, isolation and decolonization strategies in the control of MRSA in ICU	Dynamic transmission model	(A) Universal admission and weekly screening with PCR and decolonization using mupirocin was most CE Isolation of only patients at high risk of carrying MRSA was most CE when MRSA prevalence was 5 % Universal admission and weekly PCR and isolation were CE when MRSA prevalence was 10 %	MRSA control strategies that use decolonization are cost saving in an ICU provided resistance is lacking, and combining universal screening using PCR with decolonization is likely to represent good value for money if UD is considered unacceptable	Because the model ignored infections after discharge and because MRSA colonization may have longer-term health consequences, as well as potentially leading to readmissions of colonized patients, the results presented would be expected to underestimate health benefits and cost savings resulting from interventions to control MRSA For targeted strategies, a decolonization regimen of mupirocin alone was used, whereas many protocols may currently use skin antiseptics
Wassenberg et al. [78] 2001–2010 The Netherlands	To determine the CE of different preoperative <i>S. aureus</i> screening regimens with further nasal decolonization with mupirocin	Prospective study and hospital database	[1] Treat all patients [2] Treat only identified carriers Base. No treatment or screening [1] vs [2]: (k) €7,339 vs €3,330/QALY If cost of screening is <€6.23, option [2] would be dominant YA: 2004	Preoperative screening and eradication of <i>S. aureus</i> carriage to prevent deep-seated infections saves life-years and medical costs, although treating all patients without screening is the dominant option	The number of not-screened patients was not available Several assumptions regarding different parameter values had to be introduced Only direct health care costs were included Mupirocin resistance was not considered

Table 4 continued

Reference/study period ^b /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
You et al. [79] 2000–2011 Hong Kong	To examine potential clinical outcomes and costs of active MRSA surveillance with and without decolonization in NICUs from the perspective of health care providers in Hong Kong	Decision analysis modelling Sensitivity analyses and Monte Carlo simulations	Base-case analysis: surveillance and decolonization vs surveillance alone: MRSA infection rate 0.911 vs 1.759 % (c) 0.223 vs 0.431 % (d) US\$47,294 vs US\$48,031 per case Sensitivity analyses: (d) surveillance and decolonization < d) surveillance if (F) of acquiring MRSA infections in carriers after decolonization was <0.997 Monte Carlo simulations: (c) and (d) surveillance and decolonization < (c) and (d) surveillance	Surveillance and decolonization for patients admitted to NICUs appears to be cost saving and effective in reducing the MRSA infection rate and the MRSA-associated mortality rate	The model quality was limited by the sources of clinical model inputs, which were mostly obtained from retrospective observational studies Lack of cost and clinical outcomes related to toxicity of decolonization in the model, as the literature on decolonization safety in neonates is inadequate

^a Abbreviations used in the table: *BSI* bloodstream infection, *CA-MRSA* community-acquired MRSA, *CE* cost effective/cost effectiveness, *CEP* cephalosporin, *CHG* chlorhexidine gluconate, *HA* hospital-acquired, *HD* haemodialysis, *ICER* incremental cost-effectiveness ratio; *ICU* intensive care unit, *LOS* length of stay, *MSSA* methicillin-susceptible *S. aureus*, *PCR* polymerase chain reaction, *QALY* quality-adjusted life-year, *S&D* screening and decolonization, *S&I* screening and isolation, *SSI* surgical site infection, *SSTI* skin and soft-tissue infection, *TD* targeted decolonization, *TJA* total joint arthroplasty, *UD* universal decolonization, *VAN* vancomycin, *YA* year of adjustment

^b If the original paper did not include the year of the study, the cell in the table does not mention this detail

^c (a) LOS; (b) economic impact; (c) mortality; (d) direct cost; (e) treatment failure; (f) Institutionalization; (g) functional impairment at discharge; (h) indirect cost; (i) survival; (j) treatment cost; (k) cost saving; (l) cost of isolation and management of colonized patients; (m) costs of screening; (n) readmission; (o) cost after infection; (p) length of treatment; (q) chronic health problems; (r) total duration of fever; (s) systemic complication rate; (t) rates of admission to ICU; (u) longer antibiotic-related LOS; (v) saving in LOS; (w) saving in deaths; (x) cost of the strategy; (y) failure of treatment; (z) cure rate; (A) CE; (B) cost-benefit; (C) median saving-to-cost ratio; (D) saving-cost difference; (E) efficacy of prevention measures; (F) risk ratio; (G) ICER

^d The reference year for the adjustment of the estimated costs (YA) is indicated; if the original paper did not include the reference year, the relevant cell in the table does not mention the YA data

studies differed from the studies that analysed MRSA versus MSSA costs, in the sense that they generally calculated the additional costs by using the absence of infection in similar medical pathologies as a benchmark [45, 47, 51, 52, 55, 56, 58]. Furthermore, some studies calculated the cost of MRSA patients only, without comparing them with any other group [48, 53]. Nevertheless, we observed that there were many common elements in the methodology and findings of the papers that focused exclusively on MRSA costs and those that analysed MRSA versus MSSA costs.

Most of the papers, when comparing MRSA cases with MRSA-free cases, reported an important increment in direct costs, i.e. about 2 to 3 times greater; depending on the study, use of health resources, such as the LOS, was increased by 8–29 days, and the additional total cost was in the range of US\$1,900–84,000 (Table 3); in general, these values are higher than those previously shown in comparisons of MRSA and MSSA, specifically because of the high costs resulting from the management of MSSA cases.

The reviewed articles combined patients without classifying costs according to co-morbidities or patient case mix. Again, the range of the costs resulting from resistance was too broad for them to be summarized by an intuitive figure; for instance, the range of values reported by Gómez-Pavón et al. [45] was in a relationship of 1–2 (i.e. €3,611–7,517) for the period 2001–2006, and in the analysis by Lee et al. [54] the relationship was 1–3, i.e. €7,070–20,849, for 2009–2011 (indirect costs were included too). Macedo-Viñas et al. [55] found 15.3 days of incremental LOS, also in a similar period, but in a range that was quite wide, which translated into an increment of CHF 4,929–1,313,355. The work by Kim et al. [51] found an incremental LOS for colonized patients of 14 days, on average (the range was from 6 to 112 days), which meant that the additional hospitalization costs due to MRSA, across Canada, would have been \$41.7–58.7 million for the period 1996–1998.

Some papers analysed outbreaks in a hospital setting [50], while others focused on catheter-related bacteraemia [56]. In addition, some studies dealt with the incremental LOS of colonized versus non-colonized patients [47, 51] and others focused on the differences in diagnosis-related groups (DRGs) that were dependent on the MRSA issue [57]. The study by Schultz et al. [58] was one of the most specific, as it analysed the incremental costs in the neonatal ICU in an American hospital, finding an additional total cost of close to \$7 million. Other studies provided an analytical presentation of the costs, classifying and estimating the different types of health resources—namely, drugs, interventions and direct medical expenses.

The designs of the studies frequently referred to a specific setting, but in some instances, there were

extrapolations to the whole country [48, 51]. Goetghebeur et al. [48], using the costs found in a literature review, estimated the impact in Canada using a ‘cost per case of MRSA’ approach (rather than an ‘incremental cost per case’ approach). The study by Smith et al. [59] also estimated the implications of MRSA policy, nationwide, in the UK, designing a macroeconomic model in which the consequences of regulation, taxation and permits (tradable licenses that are provided to all physicians so they can prescribe up to a designated level of antimicrobials, effectively capping the total prescription) on MRSA control, as well as the implications of MRSA on the national economy, could be quantified. This study allowed an analysis of the economic repercussions of MRSA on sectors other than the health care sector. The study by Athanasakis et al. [46], which was based on a simulation model and expert opinions, estimated that, for Greece, the total cost of MRSA infections was about €29 million.

These studies generally used the hospital perspective when analysing costs, although some [54] also considered the loss of productivity due to MRSA infections and the costs borne by third parties. The incremental hospital costs due to MRSA represented up to 108 % of the average cost in the absence of that infection, as found by Gómez-Pavón et al. [45]. Again, general patterns among the papers and general conclusions regarding the total costs are difficult to establish, given the variety of study designs and jurisdictions in which the management of the infection and its associated costs were observed.

5 MRSA Prophylaxis and Decision-Making Processes

Preventive medical decisions are originally made on the basis of a risk–benefit trade-off, and lately, they have incorporated efficiency criteria from the field of economics. Pure ‘cost of illness’-type studies provide information on the general costs of treating the affected patients; they make health managers and society, in general, more aware of the implications of resistance. However, these studies are not fully useful to support a decision when several options are available. This gap is intended to be filled by studies that analyse efficiency, with the help of economic evaluation methods. To date, several surveys have also reviewed these issues, and they have assessed these prophylactic policies. In Table 4, we summarize 20 papers that we found, which were not included in those reviews [1, 2, 62–79].

There are a variety of prophylactic goals that were targeted in these studies. For instance:

1. Isolation of MRSA carriers from non-carriers in the wards of a hospital: Gurieva et al. [66], in the

Table 5 Summary of the three studies related to rapid detection of methicillin-resistant *S. aureus* (MRSA)^a

Reference/ study-period/ location	Objectives	Methods	Economic results ^c	Conclusions of the authors	Limitations and observations acknowledged by the authors
Henson et al. [81] 2011–2012 MS, USA	To compare the PCR assay and traditional microbiological culture as screening tools for the identification of MRSA in patients admitted to the paediatric and surgical ICUs at a 722-bed academic medical centre	Prospective study	PCR vs microbiological culture: (d) \$602.95 vs \$364.30 per positive carrier identified HA-MRSA vs MRSA identified on admission (a) 29.5 vs 6 days (d) \$63,810 vs \$14,561 per case (k) \$49,249 per hospitalization	A reduction of 2.9 HA-MRSA cases/month associated with PCR screening suggested potential savings in hospitalization costs of \$142,822 per month	The study was small, and it was not possible to directly relate the CE and cost–benefit analysis, because of confounding factors such as underlying patient morbidity and mortality
Shrestha et al. [82] Cleveland, OH, USA	To determine the accuracy and CE of a PCR for detecting nasal carriage of <i>S. aureus</i> directly from clinical specimens	Cross-sectional study	[1] Culture-guided therapy vs [2] PCR-guided therapy vs [3] treat-PCR vs [4] treat-culture vs [5] universal therapy (d) [1] \$22.60, [2] \$25.10, [3] \$28.60, [4] \$37.40, [5] \$49.40 per case Incremental (A) ratio: [2] and [3] were lowest (\$1.64 and \$6.98)	Rapid real-time PCR is an accurate, rapid and CE method for identifying <i>S. aureus</i> carriers for preoperative intervention Universal therapy without testing is not CE in any circumstances	The capital costs of the culture and PCR strategies were not considered in the analysis
Yossepowitch et al. [83] 2012 Israel	To study an algorithm combining two rapid methods to detect <i>S. aureus</i> and its susceptibility to OXA directly from positive blood cultures	Prospective study	Combined rapid assays produced results within 2 h and reduced cost by 75 % compared with Xpert MRSA/SA BC Assay if used alone on all blood bottles	Early notification of results in conjunction with an antimicrobial stewardship programme can potentially reduce unnecessary antimicrobial costs and improve care for patients with <i>S. aureus</i> bacteraemia	Low sensitivity of the BinaxNOW [®] assay (92 %) in detecting <i>S. aureus</i>

^a Abbreviations used in the table: CE cost effective/cost effectiveness, HA hospital-acquired, ICER incremental cost-effectiveness ratio, ICU intensive care unit, LOS length of stay, OXA oxacillin, PCR polymerase chain reaction

^b If the original paper did not include the year of the study, the relevant cell in the table does not mention this detail

^c (a) LOS; (b) economic impact; (c) mortality; (d) direct cost; (e) treatment failure; (f) institutionalization; (g) functional impairment at discharge; (h) indirect cost; (i) survival; (j) treatment cost; (k) cost saving; (l) cost of isolation and management of colonized patients; (m) costs of screening; (n) readmission; (o) cost after infection; (p) length of treatment; (q) chronic health problems; (r) total duration of fever; (s) systemic complication rate; (t) rates of admission to ICU; (u) longer antibiotic-related LOS; (v) saving in LOS; (w) saving in deaths; (x) cost of the strategy; (y) failure of treatment; (z) cure rate; (A) CE; (B) cost–benefit; (C) median saving-to-cost ratio; (D) saving–cost difference; (E) efficacy of prevention measures; (F) risk ratio; (G) ICER

Table 6 Summary of the 21 studies related to methicillin-resistant *S. aureus* (MRSA) treatments^a

Reference/ study period/ location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Bounthavong et al. [93] 2004–2009 USA	To evaluate the CE analysis of LZD, DAP, and VAN in MRSA cSSTI	Decision analytic model Univariate and probabilistic sensitivity analyses Bayesian methods	LZD vs DAP vs VAN: (d) \$18,057 vs \$20,698 vs \$23,671 per case (A) ratio: \$37,604 vs \$44,086 vs \$52,663 per successfully treated patient LZD vs VAN: LZD was dominant DAP vs VAN: DAP was dominant LZD vs DAP: LZD was dominant YA: 2009	LZD and DAP are potentially –CE on the basis of the assumptions of the decision analytic model; however, LZD appears to be more CE for MRSA cSSTIs	Consideration should be given to the potential for antimicrobial resistance Limitations of the studies included
Brown et al. [94] 2006–2008 New York, NY, USA	To determine whether there is a quantitative relationship between the duration of VAN treatment or cumulative VAN exposure and outcomes and costs in patients with complicated bacteraemia or infective endocarditis due to MRSA	Retrospective study Classification and regression tree analysis Univariate and multivariate modelling	Retrospective study VAN exposure vs no VAN exposure: (c) 16 % (f) 32 % No significant differences were observed in variables and costs	According to the model, the cumulative VAN amount and duration were associated with attributable mortality and clinical failure but not with differences in costs	The sample size of the study was small The retrospective methods of this analysis could lead to confounding and bias The data came from a single institution, possibly resulting in a loss of external validity
Campbell et al. [95] 2009 Detroit, MI, USA	To compare the clinical efficacy and potential cost savings associated with use of T/S vs LZD and DAP in MRSA infections with an MIC of 2 µg/mL for VAN	Retrospective study Univariate and multivariable analysis	Univariate analysis T/S vs DAP or LZD: (c) T/S < (c) DAP/LZD (z) T/S > (z) DAP/LZD Multivariate models: (c) NS (T/S) (k) \$2,067.40 per patient	T/S compared favourably to LZD and DAP in terms of treatment efficacy and mortality. Use of T/S could potentially reduce costs. T/S should be considered for treatment of MRSA infection with an MIC of 2 µg/mL for VAN	Retrospective study, with its inherent biases
De Cock et al. [96] Germany	To evaluate CE of LZD vs VAN in suspected MRSA nosocomial pneumonia in Germany	Decision analytic model Delphi Panel	Linezolid vs vancomycin: (a) 11.2 vs 10.8 days (c) 20.7 vs 33.9 % (d) €12,829 vs €12,409 per case (z) 73.6 vs 64.9 % YA: 2006	The cost–benefit profile suggested that LZD could be considered a CE alternative to VAN for treatment of patients with MRSA nosocomial pneumonia	The model base case scenario considered the conditions under which the clinical trials were carried out—conditions that are likely to differ in real-life German practice Limitations of the Delphi method include respondent bias and lack of consensus; it provides the opinions of physicians in particular hospital settings and patient populations and it may not be generalizable

Table 6 continued

Reference/study period ^a /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Eckmann et al. [91] 2010–2011 Austria, Czech Republic, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Slovakia, Spain and UK	To describe country-specific variations across Europe in real-world MRSA cSSTI treatment patterns, antibiotic stewardship activity and potential opportunities for (ES from IV to oral formulations and ED from hospital, using standardized data collection and criteria and economic implications of these opportunities	Retrospective study	(a) From 15.2 to 25 days (k) From €414 (Slovakia) to €2,703 (France) per case ES and ED eligibility ranged from 12.0 % (Slovakia) to 56.3 % (Greece) and from 10 % (Slovakia) to 48.2 % (Portugal), respectively YA: 2012	MRSA cSSTI treatment patterns varied widely across countries, but further reductions in IV therapy, hospital LOS and associated costs could be realized	Limitation in follow-up data availability if patients were re-admitted to a different hospital Retrospective observational design
Kullar et al. [97] 2005–2010 Detroit, MI, USA	To compare clinical outcomes and costs in patients treated with the new VAN trough recommending goal serum vs patients treated with VAN doses targeting trough concentrations of 5–20 mg/L prior to the new guidelines	Retrospective quasi-experimental study	VAN 15–20 mg/L (pre) vs VAN 5–20 mg/L (post): (a) 15 vs 13.5 days ($P = 0.28$) (d) \$32,754 vs \$27,709 per case ($P = 0.147$) [NS] (p) 13 vs 8.5 days ($P < 0.001$) (z) 45 vs 60 % ($P = 0.034$) YA: 2008	Higher VAN trough concentrations improved outcomes in patients with complicated MRSA bacteraemia. More aggressive dosing was shown to significantly decrease the overall duration of VAN therapy, which may affect total LOS and cost	Small cohort These results may not be applicable to other institutions Given the retrospective nature of this study, the information on the performed interventions might have not been collected for all patients Implementation of higher VAN trough level goals may have occurred sooner in some patients, resulting in contamination of the results between the pre- and post-period groups The results could have been different if the study had been performed after the publication of the Infectious Diseases Society of America practice guidelines for MRSA bacteraemia
Kullar et al. [98] 2005–2010 Detroit, MI, USA	To evaluate a clinical pathway using DAP in patients with bacteraemia caused by MRSA isolates exhibiting VAN MICs >1 mg/L	Two-phase quasi-experimental study	DAP (after VAN) [III] vs VAN [I]: (a) [III] $<$ (a) [I] (d) \$18,385 vs \$19,755 per case ($P > 0.05$) (m) 33 vs 21 % ($P = 0.08$) (p) [III] $<$ (p) [I] (z) 75.0 vs 41.4 % ($P < 0.001$) YA: 2010	Among the patients with MRSA bacteraemia that exhibited elevated VAN MICs, the switch to DAP improved clinical success without increasing the treatment cost	It was not known how patients' clinical outcomes and overall hospitalization costs may have been impacted if daptomycin was used empirically before any vancomycin therapy The lack of randomization in the study and the before-and-after timeline introduce the possibility of temporal confounders

Table 6 continued

Reference/study period ^a /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Laohavaleeson et al. [99] 2003–2004 USA	To determine the CE of TEL vs VAN for treatment of cSSTIs	Pharmacoeconomic analysis	TEL vs VAN: (a) 8 days for both ($P = 0.742$) (d) \$8,118 vs \$8,185 per case ($P = 0.560$) For MRSA: similar findings (A) for MRSA > (A) for total population (G) for TEL (–\$9,560) to \$27,889 (as acquisition price was increased) YA: 2006	Infection-related LOS and total cost of TEL were similar to those of VAN for treatment of cSSTIs. Particularly in those infected with MRSA, TEL may be more CE than VAN over the range of acquisition prices tested	The price of TEL was unknown at the time of their study, and the duration of treatment in clinical practice could be different from the one used in this analysis The benefit measure was disease specific and might not be easily comparable with the benefits of other care interventions
Lipsky et al. [100] 2008–2009 USA	To examine economic outcomes associated with inappropriate initial antibiotic treatment for cSSTIs, using data from adults hospitalized and treated with IV antibiotic therapy	Multicentre, prospective, observational study	Appropriate vs inappropriate initial antibiotic treatment for MRSA: (a) 6.44 vs 8.83 days Composite economic outcome (hospital admission, emergency department visits or unscheduled health care visits): 10.5 vs 26.2 % YA: 2006	Avoiding inappropriate initial antibiotic treatment is not only clinically important but also has substantial economic implications	The accuracy and completeness of the data that were collected varied with the investigators at the individual study sites Some of the subanalyses had a small sample size The study included the four most common cSSTI infection types; the findings may not be generalizable to other types of cSSTIs, uncomplicated infections or excluded populations
McKinnon et al. [101] 2004 USA	To assess the economic outcomes of LZD vs VAN and to evaluate the determinants of treatment costs for cSSTIs	Multinational, open-label, clinical trial multivariate regression analysis	LZD vs VAN: (a) LZD < (a) VAN (d) \$4,881 vs \$5,039 per case ($P = 0.041$) (p) LZD < (p) VAN YA: 2004	LZD therapy was associated with improved clinical outcomes and significantly lower treatment costs than VAN. The largest cost advantage was demonstrated in patients with MRSA cSSTIs	Patients enrolled in the study may have received medical treatment or procedures that are not consistent with standard clinical practice but were mandated by the protocol Patients included in the analysis may have displayed inherent selection bias
Międzybrodzki et al. [102] 2007 Poland	To present economic aspects of experimental phage therapy in patients infected with <i>Staphylococcus</i> and treated at the Phage Therapy Center	Retrospective study	Phage therapy vs VAN vs LZD and Q/D vs TEL: (d) PLN 2,096 vs PLN 1,376.00 per case PLN 2,076.20 vs PLN 6,235.42 PLN 7,562.80 vs PLN 10,483.40 (€1 = approximately PLN 4) YA: 2007	Experimental phage therapy could be an alternative to antibiotics for treatment of chronic MRSA infections, especially in outpatients	The study could be biased because of the selected 6 cases in which good clinical effect of the phage therapy was seen

Table 6 continued

Reference/study period ^a /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Nathwani et al. [92] 2010–2011 UK, Ireland, France, Germany, Italy, Spain, Portugal, Austria, Greece, Poland, Slovakia, Czech Republic	To document pan-European real-world treatment patterns and health care resource use and estimate opportunities for ES from IV to oral antibiotics and ED of hospitalized patients with MRSA cSSTIs	Retrospective study	Switch from IV to oral treatment vs IV-only treatment: (a) 19.1 ± 12.9 vs 21.0 ± 18.2 days; $P = 0.162$ Potential savings of €2,000 per ED-eligible patient YA: 2012	A substantial number of patients with MRSA cSSTI could be switched to oral therapy and discharged earlier from hospital, resulting in cost savings across European health care systems	Inherent limitations of a retrospective medical chart review Not all ES/ED criteria could be applied at inclusion to determine actual (rather than potential) cost savings The results could be influenced by a disease severity bias in those receiving IV-to-oral switch treatment vs IV-only treatment
Patel et al. [103] 2012 USA	To compare the economic impacts of LZD and VAN for treatment of hospitalized patients with MRSA-confirmed nosocomial pneumonia	4-week decision tree model	LZD vs VAN: (d) \$46,168 vs \$46,992 per case (G) LZD better than VAN YA: 2012	LZD has a favourable ICER compared with VAN for MRSA-confirmed nosocomial pneumonia, largely attributable to the higher clinical trial response rate of patients treated with LZD	In the model's base case scenario, they considered some conditions, which may differ in real-life US clinical practice The results may not be applicable to scenarios outside the US
Sharpe et al. [104] Louisville, KY, USA	To compare oral LZD and intravenous VAN for management of cSSTI caused by MRSA	Prospective study	LZD vs VAN: (a) 3 vs 6 days (d) Inpatient charges: \$277 vs \$160; outpatient charges: \$103 vs \$200 per day (z) 50 vs 20 %	Clinical outcomes were significantly better with LZD than with VAN. LZD was associated with reduced LOS and outpatient charges	They estimated direct costs only The study was small (60 patients) The trial was confined to a single research site, thus possibly limiting applicability of the data
Rosner et al. [105] 1997–2000 Canada	To determine the costs and consequences of LZD use vs VAN IV for treatment of infections caused by MRSA	Retrospective study	LZD vs VAN IV: (a) 21.4 vs 23.4 days (k) \$750 per case YA: 2001	The estimated LZD cost savings not only offset the higher acquisition cost of the anti-infective but may be substantial for health care systems across Canada	The data set for the LZD group was simulated on the basis of observational data collected from VAN IV-treated patients The early discharge benefits observed for patients treated with LZD relied on several key assumptions involving both the switch of therapy and the discharge algorithms
Rubio-Terrés et al. [106] Spain	To assess the efficiency of DAP vs VAN for treatment of MRSA bacteraemia	Retrospective study Monte Carlo probabilistic and deterministic analysis	DAP vs VAN: (d) €12,329 vs €12,696 per case (z) 44.4 vs 31.8 %, not statistically significant ($P = 0.2203$) Probabilistic and deterministic analysis: DAP was dominant Monte Carlo simulation: DAP was most CE YA: 2011	DAP is more CE than VAN in treating MRSA bacteraemia. The higher cost of acquisition of DAP does not imply a higher cost of treating this infection	It was not a pragmatic design The model considered the duration of antibiotic treatment for all <i>S. aureus</i> bacteraemia (14 and 15 days for DAP and VAN, respectively) because these data were not available in the publication of clinical trial based on bacteraemia MRSA

Table 6 continued

Reference/study period ^a /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
Schürmann et al. [107] Germany	To evaluate the CE of LZD vs VAN in empirical treatment of cSSTI due to suspected MRSA from the German hospital and health care system perspective	Decision analytic model	LZD vs VAN: (a) 7.2 vs 9.9 days (d) €8,232 vs €9,206 per case (z) 90.1 vs 85.5 % (after first-line treatment) and 98.4 vs 98.1 % (after two lines of treatment) YA: 2003	LZD was expected to result in a shorter IV treatment duration and shorter LOS that offset its higher acquisition cost vs VAN for cSSTI in Germany	The study relied on expert opinion for resource use estimates, particularly the length of treatment and LOS It is not possible to generalize the results The study included only direct medical costs and did not consider indirect costs Isolation is not something that is widely practiced in other European countries, mainly where MRSA is endemic
Seaton et al. [89] 2007–2009 Glasgow, UK	To explore the potential for, and relative costs of, earlier hospital discharge through switching to oral antibiotic therapy (LZD or RIF and DOX) or continuation of IV therapy (TEJ) via an OPAT service in SSTIs	Retrospective study	Patients received only inpatient care vs OPAT vs oral therapy: (d) £12,316 vs £6,136 vs £6,159 per case	A significant proportion of patients with MRSA SSTI may be suitable for outpatient management with either oral therapy or via OPAT, with a reduction in treatment costs	It is possible that there were other clinical reasons that contributed to the prolongation of hospitalization The model assumed the existence of an OPAT service; consequently, set-up costs (which may require a substantial investment) were not included
Stephens et al. [90] USA	To develop an economic model from a US payer perspective that includes all direct inpatient and outpatient costs incurred by patients with MRSA cSSTI receiving LZD, VAN, or DAP	Retrospective database analyses 4-week decision model Base-case analysis and sensitivity analyses	LZD vs VAN vs DAP: (d) \$10,571 vs \$11,096 vs \$13,612 (inpatient costs); \$7,835 vs \$7,095 vs \$7,922; outpatient costs: \$2,086 vs \$4,001 vs \$5,690 YA: 2011	Outpatient costs of managing MRSA cSSTI may be reduced by 30–50 % with oral LZD vs VAN or DAP	Only direct medical costs were included The model data were partly based on expert opinion Adverse events were assigned to the VAN arm in the empirical stage of treatment but not during the definitive phase They assumed that second-line treatment is 100 % effective and that no patients died during the 4-week model timeframe
Wright and Eiland [108] 2007 AL, USA	To compare clinical and cost outcomes associated with patients who had suspected or documented MRSA infections treated with DAP, VAN or LZD in cSSTIs	Retrospective analysis	DAP vs VAN vs LZD: (a) 12.9 vs 12.3 vs 15.7 days (d) \$5,364.48 vs \$4,703.57 vs \$6,384.79 per case (p) 6.34 vs 6.21 vs 5.93 days	Future studies are necessary to determine if MRSA treatment options can be stratified on the basis of the severity of the infectious process	The true cost of OPAT is not known The clinical effectiveness of VAN was less defined during the study period with regard to the developing data describing an MRSA MIC creep to this agent The study was affected by the decision of the Pharmacy and Therapeutics Committee, which positioned VAN as the first-line agent for cSSTIs

Table 6 continued

Reference/study period ^b /location	Objectives	Methods	Economic results ^{c,d}	Conclusions of the authors	Limitations and observations acknowledged by the authors
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Young et al. [109]
2005–2010
Edinburgh, UK

To determine whether LZD was being used in accordance with local guidelines and whether it had an effect on admissions for diabetes foot ulceration

^a Abbreviations used in the table: *CE* cost effective/cost effectiveness, *cSSTI* complicated skin and soft-tissue infection, *DAP* daptomycin, *DOX* doxycycline, *ED* early discharge, *ES* early switch, *ICER* incremental cost-effectiveness ratio, *IV* intravenous, *LOS* length of stay, *LZD* linezolid, *MIC* minimal inhibitory concentration, *NS* not statistically significant, *OPAT* outpatient parenteral antimicrobial therapy, *Q/D* quinupristin/dalfopristin, *RIF* rifampicin, *SSTI* skin and soft-tissue infection, *TEI* teicoplanin, *TEL* telavancin, *T/S* trimethoprim/sulfamethoxazole, *VAN* vancomycin, *YA* year of adjustment

^b If the original paper did not include the year of the study, the relevant cell in the table does not mention this detail

^c (a) *LOS*; (b) economic impact; (c) mortality; (d) direct cost; (e) treatment failure; (f) institutionalization; (g) functional impairment at discharge; (h) indirect cost; (i) survival; (j) treatment cost; (k) cost saving; (l) cost of isolation and management of colonized patients; (m) costs of screenings; (n) readmission; (o) cost after infection; (p) length of treatment; (q) chronic health problems; (r) total duration of fever; (s) systemic complication rate; (t) rates of admission to ICU; (u) longer antibiotic-related *LOS*; (v) saving in *LOS*; (w) saving in deaths; (x) cost of the strategy; (y) failure of treatment; (z) cure rate; (A) *CE*; (B) cost–benefit; (C) median saving-to-cost ratio; (D) saving–cost difference; (E) efficacy of prevention measures; (F) risk ratio; (G) *ICER*

^d The reference year for the adjustment of the estimated costs (*YA*) is indicated; if the original paper did not include the reference year, the relevant cell in the table does not mention the *YA* data

Netherlands, analysed four screening and isolation (S&I) strategies in relation to a ‘do nothing’ scenario—(a) patients who were previously carriers; (b) patients who were previously carriers and ICU admissions; (c) patients who were previously carriers and frequent patients; and (d) all hospital admissions—and concluded that the most cost-saving S&I strategy, with the fastest return on investment, was S&I of patients who were previously carriers and ICU admissions.

- Screening for MRSA in different settings—usually preoperative patients—as well as subsequent decolonization: Lee et al. [68–71] found a cost per quality-adjusted life-year (QALY) below US\$50,000 in the period 2008–2010, and Noskin et al. [74] and Clancy et al. [62], in budget impact analyses, found that there would be net savings if that policy were adopted in the USA.
- Preoperative antibiotic prophylaxis, with different drugs, such as mupirocin: Courville et al. [63] found that empirical nasal decolonization with mupirocin was efficient when it was administered to orthopaedic surgery patients; Wassenberg et al. [78] compared treating all patients without screening and treating only identified carriers, and they concluded that preoperative prophylaxis without screening was the most efficient strategy.
- Isolation of newly admitted patients, when they had a clinical history of MRSA infection in previous admissions, was the strategy analysed by Goldsack et al. [1]; it was found to generate annual savings of about US\$101,000 in a given hospital in the USA in the year 2013.
- Other authors, such as Petlin et al. [76], analysed the efficiency of a bathing protocol using chlorhexidine gluconate versus the impregnated-wipe option in ICU patients, and showed greater efficiency of the former.
- Finally, there are some studies [67] that measured the efficiency of several strategies of screening, isolation and decolonization in ICU patients, and concluded that universal decolonization would reduce bloodstream infections and probably health care costs.

Interestingly, the review by Farbman et al. [8] analysed 36 studies published during the period 1987–2011 and found that the incremental cost effectiveness ratios (ICERs) were sometimes negative (meaning that net savings were achieved) and sometimes positive (therefore signifying a cost per health outcome), depending on the setting. They also noted that the cost component per intervention and the cost estimation methods were very variable among the different papers. The majority of the studies analysed only two components: preventive

isolation and decolonization. Farbman et al. [8] noted that the included studies had some limitations in their designs.

The 19 studies reviewed by Chen et al. [7] focused on screening and decolonization in a specific area—orthopaedic surgery—in relation to the reduction of surgical site infections (SSIs). They concluded that preoperative screening and decolonization of *S. aureus* in orthopaedic patients is cost effective in reducing SSIs. However, they found a lack of uniformity between studies and advised that the results should be stratified by the type of surgery, because of the multiple surgery sites involved. They also emphasized that a conclusive finding regarding the most appropriate swab sites for detection of *S. aureus* colonization could not be obtained from the works. However, in other types of studies in which comparisons between different sites were performed, the nasal swab seemed to be the best option [80]. Chen et al. [7] also found that the specific studies generated results that were not always statistically significant, which limited their contribution to the general knowledge on the subject.

The review by McGinagle et al. [10] targeted the efficiency of active surveillance cultures (ASCs) in ICUs. It included 20 studies. After assessing the quality of the articles according to the US Preventive Services Task Force guidelines, they concluded that ‘poor quality’ was the dominant result, and none of the studies was classified as being of good quality. They also remarked that a clear definition of ASCs was missing, which might have been a cause of the ambiguous results found in the review. The efficiency of prophylaxis using ASCs does not seem to be clear, although evidence from multiple observation-based studies suggests that the use of ASCs reduces the incidence of MRSA infections.

In a short review, which primarily targeted German environments, Korczak and Schöffmann [9] referred to a health economic evaluation of prevention and control measures related to MRSA infections or colonization in hospitals. They analysed only eight studies, from which the reviewers could not establish clear conclusions about the break-even point of cost-effective prevention and control measurements. They also recommended additional cost-benefit analyses on this issue.

As a general comment, the time horizon of these economic evaluation studies was short, and it usually covered the duration of the infection. The health outcomes were the lives gained, which also translated into life-years gained and QALYs. Several analyses only considered prophylaxis as an investment and examined the potential savings, from the hospital perspective, when it was implemented. Some of these studies were quite ambitious, because they extrapolated their findings to the whole country, such as the study by Noskin et al. [74], which estimated a probability of 65 % that net savings would be obtained if there was

testing for *S. aureus* before elective surgery in US hospitals.

We also agree with Shorr [6] and Gould et al. [4, 5], in the area of prevention of MRSA, that the reviewed literature did not provide conclusive results that could orientate the health management of prophylactic policies. Given that the efficiency of such policies is highly dependent on the prevalence of MRSA in the region, the reason for the admission to hospital (surgical or non-surgical) and hospital costs, it is very difficult to transfer the findings of the analysed experiences to other jurisdictions. Apparently, the reviewed studies indicate that the assessed policies were cost effective in these settings, according to the threshold commonly considered. Furthermore, what could be efficient for an individual hospital is not easily transferable to the whole country.

The reviewed papers do not acknowledge the fact that the efficiency of the decolonization technique consisting of administering antibiotics to every admitted patient, without a screening test, could be reversed by an increase in the resistance of MRSA to other antibiotics (in this case, mupirocin), which would generate additional costs for society.

Therefore, as a summary of the literature in this area, it is quite common to find net savings, as well as a positive incremental cost per health outcome. Nevertheless, the design of the studies must be improved to reduce the uncertainty of the results, and more studies addressing prophylactic policies are still needed to corroborate the potential savings.

6 Rapid Detection

Rapid detection is another health management policy that may be adopted in different hospitals. The rationale for such a policy is that faster diagnosis (usually performed by polymerase chain reaction [PCR]) of the MRSA infection can be used for adoption of more effective antibiotic treatment or prophylactic intervention, which would potentially translate into a higher survival rate, better quality of life for patients and, probably, lower hospital costs. Several papers have analysed the economics of these options and extrapolated (from a rather intermediate endpoint, such as the delay in the initiation of the antibiotic treatment) the benefits derived from early administration of the right antibiotic for MRSA to life-years gained (Table 5). In our search, we found several papers that had already been reviewed by Brown et al. [11], as well as three additional papers [81–83]. The paper by Shrestha et al. [82] focused on the efficiency of avoiding a delay in diagnosis of MRSA and established that rapid real-time PCR is an accurate, rapid and cost-effective method for

identifying *S. aureus* carriers for preoperative intervention, while universal mupirocin therapy without PCR testing is not cost effective under any conditions. The study by Henson et al. [81–83] showed that rapid detection was a cost-saving technology in comparison with standard microbiological tests, although the study's conclusions were limited by the reduced number of analysed cases (fewer than 40 in each arm). Yossepowitch et al. [83] calculated the efficiency of two combined rapid assays and found that their utilization reduced costs when they were implemented together with early notification of the disease management policy.

Brown and Paladino [11] reviewed 12 papers and found that the ICERs showed that the PCR tests, in all circumstances, were a dominant option. Rapid PCR testing also had the potential to reduce mortality rates and was less costly than administering empirical therapy in studies in both the EU and the USA.

Again, in spite of the diversity of study designs and settings, it seems clear that obtaining rapid confirmation of the presence of MRSA is an efficient decision for health care systems. For the moment, PCR and other rapid techniques used for detection of MRSA are focused on detecting the *mecA* gene. Nevertheless, new strategies for rapid detection should consider the emergence of the new mechanism of methicillin resistance, which is encoded by the *mecC* gene.

7 Treatment Alternatives

Vancomycin has been one of the most important options for treatment of MRSA bacteraemia and other important types of infections. Other therapeutic alternatives have arisen in recent years for treatment of SSTIs and other types of infections, including (among others) linezolid, daptomycin and telavancin. In addition, discrepancies have been revealed, in recent years, about the efficacy of vancomycin for treatment of the bacteraemia caused by vancomycin-susceptible MRSA isolates showing a slightly increased minimal inhibitory concentration (MIC) for vancomycin ($>1 \mu\text{g/mL}$); some authors have reported increased treatment failures [84, 85], but others have not found differences [86, 87] or have associated the site of infection, rather than the vancomycin MIC, with treatment failures [88].

In the area of treatment of MRSA infections, we found four reviews, as well as various individual case studies, in which the adoption of decisions for treatment of MRSA patients was assessed on economic grounds. Although there have been a variety of studies, not all of them were full economic evaluations (i.e. comparing alternative options and studying their costs and health outcomes) and,

hence, in purity, their utilization in the decision-making process is limited and could lead to biases due to the designs of the analyses. Some examples of this type of economic study are those by Seaton et al. [89] and Stephens et al. [90], which dealt with the potential savings derived from earlier discharges due to switching to an oral antibiotic regime; in this sense, in two recent studies, Eckmanna et al. [91] and Nathwani et al. [92] analysed this issue in several EU countries in the therapeutic area of cSSTI, and they highlighted the potential cost savings of oral medication and the differences across jurisdictions (with a range of €400–2,700 for the period 2010–2011).

The majority of the 21 analysed studies [89–109] (Table 6) focused on the efficiency of vancomycin, linezolid, daptomycin or telavancin treatment regimens in targeting different kind of infections, especially SSTIs [89, 90, 93, 99, 101, 104, 105, 107, 108], but also pneumonia or bacteraemia [96, 106]. Other studies provided economic data related to alternative treatment regimens for bacteraemia caused by MRSA with a vancomycin MIC $>1 \text{ mcg/mL}$ [94, 95, 97, 98] or non-antibiotic alternatives for MRSA infections [102].

The two available Cochrane reviews in this area were performed by Gurasamy et al. [13] and Yue et al. [15], and they dealt with treatment of non-surgical wounds and the administration of linezolid and vancomycin for SSTIs, respectively. In the second study, the review included nine randomized controlled trials (RCTs), and their companion studies concluded that total hospital charges per patient were lower with linezolid treatment than with vancomycin therapy, mostly because of a reduction in the LOS by 3 days with linezolid treatment. Regarding MRSA-infected non-surgical wounds, no differences were detected between daptomycin and vancomycin. As a consequence, the economic results were uncertain.

Another review by Watkins et al. [14] noted that linezolid was apparently the preferred option from the efficiency perspective, although they also found discrepancies in the analysed texts that might generate some uncertainty. They finally claimed that additional large studies were needed to clarify whether linezolid is more or less cost effective than other agents. Ager and Gould [12] performed a wide review on Gram-positive bacterial infection, and they too found that linezolid was a cost-effective treatment option in several analysed studies.

We also learned from the literature review that administering oral antibiotics to MRSA patients contributes to early discharge of patients and, consequently, may reduce the LOS (depending on the reason for the admission). Therefore, in spite of the higher cost of oral treatments, the total cost seems to be offset by the lower hospitalization costs. This indicates that oral treatments will be more efficient than parenteral ones. However, these findings,

which were also highlighted by Shorr [6], are somewhat controversial because in some cases, the design of the studies relied on expert opinions or used weak evidence with respect to the clinical outcomes (which does not come from well-designed RCTs). As efficacy is a crucial element for calculation of the efficiency of a treatment, important variables such as the specific susceptibility to the antibiotic (measured by the MIC), the type of infection and the possibility of the emergence of antimicrobial resistance in the medium and long term should be considered in all of the studies, but frequently those aspects are scarcely addressed in the cost-effectiveness literature.

In other words, basing antibiotic policy on short-term-designed cost-effectiveness studies—which mostly capture the incremental antibiotic costs that are usually offset by LOS reductions and their associated costs—is risky, because omitted future health outcomes could soon change the evaluation of efficiency. Hence, if the duration of the analysis is not prolonged, criteria other than economic factors should be more influential in setting that policy.

8 Discussion

We found several previous reviews in this area, and we observed, in our update of the literature, that there is increasing research regarding the economic issues related to MRSA infections that covers new infection sites, settings, target populations and the management of disease patterns.

According to our analyses and other literature reviews, there are a significant number of papers dealing with the calculation of the economic burden resulting from MRSA (either MRSA versus MSSA or pure ‘cost of illness’-type studies). These kinds of studies are aimed at attracting attention to this area and highlighting the importance of the health care resources needed to treat these infections; their results are not easily transferable to other settings that are different from those where they were obtained, and we consider their direct contribution towards improving the management of the disease to be limited. We must also remark that the year of the cost calculations in the reviewed studies is not clearly stated in some papers, which makes it more difficult to compare the results between different settings. However, the other kind of texts found in the literature analyse different options (prophylaxis, rapid detection and treatments) from the economic perspective, and the results of these studies constitute an informative tool in the decision-making process. As such, it would be desirable for those analyses to be easily transferable to other settings, so that the accumulated knowledge in the field could be used to improve the management of the infection.

Given the diversity of settings, the application of different antibiotic regimes, the design of the economic studies, the cost calculation and health outcome measures, and, importantly, the diversity of the patients infected by MRSA, the results of the economic evaluation studies (mostly those dealing with treatment strategies) are difficult to translate into straightforward (i.e. unambiguous) conclusions that can be used directly in real medical practice and health management. It has been determined that the reviewed articles based their economic estimations on rather weak epidemiological data that primarily came from observational and uncontrolled studies. It would be desirable for the economic studies to be based on well-designed clinical trials from which health outcomes could be derived so that the economic evaluation models could be populated with more reliable figures. This would reduce the uncertainty in the generated information regarding the efficiency of the policies and would be helpful for building a framework to rationalize the decision-making process. Moreover, it seems necessary for future articles to also consider new problems that are derived from the changing epidemiology of this microorganism. For example, it is still unknown how much it costs to manage MRSA infections in the community (not in hospitalized patients), as well as in livestock farms, and how much it would cost to avoid the increasing incidence in both non-hospitalized humans and farm animals.

We understand that medical variations in practice, as well as the heterogeneity of MRSA-infected patients, are two reasons for the large cost differences found in the literature review, but there are probably more explanatory reasons. In this sense, the methodology used in many of the reviewed studies suggests that improvement is needed.

9 Conclusions

We found a wide range of incremental LOS of 2–10 days when comparing the consequences of MRSA and MSSA infections in hospitalized patients; this meant that the direct costs of MRSA were 1.5 to 3 times greater (in the range of approximately €1,200–50,000). The incremental LOS and its associated costs were greater when comparison was established between MRSA-infected and MRSA-free patients (the range of incremental LOS was 8–29 days and the direct costs were 2 to 3 times greater; the range of direct costs was approximately €1,500–2,000). Few studies have calculated the total costs derived from resistance in the context of a country; furthermore, the accuracy of those calculations is limited.

We analysed studies of other areas of economic interest related to MRSA infection, the results of which are useful

to inform the decision-making processes (selection of rapid diagnostic techniques, prophylactic policies and treatment options); in spite of the abundant literature on these topics, the results we found only highlighted the greater efficiency of the PCR method for rapid diagnostic techniques—the results regarding efficiency in other cases (i.e. prophylaxis and treatment options) being highly dependent on the characteristics of the centres and patients, the epidemiology of the infection and the management of the disease.

Finally, extrapolation of the findings from the settings where the studies were carried out to other jurisdictions is not immediately possible, and local data are needed for calculation of the effects on the efficiency of health policies related to MRSA.

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Carmen Torres has no conflicts of interest (including non-financial). Her contributions consisted of summarizing the texts that were found, classification of the papers into different categories and general review of the written text.

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