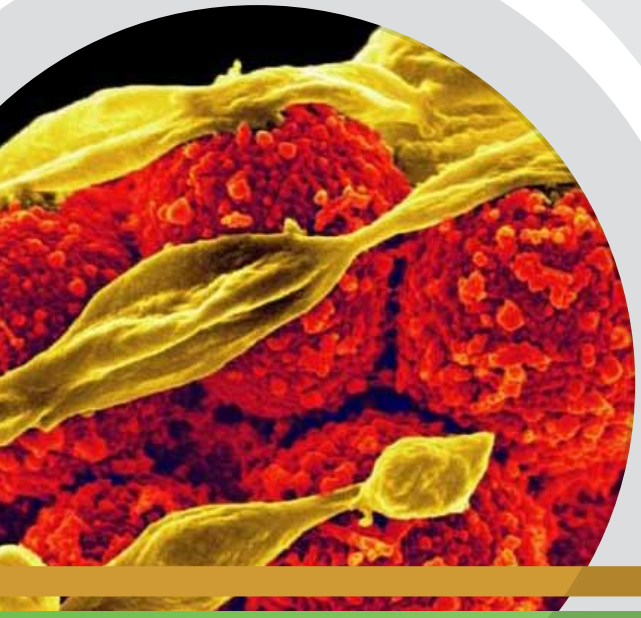

TECHNICAL REPORT

Economic evaluations of interventions to prevent healthcare-associated infections

Literature review

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ECDC TECHNICAL REPORT

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Literature review

This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Tek-Ang Lim, Dominique Monnet and Alessandro Cassini, and produced by the Centre for Reviews and Dissemination, University of York, following an open call for tender (Contract ECD.3450).

Contributing authors: Dawn Craig, Joanne O'Connor, Steven Duffy, Gavin Barlow, Alessandro Cassini, Tek-Ang Lim and Dominique Monnet.

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Yehuda Carmeli	Tel-Aviv Medical Center, Israel
Isabelle Durand-Zaleski	AP-HP Santé Publique Hôpital Henri Mondor, France
Alastair Gray	University of Oxford, UK
Lázló Gulácsi	Corvinus University of Budapest, Hungary
Sarah Deeny	Health Protection England, United Kingdom
Sara Cosgrove	Johns Hopkins University, Baltimore (MD), USA
Walter Zingg	University of Geneva, Switzerland

Additional information on the search strategy for this project and a methodological quality assessment of the articles reviewed is available in a digital format and can be obtained by writing to ECDC (ARHAI@ecdc.europa.eu) with 'A literature review of economic evaluations of interventions to prevent healthcare-associated infections' in the subject line of the e-mail.

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Abbreviations

CR-BSI	catheter-related bloodstream infection
CVC	central venous catheter
ECDC	European Centre for Disease Prevention and Control
HAI	healthcare-associated infection
HEED	Health Economic Evaluation Database
ICER	incremental cost-effectiveness ratio
MRSA	meticillin-resistant *Staphylococcus aureus*
MSB	maximal sterile banners
NHS EED	National Health Service Economic Evaluation Database
PCR	polymerase chain reaction
QALY	Quality-adjusted life-year
VRE	Vancomycin-resistant *Enterococcus* spp.

Executive summary

Background

Healthcare-associated infections (HAIs) are defined as infections that occur after exposure in hospital environments and/or healthcare facilities. Based on the data from the HAI surveillance network in Europe, over 3.2 million patients are infected at least once following exposure in healthcare facilities across the European Union every year [1]. A total of 37 000 of them die as a direct consequence of the infection [2]. Thus, HAIs are of considerable concern to patients, healthcare professionals and policy-makers alike. The most frequent types of HAI are surgical site infections, urinary tract infections, pneumonia, bloodstream infections and gastrointestinal infections.

Initiatives to prevent and control HAIs are resource intensive and it is not always clear which interventions are economically sound. To date, initiatives mainly focus on key preventive measures for HAIs, such as hand hygiene, screening, isolation and decolonisation, personal protective equipment, cleaning and decontamination, and antibiotic stewardship. In some European countries, this appears to have led to a subsequent reduction in the incidence of HAIs due to meticillin-resistant *Staphylococcus aureus* (MRSA) in recent years.

Whilst this is encouraging and desirable, healthcare systems and individual hospitals have used considerable financial and human resources in a heterogeneous manner in attempting to tackle HAIs. Moreover, it is unclear whether the strategies employed in both the successful and unsuccessful attempts to prevent and control these infections are cost-effective. At a time of European economic austerity, an assessment of the existing economic literature is pertinent in order to highlight those areas that already have a robust economic evidence base and those that should be the target of future research initiatives.

Objectives

The aim of this review was to assist decision-makers by identifying and summarising existing economic evaluations and cost-effectiveness analyses associated with the control and/or prevention of HAIs. Moreover, we identified common assumptions which would be desirable for a common framework to enable future cost-effectiveness analyses in European hospital settings.

Methods

A literature review took into account all full economic evaluations which met the inclusion criteria for the UK National Health Service Economic Evaluation Database (NHS EED). Additional inclusion criteria were: populations restricted to those in or being admitted to a hospital setting; interventions restricted to three broad types aimed at prevention and/or control of HAIs (hand hygiene/screening, isolation and decolonisation/personal protective equipment). Two researchers independently screened studies for relevance based on the pre-specified inclusion criteria. NHS EED abstracts formed the basis of the data extraction and quality assessment. In addition, an appropriate checklist was completed for each study meeting the inclusion criteria and a narrative summary was written for each of the studies included.

Results

The searches identified 1 973 records, 28 of which met the inclusion criteria. Four economic evaluations assessed the cost-effectiveness of hand-hygiene measures; three economic evaluations investigated the use of personal protective equipment; two studies investigated the cost-effectiveness of isolation interventions; and 19 studies evaluated screening, isolation and decolonisation strategies.

Both hand-hygiene evaluations, designed as interventions targeting surgeons, were not cost-effective. The evaluations targeting hospital staff were found to be cost-saving. All of the hand-hygiene evaluations were considered to be poor-quality. Further, the heterogeneity across the four studies precluded any quantitative synthesis. In brief, none of the studies comprehensively addressed the issue of uncertainty and all suffered from poor reporting of important methodological details.

The three evaluations of personal protective equipment were of variable quality and heterogeneous in terms of resource use and perspective – e.g. settings, interventions (gown versus apron). This was reflected in their contradicting conclusions, with personal protective equipment described as cost-effective or cost-ineffective depending on the intervention. It would therefore be difficult to draw strong conclusions based on these evaluations.

Twenty-one studies were identified which evaluated some form of screening, isolation and/or decolonisation strategy. The complexity of the strategies varied from two evaluations focusing on the isolation of patients but not

dealing with screening and decolonisation, to strategies undertaking screening, followed by isolation and/or decolonisation. A total of 13 studies evaluated strategies which included screening for MRSA; five accessed screening during hospital admission; five accessed screening in high-risk/intensive care units; and three evaluated screening in surgical patients. Five studies evaluated strategies which included screening for *Staphylococcus aureus,* all in pre- or post-operative patient populations, and one study evaluated a strategy which included screening for vancomycin-resistant *Enterococcus* spp. (VRE).

In general, the results of these evaluations suggested that screening upon admission to hospital followed by isolation/decolonisation is cost-effective. However, the variation in methods and strategies evaluated made it difficult to determine the extent to which adding decolonisation improves the effectiveness of screening and isolation. Moreover, the additional benefits of universal screening, as opposed to targeted screening, were unclear. There are several issues that varied across the evaluations and would need to be considered if further evaluations are to be undertaken. These include baseline prevalence rates, screening test selection, sensitivity and specificity of the selected test, effectiveness of decolonisation, adherence levels, mupirocin resistance and efficacy, turnaround time of test, transmission, compliance, time horizon and outcome considered.

These issues were similar for all of the screening, isolation and decolonisation studies, regardless of the population being screened or the microorganism identified. Drawing strong conclusions on the basis of heterogeneous and weak evidence could lead to inappropriate decision making.

Only one evaluation investigated screening for VRE and it was therefore difficult to draw conclusions on the cost-effectiveness of alternative strategies. The results of the analysis presented are valid, but it may be difficult to generalise and apply them to other clinical settings.

Conclusions

The review identified a total of 28 evaluations which met the inclusion criteria: four evaluating hand-hygiene interventions, three evaluating personal protective equipment and 21 evaluating screening and/or isolation and/or decolonisation strategies. The evaluations identified suggested that interventions were either cost-saving (hand hygiene for hospital staff), cost-effective (most isolation/decolonisation interventions and some interventions with personal protective equipment), cost-equivalent (hand hygiene for surgeons) or cost-ineffective (some isolation/decolonisation interventions). However, there was only a limited number of high-quality economic evaluations. The studies identified were generally of either poor or only inadequate quality and very heterogeneous.

Development of a European framework for future economic evaluations of HAI control and/or prevention to provide researchers with common assumptions would only support research in this area if it were based on high-quality studies, providing evidence not only on cost-effectiveness, but also clinical effectiveness of the interventions. Drawing conclusions on the clinical effectiveness of specific interventions based on heterogeneous, weak evidence could lead to inappropriate decision-making. In addition, given the diversity of health systems across Europe and the country-specific assumptions that may be required, it is likely that several frameworks for economic evaluations would need to be developed.

Therefore, we recommend that future attempts to establish the cost-effectiveness of such interventions are underpinned by robust evidence of clinical effectiveness. High-quality primary research combining robust study designs to assess both clinical effectiveness and cost-effectiveness would then be required.

1. Introduction and background

Healthcare-associated infections (HAIs) are defined as infections that occur after exposure to healthcare - i.e. hospitals or other healthcare facilities. Based on data from the HAI surveillance network in Europe, over 3.2 million patients are infected at least once following an exposure in healthcare facilities across the European Union every year. A total of 37 000 of them die as a direct consequence of the infection [2]. Major causes of HAIs in Europe are meticillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*, and increasingly highly resistant Gram-negative bacteria. The published literature highlights the effects that HAIs have on patient outcomes, the difficulties in reducing the incidence of these infections and the huge potential clinical and economic benefits if a reduction could be achieved. HAIs are of considerable concern to patients, healthcare professionals and policy-makers alike and have become important targets for quality improvement and patient safety initiatives across Europe during the last decade. Such initiatives have mainly focused on what are generally considered to be the key preventive measures for HAIs, such as hand hygiene, screening, isolation and decolonisation, personal protective equipment, cleaning and decontamination, and antibiotic stewardship. In some European countries, this appears to have led to a subsequent reduction in the incidence of these infections in recent years.

Whilst this is encouraging and desirable, healthcare systems and individual hospitals have used considerable financial and human resources in a heterogeneous manner in attempting to tackle HAIs. Moreover, it is unclear whether the strategies employed have been cost-effective. At a time of European economic austerity, an assessment of the existing economic literature is therefore pertinent in order to highlight those areas that already have a robust economic evidence base and those that should be the target of future research initiatives.

The aim of this technical report is to provide a literature review on cost-effectiveness analysis of prevention and control interventions for healthcare-associated infections. The report also describes the results of a number of interventions in terms of cost-effectiveness, as well as the quality of the studies identified.

2. Review methods

2.1 Overview

There were two planned components of this project. Firstly, a mapping of the economic evaluation literature included all interventions aiming to prevent and/or control HAIs in a hospital setting (mapping review available in digital format upon request). Secondly, a literature review was performed, focusing on economic evaluations of hand hygiene, screening and isolation interventions and personal protective equipment. Throughout all stages of the project, a clinical expert was consulted (Gavin Barlow) in an attempt to ensure the usefulness and validity of the work.

2.2 Review of literature

The review work was undertaken in accordance with the general methods outlined in the Centre for Reviews and Dissemination (CRD) guidance[3] by the University of York.

2.2.1 Literature searches

The purposes of the searches was to identify economic evaluations of interventions used to prevent or control HAIs. Full economic evaluations of hand hygiene, screening, isolation and decolonisation, or personal protective equipment interventions were eligible for inclusion in the literature review.

Two specialist economic databases were searched using the CRD interface for the NHS Economic Evaluation Database (NHS EED)[i] and the Wiley Online Library interface for the Health Economic Evaluation Database (HEED). There was no restriction by country or language.

The searches were performed in July 2012. Following the expert elicitation meeting on 9–10 October 2012, further searches were undertaken specifically for the term 'hand hygiene' interventions. The search strategies are presented in Appendix 1.

Inclusion criteria
Studies were included in the review if they met the criteria outlined below.

Population
- Populations were restricted to those in or being admitted to a hospital setting.

Interventions
- Based on the preliminary mapping exercise, three types of intervention were eligible for inclusion
  - Hand-hygiene interventions targeting prevention and/or control of HAIs.
  - Screening, isolation and decolonisation interventions targeting prevention and/or control of HAIs.
  - Personal protective equipment targeting prevention and/or control of HAIs.

Comparator
- There were no restrictions on the type of comparator.

Outcomes
- All reported outcomes were included.

Study design
- All full economic evaluations (studies which compare two or more treatments or care alternatives and examine and present sufficient details on both the costs and outcomes of the alternatives being compared) were included.

2.2.2 Screening and study selection

Two health economists independently screened all titles and database (NHS EED/HEED) abstracts identified from the searches. Disagreements were resolved by consensus. Full manuscripts were obtained for all evaluations meeting the inclusion criteria of the literature review.

[i] http://www.crd.york.ac.uk/crdweb/

2.2.3 Data extraction

The NHS EED abstracts laid the basis for data extraction for this literature review but, where relevant, these were supplemented with further details on key modelling and analytical assumptions from the full papers, such as:

- Scenario assumptions
- Thresholds
- Key structural assumptions.

The process of NHS EED abstract production requires that the abstract is written by one health economist and independently checked by a second health economist. For the purpose of this review a third economist read and supplemented the abstracts where necessary.

2.2.4 Quality assessment

The NHS EED database provides critical abstracts, which are written and checked by experienced health economists. These structured NHS EED abstracts provide a critical commentary of an economic evaluation, summarising the overall reliability and the possibility of generalising the study. The structured abstract provides a critical assessment of the economic evaluation in each of the following areas:

- Analytical approach;
- Inclusion of effectiveness data;
- Benefit measure used and method used to estimate this benefit measure;
- Study results presented;
- Analysis of uncertainty undertaken.

Critical structured NHS EED abstracts for each of the studies included are available from the NHS EED website and the critical commentary of the NHS EED abstracts for the studies in this report formed the basis for the quality assessment of this report. In addition, the Drummond checklist [4] was completed for each study included and summary results for the quality assessment using the Drummond checklist are available in Appendix 2.

2.2.5 Synthesis and formulation of framework

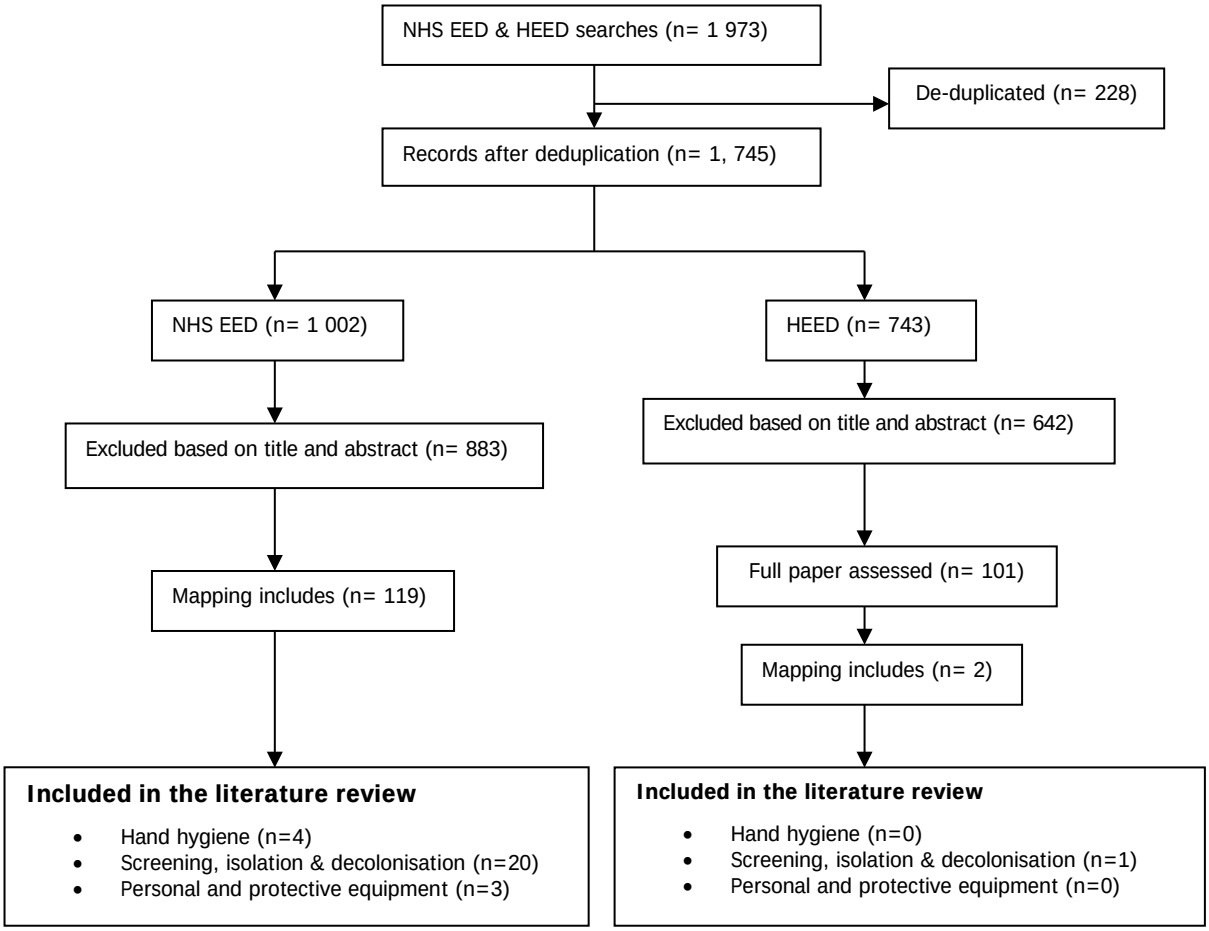
A narrative synthesis was undertaken. The synthesis drew together the common themes, important assumptions and differences across the included studies. The synthesis was guided by a clinical expert, based on the quality of the economic evaluations and whether or not general conclusions could be drawn from the assumptions.

A discussion is provided on whether the assumptions could be generalised and the potential impact that the issues highlighted in the synthesis may have on the use of a framework for evaluating strategies across Europe.

3. Review results

The searches identified 1 973 records. Following de-duplication this was reduced to 1 745, of which 1 002 were from NHS EED and 743 from HEED (Figure 1). After reviewing the title and the NHS EED or HEED abstract, 1 525 records were excluded (883 from NHS EED records and 642 from HEED). Of the 119 NHS EED records retrieved, 28 met the inclusion criteria. Of the 101 manuscripts from HEED that were ordered to enable more in-depth screening, only one met the inclusion criteria for the literature review.

Figure 1. Flow diagram for study inclusion



The additional searches undertaken after the expert elicitation meeting held at ECDC on 9–10 October 2012 focused on the intervention term 'hand hygiene' and identified 40 potential studies to include; three were duplicates. Of the remaining 37, only one met the inclusion criteria [5] but this was an article reporting on a study which had already been included [6]. To avoid duplication, this second article on the same study [5] was not included in the review.

3.1 Hand hygiene

3.1.1 Study characteristics

The review identified four economic evaluations which assessed the cost-effectiveness of hand-hygiene measures (Tables 1 and 2). The interventions evaluated included two targeting surgeons and two targeting hospital staff:

- a water-less, scrub-less and brush-less antiseptic hand-rub system for use in preparing for inpatient and outpatient paediatric urological operations;
- an alcohol-based hand-rub for surgery preparation;
- a hospital-wide hand-hygiene programme which included disposable alcohol-based hand sanitisers mounted between beds and to trolleys; lectures and web-based self-learning tools; reminder notices compliance statistics audits and feedback;
- enforcement of compliance with strict hand-hygiene protocols, implementing a ventilator-associated pneumonia-preventive bundle and ensuring compliance with care practices and standard guidelines for accessing and maintaining the dressings of central-line catheters.

Interventions aimed at surgeons

One of the studies was conducted in the United States of America (USA)[6] and one in Kenya.[7] The setting of rural Kenya, which is poor in water resources, was deemed unlikely to produce findings which could be generalised to a European setting. Both economic evaluations were conducted alongside single clinical studies; none of the evaluations used decision analytical models. Both of the studies were cost-effectiveness analyses; no utility outcomes were evaluated. Neither of the studies synthesised costs and effects; consequently neither of the studies undertook an incremental analysis.

Both studies looked at interventions which included a hand-hygiene component aimed at changing the behaviour of surgeons and evaluated the impact of those interventions on various patient populations, one assessed a paediatric population[6] and the other a general inpatient population.[7]

In their evaluation of hand-hygiene regimes, Nthumba et al. [7] targeted surgeons. The analysis was undertaken in a rural hospital in Kenya. Six operating theatres from a single institution were assigned randomly to one of the regimes, with a cross-over every two months. There were 10 clusters analysed during the five two-month intervals. Clusters were defined by operating theatre. It is unclear whether it would be possible to make generalised conclusions on the interventions compared or the analysis undertaken or whether it would be useful in a European setting, so full details are not presented. However, for the sake of completeness the study has been included. No sensitivity analysis was undertaken, despite the presence of uncertainty.

Weight et al. [6] looked at two alternative hand-rub regimes for surgeons. The evaluation was undertaken at one institution, where all procedures were undertaken by one surgeon. Incidence of wound infection was the primary outcome. Costs were presented separately from outcomes and only included the costs of applying the antiseptic rubs, not the process. Resource use was derived from the hospital database and while no perspective was stated, it is clear that it was very limited. No price year or other cost adjustments were reported and, once again, uncertainty was not investigated by undertaking sensitivity analyses.

Table 1. Study characteristics – hand hygiene (surgeons)

Study	Study year	Targeted population	Outcome population	Effectiveness evidence	Intervention
Nthumba et al. [7] Kenya CEA	2010	Surgeons	Inpatients	Cluster RCT	Pre-operative alcohol-based hand rub
Weight et al. [6] USA, CEA	2010	Paediatric surgeons	Paediatric surgical inpatients and outpatients.	Controlled cohort (historical control)	Water-less, scrub-less and brush-less antiseptic.

Interventions aimed at frontline staff

One of the studies was undertaken in the USA [8] and the other in Taiwan [9]. Both were conducted alongside clinical studies, so neither utilised decision modelling. Both were cost-effectiveness analysis studies, so no utility outcomes were captured. Neither of the studies synthesised costs and effects, so neither undertook an incremental analysis.

Both studies looked at interventions to change the behaviour of frontline staff with a view to improving health outcomes for the patient population; one in a paediatric population and one in a general inpatient population.

Chen et al. [9] undertook a study-based evaluation of a hand-hygiene programme targeting hospital staff. They used a before-and-after study design to obtain clinical effectiveness data, which was conducted in a large teaching hospital. To overcome the issues of confounding and bias with this type of study design, they used regression methods. The main outcome was rates of infection; this outcome was used to derive a cost per infection prevented outcome. Again, no perspective was reported but direct costs relevant to the hospital were included. Only the costs of the interventions and promotional efforts were included. No staff costs were considered. Once again, costs were derived from the hospital database. The price year was reported and costs discounted at a rate of 3%, due to the longer time horizon (>1 year). Limited one-way sensitivity analyses were undertaken to try and evaluate some of the uncertainty that was present. Harris et al. [8] considered a wider programme of infection control measures aimed at all paediatric staff. The programme included enforcement of compliance with strict hand-hygiene protocols, implementing a ventilator-associated pneumonia preventive bundle, and ensuring compliance with care practices and standard guidelines for accessing and maintaining the dressings of central-line catheters. The clinical effectiveness data were derived from a small retrospective cohort study undertaken in a single hospital. The primary outcomes were probability of ventilator-associated pneumonia or central-line catheter infection and in-hospital mortality. The authors state that the evaluation was undertaken from the perspective of the hospital and they included all relevant costs. Details of resource use were obtained from the hospital database and presented in full. No unit costs were presented, however the price year was reported. Limited sensitivity analysis was conducted.

Table 2. Study characteristics – hand hygiene (frontline staff)

Study	Study year	Targeted population	Outcome population	Effectiveness evidence	Intervention
Chen et al. [9] Taiwan, CEA	2011	Hospital wide (staff)	Inpatients	Before and after study	Hospital-wide hand-hygiene programme, equipment, reminders, lectures, rewards & fines.
Harris et al. [8] USA, CEA	2011	Paediatric staff	Paediatric patients	Retrospective controlled cohort (historical control)	Strict compliance with hand-hygiene regime and two other target guidelines (ventilator & catheter).

3.1.2 Outcomes

Interventions aimed at surgeons

Both economic evaluations reported the results in a disaggregated manner (i.e. no summary outcome was derived). A summary of the results is presented in Table 3.

Nthumba et al. [7] found that, in the intervention group, the crude rate of surgical site infections was 8.3% (95% CI, 6.9–9.8%) compared with 8.0% (95% CI, 6.7–9.5%) in the control group. The difference in the crude odds ratios (ORs: 1.03; 95% CI, 0.80–1.33) did not reach statistical significance. A similar result was observed in the adjusted analysis. Predictors of occurrence of a surgical site infection were duration of surgery and surgical-site contamination class. Total weekly costs were similar in the two groups: EUR 4.60 in the intervention group and EUR 3.30 in the control group.

Weight et al. [6] demonstrated that the incidence of wound infections was 2/1800 (0.11%) in the intervention group and 3/1800 (0.17%) in the control group. The difference was not statistically significant (P>0.99). The application of the antiseptic studied (Avagard™) was completed in two minutes versus six minutes for the traditional hand antisepsis (control group). The intervention cost was USD 0.59 per application, while the control cost was USD 1.04 per application. In addition, no waste was generated with the brush-less technique, while the control strategy required water, and the disposal of the scrub brush, packaging and drying towel.

Table 3. Summary results – hand hygiene (surgeons)

Author	Study year	Intervention(s) & comparators	Results
Nthumba et al. [7]	2010	A: Pre-operative alcohol-based hand rub B: Standard practice	No difference in surgical site infection rates Average weekly intervention costs = EUR 4.60 Average weekly comparator costs = EUR 3.30
Weight et al. [6]	2010	A: Water-less, scrub-less and brush-less antiseptic B: Standard practice	No difference in infection rates A = USD 0.59 B = USD 1.04

Interventions aimed at hospital staff

Once again, both of the economic evaluations reported the results in a disaggregated manner (i.e. no summary outcome was derived). A summary of the results is presented in Table 4.

Chen et al. [9] found that the number of HAIs was 14 608 with the programme, compared with 16 032 without the programme. Therefore, the savings from the extra costs incurred with HAIs were USD 5 522 408, while the extra costs of the hand-hygiene programme were USD 233 044. The extra cost of the programme to prevent one episode of HAI was USD 163.60. However, when savings from future costs associated with HAIs were considered, the programme appeared more cost-effective. The economic benefits from savings were estimated to have been USD 5 289 364, and the benefit-cost ratio was USD 23.7, meaning that every USD 1 spent on the programme resulted in a USD 23.70 economic benefit to the hospital. The sensitivity analysis showed that the programme remained cost-saving in all alternative scenarios.

Harris et al. [8] found that all clinical and economic outcomes improved in the post-intervention period compared with the baseline period and the differences were statistically significant. In the adjusted analysis, the odds ratio (OR) of ventilator-associated pneumonia risk was 0.37 (95% CI, 0.15–0.97), the OR of central-line catheter site infection was 0.42 (95% CI, 0.22–0.80), and the OR of in-hospital mortality was 0.51 (95% CI, 0.30–0.85). Adjusted hospital direct cost-savings were estimated at USD 12 136 per patient. Differences in costs were statistically significant for the comparison between the baseline period and the post-intervention period, both for paediatric intensive care units considered separately, and paediatric intensive care units and normal wards together ($p<0.001$). The results of the sensitivity analysis did not substantially alter the base case findings.

Table 4. Summary results – hand hygiene (frontline staff)

Author	Study year	Intervention(s) & comparators	Results
Chen et al. [9]	2011	A: Hospital-wide hand-hygiene programme, equipment, reminders, lectures, rewards & fines B: Standard practice	Reduction in HAI episodes = USD 1 504 Total cost of programme = USD 244 470 Average cost of preventing one episode = USD 163.60.
Harris et al. [8]	2011	A: Strict compliance with hand-hygiene regime and two other target guidelines (ventilator & catheter) B: Standard practice	Post-intervention: OR: 0.37 Ventilator-associated pneumonia; 0.42 Central line bloodstream infection; 0.51 mortality compared with baseline. Total intervention period reduction in costs = USD 12 136 compared with baseline; post intervention period reduction costs = USD 7 697 compared with baseline.

OR: odds ratio

3.1.3 Quality assessment

For a variety of reasons the quality of the studies was considered poor. Three of the four studies included limited costing information and, although these three studies broadly met the definition of an economic evaluation, their main focus was on clinical outcomes [6,7,9,10]. Only one study reported a perspective and the methods used to estimate resource use and costs; Harris et al. [8] clearly set out to conduct an economic evaluation as part of their study and presented these relevant details. However, as with all of the other studies, while they did present the methods, they did not present the volume of resource use and/or the associated unit costs, making it difficult to generalise.

Three of the evaluations were undertaken alongside observational studies, cohort with historical control or before-and-after studies[6,8,9], and one alongside a cluster-randomised crossover-control trial[7]. Nthumba et al. [7] used the most robust clinical study design, however the lack of detailed reporting and poor randomisation method may mean that the results are still prone to bias. Moreover, these results may be specific to the setting in which the evaluation was undertaken (rural Kenya).

Chen et al. [9] used sophisticated regression methods to try and ensure that issues of bias which might be introduced through their choice of study design could be limited. However, they did not report sufficient methodological details regarding the costing element of the evaluation. Absence of perspective, limited resource use data, and the use of macro-costs all impacted on the quality of the results and the extent to which they could be generalised.

In general, the three evaluations which clearly focused on the clinical effectiveness component of their analysis suffered from the same lack of detail surrounding the economic component [6,7,9]. None of the evaluations comprehensively addressed the issue of uncertainty, two failed to undertake any analysis of uncertainty [6,7] and two undertook limited analyses.[8,9] Due to the lack of reporting of important methodological details, the high likelihood of bias in the clinical data and the lack or limited sensitivity analyses undertaken, the quality of these evaluations was considered poor.

3.1.4 Summary evidence statements

Interventions aimed at surgeons

Nthumba et al. [7] examined the clinical and economic impact of a waterless, alcohol-based hand rub for surgical hand preparation with conventional plain soap and water in a resource-poor setting without continuous, clean water. There was no statistically or clinically significant difference in surgical site infection rates between the two methods and costs were very similar. The clinical analysis methodology was adequate, although the method of randomisation was poor. The economic side of the analysis adopted a very limited perspective. Consequently, the authors' conclusions appear valid within the limited scope of the analysis, but it may not be possible to make broader generalisations.

Weight et al. [6] examined the clinical and economic impact of a waterless, scrubless, and brushless hand antiseptic for paediatric urological operations. The authors concluded that waterless, scrubless, and brushless hand antiseptic provided comparable antisepsis to the traditional brush hand scrub, which required a longer application time and a higher cost. The study has some methodological drawbacks, mainly related to design of the clinical study and the lack of sensitivity analyses. Caution is advised when interpreting the authors' conclusions.

Interventions aimed at hospital staff

Chen et al. [9] examined the cost-effectiveness of a hand-hygiene programme to reduce the burden of HAIs. The authors concluded that the hand-hygiene programme was feasible and reduced both HAI rates and hospital costs.

The authors utilised a sophisticated methodology to try to overcome issues related to the clinical design of the study. The overall quality of the study was considered poor due to the lack of details on the costing methodology used.

Harris et al. [8] examined the clinical and economic impact of improving practices of hand hygiene, oral care, and central-line catheter care to reduce HAIs (ventilator-associated pneumonia and central-line bloodstream infections) in the setting of a paediatric intensive care unit. The authors concluded that the quality improvement programme improved clinical outcomes and reduced both mortality and hospital costs. The study methodology presents some limitations that might potentially affect the validity of the authors' conclusions.

3.1.5 Overall summary

The heterogeneity across these four studies precludes any quantitative synthesis. Furthermore, as they have not employed decision modelling methodology there are no underlying assumptions or similarities of data input for discussion.

Given the lack of reported information on perspective, resource use data, price year and costing adjustments, a comparison of cost results across studies would not be meaningful. Furthermore, given the variation in standard practice in the hospitals where these evaluations were undertaken, it would be difficult to draw any conclusion about which interventions, if any, would be cost-effective in alternative hospital settings. The limitations of the studies mean that strong conclusions cannot be drawn.

3.2 Personal protective equipment

3.2.1 Study characteristics

We identified three economic evaluations which investigated the use of personal protective equipment (Table 5). The interventions evaluated were variable and included:

- the use of gown and gloves when entering the rooms of patients colonised or infected with vancomycin-resistant *Enterococcus* (VRE), to prevent the transmission of VRE;
- two techniques for reducing central venous catheter (CVC)-related infections. The 'maximal sterile barriers' (MSB) technique requires the person who performs the catheterisation to wear a head cap, a facemask, a sterile body gown and sterile gloves, and the insertion site to be covered with a full-size drape;
- the use of routine gowning (defined as hand washing and wearing a plastic apron) before entering a neonatal nursery.

The evaluated populations and settings were not comparable. They included (a) neonates in a neonatal intensive care unit, (b) isolated, colonised or infected VRE inpatients, and (c) a hypothetical inpatient population. Two of the studies were conducted in the USA [11,12] and one in Singapore [13]. Both Puzniak et al. and Tan et al. [13] undertook economic evaluations alongside clinical studies, although Puzniak et al. used a decision tree framework to facilitate the economic evaluation. In both instances, costing appeared to be undertaken retrospectively on the same population used to derive the clinical estimates [11,13]. Hu et al. [12] also used a decision analytical model to evaluate a hypothetical inpatient population. All the data used for the model were derived from published sources; a systematic review was used to derive clinical input estimates.

All the studies were cost-effectiveness analyses; utility outcomes were not evaluated. Only one study synthesised costs and effects [11], the other two presented disaggregated results [12,13]. The evaluated clinical outcomes varied, but on the whole appeared relevant to the intervention and population being considered. Both of the studies which used decision modelling undertook sensitivity analysis [11,12].

Table 5. Study characteristics – personal protective equipment

Study	Study year	Targeted population	Outcome population	Effectiveness evidence	Intervention
Hu K K;[12] USA; CEA	2004	Staff member undertaking procedure	Hypothetical inpatient	Literature review	Use of head cap, facemask, sterile body gown and sterile gloves when undertaking procedures; plus coverage of site with full-size drape.
Puzniak L A;[11] USA; CEA	2004	Staff & visitors	Inpatients colonised or infected with VRE	Controlled cohort (non-concurrent control)	Routine gowning and gloves
Tan S G;[13] Singapore; CEA	1995	Staff, parents & visitors	Neonates (intensive care)	Controlled trial (historical control)	Routine gowning and hand washing.

All three studies included direct costs; two stated that costing was calculated from a hospital perspective and included relevant direct costs, and one [13] did not report the perspective and only included the cost of the intervention (i.e. apron). The level of detail provided on costing varied, with both modelling studies [11,12] providing significantly more detail on cost derivation, sources and adjustments than the single-study evaluation [13].

In addition to hand washing, Tan et al. [13] undertook an evaluation of aprons using a cohort study with a historical control. The data were collected over a one-year period. The clinical outcomes of interest were nosocomial infection rates, MRSA colonisation and infection rates, and mortality rates. These outcomes were not summarised with costs, but presented separately. No perspective was reported and only the cost of the apron was considered. No details of a price year or costing adjustments were given and no sensitivity analysis was undertaken.

Puzniak et al. [11] evaluated the use of gowns in combination with gloves. It is likely that gowning is more comprehensive than the wearing of an apron, but this was not explicitly discussed. The study was undertaken in a single centre and, although this was not explicitly mentioned, may have been retrospective. The outcomes of interest were the number of VRE-positive and VRE-negative patients on admission, and the number of patients who acquired VRE during hospitalisation. Data from the clinical study were used as inputs in a simple decision model. The time horizon of the model (and clinical study) was 30 months. The summary measure of benefit was the number of VRE cases averted per 1000 intensive care unit-days. The perspective was that of the hospital and all relevant costs appear to have been included. Parameter uncertainty was investigated through the use of one-way sensitivity analysis.

Hu et al. [12] also undertook a model-based analysis which was populated using published data, rather than a single clinical study. Their evaluation focused on two techniques for reducing central venous catheter (CVC)-related infections: the 'maximal sterile barriers' technique - which required the person who performs the catheterisation to be wearing a head cap, a facemask, a sterile body gown and sterile gloves, and the insertion site to be covered with a full-size drape – and a less stringent method which involved the wearing of gloves and the use of a small regional sterile drape. The evidence to populate the model was derived from the literature. The outcomes of the economic evaluation were the incidence of catheter-related bloodstream infection, catheter colonisation and mortality related to catheter-related bloodstream infection. A hospital perspective was adopted and all relevant costs appear to have been included. Unit costs and resource use were presented for some components, but for other components only summary costs were presented. The price year and other relevant adjustment details were reported. Sensitivity analysis was undertaken.

3.2.2 Outcomes

Only one of the studies synthesised costs and effects [11]. A summary of the results is presented in Table 6. Puzniak et al. [11] undertook an incremental analysis and presented cost per VRE case averted. The findings show that the incremental annual cost between gown and no-gown interventions was USD 73 995. Incremental cost-effectiveness ratios (ICERs): the incremental cost per case of VRE averted with gown use versus no-gown use was USD 1 897. The annual net benefit of the gown policy (defined as the difference between the averted costs derived from the use of gowns minus the incremental costs incurred) was USD 419 346. The results were most sensitive to the probability of acquiring VRE. With a no-gown transmission rate of 40%, the incremental cost per case of VRE colonisation averted was USD 3 217 and the net benefit was USD 546 182. The use of gowns became a cost-saving strategy when the no-gown transmission probability was approximately 88% (corresponding to the prevention of seven cases of VRE colonisation).

In Singapore, Tan et al. [13] found no statistically significant difference between groups for the evaluated clinical outcome and therefore presented cost results separately. The costs of the intervention over the six-month period were greater than that of the comparator (SGD 3 708 compared with SGD 2 012).

Hu et al. [12] focused on catheter-related bloodstream infection (CR-BSI), catheter colonisation and mortality due to CR-BSI, all of which were shown to be lower in the intervention group. The outcomes were presented separately from costs and no summary ratio was calculated. The results suggest that incidence of CR-BSIs was 2.81% with 'maximal sterile barriers' versus 5.3% for less-stringent techniques; catheter colonisation incidence was 2.9% of patients with 'maximal sterile barriers' versus 5.48% for less-stringent techniques; and death due to CR-BSI was 0.42% for patients with 'maximal sterile barriers' versus 0.80% for less-stringent techniques. The total intervention costs were reported per patient (per catheter) and were USD 369.34 in the 'maximal sterile barriers' group and USD 621.39 in the less-stringent techniques group.

Table 6. Summary results – personal protective equipment

Author	Study year	Intervention(s) & comparators (s)	Results
Hu KK et al. [12]	2004	A: Use of head cap, face mask, sterile body gown and sterile gloves when undertaking procedures; plus coverage of site with full-size drape. B: Use of sterile gloves and small regional sterile drape.	Total cost of intervention per patient (per catheter) = USD 369.34 Total cost of comparator per patient= USD 621.39 Incidence of CR-BSI: A = 2.81%; B = 5.3% Incidence of CR- colonisation: A = 2.9%; B = 5.48% Mortality related to CR-BSI: A =0.42%; B = 0.8%
Puzniak LA et al. [11]	2004	A: Routine gowning and gloves B: Use of gloves only	Total annual cost of intervention = USD 179 816 Total annual cost of comparator = USD 105 821 VRE colonisation averted = 5.96 cases per 1 000 hospital-days VRE bacteraemia averted = 0.61 cases per 1 000 hospital-days ICER cost per case of VRE averted = USD 1 897
Tan SG et al. [13]	1995	A: Routine gowning and hand washing B: No routine use of gown.	Total cost of intervention = SGD 3 708 (six months) Total cost of comparator = SGD 2 012 (six months) No statistically significant difference in infection rates.

CR: catheter related; CR-BSI: catheter-related bloodstream infection; ICER: incremental cost-effectiveness ratio

3.2.3 Quality assessment

Quality varied across the studies, from adequate to poor. The quality of the two modelling studies, Puzniak et al. [11] (informed from a single clinical study) and Hu et al. [12] (informed by a literature review), was adequate, while that of Tan et al. [13], which was undertaken concurrently with a clinical study, was poor. The main focus of Tan et al. [13] was the clinical study; the methodology employed in the economic evaluation was weak and the detail limited, with no more than the cost of aprons throughout the considered intervention and non-intervention periods. This partial approach to undertaking an economic evaluation restricts the usefulness and scope for generalisation of the results.

The two modelling studies clearly stated the perspective, the form of economic evaluation and the rationale for undertaking the analysis. They provided details of how the effectiveness and cost data were derived, and presented a rationale for the chosen outcome measure for the economic evaluation. Puzniak et al. [11] derived costs using their hospital's step-down costing allocation system, which subsequently enabled them to present unit costs and resource use separately for the majority of items, making it easier to generalise. Hu et al. [12] undertook a less precise costing analysis, using physicians' assumptions regarding time and the literature to obtain relevant cost estimates. The possibility of generalising assumptions on resource use and costs from one setting to another can be problematic. If unit costs and resource use are presented separately, as in Puzniak et al. [11], this can aid transferability. Both undertook a one-way sensitivity analysis, which enabled them to ascertain the robustness of their results to variations in one estimate. However, probabilistic methods would have been more appropriate and are widely regarded as the gold standard.

Both Puzniak et al. [11] and Hu et al. [12] highlighted many of the limitations of their analyses and acknowledged the uncertainty in their results. Tan et al. [13] focused primarily on the clinical analysis, which left the economic evaluation lacking in many key components. However, these authors also acknowledged that there were limitations in their methodology. All three evaluations were subject to limitations which may have affected the validity of the findings.

3.2.4 Summary evidence statements

Puzniak et al. [11] examined the use of gown and gloves when entering the rooms of patients colonised or infected with VRE, to prevent the transmission of VRE. The authors concluded that the use of gowns adds costs to the delivery of health services, but the benefits from averting VRE transmission outweigh those costs. The study was subject to some limitations and these should be considered carefully when interpreting the results.

Hu et al. [12] studied the use of 'maximal sterile barriers' in a hypothetical cohort of intensive care unit patients (i.e. a head cap, a face mask, a sterile body gown and sterile gloves, and the catheter insertion site to be covered with a full-size drape.) The authors concluded that the use of 'maximal sterile barriers' during central venous catheterisation was effective in reducing relevant outcomes and costs, when compared with less-stringent sterile barrier techniques. The quality of the evaluation was adequate.

Tan et al. [13] compared the use of routine hand washing and wearing a plastic apron with no plastic apron before entering a neonatal nursery. The authors concluded that an apron is an ineffective and expensive method of reducing nosocomial infection, MRSA colonisation and infection, and mortality rates in this setting. However, the quality of this evaluation was poor and its results are not robust.

3.2.5 Overall summary

Due to the diversity in outcomes and populations, it is not possible to derive any global conclusion regarding the cost-effectiveness of personal protective equipment. One study suggests that protective equipment produces no significant difference in clinical outcomes, but higher costs [13]; while the other two suggest a benefit in terms of clinical outcomes, one at an increased cost [11] and the other at a decreased cost [12]. These differences are a reflection of the different settings, interventions (gowning versus apron), resource use, perspective, and potentially also price years. The studies are of variable quality and all suffer from issues with regard to scope for generalisation. Due to the limitations outlined in this section, any conclusion reached is likely to be highly uncertain.

Furthermore, despite that fact that two of these evaluations employ decision modelling methods, there is no value in discussing or comparing underlying assumptions or data inputs due to the diversity of the evaluated interventions.

3.3 Isolation

3.3.1 Study characteristics

Two studies were identified that investigated the cost-effectiveness of isolation interventions in reducing HAI rates (Table 7) [14,15]. The interventions compared included:

- the use of an isolation ward with designated staff to control MRSA transmission;
- the discontinuation of isolation procedures post heart transplant.

Table 7. Study characteristics – isolation

Study	Study year	Population	Economic evaluation design	Effectiveness evidence	Intervention
Cooper et al. [14] UK, CEA	2003	Homogenous inpatients	Model (dynamic state transition model)	Literature review	Isolation ward for MRSA
Williams et al. [15] USA, CEA	1995	Heart transplant recipients	Study based	Retrospective cohort	Isolation post transplantation

The populations evaluated were not comparable. One was a homogenous group of hospital inpatients [14] and the other a cohort of heart transplant recipients [15]. One was conducted in the UK [14] the other in the USA [15].

Cooper et al. [14] built on previously published mathematical models, developing them further to capture elements such as persistence and transmission of MRSA within and between wards in hospitals. The model was fully described and populated using data from an accompanying systematic review. There were a number of data limitations which the authors overcame with simplifications and assumptions. Both a deterministic and stochastic version of the model was presented. The impact of ward capacity and variation in detection rates were considered. The outputs of models were presented as a number of alternative scenarios and the costs saved when compared with no isolation ward.

Williams et al. [15] evaluated the impact of discontinuing an existing isolation post heart transplant. A retrospective cohort study was undertaken to obtain clinical estimates.

Both studies [14,15] were cost-effectiveness analyses; no utility outcomes were derived. Neither of the studies stated a perspective, but both included only direct costs and appear to have been undertaken from the perspective of the hospital.

Cooper et al. [14] presented many alternative scenarios, some of which included only infected patients while others included both infected and colonised patients. Alternative transmission and prevalence rates, variation in isolation ward capacity and the use of stochastic methods enabled the presentation of a range of graphical results illustrating these various assumptions on transmission rate.

3.3.2 Outcomes

The results of Cooper et al. [14] focused on the cost savings acquired as a result of using isolation wards. In general, the authors' results suggested that use of an isolation ward was cost-saving; however, the amount saved was uncertain and depended on the underlying assumptions of the model. Williams et al. [15] presented results in a disaggregated manner. They showed no statistically significant difference in HAI rates and therefore focused on the cost differences; presenting total costs for each intervention. Their results suggested that discontinuing isolation procedures had no impact on HAI rates but seemed to save money. A summary is presented in Table 8.

Table 8. Summary results – isolation

Author	Study year	Intervention(s) & comparator(s)	Results
Cooper et al. [14]	2003	A: Isolation ward B: No isolation ward	Subset of results for infected MRSA patients, high transmissibility and low virulence Total cost saving – 5 bed ward = GBP 9.6million Total cost saving – 10 bed ward = GBP 8.6million Total cost saving – 15 bed ward = GBP 4.8million Total cost saving – 20 bed ward = GBP 1.4 million
Williams et al. [15]	1995	A: No isolation B: Standard practice (isolation)	Total mean nursing time intervention costs = USD 8 340 Total mean nursing time comparator costs = USD 4 265 No statistical difference in infection rates.

The two studies undertook very different analyses in very different settings. The assumptions used in the modelling may not be reflective of a clinical setting, but may add to the understanding of how MRSA is transmitted. The scenario evaluated by Williams et al. [15] was quite hospital-specific and may be difficult to apply more generally. It is impossible to draw general conclusions based on these two studies.

3.3.3 Quality assessment

The quality of the two studies was adequate for Cooper et al. [14] but poor for Williams et al. [15]. Cooper et al. [14] undertook sophisticated mathematical modelling to evaluate the transmission of MRSA throughout a hypothesised hospital setting in a homogenous population of patients. They then evaluated the impact of using isolation wards (of various capacities) on transmission rates. They did not undertake detailed costing, but presented average costs obtained from a UK National Health Service hospital. They reported a price year and conducted their analysis over a 10-year time horizon; however, they did not discount costs which, given the time horizon, was inappropriate. The authors acknowledged that they may have overestimated savings due to the lack of discounting. The data used to populate the model were limited. The authors stated that their main aim was a theoretical understanding of the dynamics of transmission. The lack of reliable data to inform the model makes the resulting outcomes uncertain. The methodological quality was adequate, but the results are not robust.

Williams et al. [15] undertook a retrospective analysis of clinical data and evaluated the difference in nursing time costs for the two interventions. The nursing time costs were derived from a hospital monitoring system and are likely to be accurate. However, the authors did not present any further costing details and the economic evaluation was clearly a secondary component of the study. They undertook no sensitivity analysis and acknowledged that there were uncertainties in their data. The question posed was very setting-specific and the limited costing undertaken would make it problematic to apply the results more generally. Overall, the quality of the economic evaluation was poor.

3.3.4 Summary evidence statements

Cooper et al. [14] evaluated the cost-effectiveness of various patient isolation and screening strategies through the use of mathematical modelling. The authors did not draw firm conclusions from their analyses, but suggested that their model aided the theoretical understanding of the behavioural and relationship patterns between outcome measures. The methodology used was adequate, but limitations in the data meant that the results were not robust.

Williams et al. [15] evaluated the policy of isolation for heart transplant recipients during their intensive care stay. The authors concluded that abandoning the isolation policy had no significant impact on HAI or on rejection rates, and saved nursing costs. The retrospective nature of the study may have introduced bias. This along with other elements of limited reporting means that the economic evaluation should be considered poor quality.

3.3.5 Overall summary

These two studies undertook very different analyses in very different settings. The assumptions used in the modelling of Cooper et al. [14] may not be reflective of a clinical setting, but may add to the understanding of how MRSA is transmitted. The scenario evaluated by Williams et al. [15] was quite hospital-specific and may be difficult to apply more generally. It is impossible to draw any general conclusion based on these two studies.

In addition, due to the nature of the evaluations, there are no common assumptions or data inputs to discuss.

3.4 Screening, isolation and decolonisation

3.4.1 Overall study characteristics

A total of 19 studies evaluating screening, isolation and decolonisation strategies were identified [16-34]. Fourteen studies were conducted in the USA [16,19-25,27-29,31,33,34], two in the UK [17,26], two in the Netherlands [30,32] and one in Switzerland [18]. Four studies were evaluations based on a single clinical study [16,17,29,32], while the other 15 studies used decision modelling frameworks for the evaluation [18-28,30,31,33,34]. Of these, 15 studies used decision models, three derived effectiveness data from a single study [18,20,25] and the other 12 studies all undertook literature reviews [19,21-24,26-28,30,31,33,34]. The time horizon most often used was the duration of hospitalisation, which can be considered short-term. Only five of the studies used a lifetime horizon [22,24,26,27,31]. The populations screened were variable: six of the studies evaluated strategies aimed at hospital admissions or immediately post admission [20,22-24,29,34], eight evaluated individuals admitted for a variety of surgical procedures [17,18,25,27,28,30,31,34] and the remaining five studies performed the evaluation in an intensive-care setting or for high-risk admissions [16,19,21,26,32]. The majority of the analyses were undertaken from a hospital perspective, with only four studies reporting a broader societal perspective [22,28,30,33]. The evaluated interventions included variations of:

- surveillance strategies for identifying carriers of vancomycin-resistant enterococci (VRE) (not reported if decolonisation or isolation was involved);
- screening for *S. aureus* colonisation with nasal culture, followed by mupirocin treatment (decolonisation) for positive screens;
- empirical treatment (decolonisation) with mupirocin for all patients prior to surgery;
- rapid MRSA screening (polymerase chain reaction - PCR) of all surgical admissions;
- universal screening with PCR (plus isolation and/or decolonisation);
- universal screening with chromogenic agar (plus isolation and/or decolonisation);
- targeted screening with PCR (plus isolation and/or decolonisation);
- targeted screening with chromogenic agar (plus isolation and/or decolonisation).

Thirteen of the evaluations focused on MRSA, five on *S. aureus*; and one on VRE.

3.4.2 Screening to detect meticillin-resistant *S. aureus* (MRSA)

A total of thirteen studies evaluated the cost-effectiveness of screening strategies for MRSA [16-19,21-24,26,29,31,32,34]. Nine of the evaluations were conducted using decision models [18,19,21-24,26,31,34], the remaining four were conducted alongside clinical studies of varying design including: a case-series [32], a retrospective cohort [16], a controlled cohort (with historical control) [17], and a prospective, interventional study, difference-in-differences, and cost-benefit analyses [29]. All four study-based evaluations were conducted over a short time horizon of less than one year. Three of the four studies did not explicitly report the perspective of the evaluation [16,17,29], the fourth study stated that it was undertaken from a hospital perspective [32].

Of the nine modelling evaluations, one was undertaken from a societal perspective,[22] the other eight either failed to explicitly report a perspective [21,23,31] or were stated to be from a hospital [18,19,24,34] or a regional/national healthcare manager's perspective [26]. Four of the modelling studies were conducted over a lifetime or long-term time horizon (>15-years) [22,24,26,31] and the remaining five studies were conducted over a shorter time horizon; four using the period of inpatient stay [18,21,23,34] and one using a one-year period [19].

Five studies evaluated screening strategies at hospital admission [22-24,29,34], five evaluated strategies in high-risk wards, including intensive care units [16,19,21,26,32], and three evaluated strategies in surgical populations [17,18,31]. The studies will be presented in these sub-groupings.

3.4.3 Screening for MRSA at hospital admission

Overview of study characteristics

Four of the five studies evaluating screening on admission were conducted using decision models [22-24,34]. The fifth study was conducted alongside a prospective case-control study [29]. All five studies were conducted in the USA [22-24,29,34]. A brief summary of key characteristics is presented in Table 9.

Lee et al. [22] evaluated the cost-effectiveness of universal MRSA screening for all adult patients on admission. Positively screened patients were isolated. This was compared to a strategy of no screening. The authors were not specific about the test used to screen. The analysis was conducted using a decision model over a lifetime horizon, from both a societal and third party-payer perspective. A review of the literature was undertaken to obtain both clinical and utility data for the model. Costs were also identified from the literature. Resource use was not presented, but costing adjustments, discount rate and price year were all stated. Extensive sensitivity analysis was undertaken, including a probabilistic analysis. An incremental analysis was undertaken and the results of numerous scenarios presented.

Table 9. Study characteristics – MRSA at hospital admission

Study	Study year	Population	Economic evaluation design	Effectiveness evidence	Intervention
Hubben et al. [24], USA CEA	2011	Hospital admissions	Model	Selected published studies	A: Universal screening with PCR (+isolation) B: Universal screening with chromogenic agar (+isolation) C: Targeted screening with PCR (+isolation) D: Targeted screening with chromogenic agar (+isolation) E: No screening
Kang et al. [34], USA CEA	2012	Hospital admissions	Model	Selected published studies	A: Universal screening with PCR (+isolation) B: Targeted screening with PCR (+isolation) C: No screening
Lee et al. [22] USA, CUA	2010	Hospital admissions	Model	Selected published studies	A: Single culture of an anterior nares specimen (+isolation) B: No screening
Leonhardt et al. [29], USA CEA	2011	Hospital admissions	Study based	Prospective interventional case-control	A: Universal screening with PCR (+isolation/ decolonisation) B: Targeted screening with PCR (+isolation/ decolonisation)
Nelson et al. [23], USA CEA	2010	Hospital admissions	Model	Selected published studies	A: Universal screening with PCR plus decolonisation B: Universal screening with PCR C: No screening

The other four studies in this group also included a targeted screening strategy and therefore undertook their analyses comparing universal screening, targeted screening and no screening. Hubben et al. [24] undertook an analysis based on a published discrete event simulation model that some of the authors had been involved in developing. Strategies were evaluated over a 15-year time horizon from a hospital perspective. Only limited details of the model were presented in this article. The authors opted to evaluate two alternative screening tests (PCR and chromogenic agar) for both the universal and targeted screening strategy. For all screening strategies, positive patients were isolated. Most of the clinical data appear to have been derived from the University Medical Centre, Utrecht. Sensitivity/specificity of screening were taken from a published meta-analysis. Clinical, rather than utility outcomes were used in the evaluation. Direct costs were included and derived from data sources in the USA. Costing adjustments, discounting and price year were all presented. An incremental analysis was conducted, the results of which were presented along with extensive sensitivity analyses. This was the only evaluation in this broader group of studies that was conducted over a longer-time horizon.

Kang et al. [34] followed a similar methodology, opting to model the same strategies (including isolation for positive screens) from the perspective of the hospital, but over a short time horizon. Unlike Hubben et al. [24], they elected to undertake the evaluation assuming PCR would be used for screening. The authors used published studies from the USA to derive their model inputs, including costs. All cost adjustments and a price year were reported. An incremental analysis was undertaken, along with both one-way and probabilistic sensitivity analyses, the results of which were fully presented.

Nelson et al. [23] evaluated a more comprehensive strategy and this was the only modelling study to add decolonisation to the evaluated strategies. The authors compared screening and isolation with no decolonisation, and screening and isolation with decolonisation but no screening from a hospital perspective. Decolonisation was undertaken with topical treatments, such as mupirocin and chlorhexidine bathing. They utilised a decision model evaluated over a short time horizon, defined as duration of inpatient stay. Clinical data were derived from the published literature. To facilitate modelling the authors made an assumption regarding the reduction in risk of infection in non-colonised patients. Two summary measures of benefit were used: avoided MRSA infections and infection-related mortality. Relevant direct costs were included. These were derived in most instances from published sources; however, decolonisation costs were based on local estimates. An incremental analysis was conducted, along with extensive one-way, multi-way and probabilistic sensitivity analyses.

Leonhardt et al. [29] conducted their evaluation alongside a prospective, interventional study, using a case-control design, over a short time horizon (<15 months). They also evaluated universal or targeted screening, using PCR,

followed by isolation for positive screens and perioperative decolonisation and antibiotic prophylaxis, as appropriate. To account for differences in the two evaluated hospital sites, the authors undertook a difference-in-difference analysis. The primary outcome for the clinical effectiveness was the number of hospital-acquired MRSA infections per 100 adult patients. Costs appear to have been derived from the hospitals involved in the study; although this was not explicitly reported. The results were presented in terms of a ratio of incremental net savings/incremental cost of universal screening relative to target screening. An incremental analysis was not conducted and clinical results were not summarised as a cost-effectiveness ratio. A price year was reported, but only limited costing details were presented.

Outcomes

The results of the five studies are summarised in Table 10. The study by Lee et al. [22] was the only one evaluating universal screening compared with no screening. The analysis was undertaken for various combinations of MRSA prevalence and reproductive rates, and this is how the results were presented. Screening was found to be the dominant strategy (simultaneously more effective and less expensive than 'no surveillance') in the following scenarios: (a) when the basic reproductive rate was 1.5 or greater and the prevalence was 15% or greater; (b) when the basic reproductive rate was 2.0 or greater and the prevalence was 10% or greater; and (c) when the basic reproductive rate was 2.5 or greater and the prevalence was 5% or greater. At a threshold of USD 50 000 per QALY, screening was shown to be cost-effective when the basic reproductive rate was 0.25 or greater and the prevalence was 1% or greater. The probabilistic analysis showed that if the MRSA prevalence was 1%, screening was the preferred strategy for more than 50% of simulations at a threshold of USD 10 000 or greater. Baseline prevalence was varied from 1–90%, with the full range of results presented.

Hubben et al. [24] also evaluated a range of strategies, which included universal and targeted screening with either chromogenic agar or PCR testing. For the high prevalence analysis, the baseline prevalence rate was assumed to be 15%, and for the medium prevalence analysis it was assumed to be 5%. The analyses found that the number of infections avoided ranged from 2 085 to 2 252 for hospitals with a high prevalence of MRSA; and 622 to 709 for hospitals with a medium prevalence of MRSA. The total investment costs for the different screening and isolation strategies ranged from USD 8.64 million to USD 16.30 million for hospitals with a high prevalence of MRSA, and from USD 6.38 million to USD 15.03 million for hospitals with a medium prevalence of MRSA.

An incremental analysis was undertaken and the cost per averted additional infection was presented. Compared with selective chromogenic-based testing, selective PCR-based testing had an ICER of USD 13 000 per additional infection averted in a high-prevalence setting, and USD 36 200 per additional infection averted in a medium prevalence setting. Compared with selective PCR-based testing, universal PCR-based testing had an ICER of USD 131 000 per additional infection averted in a high-prevalence setting, and USD 232 700 per additional infection averted in a medium-prevalence setting. The authors concluded that if savings of USD 17 645 were generated by avoiding one infection, the most cost-saving intervention was selective PCR screening in settings with high prevalence, and selective chromogenic screening in settings with medium prevalence.

Kang et al. [34] evaluated a hypothetical large academic hospital with approximately 800 beds and estimated that total costs and MRSA HAIs were USD 6 741 630 and 516.6 with no screening, USD 6 458 860 and 457.2 with targeted screening, and USD 8 133 372 and 423.5 with universal screening. In comparison with no surveillance, targeted screening was dominant (more effective and less expensive) while the incremental cost per MRSA HAI prevented with universal screening was USD 14 955. The baseline prevalence rate for targeted screening was assumed to be 8.3%, whereas the baseline rate for universal screening was assumed to be 6.3%. When screening strategies were compared, the incremental cost per MRSA HAI prevented with universal versus targeted screening was USD 49 748. The deterministic sensitivity analyses confirmed the base case findings and the targeted strategy remained the most cost-effective strategy, as long as the effectiveness of screening in intensive care units was above 21%, the cost of one MRSA HAI above USD 8 291 and the length of stay less than 11.4 days. Similar results were shown in the probabilistic analysis, whereby targeted screening was more cost-effective than universal screening (compared with no screening). The universal screening strategy was the most cost-effective strategy but only if a decision-maker was willing to pay more than USD 71 300 per MRSA HAI prevented.

Leonhardt et al. [29] used baseline prevalence rates of MRSA of 3.24% at the control hospital and 1.76% at the intervention hospital, and the subsequent infection rates were 0.1% at the control hospital and 0.27% at the intervention hospital (P=0.06). Over the intervention period, the infection rate fell to 0.15% at the intervention hospital, but the difference with the control hospital remained non-significant (P=0.23). The incremental cost-saving of universal versus targeted screening was USD 15.44 per hospitalised patient. As the incremental cost of screening (universal versus targeted) was USD 31.19 per hospitalised patient, the ratio was estimated to have been USD 0.50, suggesting that for every additional dollar (USD 1.00) spent on universal versus targeted screening, only USD 0.50 would be recovered in costs avoided from hospital-acquired MRSA infections.

Nelson et al. [23] also undertook an incremental analysis, but unlike the other four studies in this section, included decolonisation as part of one of their screening strategies. The baseline prevalence at admission was assumed to be 7.5%. The expected costs of screening plus decolonisation were USD 93 538; whereas the cost of screening alone was USD 107 971; and the cost of no screening was USD 141 300. The projected rates of avoided MRSA

infections were USD 96.07 with screening and decolonisation, USD 95.69 with screening and USD 92.94 without screening. The number of avoided infection-related deaths was 99.57 with screening and decolonisation, 99.49 with screening and 99.29 without screening. The incremental analysis demonstrated that screening and decolonisation was the dominant strategy as it was simultaneously more effective and less expensive than both comparators. These conclusions held in almost all scenarios; the only exceptions being when assuming (a) extremely low estimates for the direct benefit of decolonisation (screening dominated in this case), or (b) very low risk of hospital-acquired MRSA infection in non-carriers, or (c) a very low cost of hospital-acquired MRSA infection; the 'no screening' strategy dominated in these three cases. A probabilistic sensitivity analysis was undertaken and showed that screening and decolonisation was the dominant strategy in all simulations.

Table 10. Summary results – MRSA at hospital admission

Author	Study year	Population	Economic evaluation design	Effectiveness evidence	Intervention
Hubben et al. [24], USA CEA	2011	Hospital admissions	Model	Selected published studies	A: Universal screening with PCR (+isolation) B: Universal screening with chromogenic agar (+isolation) C: Targeted screening with PCR (+isolation) D: Targeted screening with chromogenic agar (+isolation) E: No screening
Kang et al. [34] USA, CEA	2012	Hospital admissions	Model	Selected published studies	A: Universal screening with PCR (+isolation) B: Targeted screening with PCR (+isolation) C: No screening
Lee et al. [22]	2010	A: Universal screening B: No screening	Numerous scenarios were presented. In the majority of base-case scenarios where prevalence was >5% and the basic reproductive rate >1.5%, universal screening was the dominant strategy (i.e. more beneficial and less costly).		
Leonhardt et al. [29]	2011	A: Universal screening B: Targeted screening	Prior to intervention baseline MRSA rates at intervention hospital = 0.27% Post interventions MRSA rate reduced to 0.15% (decrease of 0.12%) Incremental cost savings of universal compared to targeted screening was USD 15.44 per hospitalised patient Incremental cost of universal compared to targeted screening was USD 31.19 per hospitalised patient The ratio of savings to cost was USD 0.5 which suggests that for every dollar spent only USD 0.5 could be recouped in avoided costs.		
Nelson et al. [23]	2010	A: Screening plus decolonisation B: Screening C: No screening	**Per 100 patients** **Screening plus decolonisation:** infections avoided = 96.07; deaths avoided = 99.57 **Screening:** infections avoided = 95.69; deaths avoided= 99.49 **No screening:** infections avoided = 92.94; deaths avoided = 99.29 Screening plus decolonisation cost = USD 93 538 Screening cost = USD 107 971 No screening cost = USD 141 300 For both outcomes screening plus decolonisation dominated the other strategies (i.e. more beneficial, less costly).		

Quality assessment

The quality of the studies ranged from poor to good. Lee et al. [22] undertook their evaluation using a stochastic simulation model, which analysed the interventions over the lifetime of the patient from two perspectives (societal and third-party payer). The authors undertook an extensive review of the literature to populate the model and used quality-adjusted life-years (QALYs) as a summary measure of benefit. The costs were presented from a third-party payer perspective, and non-medical costs and productivity costs were excluded. Cost data was obtained from relevant literature from the USA. Details such as price year and discount rate were provided. Extensive sensitivity analyses were undertaken and a range of results were presented. Although it may not be possible to generalise the results, the quality of the study was good overall.

Kang et al. [34] used a simpler modelling approach, but like Lee et al., [22] they clearly reported the key elements of their evaluation. A comprehensive non-systematic review of the literature was undertaken to populate the model. The authors highlighted some limitations in the clinical data and undertook extensive sensitivity analyses in an attempt to characterise the impact of uncertainty. They elected to use a disease-specific outcome (i.e. infection rates) and presented a good level of detail regarding costs inputs. They presented an explicit price year and relevant costing adjustments. An incremental analysis was undertaken and the results were fully presented. The authors acknowledged that it could be difficult to generalise the results outside of large hospitals in the USA, but the quality of the study was good overall.

The remaining two modelling studies [23,24] were considered to be of adequate quality. Nelson et al. [23] reported very limited information regarding the derivation of the clinical inputs to their model. In addition, the lack of a detailed cost breakdown and the absence of information on price year or cost adjustments impacted on the ability to assess quality. The authors undertook extensive sensitivity analyses and presented and conducted an appropriate incremental analysis. However, due to the limitations in reporting of the clinical data, the quality was only considered adequate. The study by Hubben et al. [24] was also considered to be only of adequate quality due to poor reporting of the model structure, underlying assumptions and justification for the choice of clinical data. In addition, while these authors undertook both one-way and scenario-based sensitivity analyses, they did not use probabilistic methods. Due to these limitations, there remains a level of uncertainty in the study findings.

Unlike the other studies, Leonhardt et al. [29] undertook their analyses as part of a prospective single study. The study was well reported and the authors employed appropriate methods to try and deal with confounding factors and time trends. They did not report a perspective and generally presented little information on resource use and unit costs. Finally, these authors did not undertake any sensitivity analysis despite highlighting areas of uncertainty. Due to these limitations, the quality of the study was considered poor.

Evidence statements

Lee et al. [22] examined the cost-effectiveness of universal MRSA screening of all adult patients at hospital admission. The authors concluded that universal screening of adults at hospital admission was cost-effective at a wide range of prevalence and basic reproductive rate values. The analysis used a valid cost-effectiveness methodology and the authors' conclusions appear robust.

Hubben et al. [24] determined the cost-effectiveness of selective and universal screening for MRSA upon hospital admission. The authors concluded that if the financial benefits from infections avoided were taken into account, MRSA screening could be cost saving. The methods were adequate, but could have been reported in more detail. The authors' conclusions seem valid within the scope of the analysis, but in a wider context there was uncertainty concerning the clinical estimates and therefore the results.

Kang et al. [34] examined the cost-effectiveness of targeted versus universal screening for MRSA at a hospital level. The authors concluded that targeted screening provided the best value for money as it improved clinical outcomes and saved costs from the perspective of the hospital. The study was based on a valid modelling framework that investigated key areas of uncertainty. The authors' conclusions appear robust.

Leonhardt et al. [29] examined the clinical/economic impact of universal versus targeted screening for MRSA to prevent hospital-acquired MRSA infections. Universal screening did not significantly reduce the rate of hospital-acquired MRSA compared with targeted screening and was more expensive because of higher costs of care. The study adopted a transparent framework that considered various methodological issues, but cost-effectiveness ratios were not derived and the issue of uncertainty was not investigated. Thus, caution is required when interpreting the authors' conclusions.

Nelson et al. [23] examined the cost-effectiveness of adding MRSA decolonisation to a universal screening programme at hospital level. The authors concluded that the model results strongly support the implementation of universal screening plus decolonisation from the perspective of the hospital. Overall, the study was based on a valid methodology that considered various areas of uncertainty although data sources were not clearly described. The authors' conclusions appear robust.

Overall summary

In general, the results of these evaluations suggest that MRSA screening on admission to hospital, followed by isolation if the result of MRSA screening is positive, is cost-effective. The variation in methods and strategies evaluated make it difficult to determine how much the addition of decolonisation improves the effectiveness of screening and isolation. In addition, it is not clear what the benefits of universal screening are, over and above those of targeted screening. There are several issues that varied across the evaluations and need to be considered if further evaluations are to be undertaken. These include:

- baseline prevalence rates;
- screening test selection:
  - rapid screening by PCR, chromogenic agar, culture screening;
- sensitivity and specificity of the selected test;
- effectiveness of decolonisation:
  - dependence on adherence assumption;
  - resistance to mupirocin;
- turn-around time of test;
  - 12 hours, 24 hours, 36 hours, 48 hours;
- compliance with treatment not being explicitly considered in all of the studies;
- appropriate time horizon:
  - short-term, long-term;
- appropriate outcomes:
  - infection rates, QALYs;
- reproductive rates.

These issues are similar across all of the screening, isolation and decolonisation studies regardless of population screened. Drawing any strong conclusion on the basis of heterogeneous, weak evidence can lead to inappropriate decision-making. In this instance, due to the huge economic benefits of avoiding infection, screening, isolation, and/or decolonisation strategies are likely to be cost-effective. What is not clear is which strategy or which set of assumptions are the most appropriate.

3.4.4 Screening for MRSA in high-risk patients and wards

Study characteristics

Of the five studies that evaluated screening in high-risk populations or wards, three were evaluations conducted alongside clinical studies [16,21,32] and two were undertaken using decision models [19,26]. Two of the analyses were undertaken from the perspective of the hospital [19,32]; two did not explicitly report the perspective but included direct costs relevant to a hospital perspective [16,21], and the fifth analysis was reported to have been conducted from a regional/national healthcare manager perspective [26]. Four of the five analyses were over a short-time horizon [16,19,21,32], the fifth analysis was undertaken over a lifetime horizon [26]. Three studies were undertaken in the USA [16,19,21], one in the UK [26] and one in the Netherlands [32]. A summary of key characteristics is presented in Table 11.

Two of the three evaluations undertaken alongside clinical studies considered screening at admission, followed by weekly screening of high-risk patients and wards [16,21]. The definition of high risk differed between the two studies. Using a controlled cohort (historical control), Clancy et al. [21] evaluated a screening strategy targeting all patients admitted to adult medical or surgical intensive care units. Patients identified as colonised or infected were placed in isolation. The primary outcome measure was the incidence of MRSA infection. The authors included the costs of screening and costs of isolation as well as cost avoidance (i.e. excess costs avoided). No summary measure of benefit was derived, so costs and outcomes were presented separately. Intervention costs were derived retrospectively using data from the same patients that were used to estimate the clinical outcomes. Direct hospital costs were included and, although a perspective was not reported, it is likely to be that of the hospital.

The other study by West et al. [16] defined high-risk patients as patients transferred from other hospitals, or admitted from long-term care facilities, or readmitted to a nephrology service within 30-days of discharge. Although this was not explicit, the analysis seemed to have been conducted over the short-term from what appeared to be a hospital perspective. The evaluation was undertaken alongside a controlled cohort (historical control) conducted across two hospitals in the USA. The primary outcome measure was the rate of MRSA infection. No summary measure was derived, so like Clancy et al., [21] these authors presented costs and outcomes separately. They included the costs of screening and the costs of isolation. The costs of screening were derived from the cohort study, whilst the costs of isolation were derived from the literature.

Both of the above-mentioned studies were undertaken in the USA from what appeared to be a hospital perspective. One of the modelling studies by Nyman et al. [19] was also undertaken in the USA and evaluated a similar screening and isolation policy from the same perspective. The focus of the modelling was the costs of MRSA screening and the authors evaluated what they stated to be the typical MRSA intervention in the USA: screening of

all intensive care unit patients and isolation of colonised/infected patients. They constructed a Markov model to capture the impact of screening on the incidence of MRSA hospital-wide. Clinical data were derived from published studies, whilst cost data were derived from the hospital database and patient medical records. Costs included the cost of screening, isolation and treatment. Once again, no summary measure was derived, as the main aim of the study was to estimate costs.

Table 11. Study characteristics – MRSA in high-risk patients and wards

Study	Study year	Population	Economic study design	Effectiveness evidence
Clancy et al. [21] USA CEA	2006	High-risk targeted screening	Study based	Controlled cohort (historical control)
Nyman et al. [19], USA CEA	2011	Intensive care patients	Model (Markov)	Selected published studies
Robothem et al. [26], UK CUA	2011	Intensive care unit patients	Model	Selected published studies
Van Rijen et al. [32] Netherlands CEA	2009	High-risk patients	Study based	Prospective case series
West et al. [16] USA CEA	2006	High-risk patients	Study based	Controlled cohort (historical control)

The two remaining studies [26,32] were undertaken outside of the USA and considered slightly different strategies. Van Rijen et al. [32] evaluated the Search and Destroy policy which is widely used in the Netherlands and Scandinavian countries. The policy is outlined in the national guidelines of the Dutch Working Party on Infection Control. The policy focuses on screening and isolation of patients considered at risk for the carriage of MRSA, especially those who have been treated in a hospital abroad and those who have been exposed to pigs or veal calves. In addition to isolation, patients identified as carriers are prescribed antibiotics for decolonisation, as defined in the guidelines of the Dutch Working Party on Antibiotic Policy. The analysis was undertaken over a short period, using what appeared to be a single cohort of patients, from a hospital perspective. The primary clinical outcome was the rate of MRSA. No summary measure of benefit was derived; the authors elected to present the number of lives saved and cases avoided separately from costs. All relevant direct costs appeared to have been included. Elements considered were the costs of screening, isolation, contact tracing and treatment.

Finally, the fifth study evaluating MRSA control in an intensive care unit was undertaken in the UK, using an individual patient model [26]. This analysis considered a broader range of screening strategies, some of which included decolonisation; in total 21 strategies were evaluated. The clinical data were derived from a systematic review of the literature. Epidemiological data were from UK sources (mainly the Intensive Care National Audit and Research Centre) and cost data were also derived from UK-specific sources, which included published studies and national reference costs. Of the five studies in this section, this was the only one to use an utility outcome measure (i.e. QALYs). Utility data were obtained from a published cohort study that estimated morbidity and mortality for the five years after discharge from the intensive care unit. The analysis was undertaken over a long-term (lifetime) horizon. Extensive sensitivity analysis, including probabilistic analysis, was presented.

Outcomes

The results of the five studies evaluating MRSA screening on admission are presented in Table 12. The two study-based evaluations by Clancy et al. [21] and West et al. [16] evaluated very similar strategies and both demonstrated that screening was cost-saving in these patient populations. Clancy et al. [21] presented the results for total infection and nosocomial infection. We will only discuss the results of the intervention on nosocomial MRSA. Following the implementation of screening, the rate of MRSA nosocomial infection decreased from 4.5 to 2.8 infections per 1 000 census-days ($p<0.01$). Rates were calculated as the number of clinical specimens positive for MRSA in a unit divided by the total number of census-days per month in that unit. The monthly costs of the programme were stated to be USD 3 475. The authors reported that published data showed that the attributable excess cost of treating patients with MRSA varied from USD 9 275 to USD 27 000. Using the lowest cost estimate (USD 9 275), they suggested that the screening programme saved intensive care units USD 19 714.

West et al. [16] presented their evaluation results separately for two hospitals. Results were again favourable to the screening intervention across both hospital settings. At the first hospital, screening resulted in a mean post-intervention MRSA infection rate of 0.46 per 1 000 patient-days compared with 0.76 per 1 000 before the intervention, or a statistically significant 39% relative decrease ($p=0.05$). The second hospital showed a non-statistically significant 21% relative decrease of the MRSA infection rate (from 0.72 to 0.57 per 1 000 patient-days). The total cost of the screening programme (across hospitals) was USD 113 955. Over a 16-month period, West et al. [16] estimated an overall cost saving of USD 483 005 attributable to the screening programme. The authors

concluded that expanded surveillance was cost-effective, preventing 13 nosocomial MRSA bacteraemia and nine surgical site infections, at a saving of USD 1 545 762.

To enable comparison with the study by Clancy et al. [21] we calculated a monthly cost of USD 113 955/16 or approximately USD 7 122 for the study by West et al. [16]. However, neither of these studies reported a perspective or price year so it is not clear whether it is appropriate to compare cost results. The difference in costs may be indicative of a number of factors including different settings, resource use and price year.

Nyman et al. [19] presented results for three alternative screening test strategies evaluated using a decision model. The focus of the study was the costing element of the economic evaluation. The study showed that the total annual cost of screening was USD 126 788 with standard culture, USD 135 906 with chromogenic agar and USD 192 709 with PCR. The base case results showed that a 'no screening' strategy resulted in 0.0480 new MRSA infections per hospital admission, compared with screening which resulted in 0.0159 new MRSA infections per hospital admission. The effectiveness of the tests was not evaluated as the authors stated that the current published literature did not provide statistically significant effect data for these tests. The various costs of the tests were incorporated into the model. The base case results showed that screening resulted in a net saving per hospital admission of USD 484 with standard culture, USD 483 with chromogenic agar and USD 476 with PCR.

Van Rijen et al. [32] evaluated the Dutch Search and Destroy policy. Based on the assumptions used to determine the estimates of a 'no screening' strategy, the screening programme was found to prevent 36 additional nosocomial MRSA bacteraemia cases and save an additional ten lives. The authors estimated that the total cost of the programme was EUR 215 559 and the total savings to the hospital from the implementation of the programme were EUR 211 797.

Robotham et al. [26] undertook an extensive modelling exercise which considered 21 strategies. Due to the large number of results, not all were presented. Results were presented separately for the screening and decolonisation strategies, and the screening and isolation strategies, as a narrative and as cost-effectiveness curves and frontiers. The authors found that universal decolonisation (pre-emptive decolonisation) with chlorhexidine had the highest probability (70%) of being cost-effective at a threshold of GBP 30 000 per QALY gained. The next best strategy was screening all patients with PCR, combined with mupirocin treatment for MRSA-positive patients (30% probability of being cost-effective at threshold of GBP 30 000). The results for those strategies comprising screening and isolation demonstrated considerable uncertainty in determining which strategy would be the most cost-effective. Up to a threshold of GBP 17 000, the results suggested that the most cost-effective strategy would be to do nothing. However, within the range of GBP 20 000 to GBP 30 000, which is widely accepted as an appropriate threshold in the UK, the results suggested that either pre-emptive isolation of high-risk patients or a strategy combining screening of high-risk patients using chromogenic agar followed by isolation of MRSA-positive patients were the most cost-effective. Extensive analyses were conducted and presented.

Table 12. Summary results – MRSA in high-risk patients and wards

Study	Study year	Intervention(s)/comparator(s)	Results
Clancy et al. [21]	2006	A: Screening on admission and then on a weekly basis plus isolation for MRSA-positive patients. B: No screening	Average nosocomial MRSA infection rate with screening = 2.8 per 1 000 census-days; compared with no screening = 4.5 per 1 000 census-days. Overall cost savings for intensive care units = USD 19 714
Nyman et al. [19]	2011	A: Screening (chromogenic, PCR & standard culture) and isolation for MRSA-positive patients. B: No screening	New MRSA infections with screening = 0.0159; without screening = 0.0480. Total cost of screening with chromogenic = USD 135 906. Total cost of screening with PCR = USD 192 709. Total cost of screening with standard culture = USD 126 788. Cost per admission without screening = USD 18 051; with standard culture = USD 17 567; a net saving of USD 484. Net saving with PCR was USD 476; and with chromogenic = USD 483.
Robothem et al. [26]	2011	A: High-risk patients with a) conventional culture; b) chromogenic agar; c) PCR with each of the three strategies followed by isolation or decolonisation (MRSA-positive patients received mupirocin immediately after the result or at 24 or 48 hrs). B: All patients with a: conventional culture; b) chromogenic agar; c) PCR with each of the three strategies followed by isolation or decolonisation (MRSA-positive patients received mupirocin immediately after the result or at 24 or 48 hrs) C: All high-risk patients with a: conventional culture followed by pre-emptive isolation. D: No screen –conventional culture of clinical swab, pre-emptive isolation for high risk patients (chlorhexidine) E: No screen – conventional culture of clinical swab, pre-emptive isolation of all patients (chlorhexidine) F: No screen – conventional culture of clinical swab, isolation or decolonisation for MRSA-positive patients (chlorhexidine)	**Screening and decolonisation strategies:** All screening and decolonisation strategies improved health outcomes and reduced costs. Universal decolonisation with chlorhexidine had the highest probability of being cost-effective (70% of simulations below a threshold of GBP 30 000). **Screening and isolation strategies:** All screening and isolation strategies improved health outcomes, but at increased costs. These results were more uncertain. At thresholds of GBP 20k to GBP 30K, isolation of high-risk patients without screening or chromogenic screening for high risk patients followed by isolation for positive screens were likely to be the most cost-effective options.
Van Rijen et al. [32]	2009	A: Screen and isolate from admission ('Search and Destroy' policy). B: No screening (No 'Search and Destroy' policy).	Screening and isolation followed by antibiotic treatment was found to prevent 36 additional infections and save 10 additional life years. Total annual costs = EUR 215 559. Total annual savings due to reduction in MRSA = EUR 427 356. Net savings to hospital = EUR 211 797
West et al. [16]	2006	A: Screening all high-risk patients on admission and weekly thereafter plus isolation for MRSA-positive patients. B: Screening only intensive care unit admissions.	Hospital one: Screening all high-risk patients led to a 39% relative decrease in infections (mean 0.76 per 1 000 patient-days compared with mean 0.46). Hospital two: Screening all high-risk patients led to a 21% relative decrease in infections (mean 0.72 per 1 000 patient-days compared with 0.57). Numbers of nosocomial pneumonia, surgical site infection, urinary tract infection and skin/soft tissue infections were reported for both intervention and comparator. Total cost of screening all high-risk patients = USD 113 955. Overall savings = USD 483 005.

Quality assessment

The quality of the studies varied from poor to good. West et al. [16] undertook a retrospective analysis of patient charts across two time points. They did not demonstrate that the two groups were comparable at baseline and did not deal with the potential issues of confounding and bias. In addition, the authors did not report a perspective or any details on the price year or adjustments undertaken. These authors did not include a sensitivity analysis and did not address the issue of generalisability. The quality of the study was considered poor.

Clancy et al. [21] also undertook their analyses based on a single retrospective study. They provided some limited data on the baseline comparability of the two groups. The authors did not report a perspective, although they did report extensively on the resource use and associated unit costs. Like West et al. [16], the authors did not report a price year, the details of any costing adjustments or a sensitivity analysis. The quality of this study was considered poor.

Van Rijen et al. [32] also used a study based approach to undertake their evaluation. The clinical estimates were derived from a prospective analysis of patients admitted to the authors' hospital. The estimates for the control group were based on the literature, assuming that MRSA cases without screening would be similar to those in other settings. The economic evaluation methodology was reported transparently, with much of the cost data being derived from the hospital system. Full details of resource use and unit costs were presented. However, no sensitivity analysis was conducted and the issue of generalisability was not discussed. The overall quality of the analysis was considered poor.

Both modelling studies by Nyman et al. [19] and Robotham et al. [26] undertook more comprehensive analyses which can be considered of adequate [19] and good [26] quality. Both studies derived the clinical estimates for their models from the literature; one using published systematic reviews and other high-quality studies [26] and the other using literature identified from a database in the USA [19].

The details presented by Nyman et al. [19] made it more difficult to be sure that all relevant evidence had been identified and used. The main focus of Nyman et al. [19] was the cost analysis, for which the authors provided a thorough description of how costs were measured and which sources were used. They did not present information on resource use. The authors utilised a previously published model, which was not reported in detail in the article, but is available from other publications. Overall, the methods for the costing component were well reported and of good quality. However, cost analysis relies on robust clinical data and it was not clear whether the data used were adequate. For this reason, the study was considered to be only adequate in terms of quality.

Robotham et al. [26] undertook a more thorough review in order to populate their model, using epidemiological data and patient-level data relevant to their UK setting. However, their determination of costing relied on published categories of costs rather than an evaluation of resource use and associated unit costs. The authors evaluated numerous strategies and presented many incremental results. The use of probabilistic methods allowed for characterisation of uncertainty and for the results to be presented using cost-effectiveness frontiers. Due to the less comprehensive costing, it may not be possible to apply the results more generally outside of the UK setting, but the quality of the study was considered good.

Evidence statements

West et al. [16] examined the cost-effectiveness of an MRSA screening programme targeting high-risk patients upon admission into a hospital system. The authors concluded that the screening programme reduced the rate and costs of MRSA infections in a community hospital system. The study methodology presented some potential limitations that should be considered when assessing the robustness of the authors' conclusions.

Clancy et al. [21] examined the clinical and economic impact of an MRSA screening programme in high-risk hospital wards such as intensive care units. The authors concluded that the screening programme reduced the rates of MRSA infections and led to cost savings throughout the hospital. Although well-presented, the analysis had some methodological limitations and the authors' conclusions should be interpreted with caution.

Nyman et al. [19] assessed the costs of screening patients for MRSA in the intensive care unit and concluded that screening, using any of three tests, produced net savings for the hospital, but that further research was needed. The selection process for the effectiveness data was poor, but other methods were satisfactory and these methods and the results were adequately reported. Given the scope of the analysis, the authors' conclusions may be valid but remain uncertain.

Van Rijen et al. [32] examined the cost-effectiveness of a screening and decolonisation treatment programme against MRSA in a large teaching hospital in a country with low MRSA prevalence. The authors concluded that the MRSA screening and decolonisation treatment programme saved money and lives from the hospital's perspective. The study relied on several assumptions and was not based on an explicit comparison between the programme and the control strategy. Thus, caution is required when interpreting the authors' conclusions.

Robotham et al. [26] assessed the cost-effectiveness of screening strategies, with isolation or decolonisation, to control MRSA in intensive care units. Decolonisation strategies were likely to be cost saving in an intensive care unit setting provided that there was no resistance to meticillin. Universal screening for MRSA by PCR, followed by decolonisation for MRSA-positive patients, could be cost-effective. The evidence on effectiveness of isolation was insufficient to support universal screening. The cost-effectiveness framework was robust and the uncertainty was considered. The conclusions therefore seem valid.

Overall summary

As stated previously, all of the results suggest that in a high-risk patient population, targeted screening for MRSA, followed by isolation and/or decolonisation of MRSA-positive patients, is likely to be cost-effective and produce net savings for the hospital. However, there was a large degree of variation across the studies which underlines that more research is necessary to provide additional data on effectiveness before undertaking further economic evaluations. These data include: prevalence rates, sensitivity and specificity of tests, treatment efficacy and compliance rates.

3.4.5 Screening for MRSA in surgical patients

Study characteristics

Three studies evaluated screening followed by decolonisation of MRSA-positive patients in surgical populations [17,18,31]. The strategies studied included:

- Universal screening for MRSA using PCR;
- Chromogenic agar screening based on risk profile plus pre-emptive isolation;
- Screening of all (unspecified test) and decolonisation of MRSA-positive patients prior to surgery.

A summary of the key characteristics of these studies is presented in Table 13. One focused on vascular surgery patients [31], whereas the other two studies evaluated more general surgical populations (including both emergency and elective procedures) [17,18]. Two of the three studies used decision models to undertake the evaluation [18,31]; the third study was conducted alongside a clinical study [17]. Two studies were undertaken over a short-term time horizon [17,18] and one used a long-term, lifetime, horizon [31]. Two of the studies used infection rates as the outcome measure [17,18] and one used QALYs [31]. The evaluations were undertaken in the USA [31], the UK [17] and Switzerland [18].

Table 13. Study characteristics – MRSA in surgical patients

Study	Study year	Population	Economic study design	Effectiveness evidence
Keshtgar et al. [17] UK CEA	2008	Surgery admission patients	Study based	Controlled cohort (historical control)
Lee et al. [31] USA, CUA	2009	Vascular surgery patients	Model (Tree)	Selected published studies
Murthy et al. [18] Switzerland, CEA	2010	Surgery admission patients	Model (Markov)	Prospective cohort

Lee et al. [31] evaluated screening in patients admitted for vascular surgery, followed by decolonisation of MRSA-positive patients. They used a decision-tree evaluated over the lifetime of the patient; no perspective was reported. Clinical parameters, such as probability of screening, successful decolonisation and survival were obtained from the published literature. The summary outcome measure was QALYs, which were taken from the published literature. Direct costs relevant to a hospital perspective were included. An incremental analysis was presented. In addition, both univariate and probabilistic sensitivity analyses were undertaken in an attempt to characterise parameter uncertainty.

Murthy et al. [18] also undertook a decision model analysis, but over a short time horizon (hospitalisation period) in a more general surgical population. The analysis was undertaken from a hospital perspective and considered three screening strategies: (a) universal screening with PCR for all patients admitted for surgery; (b) screening for risk factors (prior hospitalisation or antibiotic use) combined with pre-emptive isolation and contact precautions pending chromogenic agar results; or (c) no screening. The majority of clinical data were derived from one large prospective cohort study and the study details were not fully reported. The screening test used was PCR and the sensitivity/specificity of this PCR test was taken from the cohort study. The measure of benefit used in the economic evaluation was avoided MRSA infections. All relevant direct costs were included and these were derived from the hospital accounting system, supplemented by data from staff interviews. A price year was reported. An incremental analysis was undertaken and a one-way sensitivity analysis was conducted.

Keshtgar et al. [17] also undertook an evaluation in a more general surgery population, but did so alongside a cohort study, with historical controls. They evaluated rapid screening by PCR followed by decolonisation of MRSA-positive patients compared with an existing culture screening that had a three-day turnaround for results. The primary outcome was the rate of MRSA bloodstream infections. The perspective of the analysis was not reported,

but direct costs relevant to a hospital perspective were given. Resource data were derived from the cohort study, but a full breakdown was not reported. The source of unit cost data was not reported and the price year was also not reported. An incremental analysis was not presented, instead costs and outcomes were presented separately. No sensitivity analysis was undertaken.

Outcomes

The results of the three studies evaluating MRSA screening of surgical populations on admission are presented in Table 14. Lee et al. [31] found that MRSA infection was associated with a mean increase in the length of stay of 5.9 days at a revenue loss of USD 2 079 per day. Their results suggested that MRSA screening following by decolonisation of MRSA-positive patients was cheaper and more effective than (dominant over) a 'no screening' strategy when the MRSA prevalence was 2.5% and the success of decolonisation was set at 50% effectiveness. At a cost-effectiveness threshold of USD 50 000 per QALY, this strategy was cost-effective with an MRSA prevalence rate of 1% or 2.5%, and with a decolonisation success rate set at 25% effectiveness. A range of scenarios for alternative MRSA prevalence rates and decolonisation success rates were presented. Given this wide range of scenarios, the results suggested that MRSA screening following by decolonisation of MRSA-positive patients was cost-effective in patients admitted for vascular surgery.

Murthy et al. [18] found that the expected costs and probability of infection with MRSA were CHF 10 358.46 and 0.0088 without MRSA screening, CHF 10 502.53 and 0.0041 with universal MRSA screening with PCR, and CHF 10 511.04 and 0.0057 with MRSA screening of selected patients based on risk factors. They estimated that, compared with the 'no screening' strategy, the incremental cost per avoided MRSA infection for universal screening was CHF 30 784. Universal screening was also more effective and less expensive than screening of selected patients based on risk factors. The sensitivity analysis showed that the most influential input was the prevalence of MRSA carriage; when MRSA carriage decreased, cost-effectiveness of universal screening decreased. Other influential inputs were the probability of cross-transmission, the efficacy of MRSA decolonisation and of contact precautions, and the costs of MRSA infections and of rapid screening.

Keshtgar et al. [17] demonstrated that, in comparison with the annual mean for the preceding six years, implementation of MRSA screening with PCR led to a 38.5% decrease of the overall rate of MRSA bacteraemia per 1 000 patient-days ($p < 0.001$) and a 12.7% decrease of the rate per 1 000 patient-days of MRSA isolation from wounds ($p=0.021$). When compared with the year preceding the intervention (2005), MRSA bacteraemia per 1 000 patient-days decreased by 38.6% ($p<0.001$) and MRSA wound infections per 1 000 patient-days by 27.9% ($p<0.001$). The authors also found that compliance with MRSA screening improved across surgical specialties. In comparison with the annual mean for the preceding six years, the observed reduction in MRSA bacteraemia per 1 000 patient-days and wound infections per 1 000 patient-days was equivalent to saving the cost of 3.78 beds per year (GBP 276 220). The annual cost of MRSA screening was GBP 302 500, which corresponded to 4.1 beds per year. Thus, the programme led to a net loss of GBP 26 280 when compared with the mean of the previous six years. When compared with the year preceding the intervention (2005, which was also the year with the highest incidence of MRSA bacteraemia and wound infections), there was a net saving of GBP 545 486. The baseline prevalence rate of MRSA carriage used in the model was 5.1%.

Table 14. Summary results – MRSA in surgical patients

Study	Study year	Intervention(s)/comparator(s)	Results
Keshtgar et al. [17]	2008	A: Rapid PCR screening; decolonisation of MRSA-positive patients B: Current culture screening	Compared to B, strategy A resulted in a decrease of 38.5% in MRSA bacteraemia and 12.7% MRSA wound infections. Reduction in MRSA bacterium resulted in a saving of GBP 276 220 Annual cost of screening GBP 302 500.
Lee et al. [31]	2009	A: Universal PCR screening; isolation and decolonisation of MRSA-positive patients B: No screening, no decolonisation.	MRSA infection resulted in a mean increase in length of stay of 5.9 days. Strategy A dominated strategy B for a wide range of prevalence rates and decolonisation success rates. A range of incremental results over a range of plausible scenarios were presented.
Murthy et al. [18]	2010	A: Universal PCR screening; isolation and decolonisation of MRSA-positive patients B: Chromogenic agar screening for high risk plus pre-emptive isolation: decolonisation of MRSA-positive patients. C: No screening.	Strategy A cost CHF 10 502 and resulted in 0.0041 MRSA infections. Strategy B cost CHF 10 511 and resulted in 0.0057 MRSA infections. Strategy C cost CHF 10 358 and resulted in 0.0088 MRSA infections. ICER for A compared with C = CHF 30 784 per infection avoided. Strategy A dominated B.

Quality assessment

Over the three studies, the quality varied from poor [17,31] to adequate [18]. Both Lee et al. [31] and Keshtgar et al. [17] did not report basic elements of economic evaluation methodology such as price year, cost adjustments, and perspective. Keshtgar et al. [17] derived clinical evidence from a cohort study with historical control, but did not deal with issues of changes in practice over time or comparability of cohorts. In addition, the authors did not attempt to deal with uncertainty through the use of sensitivity analysis. Lee et al. [31] used decision-model-based-analyses and incorporated QALYs as an outcome. However, these authors reported limited details on the derivation of clinical input values, no information on the utility estimates or how these were derived, and only limited information on costing. Due to these limitations, both studies were considered poor quality [17,31].

Murthy et al. [18] undertook a more comprehensive modelling analysis. Data were derived from published sources, although the authors relied heavily on one large cohort study. The perspective was clearly stated and all relevant costs included. Costs and resource use were derived from the hospital system, with some of the unit costs presented. An incremental analysis was undertaken and fully presented. In addition, extensive one-way sensitivity analyses were undertaken. Probabilistic methods for dealing with uncertainty would have been more appropriate, but the quality of the study overall was considered adequate.

Evidence statements

Keshtgar et al. [17] examined the clinical and economic impact of MRSA screening with PCR for the prevention of hospital-acquired MRSA in surgical patients. The authors concluded that rapid MRSA screening of all surgical admissions led to a significant reduction in MRSA bacteraemia per 1 000 patient-days, which, in turn, led to savings in treatment costs, but also to an increase in screening costs. The study had some methodological limitations, which might affect the validity of the authors' conclusions.

Murthy et al. [18] examined the cost-effectiveness of universal MRSA screening using PCR on admission to prevent nosocomial MRSA infections in surgical patients. The authors concluded that universal MRSA screening using rapid PCR on admission was unlikely to be a cost-effective option for reducing MRSA infection probability in surgical patients in their setting, but might be cost-effective in settings with a higher MRSA prevalence rate. The analysis used an appropriate methodology and was based on valid sources that reinforced the authors' conclusions.

Lee et al. [31] aimed to compare the cost-effectiveness and economic value of a strategy to screen for MRSA and decolonise MRSA-positive patients before vascular surgery. The authors concluded that pre-operative MRSA-screening in these patients was likely to be cost-effective across a range of situations. Due to limited reporting of the methods and the quality of the data inputs, the reliability of the results and the validity of the conclusions cannot be assessed.

Overall summary

Despite the limitations, these evaluations suggest that MRSA screening and decolonisation of MRSA-positive patients prior to surgery is likely to be a cost-effective option. However, the evaluated strategies and underlying assumptions were not consistent across the evaluations.

3.4.6 Screening to detect S. *aureus*

Study characteristics

Five studies [25,27,28,30,33] were identified which evaluated pre-operative screening for *S. aureus* and subsequent decolonisation of *S. aureus*-positive patients. All five economic evaluations were conducted using decision models and evaluated over different time horizons. Four studies were conducted in the USA [25,27,28,33] and one in the Netherlands [30]. Three studies were stated as being from a societal perspective [28,30,33]. One study did not report the perspective but appeared to be undertaken from a hospital perspective [25], whereas the remaining study was from the perspective of a third-party payer [27]. In all five studies the treatment evaluated for decolonisation of *S. aureus*-positive patients was based on mupirocin. Four of the studies did not allow for a distinction of *S. aureus* between meticillin-susceptible *S. aureus* (MSSA) and MRSA. [27,28,30,33]. Slover et al. [25] presented a pathway which enabled patients to be distributed into one of these two groups; however, results were not presented separately. A brief summary of key study characteristics is presented in Table 15.

Courville et al. [28] undertook a one-year analysis using a decision modelling framework focused on screening for *S. aureus* to reduce surgical site infections in patients undergoing total hip or knee arthroplasty. They compared three strategies: (a) screen and then only treat *S. aureus*-positive patients; (b) treat all patients; and (c) no screening or treatment. The analysis was stated to be from a societal perspective, although limited to costs and health effects directly affecting the target population. The price year was reported, along with details on other relevant cost adjustments. Resource use and unit costs were not presented separately. The clinical data were derived from the literature. Utility outcomes were based on quality of well-being index scores, also derived from the literature. An incremental analysis was undertaken and uncertainty explored through the use of one-way sensitivity analysis.

Slover et al. [25] also evaluated a pre-operative *S. aureus* screening and decolonisation programme for patients undergoing hip or knee arthroplasty, but also included patients undergoing spinal fusion. They utilised a decision model with a short time horizon, but did not state a perspective. The clinical data were mainly derived from a cohort of patients attending the authors' hospital. The clinical outcome of interest was a reduction in surgical site infections. The costs of screening and treatment were also derived from the authors' hospital and were further augmented with average costs of surgical procedures from the literature. There was no discounting and a price year was not reported. A two-way sensitivity analysis was conducted and this was presented as the final result. The results demonstrated that *S. aureus* screening and decolonisation reduced the number of infections and resulted in cost savings.

Both of these studies modelled similar populations. Courville et al. [28] evaluated a hypothetical population aged 65 years and ran separate models for patients undergoing hip and knee arthroplasty respectively. Slover et al. [25] did not report patient characteristics and evaluated patients undergoing hip and knee arthroplasty together and patients undergoing spinal fusion separately. Only Courville et al. [28] reported the time horizon, but both studies were short-term and hence comparable. Slover et al. [25] did not report the perspective, but included direct costs. Despite stating a broader perspective, Courville et al. [28] only included direct costs, thus the costing components are potentially comparable. However, we did not compare the studies for the following reasons: lack of reporting on price year and price adjustments, inconsistencies in presenting the results and high variability.

Table 15. Study characteristics – *S. aureus* screening

Study	Study year	Population	Design	Effectiveness evidence
Courville et al. [28] USA, CUA	2012	Preoperative patients (total hip/knee arthroplasty)	Model	Selected published studies
Lee et al. [27] USA CUA	2011	Women who underwent planned Caesarean section	Model	Selected published studies
Slover et al. [25], USA, CEA	2011	Elective arthroplasty patients	Model	Hospital cohort
Wassenberg et al. [30] Netherlands, CEA	2011	Pre-operative patients	Model	Selected published studies
Young et al. [33], USA, CEA	2006	Post-operative patients	Model	Selected published studies

Wassenberg et al. [30] examined a variety of pre-operative *S. aureus* screening and treatment strategies focusing on deep-seated cardiac and prosthetic infections. They employed a decision model evaluating 1 000 patients over a one-year time period from a societal perspective. Epidemiological data were derived from a hospital database, while other clinical data were taken from the published literature. The summary measures of benefit were life-years saved and infections prevented. Only direct costs were included. Details regarding the derivation and source of cost data were reported, along with the price year and exchange rate. A number of one-way sensitivity analyses were conducted to identify influential parameters. The results were shown to be robust to the variation undertaken in the sensitivity analysis.

The patient population evaluated by Wassenberg et al. [30] included some patients who may be comparable to the patient population evaluated in Courville et al. [28] and Slover et al. [25]. The clinical data were derived from a population that included patients undergoing total knee and hip prosthesis; this may add additional weight to the conclusions reached by the other two studies [25,28]. The baseline prevalence rate utilised in Wassenberg et al. [30] was 18.5%, which is closer to the rate of Courville et al. [28] (23%) than that of Slover et al. [25] (3.3% hip and knee arthroplasty, 1.7% spinal fusion).

Young et al [33] evaluated pre-operative *S. aureus* screening and treatment strategies in a more general surgical population, including non-emergent cardiothoracic, neurological, general and gynaecological patients, in another modelling study that may add weight to the conclusions of other studies. The authors used a short-term decision model to compare the strategies from a societal perspective. The model structure was presented, along with details of the clinical and cost data used to populate the model. The clinical and cost data were derived from the published literature. Resource use was not presented. The price year and details of costing adjustments were reported. Direct costs and productivity costs were included. Several one-way, multi-way and scenario sensitivity analyses were presented. The model results were sensitive to the efficacy of mupirocin. In this more general population of surgical patients, Young et al. [33] demonstrated that *S. aureus* screening and treatment of *S. aureus*-positive patients, or treatment of all patients without screening for *S. aureus* were both cost-effective. The evaluated patient population was more heterogeneous in the other three studies [25,28,30] but the baseline prevalence of 23.1% was similar.

The last of the five studies in this group considered a different surgical population. Lee et al. [27] evaluated routine pre-operative *S. aureus* screening and decolonisation for women with a planned Caesarean section. They used a decision model with a lifetime horizon to compare a *S. aureus* screening and treatment strategy to a 'no screening'

strategy from a third-party payer perspective. The clinical data used to populate the model were derived from a variety of published sources, details of which were presented. Baseline prevalence data varied from 1–50%. This was the only of the five studies to used QALYs as an outcome measure. The utility weights were derived from the published literature. Costs were derived from well-known US sources, such as the Red Book and the Medicare database. The resource use data were derived from the literature. Both costs and benefits were discounted at a rate of 3%, but no price year was reported. Probabilistic sensitivity analysis was conducted, an incremental analysis was undertaken and the results were fully presented.

Outcomes

The results of the four studies evaluating *S. aureus* screening in similar surgical populations are summarised in Table 16. Courville et al. [28] presented the results for two separate patient populations: total hip and total knee arthroplasty. In both patient populations, the strategy of treating all patients without screening was more effective and less costly. The sensitivity analysis demonstrated that the results were robust. The findings suggest that pre-operative screening for *S. aureus* was cost-effective. Slover et al. [25] presented their results in a graphical format, which clearly demonstrated the relationship between costs and *S. aureus* infection rates. The findings suggested that pre-operative screening followed by treatment for decolonisation of *S. aureus*-positive patients and an approach consisting of treating all patients without prior screening were both cost-effective strategies compared with absence of intervention.

Although a synthesis of these two evaluations was not possible, both studies independently demonstrated that screening for *S. aureus* followed by decolonisation of *S. aureus*-positive patients in a general hip/knee arthroplasty population was likely to be cost-effective.

Wassenberg et al. [30] evaluated a broader patient population, which included prosthesis recipients and found that, compared with absence of screening, universal screening for *S. aureus* prevented seven surgical site infections, resulted in a gain of 14 life-years and savings of EUR 47 746, whereas empirical treatment of all patients prevented three surgical site infections, resulted in a gain of 24 life-years and savings of EUR 178 970. Both strategies were more effective and less costly than absence of screening.

Although it was impossible to make direct comparisons or a synthesis of results, these three evaluations suggested that screening for *S. aureus* and treating *S. aureus* -positive patients pre-operatively was cost-effective in a hip/knee prosthesis patient population. The heterogeneous evaluated populations may suggest that the results are generally robust to a broad population of hip and knee prosthesis patients.

Young et al. [33] evaluated screening for *S. aureus* in a more general surgical population and found that both strategies (screening then treatment, and treating all patients without prior screening) were more effective and less costly than absence of screening. The results showed that both strategies were cost-saving due to the high cost of treating healthcare-associated infections.

In these four modelling studies, efficacy of the decolonisation treatment was an important parameter, along with the assumptions regarding the cost of infections. Despite variations in quality, as well as the different underlying modelling assumptions and structure, the results of these studies all suggested that pre-operative screening and decolonisation may be a cost-effective strategy in some surgical populations. Additionally, three of the studies suggested that a ‘treat all’ approach may be an attractive strategy.

Table 16. Summary results – *S. aureus* screening

Author	Study year	Intervention(s)/comparator(s)	Results
Courville et al. [28]	2012	Strategy A: Screening for *S. aureus* and treatment of carriers Strategy B: Treatment of all patients Strategy C: No intervention.	For both evaluated populations: Strategy A dominated C. Strategy B dominated A and C Total cost for strategy A = USD 24 471(THA) & USD 24 611(TKA) Total cost for strategy B = USD 24 258(THA) & USD 24 378(TKA) Total cost for strategy C = USD 24 506(THA) & USD 24 667(TKA) Total QALY for strategy A = 0.7983(THA) & 0.6785(TKA) Total QALY for strategy B = 0.7985(THA) & 0.6787(TKA) Total QALY for strategy C = 0.7980(THA) & 0.6783(TKA).
Lee et al. [27]	2011	Strategy A: Screening for *S. aureus* and treatment of carriers Strategy B: No screening.	Results were presented for a range of decolonisation and colonisation prevalence rates. High colonisation prevalence and high decolonisation rates were required to get results that may be cost-effective at thresholds of USD 100 000.
Slover et al. [25]	2011	Strategy A: Screening for *S. aureus* and treatment. Strategy B: No screening	Results were presented graphically. For both populations evaluated the findings suggest only a small reduction in infection is required to achieve cost savings.
Wassenberg et al. [30]	2011	Strategy A: Screening for *S. aureus* and treatment of carriers. Strategy B: Treatment of all patients. Strategy C: No intervention	Strategies A and B dominated strategy C Strategy A prevented seven surgical site infections and gained 14 life-years. Strategy B prevented three surgical site infections and gained 24 life-years. Strategy A saved EUR 47 746 compared with C Strategy B saved EUR 178 970 compared with C.
Young et al. [33]	2006	Strategy A: Screening for *S. aureus* and treatment of carriers. Strategy B: Treatment of all patients. Strategy C: No intervention	Strategies A and B dominated strategy C. Strategy A prevented 86 infections compared with C. Strategy B prevented 86 infections compared with C. Strategy A saved USD 1 019 207 compared with C Strategy B saved USD 877 052 compared with C.

Lee et al. [27] analysed a very specific population (i.e. women undergoing a planned Caesarean section) and their findings may not be comparable with those of the other four evaluations. Lee et al. [27] presented incremental cost-effectiveness ratios that ranged from USD 184 171 per QALY to USD 761 849 per QALY depending on prevalence of colonisation, decolonisation success rate and culture method. These findings suggested that a strategy of routine screening for *S. aureus* followed with decolonisation of *S. aureus*-positive patients was not cost-effective. As the only analysis in this patient population, it is difficult to draw conclusions for all women undergoing planned Caesarean section.

Quality assessment

Quality of the studies ranged from poor to adequate. The quality of the evaluation by Courville et al. [28] was adequate. The details of the model and input parameters were clearly reported, along with the perspective and form of the economic evaluation. The derivation of the effectiveness inputs was not systematic; however, relevant studies were identified and included. The authors acknowledged the uncertainty surrounding the main clinical effect parameter (i.e. efficacy of mupirocin) and a large proportion of the sensitivity analyses focused on this parameter. The use of local data and the lack of information on resources used limited the possibility to generalise on the basis of the study findings. In addition, more robust methods of dealing with uncertainty may have allowed stronger conclusions to be drawn. The results were uncertain and would be difficult to generalise to other settings.

The quality of the study by Slover et al. [25] was poor. The details of the model and input parameters were well presented. However, there was no information on the population from which the clinical data were derived. Furthermore, only limited cost data were reported and no information on cost adjustments or price year was reported. Some sensitivity analysis was undertaken and was presented as the findings rather than as an incremental analysis, which is the more usual manner of presenting cost-effectiveness results. The focus of the study appeared to be the potential cost-savings of the screening strategy rather than the cost-effectiveness of the screening strategy. A time horizon was not reported, making it difficult to determine if all relevant costs and effects had been incorporated into the model. The results may be indicative of cost-savings, but are unlikely to be robust enough to inform decision making.

Overall, the quality of the study by Wassenberg et al. [30] was considered adequate. The details of the model structure and input parameters were well presented. The derivation of the clinical inputs was not systematic, leading to some uncertainty and potential issues with the generalisation of the results. However, the results were valid for the authors' setting. The perspective was stated to be societal even though only direct costs were considered. Exclusion of productivity costs was justified by the authors based on the fact that the population studied was over 70 years old. Nevertheless, inclusion of productivity costs would probably have helped increase the cost-effectiveness of the intervention. Detailed information on the costing adjustments and price year were reported, along with a limited amount of resource use data. Although the methods were adequate and the results appropriate, it may not be possible to generalise the results to other settings.

The quality of the study by Young et al. [33] was considered adequate. The model structure and the input parameters were fully reported. A review of the literature was undertaken to obtain clinical estimates and, in the majority of cases, randomised clinical trial data were used. The summary measures of benefit used were infection cases prevented and life-years saved. The estimation of life-years saved was not discussed, making it unclear how these were derived. The analysis was undertaken from a societal perspective and all relevant costs were included. Costs were taken from the literature and, whilst fully referenced, only limited information was reported on resources used. However, all adjustments and a price year were reported. The lack of detailed information on resource use had an impact on the potential for generalising the study findings. The authors undertook a range of sensitivity analyses. They did not include a probabilistic analysis, which is widely considered to be the gold standard for this purpose, but included a variety of one-way, multi-way and scenario analyses which all demonstrated the general robustness of the findings. The study was generally well reported and the results are likely to be valid.

The quality of the study by Lee et al. [27] was considered adequate. Information on the structure of the model and the input parameters was presented in full. The clinical data were derived from the published literature. The details of the individual studies were not presented. The authors elected to use QALYs as the measure of benefit. However, they did not present detailed information on the derivation of the utility weights, opting instead to provide limited information on the populations from which the estimates were obtained. All costs relevant to the perspective were included and some unit costs/resource use data were also presented. Transparent costing would have helped when drawing conclusions on possible generalisation. An appropriate incremental analysis was undertaken, although due to the large number of scenarios only some of the results were presented. All parameters were assigned distributions and the results of the probabilistic analysis were presented narratively. No scatterplot or cost-effectiveness acceptability curves were presented. Use of probabilistic analysis would have helped to better characterise the uncertainty in the model inputs and improve the reliability of the results.

Evidence statement

Courville et al. [28] assessed the cost-effectiveness of pre-operative screening for *S. aureus* and treatment with mupirocin of *S. aureus*-positive patients undergoing total hip arthroplasty or total knee arthroplasty. The authors concluded that pre-operative treatment of all patients was cost-effective compared with screening for *S. aureus* and only treating *S. aureus*-positive patients. The analysis was based on a robust methodological framework that reported all model assumptions, but did not fully account for uncertainty. The authors' conclusions appear valid within the scope of the analysis undertaken.

Slover et al. [25] evaluated the cost-savings associated with a pre-operative *S. aureus* screening and decolonisation strategy for patients undergoing arthroplasty and spinal fusion. The authors concluded that, in the evaluated patient population, screening for *S. aureus* and decolonisation of *S. aureus*-positive patients only needed to achieve a small reduction in the infection rate to be cost-saving. However, elements of methodology were not fully reported, making it difficult to draw strong conclusions from this study.

Wassenberg et al. [30] examined the cost-effectiveness of pre-operative screening for nasal *S. aureus* carriage followed by eradication treatment of identified carriers versus empiric treatment of all patients without screening for *S. aureus* carriage. The authors concluded that pre-operative screening and eradication of carriage saved both life-years and costs compared to other strategies. Overall, the study used a conventional cost-effectiveness methodology and the authors' conclusions appeared robust. However, the study would have benefited from a more extensive sensitivity analysis.

Young et al. [33] examined three strategies for the prevention of healthcare-associated *S. aureus* infections: screening for *S. aureus* and treatment of *S. aureus*-positive patients, treatment of all patients without screening; and absence of intervention (no treatment). The authors concluded that both interventions were cost-effective alternatives to no treatment. The quality of the study was adequate, although there was some uncertainty in the outcomes.

Lee et al. [27] assessed the cost-effectiveness of routine pre-operative *S. aureus* screening and decolonisation of *S. aureus*-positive patients for women who underwent planned Caesarean section. The authors concluded that routine screening and decolonisation was not cost-effective from the perspective of the third-party payer. The study used transparent methods that considered the impact of alternative assumptions on the model results, although little information on clinical sources was reported.

Overall summary

In general, the results of these evaluations suggested that screening for *S. aureus* and decolonisation of *S. aureus*-positive patients in surgical populations is cost-effective.

However, there were several issues that varied across the evaluations and would need to be considered if further evaluations are to be undertaken. These include:

- baseline prevalence rates – these were variable across the studies ranging between 1% and 26%;
- muprocin efficacy rate – treatment efficacy was incorporated in different ways, but was not consistent across studies;
- screening test selection, sensitivity and specificity and turnaround time were all variable:
  - rapid screening (PCR), chromogenic agar, culture screening;
  - 24 hours, 36 hours, 48 hours;
- compliance with treatment was not explicitly considered in all of the studies;
- appropriate time horizon – short-term, long-term;
- appropriate outcomes – infection rates, QALYs.

3.4.7 Screening to detect VRE

Study characteristics

Only one study evaluating screening for VRE, followed by isolation of VRE-positive patients was identified. Lee et al. [20] used a Markov model to evaluate the cost-effectiveness of three alternative screening strategies over a non-specified, but short time period. Strategies for weekly VRE screening varied by target population: (a) all patients in high-risk areas, (b) all patients in high-risk areas plus patients with history of renal disease and (c) all patients in high-risk areas plus patients hospitalised in the previous two years. Data on effectiveness were obtained from published sources; some details were reported. A summary of key characteristics is presented in Table 17. The summary outcome measure was survival rate. Resource use and unit costs were presented and all costs relevant to the adopted hospital perspective were included. The price year and relevant discounting were reported. Probabilistic methods were employed to characterise uncertainty in the model input parameters. An incremental analysis was not undertaken. Results were presented in a disaggregated manner (i.e. costs and outcomes were presented separately).

Table 17. Study characteristics – VRE screening

Study	Study year	Population	Economic evaluation design	Effectiveness evidence	Intervrvention
Lee et al. [20] USA, CEA	2005	Hospitalised patients	Model	Epidemiological study	A: Screening patients in high-risk areas B: Strategy A plus patients with renal disease history C: Strategy A plus patients hospitalised in the previous two years.

Outcomes

The survival rate ranged from 87.4–87.6% and total costs per patient ranged from USD 4 064 to USD 5 180, depending on the strategy. The results demonstrated that screening all patients in high-risk areas plus those hospitalised in the two years prior to this hospitalisation was the most effective and least costly strategy. The outcome of the probabilistic analysis suggested that the results were robust. The results are summarised in Table 18.

Table 18. Summary results – VRE screening

Author	Study year	Intervention(s) & comparator(s)	Results
Lee et al. [20]	2005	Strategy A: screening patients in high-risk areas Strategy B: strategy A plus patients with renal disease history Strategy C: strategy A plus patients hospitalised in the previous two years	Strategy C dominated both Strategy A and Strategy B (i.e. more effective and less costly) Survival rate for Strategy A = 87.50% Survival rate for Strategy B = 87.41% Survival rate for Strategy C= 87.56% Total cost for Strategy A = USD 4 544 Total cost for Strategy B = USD 5 180 Total cost for Strategy C = USD 4 064.

Quality assessment

The quality of the study was good. The authors presented full details of their model structure, inputs parameters, sources, sensitivity analyses and results. The use of hospital-specific data might have introduced issues making it difficult to generalise the results, but much of the uncertainty was characterised by the use of probabilistic methods. No time period was reported, but the analysis appeared to be conducted over the short-term and the authors stated that discounting was not relevant. A more systematic approach to identifying model inputs and further information on resource use would have made it easier to generalise the findings, but overall the methods were robust and the findings appropriate.

Evidence statement

Lee et al. [20] evaluated three screening strategies for identifying VRE carriers among hospitalised patients. Strategies included weekly screening of high-risk patients plus other defined patient groups. The authors concluded that weekly screening of high-risk patients plus those hospitalised in the two-year period prior to the current hospitalisation were the most cost-effective option. The conclusions were appropriate and the overall quality of the study was good.

Overall summary

Given the lack of evaluations investigating screening for VRE, it was difficult to draw general conclusions on the cost-effectiveness of alternative strategies. The results of the only analysis available were valid, but it may not be possible to generalise them to other clinical settings.

4. Discussion

The aim of the project was to review the available cost-effectiveness literature with a view to informing discussion at an expert meeting and a framework for future cost-effectiveness analysis.

The interventions which were the focus of this report included (a) hand-hygiene interventions; (b) screening, isolation and decolonisation, and (c) personal protective equipment targeted at prevention and/or control of HAIs. This report is supplemented by a mapping report (available in digital format upon request) which includes details of all published economic evaluations reviewing interventions to prevent and control HAIs (see Supplementary Information).

4.1 Principle findings of the review

The review identified a total of 28 evaluations which met the inclusion criteria: four evaluating hand-hygiene interventions, three evaluating personal protective equipment, 21 evaluating screening and/or isolation and/or decolonisation strategies. There was a limited number of high-quality economic evaluations. The studies identified were generally of either poor or adequate quality, and were very heterogeneous.

The hand-hygiene interventions evaluated were variable, including two preparation interventions targeting surgeons and two very different programmes targeting hospital staff. The heterogeneity across the four studies precluded any quantitative analysis. It was also not possible to draw any general conclusions because three economic evaluations were underpinned by poor quality clinical data [6,8,9], whilst the remaining evaluation was undertaken in a country with poor water resources and it is therefore unlikely that it would be possible to apply the results in a European setting.

The three studies evaluating personal protective equipment also considered very heterogeneous interventions and populations. The populations ranged from neonates, in a neonatal intensive care unit, to a hypothetical inpatient population. None of the economic evaluations were of good quality and the clinical evidence underpinning the evaluations was weak. Due to the high level of heterogeneity in the methods, populations and interventions no general conclusion could be made. Furthermore, and despite the use of decision modelling, a comparison of underlying assumptions was not feasible.

Two studies evaluated isolation interventions; however, the two interventions were not similar and considered two different populations: one intervention aimed to reduce infections through the use of an isolation ward for a homogenous inpatient population [14] whereas the other intervention evaluated the impact of discontinuing isolation for heart transplant patients [15]. The two studies were not high quality; however, the disease modelling undertaken by Cooper et al. [14] did appear robust and may provide some insight into the transmission of MRSA and a solid base on which to build should further work be done in this area. For the purpose of this review, neither study enabled any general conclusions to be drawn.

The remaining 19 studies evaluated screening, isolation and decolonisation strategies for MRSA, all *S. aureus* infections and VRE [16-34]. The strategies evaluated varied from universal rapid testing with PCR to targeted screening with chromogenic agar, with or without isolation and/or with or without decolonisation treatment. Thirteen of the studies focused on MRSA, five on all *S. aureus* infections and one on VRE. Of the 19 studies, 15 used decision modelling. The heterogeneous nature of these studies made comparison and conclusions difficult. The results of the cost-effectiveness analyses were influenced by the structural assumptions and the data in the model. However, the results were not comparable, even in studies conducted within the same country. Five studies conducted in the USA evaluated strategies for screening hospital admissions for MRSA colonisation [22-24,29,34]. The studies evaluated a variety of strategies to screen, isolate and decolonise patients; no two studies evaluated the same type of intervention. In addition, the model structures, underlying assumptions and data inputs were heterogeneous. For example, the baseline prevalence rate for universal screening for MRSA across the five studies ranged from 1.8–8.3%; while the baseline rate for targeted screening for MRSA ranged from 3.2–15.0%. Furthermore, the rate of infection after colonisation also varied greatly. This level of heterogeneity between studies did not allow comparisons to be made. The evidence in this report suggests that some form of screening for MRSA, *S. aureus* and/or VRE, followed by some form of intervention is likely to be cost-effective; although there is insufficient evidence to determine which screening strategy or intervention would be the most cost-effective. Comparison of the economic evaluations was difficult due to the high levels of heterogeneity. To inform the discussion, some areas warrant further exploration of the heterogeneity of data on clinical effectiveness.

4.2 Limitations

One of the aims of this project was to assess the feasibility of using the economic evidence base to inform a framework for future economic evaluations. The high level of heterogeneity across studies made this impossible. The scope of the project was limited to economic evaluations, however the clinical effectiveness data underpinning

many of the evaluations was of poor quality and potentially biased. In this review, no attempt was made to review evidence of clinical effectiveness, however a systematic review with a wider scope including such evidence would be useful in informing further research. The scope was further limited to three types of interventions, which were selected based on an a priori belief that these would be the areas of most interest to ECDC's target audience. However, it is possible that limiting to specific interventions rather than broader organisational/service delivery interventions may have led to results that proved difficult to generalise across Europe. Establishing the effectiveness of interventions prior to evaluating their cost-effectiveness is an obvious need. However, whether this would be feasible at an intervention level is unclear. Assessing the effectiveness of many of the interventions would require reliable prevalence and incidence data, which are likely to vary across settings. Furthermore, current practice, even within the same country, is inconsistent which only compounds this issue since prevalence and incidence rates would be affected by current hospital policies.

The review was undertaken using NHS EED as a source to identify economic evaluations. The comprehensive coverage of NHS EED makes it unlikely that any published economic evaluation was missed; however, grey literature was not searched.

4.3 Principle findings of the expert meeting

The literature review was circulated to all the participating experts prior to the meeting. Initial discussion focused on the lack of good quality evidence found in the review. It was felt that the focus of the review was potentially too narrow, and that inclusion should not have been limited solely to economic evaluations but should have also included economic analyses (i.e. cost studies). The experts also felt that, given the needs of ECDC to provide evidence-based scientific advice that could be generalised across Europe, switching the focus to management issues, infrastructure, staff training and policy evaluation might be useful. In addition, data relating to resource use and costs of such prevention programmes, even without a full economic analysis, may aid decision-makers. The experts felt that it was not clear from the review whether the clinical effectiveness underpinning the types of intervention evaluated was robust. The evidence base for clinical effectiveness was not reviewed and the experts considered that many of the economic evaluations were conducted or informed by poor-quality clinical evidence. The expert meeting concluded that there was a need to establish the effectiveness of interventions before evaluating their cost-effectiveness.

4.4 Further research needed

We identified many studies assessing the cost-effectiveness of a variety of interventions to prevent and control of HAIs. However, many of the economic evaluations were underpinned by poor-quality evidence of clinical effectiveness, and the studies that provided better quality evidence of clinical effectiveness could not be generalised. A systematic review of the clinical effectiveness of interventions would enable ineffective interventions to be excluded from further discussion. It would also facilitate further cost-effectiveness research to focus on those interventions established as being effective.

Taking a Europe-wide perspective, there is a strong need for cost-effectiveness research across healthcare settings and patient populations. It might be beneficial to achieve a consensus amongst researchers, practitioners and policymakers as to which healthcare settings and patient populations should be the focus of future research. Most of the cost-effectiveness analyses reviewed focused on *S. aureus*, but other microorganisms are also clinically relevant. It is significant that we did not identify cost-effectiveness studies focusing on *Clostridium difficile* infection, which may be more prevalent than MRSA in some European hospitals [35,36]. Questions for future research should focus on the nature of the intervention (whether to increase efforts to target a broad range of HAIs through promotion of hand hygiene or to focus on screening and isolation and, if so, for which microorganisms) and on its implementation (individual or multi-component interventions). If the latter, any primary research should be designed to ensure that the contribution of each individual component of the intervention can be assessed and that appropriate intermediate outcomes are measured.

It is likely that, at a hospital level across Europe, there is considerable variation in current procedures which may make evaluation of individual interventions impractical, although an exploration of this heterogeneity may potentially be informative. Furthermore, there may be some value in establishing the effectiveness and cost-effectiveness of prevention and control of HAIs at a policy level, before looking at individual interventions.

5. Conclusions and next steps

The review identified a total of 28 evaluations which met the inclusion criteria: four evaluating hand hygiene interventions, three evaluating personal protective equipment, 21 evaluating screening and/or isolation and/or decolonisation strategies. There was a limited number of high-quality economic evaluations. The studies identified were generally of either poor or adequate quality, and were very heterogeneous.

The identified economic evaluations for this report were generally of poor quality and displayed a high level of heterogeneity across interventions, populations, settings, model structures, prevalence, incidence rates, and other modelling inputs. This heterogeneity precluded the possibility of making any general recommendation on the cost-effectiveness of the interventions to prevent and control HAIs.

Our aim of facilitating the development of a coherent framework for future economic evaluations across Europe was also hindered by the poor quality and heterogeneous evidence base. One of the main limitations was that many of the evaluations incorporated such poor-quality evidence of effectiveness that it was unclear whether those interventions being evaluated for cost-effectiveness were in fact effective at preventing HAIs. Indeed, there is little value in undertaking cost-effectiveness analyses for interventions which are not deemed clinically effective. Discussions with experts demonstrated agreement that the lack of evidence for clinical effectiveness of the interventions in the studies greatly limited the usefulness of the literature review. Due to these limitations, no attempt was made to develop a framework for future economic evaluations across Europe.

Development of a European framework for future economic evaluations of control and/or prevention of HAIs, intended to provide future researchers with common assumptions, would only support research in this area if based on high-quality evidence of the effectiveness of interventions. Common assumptions include baseline prevalence rates, screening test selection, sensitivity and specificity of the selected test, effectiveness of decolonisation, adherence levels, mupirocin resistance and efficacy, turnaround time of test, transmission, compliance, time horizon and outcome considered. As previously stated, drawing conclusions on the basis of heterogeneous, weak evidence on the effectiveness of specific interventions could lead to inappropriate decision making. Given the diversity of health systems across Europe and the country-specific assumptions required, it is likely that several frameworks would need to be developed for economic evaluations. Each framework could provide future research, with the common assumptions to be used for specific or similarly grouped health systems and/or specific patient populations/study settings across the Europe, whilst enabling less generalisable elements/data to be varied accordingly. To undertake this work requires a better understanding of the current state-of-play in all settings (i.e. health systems, country and population specificities), including prevalence and incidence rates, hospital practices and procedures. The current evidence base, containing results from only a few studies which cannot be generalised across Europe, makes it difficult to provide clear advice on general implications for practice.

Further research in this area is obviously needed. However, to progress efficiently some consensus must be established, both on relevant decision questions and effective interventions to be subjected to economic evaluation. The latter point is crucial as high-quality research on the potential effectiveness of the various interventions for preventing and/or controlling HAIs is fundamental to establishing cost-effectiveness. Although establishing clinical effectiveness of interventions was beyond the scope of this project, we would recommend that future attempts to establish the cost-effectiveness of such interventions are underpinned by robust evidence of clinical effectiveness. A high-quality systematic review may provide such robust evidence. Failing this, high-quality primary research would then be required.

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Appendix 1. Search strategies

Search strategy for NHS EED using the CRD interface (used to identify potential includes for this project)

1	MeSH DESCRIPTOR Cross Infection EXPLODE ALL TREES
2	MeSH DESCRIPTOR Infection Control EXPLODE ALL TREES
3	infection NEAR3 control*
4	hospital* NEAR3 infect*
5	healthcare NEAR3 infect*
6	health care NEAR3 infect*
7	nosocomial
8	cross NEAR3 infect*
9	MeSH DESCRIPTOR Catheter-Related Infections
10	catheter* NEAR3 infect*
11	(central line or intravenous or intravascular) NEAR3 infect*
12	(pacemaker* or stent* or shunt* or intracardiac) NEAR2 infect*
13	MeSH DESCRIPTOR Surgical Wound Infection
14	(surg* or operat*) NEAR2 infect*)
15	MeSH DESCRIPTOR Prosthesis-Related Infections
16	(prosthe* or arthropla*) NEAR3 infect*
17	(postoperative or post-operative or postsurg* or post-surg*) NEAR2 infect*
18	(intensive care or critical care or ICU) NEAR2 infect*
19	((ventilator or ventilation or hospital or health care or healthcare or surg*) NEAR2 pneumon*) or VAP or HAP
20	MeSH DESCRIPTOR Bacteremia EXPLODE ALL TREES
21	bacteremia* or bacteraemia*
22	(blood* NEAR2 infect*)
23	MeSH DESCRIPTOR Methicillin-Resistant Staphylococcus aureus
24	MeSH DESCRIPTOR Staphylococcus aureus EXPLODE ALL TREES
25	staphylococc* NEAR2 (infect* or aureus)
26	mrsa or emrsa or mssa or orsa
27	MeSH DESCRIPTOR Clostridium difficile EXPLODE ALL TREES
28	clostridium difficile or C difficile or C-difficile or C-diff
29	bacillus difficilis or bacillus difficile
30	MeSH DESCRIPTOR Escherichia coli EXPLODE ALL TREES
31	MeSH DESCRIPTOR Escherichia coli Infections EXPLODE ALL TREES
32	escherichia coli or e coli
33	MeSH DESCRIPTOR Listeria EXPLODE ALL TREES
34	MeSH DESCRIPTOR Listeria Infections EXPLODE ALL TREES
35	listeria
36	MeSH DESCRIPTOR Adenoviridae EXPLODE ALL TREES
37	MeSH DESCRIPTOR Adenoviridae Infections EXPLODE ALL TREES
38	adenovirus* or adenoviridae
39	MeSH DESCRIPTOR Enterococcus EXPLODE ALL TREES
40	enterococci or enterococcus
41	MeSH DESCRIPTOR Legionnaires' Disease EXPLODE ALL TREES 2
42	MeSH DESCRIPTOR Legionella EXPLODE ALL TREES
43	legionella or legionnaire*
44	MeSH DESCRIPTOR Norovirus EXPLODE ALL TREES
45	norovirus* or norwalk
46	MeSH DESCRIPTOR beta-Lactamases EXPLODE ALL TREES
47	beta lactamase* or EBSL
48	MeSH DESCRIPTOR Klebsiella Infections EXPLODE ALL TREES
49	(klebsiella NEAR2 infect*) or rhinoscleroma* or (nasal NEAR2 scleroma*)
50	MeSH DESCRIPTOR Pseudomonas Infections
51	MeSH descriptor Pseudomonas aeruginosa explode all trees
52	pseudomonas NEAR3 (aeruginosa or pyocyanea or infect*)
53	MeSH DESCRIPTOR Stenotrophomonas EXPLODE ALL TREES
54	strenotrophomonas
55	MeSH DESCRIPTOR Acinetobacter Infections
56	(acinetobacter or mimae) NEAR2 infect*
57	MeSH DESCRIPTOR Candida albicans
58	candida* NEAR2 albican*
59	MeSH DESCRIPTOR Streptococcus pneumoniae

60 (streptococcus or diplococcus) NEAR2 (pneumoniae or pneumococc*)
61 coagulase negative staphylococci
62 MeSH DESCRIPTOR Enterobacteriaceae EXPLODE ALL TREES
63 MeSH DESCRIPTOR Enterobacteriaceae Infections EXPLODE ALL TREES
64 MeSH DESCRIPTOR Enterobacter EXPLODE ALL TREES
65 coliform* or enterobacter* or aerobacter*
66 MeSH DESCRIPTOR Serratia EXPLODE ALL TREES
67 MeSH DESCRIPTOR Serratia Infections
68 serratia
69 MeSH DESCRIPTOR Citrobacter EXPLODE ALL TREES
70 citrobacter
71 MeSH DESCRIPTOR Bacteroides EXPLODE ALL TREES
72 MeSH DESCRIPTOR Bacteroides Infections
73 bacteroides
74 MeSH DESCRIPTOR Bacteria, Anaerobic
75 (anaerobic NEAR2 (bacteria* or infect*)) or anaerobe or anaerobes
76 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34
77 #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75
78 #76 OR #77
79 * IN NHSEED
80 #78 AND #79

Hand hygiene search strategies

NHS EED (CRD interface: http://www.crd.york.ac.uk/crdweb/ searched 25 October 2012).

Study	Study year	Population
1	MeSH DESCRIPTOR Handwashing EXPLODE ALL TREES	30
2	hand* NEAR3 (hygiene or wash* or clean* or disinfect* or antisep* or saniti* or steril* or scrub*)	72
3	handwash*	38
4	surgical* NEAR3 scrub*	6
5	#1 OR #2 OR #3 OR #4	84
6	(*) IN NHSEED	13025
7	#5 AND #6	28

HEED (Wiley Online Library). Sep/2012. Searched 25 October 2012.

AX='hand hygiene' within 3 or 'hands hygiene' within 3 or 'hand wash' within 3 or 'hands wash' within 3 or 'hand washing' within 3 or 'hands washing' within 3 or 'hand clean' within 3 or 'hands clean' within 3 or 'hand cleaning' within 3 or 'hands cleaning' within 3 or 'hand antiseptic' within 3 or 'hands antiseptic' within 3 or 'hand antisepsis' within 3 or 'hands antisepsis' within 3 (8)

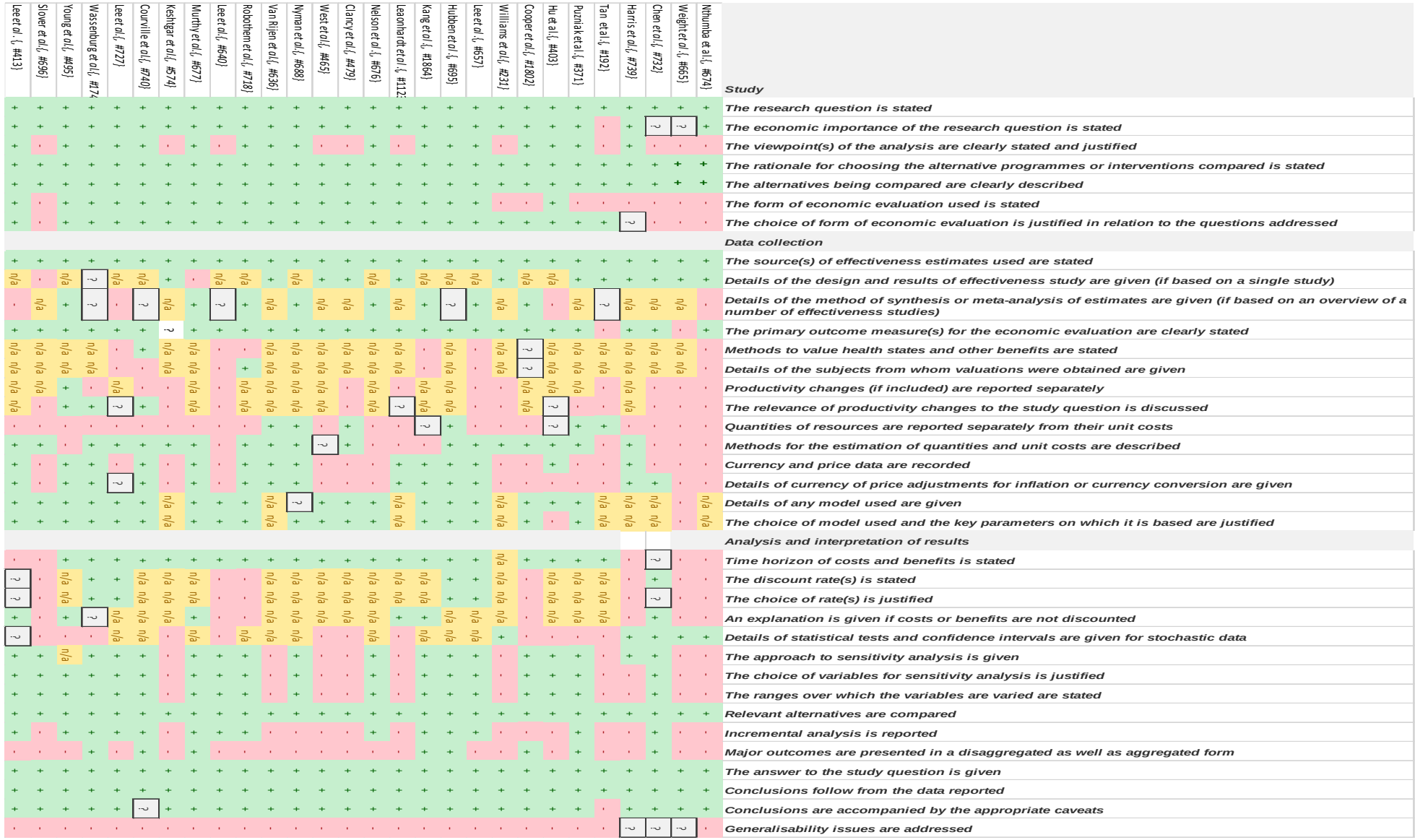
AX='hand disinfect' within 3 or 'hands disinfect' within 3 or 'hand disinfected' within 3 or 'hands disinfected' within 3 or 'hand sanitize' within 3 or 'hands sanitize' within 3 or 'hand sanitized' within 3 or 'hands sanitized' within 3 or 'hand sanitization' within 3 or 'hands sanitization' within 3 or 'hand sterilize' within 3 or 'hands sterilize' within 3 or 'hand sterilized' within 3 or 'hands sterilized' within 3 or 'hand sterility' within 3 or 'hands sterility' within 3 (0)

AX=handwash or handwashing (5)

AX='surgical scrub' within 3 or 'surgical scrubbing' within 3 or 'hand scrub' within 3 or 'hands scrub' within 3 or 'hand scrubbing' within 3 or 'hands scrubbing' within 3 (0)

CS=1 or 2 or 3 or 4 (12)

Appendix 2. Drummond checklist



European Centre for Disease Prevention and Control (ECDC)

Postal address:
Granits väg 8, SE-171 65 Solna, Sweden

Visiting address:
Tomtebodavägen 11A, SE-171 65 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
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